Written evidence submitted by Roger Shinton (RES0046)

Case study: thrombolysis to treat ischaemic stroke

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In the late 1980s acute treatment with biological agents which dissolve blood clots in the coronary vessels was introduced into mainstream clinical practice following large trials demonstrating treatment consistently reduced mortality. It was known at the time that a complication among treated heart attack patients was fatal intracranial haemorrhage. For this reason there was considerable caution in promoting the same treatments for acute ischaemic stroke, although clot formation is also often part of the stroke pathway.

Four stroke trials, each involving hundreds of stroke patients, were halted, primarily because of significantly increased mortality rates in those treated with thrombolytics. (ASK 1996, Atlantis 1999, MAST-E 1996, MAST –I 1995) The principal hazard was both fatal and symptomatic intracranial haemorrhage, the latter with a frequency of around 10 per cent in moderately severe stroke patients. (Whiteley 2016)

The FDA approval to use one particular thrombolytic, alteplase (Genentech - US, Boehringer Ingelheim - Europe), was first granted in the US in 1996 after a controversial trial run by the US National Institute of Neurological Disorders and Stroke (NINDS, published in 1995) claimed to reliably demonstrate that more patients were left free of any appreciable disability if treated within 3 hours. (NINDS 1995) The claim was mortality was unaffected. A repeat trial of alteplase treatment specifically within 3 hours has not been conducted to my knowledge.

At the time, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK declined to accept the NINDS trial constituted sufficient evidence to allow marketing authorisation for stroke in the UK, but was overruled by the European Commission in 2002 following an arbitration process. (MHRA Review 2015)

Many regarded the treatment as controversial. These concerns were re-inforced when the largest thrombolytic stroke trial (The Third International Stroke Trial with treatment up to 6 hours in 3025 patients) was published in 2012. The primary endpoint showed no statistically significant benefit but significant excess early death (a 4% increase) and intracranial haemorrhage were clear hazards. (IST-3 2012)

Having left clinical medicine in 2012, I had the time to look carefully at the background story behind the published evidence. Initial concerns were then presented to the then President of the Royal College of Physicians of London (Sir Richard Thompson) in 2012, who then also liaised with Dr Peter Wilmshurst (a UK leader in critically reviewing evidence). A letter addressing some concerns was published by myself (but with support from colleagues) in The Lancet in 2014. (Shinton 2014) The letter attracted published responses from those involved in the trials, but also a promise from the MHRA to investigate the points raised by establishing an Expert Working Group (EWG).

Concerns centred around the degree of transparency and the conduct, handling of data and presentations in the thrombolysis trials. Prior to submitting evidence to the MHRA Review
I sought key data tabulations from the Stroke Thrombolysis Trialists Collaboration (STTC), based at the Clinical Trials Service Unit and Epidemiological Studies Unit within Oxford University. This request was turned down on the basis that the corresponding author of the primary STTC publication evaluating the published evidence of pooled trial data (Professor Colin Baigent) was now a member of the EWG. (Emberson 2014) This refusal was not published with the 800 page plus MHRA report advocating minimal amendments to the marketing authorisation. (MHRA Review 2015) This, despite protestations of a transparent process.

Unable to make a complete submission, after having been refused access to evidence sought, I approached the BBC and this produced a ‘File on 4’ radio documentary in June 2015 which culminated in the Chief Medical Officer (CMO) asking the Academy of Medical Sciences to review concerns about the degree to which clinical scientists were trustworthy in how evidence was evaluated. Before ‘File on 4’ was broadcast, three senior colleagues (Drs Tom Heafield, John Lowes and David Jenkins) and I had requested in writing that the Secretary of State for Health intervene to protect patients and assist in making key trial data publicly available. The departmental written response, although acknowledging transparency was valued, indicated that the MHRA should be allowed to complete their current examination of evidence.

A colleague (Dr John Lowes) and I met with Sir John Tooke (Academy President), who had agreed to lead the Academy review requested by the CMO. He explained that, despite the impression given by the BBC documentary and main television news, the alteplase/stroke story was beyond the scope of the Academy Review, but he did agree to pass on our concerns to the CMO. A transcript of the Academy meeting was agreed.

Before and after the publication of the EWG report in the summer of 2015 both Dr Wilmshurst and Sir Richard Thompson repeatedly challenged the conduct of the EWG. Publication followed shortly after a question to the Government from the shadow minister for public health. Dr Wilmshurst had been a member of the EWG and Sir Richard an official observer. In a further meeting at the MHRA, following publication, it was agreed I would be sent details by Dr. June Raine of information sought by the MHRA for the EWG. The response revealed that key information I would have expected, relating to trial data, was not on the list.

Somewhat surprised that very considerable effort had been expended, with such an obvious lack of curiosity, by so many highly qualified professionals, I along with colleagues, looked again at the publications, but in more detail. I had previously noted some inconsistencies, which is why data were requested for clarification. It now became apparent that on the issue of mortality in the key alteplase trials, the presentation of evidence was most certainly confusing and ambiguous but was consistent with a serious misrepresentation of the evidence, especially on survival.

It was widely agreed, before the first major trials results were presented, that reduction of mortality and severe disability was the primary outcome goal of treatment, as mortality had been in the cardiac trials. In fact both early and later mortality increased in all the main trials, except in the trial which yielded regulatory approval in the US and Europe – the NINDS trial. (NINDS 1995) The extent and handling of missing data on vital status (alive/dead), survival time and how severe disability was assessed and presented remain of concern both in NINDS and other key trials. The NINDS survival figure, in particular,
Following a meeting of Sir Richard Thompson and myself with the CMO and MHRA in early 2017 our deepening concerns were to be examined quickly by the Commission on Human Medicines (CHM at the MHRA). At the CHM presentation in July 2017 by myself, accompanied by Sir Richard Thompson and Dr Peter Wilmshurst, we made perfectly clear that ongoing lack of trial protocols and key data (e.g. accurate individual trial mortality and missing data) led us to the view that it had not been wise to promote such a hazardous and resource demanding treatment before detailed information from the trials had been placed in the public domain. The MHRA continues to investigate, but at the time of writing we have no further information.

The above comments have just focused on mortality and missing survival data. Major problems in other areas such as randomisation, blinding, computerised tomography headscan (CT) results, disability scoring, inadequate statistical clarity, persisting and multiple numerical errors, withholding of study data/protocols and conflict of interest among trialists and reviewers merit similar concerns, too numerous to convey in detail in this report.

Publications in the New England Journal of Medicine, The Journal of the American Medical Association, The Lancet and elsewhere have presented evidence relating to stroke thrombolysis which is both unclear and seriously misleading. This problem will need addressing and correcting. Several hundred professionals, located around the world, could be involved, as trials were written up on behalf of all their collaborators. A first approach to address this with UK based editorial board members of the New England Journal of Medicine has been made and we await a response.

Reviews of the treatment appear, also, to have been superficial and have failed to explore key areas relevant to evaluating the evidence. No one will be surprised to know our old friend ‘conflict of interest’ lurks close to each report. (O’Fallon 2004, rt-PA investigators 2004, Wardlaw 2012, Wardlaw 2014) In addition, Royal College, National Institute of Health and Care Excellence (NICE), MHRA and Professional Society reviews have questions to answer.

Full disclosure of information to all parties is part of good practice at legal trials. Poor or misleading practice in relation to transparency with medical trials affects more than a defendant’s liberty.

Clinical staff and patients continue to follow the alteplase stroke guidelines on this hazardous, controversial and expensive treatment, enveloped in a fog of uninterpretable data which renders an assessment of the true picture of the balance of evidence quite impossible. The story around treatment for stroke provides a stark example of the challenges we all now face given the rapid expansion in the use of powerful medicines. A new strategy to better protect patients and provide affordable and effective treatments is now needed.
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References

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IST-3 2012  The IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial ((IST-3)): a randomised controlled trial. Lancet 2012; 379:2352-63


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Conflict of Interest

When working as a stroke physician I felt it was inappropriate to offer alteplase to stroke patients. In 2015 I publicly called for routine use of alteplase to be suspended pending the release of trial data.
My research investigating the background evidence on stroke thrombolysis has not received funding.
Addendum. Presentation at the International Stroke Conference 2018 on 25.1.18. concerning thrombolysis in the treatment of ischaemic stroke presenting with less severe neurological deficits within 3 hours (PRISMS).

In the initial report on 22.1.2018, it was stated that the author was not aware of a follow up study to NINDS specifically looking at treatment within 3 hours. In the last few days a report has come to light on the internet platform ‘Medscape’ (PRISMS: No benefit of tPA in Mild Stroke Without Disability – Medscape - Jan 31, 2018) of the results of a relevant study - PRISMS. An addendum has, therefore, been submitted to my initial report to the Science and Technology Committee enquiry.

The more reputable intial thrombolysis trials hoped to reduce death or death and severe disability in stroke patients treated with thrombolysis. Several of these trials were terminated early because of higher mortality rates in treated patients. This failure led to those promoting treatment to focus instead on prevention of low levels of neurological disability. These softer outcomes were based on subjective assessments and questionnaire responses. The claim was of only modest benefit and trial conduct was repeatedly under question.

The PRISMS trial (Trial Registry number NCT02072226) initially sought to examine the potential benefit of alteplase in stroke patients who presented with minimal disability within three hours. Individual patient data meta-analysis of previous questionable trials had suggested this group was the most likely of any to benefit from avoiding any substantive disability if treated (Emberson 2014). PRISMS, like so many thrombolysis trials, was terminated early. The plan was for 948 recruits, but only 307 were available for the intention-to-treat analysis. Of the 154 given alteplase 78.2% had no or minimal disability (modified Rankin Scale 0 or1) at 90 days compared to 81.5% of the 153 patients given placebo. This represented a trend towards worse outcome with treatment. None of the untreated patients suffered symptomatic intracerebral haemorrhage within 36 hours compared to 5 in the thrombolysed group. The only comment on mortality in this news report was that there was ‘no associated increase in mortality’. It should be noted to the credit of Genentech, the manufacturer of alteplase and sponsor of PRISMS, that these results have emerged.

Those promoting thrombolysis for the treatment of stroke consistently failed to show mortality could be reduced. It was increased. The hazards of thrombolysis are more frequent in more severe strokes. We now learn that an attempt to show benefit in a large trial of milder strokes, treated rapidly with alteplase, has proved unsuccessful. The treatment seemed both ineffective and hazardous. A last throw of the dice to make any substantive case for the treatment of stroke with thrombolysis, specifically alteplase, appears to have failed.
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Appendix Table I. Example of evidence for a single variable which undermines the credibility of the trial which gained alteplase approval for treatment of stroke – the NINDS trial

Before FDA approval in 1996

NINDS 1995 (NINDS 1995)

‘In cases of surviving patients with missing outcome data, outcome data after 3 months were used; if there were none, the data from the measurement closest in time, but at least seven days after randomisation, were used. Otherwise, the worst possible score was assigned.’ Note. The worst possible score for the modified Rankin disability score is 6 which means death.

‘Compliance with the protocol was excellent in this trial.’

‘Figure 2. There were 312 patients in each group, and no patient had missing data on mortality.’

Figure 2 was the graphic survival curve up to 3 months

After FDA approval in 1996

NINDS 1998 (Fagan 1998)

‘Modified Rankin disability scores and survival status at 7 to 10 days, 3 and 6 months, and 1 year were available for more than 95% of patients enrolled in the trial.’ Consequently it is likely 30 or 31 had this information missing. For some, presumably, survival status was missing but we are not told how many or how long after randomisation.

‘Discharge disposition data by Rankin disability score at 7 to 10 days were available for 535 of 572 patients alive at discharge.’ Consequently unavailable for 37.

‘Table 3. Disposition results from NINDS rt-PA Stroke Trial’

<table>
<thead>
<tr>
<th>Disposition</th>
<th>rt-PA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>35</td>
<td>40</td>
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</table>

Consequently 624 randomised into the trial minus 572 ‘alive at discharge’ means 52 had died before discharge. We are then told at disposition, i.e. discharge, 35 plus 40 i.e. 75 was the total coded as ‘dead’ in table 3. So 23 of those coded as ‘dead’ were almost certainly missing.

Conclusion. We are told in NINDS 1998 (Fagan 1998), Table 2 that 54 were ‘dead’ by 10 days, but were up to 23 of these ‘dead’ because they were missing and coded as ‘worst possible outcome’? If so the comment alongside the 1995 survival graph that ‘no patient had missing data on mortality’ is seriously misleading as is the survival curve.
Appendix Table 2. Further concerns around mortality data in the NINDS trial with reference to the MAST-I streptokinase trial


'Although it is recognised that the pathogenesis is not similar in all respects, an analogy can be made with acute myocardial infarction. In this latter condition it is well established that thrombolytic treatment significantly decreases early and late mortality. A potential benefit could likewise be expected in ischemic stroke.’

This Group included experienced trialists such as HJM Barnett, R Peto and C Warlow. Early on the hope was to reduce mortality. It is now widely accepted stroke thrombolysis increases mortality rather than decreasing it.

'The MAST-I design and administration is, therefore, very simple and practicable within the framework of busy routine clinical practice. However, this pragmatic approach makes close supervision of the conduct of the study necessary and also scrupulous analysis of the data from each patient.’

A similar clear statement has not been made by NINDS trialists, who have declined to release the study protocol to date.

In MAST-I we were told no patient was lost to follow up, although outcomes recorded before the end of the 6 month trial were used for 29 of the 622 patients. (MAST-I 1996) In NINDS this information has not been clarified.

NINDS has not performed a ‘worst-case scenario’ sensitivity analysis for mortality in which missing patients who were treated are coded ‘dead’, and missing patients who were not treated are coded ‘alive’. The individual patient data based meta-analysis of all larger alteplase trials has not published this either. (Emberson 2014) This analysis checks for bias in trial conduct. It appears this analysis could be a game changer.