

Trial Scenarios for 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 of 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

2. Trial of prescribing strategies in managing sore throat²

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 their 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 Grp 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:

- 1 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.
- 2 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.

² 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.

- 3 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

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 is suggested:

	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.

At the end of the trial

Local PCT arrangements for archiving of documents should be followed.

3. Trial of preoperative chemotherapy in oesophageal cancer³

Background:	It has been reported that preoperative chemotherapy improves ³ 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

Trial Oversight:

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

Before the start of recruitment:

³ 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.

Minimum

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

Optimal

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

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 investigators meetings, if feasible (alternative - several teleconferences)	Annual site visits
Verification of participant existence	<ul style="list-style-type: none">• Collect signed consent form at coordinating centre (with patient consent)• Collect pathology reports• Central registry (eg 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	<ul style="list-style-type: none">• 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.

At the end of the trial

Written confirmation from each site regarding archiving

4. Trial of aspirin and heparin in acute ischaemic stroke⁴

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?⁴

- 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
- Potentially hazardous interventions, although considerable clinical experience of drugs

⁴ This scenario was based on the International Stroke Trial (*Lancet* 1997; 349:1569), but some of the details have been altered or invented.

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
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- Centralised classification of outcomes blind to treatment group

At the end of the trial

- Written confirmation from each site regarding archiving

5. Trial of fish oil supplementation in normal pregnancy⁵

Background:	Gestational age and birthweight 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 birthweights.
Design:	RCT
Setting:	A single large antenatal clinic
Study population:	600 healthy pregnant women attending for 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 that corresponding to a treatment pack or indicating no supplementation.
Trial supplies:	Pre-numbered boxes of oil capsules given to the 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:

- 1 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.

⁵ This 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

- 2 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

Trial Oversight:

- A trial management group, **and**
- An independent DMC (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).

Before the start of recruitment:

Because it is a large antenatal clinic a large number of midwives and obstetricians will be involved in the study and they 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.

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.

At the end of the trial

Record of destruction of unused treatment packs