

Project Title:	Imaging perfusion deficits and thrombolysis safety and efficacy in acute ischaemic stroke. The Third International Stroke Trial (IST-3).
Project Ref:	08-43-52
Cost:	£263,974
Lead Applicant & Institution:	Professor Joanna Wardlaw Clinical Neurosciences University of Edinburgh
Start Date:	1 September 2009
Plain English Summary:	<p>Stroke is a devastating disease with few effective treatments. In most patients, the stroke is caused by a blockage to a blood vessel in the brain. One of the main treatments is thrombolytic (or "clot busting") drugs. Although one of these drugs, alteplase (or rt-PA for short), has been licensed for use within three hours after stroke for over ten years, it is not widely used because of fears about its safety, doubts about the benefits and concerns about which patients most benefit from treatment.</p> <p>The Third International Stroke Trial (IST-3) aims to provide convincing evidence on the benefits and safety of alteplase if given intravenously up to six hours after stroke in patients who have had a CT scan to exclude bleeding as the cause of the stroke. IST-3 is now in its main phase, funded by the Medical Research Council and has recruited 1570 patients so is already the largest ever randomised trial of a thrombolytic drug, a reflection of the substantial expertise amongst the trial organisers and participating centres (target total over 3100 by mid 2011). CT scanning is the most widely available brain scanning method and so it is imperative that the main trial tests selection on the basis of careful clinical history and examination and plain CT scanning. However, newer imaging techniques may show parts of the brain where the blood flow has been reduced by the blockage but the brain has not yet died (so would benefit from treatment), as well as areas where the brain has already died (so cannot benefit from treatment). This can be done with CT perfusion or magnetic resonance (MR) diffusion and perfusion imaging. Using these imaging methods might increase the chance of better outcome after alteplase and reduce the risks. However, several recent smaller trials that tried using this approach did not show improved benefits. This may be because they were too small or gave the treatment later, or did not include the right patients to make a comparison with.</p> <p>IST-3 has well-established, streamlined and effective trial management organisation including a lay representative Mrs Heather Goodare on the Steering Committee. Its ethics have undergone extensive amendment by ethics committees in many countries and the public. Many IST-3 and other centres are interested in using these newer imaging techniques to see if</p>

	<p>they do improve patient selection. Our proposal is for very modest extra funding (<7% of the trial total cost) to enable us to collect and analyse data from these newer imaging methods in the IST-3 trial centres around the world where they are being used already. It will enable us to form a group of interested clinicians and expert image analysts to fully analyse the data to test a range of different analysis approaches that are currently available. Progress in IST-3 so far suggests that we will be able to collect data on up to 300 patients which would double the amount of information available on this topic and provide a definite answer to the question of whether these newer, less available and more expensive techniques should be used more routinely in patients being considered for thrombolytic treatment.</p>
<p>Abstract:</p>	<p><u>Design:</u> Main trial: IST-3 is an international, prospective, randomised, open, blinded end-point (PROBE) controlled trial of i.v. rt-PA within 6 hours of onset of acute ischaemic stroke (www.ist3.com). Plain CT brain scanning is the prime imaging modality for the main trial. Perfusion study: In centres where MR or CT perfusion are part of routine acute stroke care, the data from patients who have MR diffusion weighted imaging (DWI) and perfusion weighted imaging (PWI), or CT with perfusion (CTP) imaging at baseline before entry in IST3 will be collected and analysed centrally in addition to their non-contrast CT or MR DWI. We will measure infarct growth between baseline and 24-48 hour follow-up imaging, among patients with versus without DWI/PWI or CTP mismatch, with rt-PA versus control in patients with perfusion data.</p> <p><u>Setting:</u> Main trial: Hospitals in the UK, Europe, North America, Australia, with stroke units where evidence-based care pathways for stroke (including for administration of rt-PA) are in use. IST-3 currently has 97 active centres (+ 86 who may join) in 12 countries worldwide. Perfusion study: Of these, 12 centres are using MR for baseline assessment instead of CT, eight have already sent 12 MR PWI data and five have sent 23 CTP scans in acute stroke.</p> <p><u>Target population:</u> Perfusion study: Inclusion and exclusion criteria for patients will be as for IST-3 main trial. Inclusion: a) symptoms and signs of clinically definite acute stroke, b) known time of stroke onset and less than six hours previously (patients awaking with stroke are not eligible), c) CT or MR brain scanning has excluded intracranial haemorrhage and common stroke mimics, d) treatment can be started within 6 hours of stroke; exclusion: age <18, and the usual contraindications to rt-PA, please see www.IST3.com). Patients with contraindications to contrast agents, e.g. impaired renal function or on oral hypoglycaemic agents are to be excluded from perfusion imaging.</p> <p><u>Interventions being evaluated:</u> Main trial: rt-PA (total dose 0.9mg per kg of body weight up to a maximum of 90mg) versus 'open control'. Perfusion study: whether an imaging measure of mismatch between "core unsalvageable tissue" and "at risk but viable tissue" should be used routinely to guide rt-PA treatment.</p> <p><u>Measurement of outcomes and duration of follow-up:</u> Main trial: IST-3 primary outcome is functional outcome (alive and independent, Modified Rankin Scale score of 0, 1 or 2) at 6 months after randomisation; secondary outcomes are a) death from any cause, neurological deterioration and cause, symptomatic intracranial haemorrhage (fatal or non-fatal) and massive infarct swelling; at 7 days; and b) death from any cause, Health Related Quality of Life (HRQoL) at 6 months. IST-3 requires repeat CT or MR imaging at 24-48 hours to detect any intracranial haemorrhage, cerebral infarction, oedema or midline shift</p>

	<p>using validated rating scales. Perfusion study: outcome is infarct size at 24-48 hours and median relative and absolute infarct growth from baseline (the most sensitive measures in EPITHET).</p> <p><u>Project timetables including recruitment rate:</u> Main trial: stops recruitment in late 2011. Recruitment is on target. All regulatory approvals (including Human Research Ethics Committee approvals in 97 centres in 12 countries), randomisation, central data collection are in place. Perfusion study: can start immediately. The centres that are already using perfusion imaging are some of the most active in IST-3. Therefore we estimate that over the next 3 years, in 15 active centres, recruiting between four and eight patients per year each, the perfusion study will include between 100 and 300 patients. Based on scan data received so far, we anticipate a rate of two CTP to one MR PWI although a higher rate of four CTP to one MR DWI is possible. Both will provide valuable data. Ultimately, we will contribute the perfusion data to an international collaboration performing an individual patient data meta-analysis of perfusion imaging.</p>
ISRCTN:	25765518
Project Protocol:	www.eme.ac.uk/projectfiles/084352protocol.pdf
Project website:	http://www.dcn.ed.ac.uk/ist3/default.asp
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