Trial Scenarios for Monitoring

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Pilot randomised trial of streptokinase, aspirin and heparin in acute myocardial infarction

(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.)

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.

Design: 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; less than 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: 4 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
- Complex design and double blind trial, therefore it is particularly important to ensure that the patients receive the allocated treatment

Suggested Approaches to Monitoring:

1. **Trial Oversight:**

    - A Trial Steering Committee
    - An independent Data Monitoring Committee (essential)
    - A Trial Management Group

2. **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

3. **During the trial**

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

- 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

4. **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

Criteria	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	Collect signed consent form at coordinating centre (with patient consent) Collect ECG/lab results Central registry (e.g. ONS) flagging wherever possible	Clinic records
Consent	Collect signed consent at coordinating centre (patient consent	Check consent forms in patient’s clinical records

Eligibility	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

Trial of prescribing strategies in managing sore throat

(This scenario was based in part on a trial report by Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL Open randomised trial of prescribing strategies in managing sore throat(BMJ, 1977; 314:722), but some of the details have been altered or invented.)

Background: The management of sore throats in primary care is controversial and use of antibiotics varies.

Design: Open randomised trial of 3 prescribing strategies.

Setting: 11 general practices in one regional primary care research network in the UK.

Study population: Patients aged 4 years or more presenting with sore throat to GP.

Eligibility criteria: =4 yrs. old; sore throat + local sign of infection (inflamed tonsils or pharynx, exudate, or cervical adenopathy).

Intervention: Group 1 - immediate prescription for 10 day course of standard antibiotics - penicillin V (or erythromycin if allergic), Group 2 - no antibiotic prescription, Group 3 – prescription (as in Group 1) to be collected if symptoms are not starting to settle in 3 days.

Randomisation: Sealed envelopes in GP surgery containing advice sheet for the assigned treatment strategy.

Trial supplies: Prescriptions dispensed by high street chemist.

Outcomes: Patient assessed (duration of symptoms recorded by patient diary), Duration of time off work/school, Patient satisfaction.

Data management: Paper CRF - data entry at coordinating centre.

Experience: Coordinating centre and network practices have undertaken a number of similar trials previously.

What are the particular hazards of the trial?

This is a very low-risk trial – a comparison of commonly-used treatment strategies in a patient population that is not seriously ill undertaken by an experienced group of investigators. The particular concerns are:

- Randomisation process – use of sealed envelopes in an open trial makes the study vulnerable to the random allocation of treatment being compromised – either through ignorance or intentionally. Centralised process should be used if at all possible.
- Although not a vulnerable population, the inclusion of children introduces the issue of providing information about the trial for different levels of capacity to understand.
- An open trial with patient-assessed outcomes introduces the hazard of differential and biased outcome assessment. Complete follow-up and a robust data collection instrument for the primary outcome are important.

Suggested Approaches to Monitoring:

1. Trial Oversight:

- A trial management group that includes the collaborators. An independent DMC is unnecessary

- Before the start of recruitment:

    - Investigators’ meeting that includes all those who will be involved in obtaining patient consent, the randomisation procedure, and follow-up for discussion/training plus written assurance from each investigator that the practice is prepared and setup complete; or

    - Visit to each practice to undertake same

- During the trial

    - Because the trial is being conducted in a small network of practices in the same region, site visiting may pose few logistical or financial difficulties, and in view of the concern over the randomisation process may be the best way to monitor the conduct of the trial. Depending on whether or not site visiting is undertaken, one of the following plans in the table below is suggested:

- At the end of the trial

    - Local PCT arrangements for archiving of documents should be followed.

Criteria	Without site visiting	With site visiting
Understanding of and adherence to protocol and trial procedures	Annual investigator meetings	Annual site visits, including check of randomisation envelopes
Verification of participant existence	Collect signed consent form at coordinating centre (with patient consent) Alternatively, ONS flagging would be possible but generally considered unnecessary	Check practice database or clinic notes

Consent	Collect signed consent form at coordinating centre (with patient consent)	Check consent forms in patient's clinical records

Centralised classification of outcomes blind to treatment group is recommended.

Trial of preoperative chemotherapy in oesophageal cancer

(This scenario was based on a trial report by the MRC Oesophageal Cancer Working Party, Surgical resection with or without preoperative chemotherapy in oesophageal cancer. (Lancet 2002;359:1727), but some of the details have been altered or invented.)

Background: It has been reported that preoperative chemotherapy improves survival in oesophageal cancer, but there is little randomised evidence.

Design: Open simple pragmatic RCT.

Setting: 42 hospitals across Europe.

Study population: 800 patients with oesophageal cancer due to have surgery.

Eligibility criteria: Microscopically confirmed oesophageal cancer without lymph node involvement or metastatic disease; no other malignancy; normal renal function, white-cell count and platelets.

Intervention: Group 1 – immediate chemotherapy with 2 cycles of cisplatin and fluorouracil (commonly used chemotherapies in long-standing use) followed by surgical resection. Group 2 – immediate surgical resection.

Randomisation: Central telephone randomisation.

Trial supplies: From routine hospital stock.

Main outcomes: Survival time (primary) and dysphagia (secondary) recorded by treating clinician.

Follow-up: 3-monthly for first year, then 6-monthly until death.

Data management: Paper CRFs.

Experience: Coordinating centre and clinical sites all experienced in conducting and participating in clinical trials.

What are the particular hazards of the trial?

The main concern in this trial is whether pre-operative chemotherapy increases the peri and post-operative surgical morbidity.

Suggested Approaches to Monitoring

1. Trial Oversight:

- A Trial Steering Committee
- An independent Data Monitoring Committee (essential)
- A Trial Management Group

2. Before the start of recruitment:

Minimum

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

Optimal

- Investigators' meeting(s) to review trial and all procedures (it might be possible to organise a meeting in conjunction with a scientific conference)

3. During the trial
    - Depending on whether or not site visiting is undertaken, one of the following plans in the table below is suggested

4. At the end of the trial
    - Written confirmation from each site regarding archiving.

Criteria	Without site visiting	With site visiting
Understanding of and adherence to protocol and trial procedures	Annual investigators meetings, if feasible (alternative - several teleconferences)	Annual site visits
Verification of participant existence	Collect signed consent form at coordinating centre (with patient consent) Collect pathology reports Central registry (e.g. ONS) flagging wherever possible	Clinic records
Consent	Collect signed consent form at coordinating centre (with patient consent)	Check consent forms in patient's clinical records
Eligibility	Review of eligibility prior to randomisation (by telephone or faxed form) Pathology reports	Check against clinic records
Outcome	Collect death certificates	Record of death and dysphagia in clinic records
Other data	Central statistical monitoring to identify sites that may require attention or visiting	Sample of records for review of accuracy of adverse event reporting

Centralised classification of outcomes blind to treatment group is recommended.

Trial of aspirin and heparin in acute ischaemic stroke

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

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 less than 48 hours 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; some were completely inexperienced in participating in clinical trials.

Suggested Approaches to Monitoring:

1. Trial Oversight:

- A Trial Steering Committee
- An independent Data Monitoring Committee (essential)
- A Trial Management Group

- Before the start of recruitment:

Minimum

- Written assurance from each investigator that 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
- A site visit to review setup desirable for inexperienced sites

3. 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 plans in the table below is suggested

- At the end of the trial

- Written confirmation from each site regarding archiving.

Criteria	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	Collect signed consent form at coordinating centre (with patient consent) Collect CT scan Central registry (e.g. 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	Review of eligibility prior to randomisation (by telephone or faxed form) CT scan	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 sample

Centralised classification of outcomes blind to treatment group.

Trial of fish oil supplementation in normal pregnancy

(Scenario was based on a trial report by Olsen S, Sorensen N, Hedgaard M, Henriksen T, Hansen H, Grant A, Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. (Lancet 1992; 339:1003), but some of the details have been altered or invented.)

Background: Gestational age and birth weight are strong predictors of a baby's survival. Observational evidence suggests that women with a high dietary intake of oily fish have long pregnancies and babies with high birth weights.

Design: RCT.

Setting: A single large antenatal clinic.

Study population: 600 healthy pregnant women attending routine week 30 antenatal visit.

Eligibility criteria: Normal pregnancy at 30 weeks gestation based on ultrasound or LMP Exclusions – multiple pregnancy, bleeding in pregnancy, previous placental abruption, allergy to fish, regular fish oil supplementation.

Intervention: Group 1: 4g fish oils in capsule daily Group 2: 4g olive oil in capsule daily Group 3: no oil supplement.

Randomisation: Sealed opaque envelopes in antenatal clinic containing a number corresponding to a treatment pack or indicating no supplementation.

Trial supplies: Pre-numbered boxes of oil capsules given to women at each visit.

Outcomes: Duration of pregnancy, birth weight and length.

Other data: Participant interviews about lifestyle factors relevant to pregnancy outcome, compliance, food frequency questionnaire.

Data management: Paper CRF. Data entry at coordinating centre.

Experience: Experienced coordinators; clinic staff little trial experience.

What are the particular hazards of the trial?

This is a low-risk trial – a single-centre trial to assess of the impact of two different oils present in a normal diet on the outcome of normal, low-risk pregnancies. The particular concerns are:

- Randomisation process – use of sealed envelopes in an open trial makes the Study vulnerable to the random allocation of treatment being compromised – either through ignorance or intentionally. Centralised process should be used if at all possible.
- Although the women are not a vulnerable population, their babies are and their safety is of particular concern – both the risks and benefits of treatment should be carefully monitored.

Suggested Approaches to Monitoring:

1. Trial Oversight:
    - A Trial Management Group
    - An independent Data Monitoring Committee (unless the recruitment phase will be so short that no information on pregnancy outcomes would be available on the first patients randomised in time to prevent some of the patients being recruited unnecessarily should a benefit be detected).

2. Before the start of recruitment:
    - As it is a large antenatal clinic a large number of midwives and obstetricians will be involved in the study and they may have little experience of trials. An investigators' meeting or a site visit is recommended to ensure that all staff are clear about the trial procedures, in particular the randomisation process.

3. During the trial
    - Because the trial is being conducted in a single hospital, visiting the clinics periodically is likely to be an efficient way of monitoring the trial. The following could be checked:
    - Signed consent forms
    - Adherence to randomisation process
    - Patient eligibility (most of the panel would do this in a small sample)

    - Outcomes data could be checked either against the clinic records or by collecting a copy of the birth record

4. At the end of the trial
    - Record of destruction of unused treatment packs.