A collaborative meta-analysis of individual participant data from all randomised trials of intravenous rt-PA versus control

The Stroke Thrombolysis Trialists’ (STT) Collaboration

Protocol
**Background**

For the treatment of patients with ischaemic stroke, the only approved medical treatments for use within the first few hours of onset are thrombolytic therapy with intravenous (iv) recombinant tissue plasminogen activator (rt-PA) and aspirin. In 2004, a collaborative analysis of pooled individual patient data from some of the trials of iv rt-PA assessed the effects of time on benefit from treatment (1), an analysis that was subsequently updated in 2010 to include the results of the ECASS-3 (2) and EPITHET (3) trials. These analyses demonstrated reliably that thrombolysis with intravenous rt-PA is both effective and safe when administered to particular types of patient within 4.5 hours of having an ischaemic stroke, and that treatment benefit diminishes with increasing treatment delay. However, several uncertainties remain regarding the potential effects of rt-PA when administered in different circumstances, as well as in different subgroups of patients (4).

In May 2012, results from the IST-3 trial of 3035 patients randomised to rt-PA versus control were reported (5), while several other trials were still ongoing (see Appendix A). In this third phase of the collaborative analysis of pooled individual patient data from the rt-PA trials, results from the IST-3 trial (and, if possible, the TESPI trial (6)) will be included to help address several key questions, including:

1. After what treatment delay is benefit (defined by modified Rankin Score [mRS] 0-1 at final follow-up at 3-6 months) lost or does harm begin, and do age or stroke severity modify the proportional effect of rt-PA on stroke outcome?

2. What are the effects of rt-PA on a range of other secondary outcomes, including: death within 90 days; symptomatic intracranial haemorrhage, fatal symptomatic intracranial haemorrhage, symptomatic ischemic brain oedema and early oedema, effacement and/or midline shift.

These and other planned lines of investigation are described fully in the published Statistical Analysis Plan (7), which was agreed by the Stroke Thrombolysis Treatment (STT) Collaborative Group prior to becoming unblinded to the results from IST-3.

**Importance of pre-specifying the planned analyses**

To reduce the inevitable spurious findings that can result from post hoc analyses, it is important to pre-specify and limit the main subgroup analyses arising from the updated individual patient data meta-analysis. Whilst it might be tempting to suggest particular thresholds of data related to the eligibility of past and current trials, these, in general should be avoided or minimised (as these same trials will be included in the proposed analyses and circular estimation should be avoided). Furthermore, agreeing on a protocol and then progressing rapidly to data collection and organisation will allow the Collaboration to respond rapidly to the publication of new data from each of the other trials that will complete in the next few years.

**Rationale**

Good practice includes assessment of all new trial results in the context of all relevant prior completed trials. The principal aim of this new phase of analyses...
would be to provide an updated guide on whom to treat. Robust data from an
updated individual patient meta-analysis would not only provide the highest
level of evidence, but consensus from ALL the trialists would be enormously
powerful in promoting a substantial increase in the appropriate use of rt-PA and
in silencing critics who have doubted the previous data.

**Potential scope of updated meta-analysis**
The main benefits of an individual participant data meta-analysis (sometimes
referred to as a “pooled” analysis) include an ability to address some important
outstanding questions, suggest new hypotheses and help identify future
research questions. In addition to further increasing the precision of information
on time to treatment, many outstanding questions about i.v. rt-PA therapy for
acute ischaemic stroke will be informed by this collaborative meta-analysis.
These are summarised in the Statistical Analysis Plan (7).

**Study eligibility**
All randomised trials with at least one randomised comparison of intravenous rt-
PA with control that have completed and reported main results by 30th June
2012. The trials identified by the updated Cochrane Systematic review that
meet this criterion are listed in Appendix A at the end of this protocol.

**Identification of eligible trials**
It is very unlikely that there are completed and potentially eligible trials that are
not listed in Appendix A. However, for completeness, a further search of the
Cochrane Stroke Group’s Specialised Register of Trials will be conducted.

**Data collection and checking**
We will seek individual participant data for all randomised individuals in relevant
trials. The requested data will comprise: baseline neurological, physiological,
and imaging characteristics and concomitant medications recorded at
randomisation, details of randomly allocated treatments (and the time from
stroke onset that they were commenced), date and type of primary and
secondary outcomes. The data will be checked carefully for internal
consistency and completeness of individual participant records, and for other
indicators of possible anomalies. All queries regarding particular trials will be
referred back to the sponsors or principal investigators of the trials, and
computer generated outputs consisting of detailed summary tabulations and
consistency checks will be returned to each collaborator for review and
confirmation.

**Outcomes & Adjudication**
Data will be sought on key primary and secondary outcomes, as defined and
adjudicated in each trial (or adjudicated independently after trial completion [see
the Statistical Analysis Plan (7)]). If adjudicated outcomes are not available,
then the best available information on these outcomes will be recorded.

**Analytical strategy**
The analytical strategy, including definition of the primary and secondary
outcomes, can be found in the published Statistical Analysis Plan (7), which
was agreed by the STT Collaborative Group prior to becoming unblinded to the
results from IST-3.
Steering Group
The conduct of the data collection, analysis, preparation of manuscripts will be overseen by the Steering Group. This will include a lead representative from each trial, responsible for consulting with members of the trial they represent (eg to collate comments on circulated materials), for participating in manuscript preparation and editing, and for agreeing all procedural issues.

Publication policy
All publications will be in the name of the Stroke Thrombolysis Trialists’ (STT) Collaboration, with the names of collaborators listed at the end of the paper. All collaborators will be expected to participate fully in manuscript preparation and editing, and will be expected to consult with, and collate comments from, colleagues from the trials they represent. Publications will be circulated for comments and approval before submission to peer review. The principles for agreeing the text of papers are that any such papers should:

- focus on conveying clear findings on which all trial groups are agreed, with controversial findings labelled as such;
- where there is disagreement, the aim should be to moderate language to try to reach agreement; BUT
- if agreement cannot be reached, then trials have the right to remove their data from an analysis.

Confidentiality, data storage and handling
All trial data will be regarded as strictly confidential, and will not be provided to any third party without the prior written permission of the owners of the data. However, if appropriate, and agreed by the steering group, the same data set may be held elsewhere, and if so, strict confidentiality and data security at each data repository will be maintained. The secretariat will be responsible for collating and checking the data (in one location until complete, then will ensure the final locked analysis dataset is held in each data repository).

Funding and grant applications
Collaborators will be asked to fund their own travel costs for initial meetings (accommodation and meals will be provided). The secretariat will prepare grant applications as appropriate for support for the costs of research staff, data management and meeting (travel and accommodation) costs. Such applications will be submitted in the name of the group as a whole, with the members of the Steering Group named as co-applicants.
References


5. 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 randomized controlled trial. Lancet 2012; 379: 2352-2363.

6. Lorenzano S and Danilo Toni, for the TESPI trial Investigators. TESPI (Thrombolysis in Elderly Stroke Patients in Italy): a randomized controlled trial of alteplase (rt-PA) versus standard treatment in acute ischaemic stroke in patients aged more than 80 years where thrombolysis is initiated within three hours after stroke onset. Int J Stroke. 2012; 7:250-7

## Appendix A: List of eligible trials and STT lead investigators

<table>
<thead>
<tr>
<th>Trial</th>
<th>Lead investigators</th>
<th>Status in Third Phase</th>
</tr>
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<tbody>
<tr>
<td>ATLANTIS (A&amp;B)</td>
<td>Gregory Albers, James Grotta, Maarten Lansberg, Jean Marc Olivot</td>
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<tr>
<td>ECASS-1, ECASS-2, ECASS-3</td>
<td>Erich Bluhmki, Werner Hacke, Markku Kaste, Greg del Zoppo, Kennedy Lees, Ruediger von Kummer, Nils Wahlgren</td>
<td>Included</td>
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<td>EPITHET</td>
<td>Stephen Davis, Geoffrey Donnan, Mark Parsons</td>
<td>Included</td>
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<td>IST-3</td>
<td>Peter Sandercock, Joanna Wardlaw, Richard Lindley, Gordon Murray, Geoff Cohen, William Whiteley</td>
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<td>NINDS (A &amp; B)</td>
<td>James Grotta, Patrick Lyden, John Marler, Barbara Tilley</td>
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<td>TESPI</td>
<td>Danilo Toni</td>
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<td>EXTEND</td>
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<td>Mori</td>
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<td>Wang</td>
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**STT Statistical Analysis Centre and Secretariat**

Colin Baigent, Lisa Blackwell, Erich Bluhmki, Kelly Davies, Jonathan Emberson, Heather Halls, Lisa Holland, George Howard, Clare Mathews, Samantha Smith, Kate Wilson