

Trial Scenarios: Monitoring

1. Pilot randomised trial of streptokinase, aspirin and heparin in acute myocardial infarction¹

Background:	Several small trials have been undertaken of IV streptokinase in acute MI, often followed by an anticoagulant, but there was considerable heterogeneity of effect and use of these treatments is very variable.
¹Design:	2x2x2 factorial RCT to gain experience with the treatments and to collect information on common adverse effects prior to conducting a very large-scale trial
Setting:	8 hospitals (7 in UK and one in Australia)
Study population:	600 patients with suspected MI
Eligibility criteria:	Physician diagnosis of suspected MI; <24 hours of onset of symptoms; no clear indication for or contra-indication to trial drugs and not other life-threatening condition
Interventions:	IV streptokinase infused over 1 hour or matching placebo IV heparin infused over 48 hours or matching placebo Alternate day oral aspirin 325mg or matching placebo in 28 day calendar pack
Randomisation:	24 hour central telephone randomisation service which allocated the patient to a numbered pack
Trial supplies:	Treatment pack containing allocated treatments
Outcomes:	Adverse events during hospital stay – drug reactions, bleeding, stroke, arrhythmias, heart block, cardiogenic shock, cardiac arrest, reinfarction, death Deaths for up to one year following randomisation (from ONS flagging).
Data management:	Data collected on paper CRFs by investigators at each site. Data entry at coordinating centre
Experience:	Coordinating centre experienced in clinical trials. Variable experience at the clinical sites.

What are the particular hazards of the trial?

- Potentially hazardous interventions and little clinical experience of streptokinase
- Vulnerable population, some of which may not be capable of giving informed consent

¹ This scenario was largely based on the ISIS pilot study (*European Heart Journal*, 1987; 8:634-642), but some of the details have been altered.

- Complex design and double blind trial, therefore it is particularly important to ensure that the patients receive the allocated treatment

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

- Investigators meeting to review the trial procedures and discuss consent issues
- Written assurance from each investigator that the setup was complete and they are ready to start
- Investigator questionnaire to check appropriate training and skills

Optimal

- Most panel members would also consider a site visit to review setup and trial supply arrangements desirable, particularly for inexperienced sites

During the trial

Depending on whether or not site visiting is undertaken, one of the following plans is suggested:

	Without site visiting	With site visiting
Understanding of and adherence to protocol and trial procedures	Annual investigator meetings	Annual site visits (or as required)
Verification of participant existence	<ul style="list-style-type: none"> • Collect signed consent form at coordinating centre (with patient consent) • Collect ECG/lab results • Central registry (eg ONS) flagging wherever possible 	Clinic records
Consent	Collect signed consent at coordinating centre (patient consent required)	Check consent forms in patient's clinical records
Eligibility	<ul style="list-style-type: none"> • Review of eligibility (on faxed form or over the telephone) prior to randomisation • ECG/blood test results 	Check against clinic records
Outcome/adverse events	Collect death certificates, discharge summaries and lab reports	Check completeness and accuracy or AE reports against clinic records in a sample

- Unique identifier on label in each treatment pack to be attached to CRF as a check of what patient was given
- Testing of drugs in some packs to ensure accuracy of pack assembly
- Centralised classification of outcomes blind to treatment group

At the end of the trial

- Drug reconciliation by return of unused treatment packs to coordinating centre or record of destruction
- Written confirmation from each site regarding archiving.