



Third International Stroke Trial Protocol Summary

IST-3: A LARGE-SCALE, RANDOMISED CONTROLLED TRIAL OF THROMBOLYSIS FOR ACUTE ISCHAEMIC STROKE

Background: Data from over 5,000 patients are now available from trials of thrombolysis for patients with acute ischaemic stroke. A systematic review of these trials suggests that thrombolysis is very promising for patients who can be treated within 6 hours of stroke onset, but the balance of risk and benefit remains unclear. The majority of data are from trials of recombinant tissue plasminogen activator (rt-PA), also known as alteplase, which is licensed in Europe for use in selected patients aged under 80 years who can be treated within 3 hours. A further study, including at least 6,000 patients, is required to:

- Establish the balance of risk and benefit more precisely for thrombolytic therapy with rt-PA, especially among patients who do not exactly meet the current license criteria.
- Assess which categories of patients are most likely to benefit (by investigating: the interaction between stroke severity, early brain imaging appearances and other clinical features; and, to obtain better estimates of the duration of the 'therapeutic time window').

Trial design: International, multi-centre, Prospective, Randomised, Open, Blinded Endpoints (PROBE) design study of i.v. rt-PA vs control. Patients are entered into the trial by means of a telephone call to a 24-hour central computerised randomisation service (Neurosciences Trials Unit, Edinburgh) with on-line minimisation to balance key prognostic factors. Repeat brain imaging will be carried out 24-48 hours following treatment to identify early asymptomatic intracranial haemorrhage. Outcome data are collected at 7 days and six months (18 month follow-up data are collected in some countries). The primary outcome is the proportion of patients alive and independent at six months (Modified Rankin 0,1 or 2). All the scans are subject to detailed central blinded review. The study is conducted to EU GCP standards. Details of trial procedures can be found in the trial protocol, and on the trial website (www.ist3.com), and are summarised in the flowchart overleaf.

Ethical approval: The study has received approval from the UK Multicentre Research Ethics Committee and by the local ethics committees in over 30 centres worldwide.

Funding: The trial is supported by grants from the United Kingdom Medical Research Council, UK charities (The Stroke Association and The Health Foundation), the Norwegian Research Council, the Heart Foundation of Australia, The Government of Poland, AFA Insurances (Sweden), The Heart Lung Foundation (Sweden).

Sponsors: IST-3 is an independent, investigator-led trial. It is designed, and will be analysed and reported independent of the sponsors. The University of Edinburgh and the Lothian Health Board of Scotland act as joint sponsors.

Co-ordinating centre (for all information and queries)

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