

Trial Scenarios: Monitoring

4. Trial of aspirin and heparin in acute ischaemic stroke¹

Background:	Anticoagulants are widely used in ischaemic stroke to facilitate clot lysis and to inhibit clot propagation, but there is little randomised evidence on the balance of risks and benefits.
Design:	Open 2x2 factorial RCT with an additional randomisation of dose in 2 arms
Setting:	Multi-centre, international (467 hospitals in 36 countries)
Study population:	20,000 patients with acute stroke (some comatose)
Eligibility criteria:	Onset of stroke <48hours previously; CT scan to confirm absence of intracranial haemorrhage (unless severe delays and physician considered stroke very likely to be ischaemic); no contraindications to aspirin or heparin
Interventions:	Group 1 – low dose subcutaneous heparin + 300mg aspirin daily for 14 days Group 2 – medium dose subcutaneous heparin + 300mg aspirin daily for 14 days Group 3 – low dose subcutaneous heparin + avoidance of aspirin daily for 14 days Group 4 – medium dose subcutaneous heparin + avoidance of aspirin daily for 14 days Group 5 – 300 mg aspirin daily + avoidance of heparin for 14 days Group 6 – avoidance of aspirin and heparin for 14 days
Randomisation:	Central telephone randomisation
Trial supplies:	From routine hospital stock
Main outcomes:	Death from any cause within 14 days; death or dependency at 6 months (collected from patient or proxy)
Data management:	Paper CRFs. Data entry at coordinating centre.
Experience:	Experienced coordinators; some sites had participated in pilot but some were completely inexperienced in participating in clinical trials

What are the particular hazards of the trial?¹

- Vulnerable population, many of whom may not be capable of giving informed consent
- Complex design
- Very large number of centres in many different countries of very variable experience

¹ This scenario was based on the International Stroke Trial (*Lancet* 1997; 349:1569), but some of the details have been altered or invented.

- Potentially hazardous interventions, although considerable clinical experience of drugs

Suggested Approaches to Monitoring

Trial Oversight:

- A trial steering committee
- An independent DMC is essential
- A trial management group

Before the start of recruitment:

Minimum

- Written assurance from each investigator that the setup is complete and they are ready to start
- Investigator questionnaire to check appropriate training and skills

Optimal

- Investigators meeting(s) to review the trial procedures and discuss consent issues
- Some panel members consider a site visit to review setup desirable for inexperienced sites

During the trial

- The size of the trial and large number of sites makes it particularly suitable for central statistical monitoring, with targeted visits if indicated
- Depending on whether or not site visiting is undertaken, one of the following packages is suggested:

	Without site visiting	With site visiting
Understanding of and adherence to protocol and trial procedures	Annual investigator meetings	Annual site visits
Verification of participant existence	<ul style="list-style-type: none"> • Collect signed consent form at coordinating centre (with patient consent) • Collect CT scan • Central registry (eg ONS) flagging wherever possible 	Clinic records
Consent	Collect signed consent from at coordinating centre (with consent)	Check consent forms in patient's clinical records
Eligibility	<ul style="list-style-type: none"> • Review of eligibility prior to randomisation (by telephone or faxed form) • CT scan 	<ul style="list-style-type: none"> • Review of eligibility prior to randomisation (by telephone or faxed form) • Check against clinic records
Treatment	Collect sample of treatment chart to check what patients were prescribed	Check sample of treatment chart to check what patients were prescribed
Outcome/adverse events	Collect death certificates and discharge summaries	Check completeness and accuracy of adverse event

		reports against clinic records in a sample
--	--	---

- Centralised classification of outcomes blind to treatment group

At the end of the trial

- Written confirmation from each site regarding archiving.