# A risk-based approach to monitoring: the MRC/DH Joint Project

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**MRC/DH Joint Project**

# MRC / DH Joint Project

**Established:** July 2003

**Aim:** To codify good practice in publicly funded trials

**Steering group:**

- Main stakeholders in publicly-funded trials
  - funders, academic trialists, MHRA, research managers

**Objectives:**

- Practical advice for all involved in publicly-funded trials
- Examples of best practice on ways to:
  - comply with the new clinical trials legislation
  - minimise additional bureaucracy
  - avoid unnecessary waste of public resources

# MRC / DH Joint Project Workstreams

- Quality partnerships
  - Sponsorship, insurance and indemnity
  - Institutional management of trials portfolio
- Trial initiation and commencement
- Trial management and monitoring
  - Proportionate and risk-based approach to quality assurance and adherence to principles of GCP
- Trial supplies
- Pharmacovigilance
  - Proportionate and risk-based approach to safety reporting
- Whole Systems - development of Clinical Trials Tool Kit

**Website: *www.ct-toolkit.ac.uk***

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# Clinical Trials Tool Kit

DH Department of Health

MRC Medical Research Council

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## Welcome to the Clinical Trials Tool Kit

On this site you will find practical help when trying to meet the requirements of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. These regulations implement the EU Clinical Trials Directive in the UK.

The site have been developed primarily for clinical trialists and R&D managers working in the academic sector, but will also be useful to other health professionals.

To help you to navigate through the Regulations, much of the information is organised within three Route Maps. Your feedback on the content and presentation will help us improve the site.

Even if your research falls outside the Regulations, you could still find the Route Maps useful. Much of the advice they contain is relevant to clinical trials and research more generally.

The site has been developed by the UK Medical Research Council and Department of Health for use in all publicly funded academic trials. Further info...

**What's New**
Take a look at the latest additions to the Tool Kit.

**Accessibility**
Please read about the accessible features available on this site.

**First time on the site?**
Find out more about the Clinical Trials Tool Kit here...

**Ready to use a Route Map?**
To use one of these route maps, click on a link below

**Trials that Began Before 1st May 2004** | **Planning a New Trial** | **Trial Management & Closure**

**Clinical trial participants**
If you would like to find out more about taking part in a clinical trial.
More info...

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# MCR/DH Joint Project: Trial Management & Montioring

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## Working Group

Noreen Caine
Barbara Farrell
Martin Landray
Sarah Meredith
Cathy McDowell
Yolanda Moraes
Jane Robertson
Maxine Stead

## Expert Panel

Peter Brocklehurst
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Janet Darbyshire
Stephen Evans
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Peter Sandercock
Tony Soteriou
Tom Walley
Simon Wessely

# Range of non-commercial trials

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- **Stage:** ‘first in man’ studies → pragmatic comparisons of routine treatments
- **Sites:** single centre → international multi-centre
- **Funding:** slush funds → MRC / DH / research charity

# Monitoring procedures “fit for purpose“

- **Types of monitoring**
  - **oversight - e.g. TMG, TSC, DMC**
  - **‘good housekeeping’**
    - e.g. protocol compliance, data consistency
  - **central monitoring**
    - e.g. look for outlier sites, ONS to confirm pt. existence/outcome
  - **on-site monitoring**
- **Procedures should be determined by**
  - **risk assessment**
  - **trial design**
  - **number / experience of sites**
- **Coordination of monitoring to avoid duplication**
  - **Coordinating centre / Sponsor / Care organisation**

# Risk assessment (1)

**Hazard:** anything that could cause harm

**Risk:** probability that harm will be caused by the hazard

**Clinical trial risk assessment**

- Identification of trial-specific hazards
- Assessment of probability of harm
  - e.g. low, medium, high
- Assessment of the consequences
  - e.g. mild, moderate, severe
- Identification of reasonable methods to reduce risks by
  - reducing probability of harm
  - minimising its adverse consequences

# Risk assessment (2)

- **Rights of participants**
  - **consent process** ***- vulnerability of study population***
    - control risk by quality of patient info and staff training
  - **privacy** ***- systems for data protection & anonymisation***
    - **control risk by good data management & staff training**
- **Safety of participants**
  - **hazards of intervention** ***- inherent danger, clinical experience***
  - **hazards of assessment**
    - **control risk by staff training, AE monitoring, DMC**
- **Reliability of results**
  - **inaccuracy, bias, fraud, protocol adherence**
    - ***complexity, eligibility criteria, randomisation process, objectivity of outcome assessment, level of detail on CRFs***
    - **control risk by robust trial design, staff training & monitoring**

# Monitoring assessment by Expert Panel

Aim: to develop advice on the use of different approaches to monitoring in individual trials

- **Expert Panel**
  - **mainly experienced trialists**
  - **plus MHRA inspector, major funder and R&D director**
- **Trial scenarios reflecting broad range of trials**
- **Individual assessment of appropriate monitoring**
- **Group discussion of areas of disagreement**
  - **Attempt to achieve consensus**
- **Use results to expand and illustrate workstream advice**

# General guidance

- **Oversight** - always necessary, but structures will vary
  - TSC as well as a management group for large, multi-centre trials
  - DMC independent of investigators & sponsor if safety issues
- **Personnel** - ensure all understand protocol & responsibilities
  - investigator meetings or at sites visits
- **Confirmation of participant existence** - highly desirable
  - signed consent form, medical record, investigation report or ONS
- **Consent procedures vital** - training of all involved
  - copy of signed form to coordinating centre (if patient agrees)
  - check at site by R&D staff or on site monitoring visit (if done)
- **Eligibility** - importance will vary according to trial
- **Randomisation** - essential assignment cannot be predicted
- **Trial supplies** - storage and check on what patient received
- **Data accuracy** - needs will vary according to trial
  - identify key items and develop checks (central or SDV)

# Example 1 - RCT of streptokinase, aspirin & heparin in acute MI (ISIS)

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| | |
|---|---|
| **Design:** | 2x2x2 factorial placebo-controlled trial |
| **Population:** | 600 patients with suspected acute MI |
| **Sites:** | 8 hospitals (7 in UK 1 in Australia) |
| **Entry criteria:** | Dr diagnosed suspected MI <24hrs of onset |
| **Randomisation:** | 24 hr central telephone service |
| **Interventions:** | 8 groups - IV streptokinase or placebo (1 hr)<br>- IV heparin or placebo (48 hrs)<br>- oral aspirin or placebo (28 day) |
| **Supplies:** | Treatment packs held in ER |
| **Outcomes:** | SAEs in hospital + deaths < 1 yr |
| **Data:** | Paper CRFs. Data entry at coordinating centre |
| **Experience:** | Very experienced coordinating centre<br>Variable experience at sites |

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# What are the main hazards?

- 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

# Monitoring 1 - Before recruitment

*Oversight*

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

*Before the start of recruitment: Minimum*

- **Investigators meeting - trial procedures and consent**
- **Written assurance from each investigator that setup was complete**
- **Investigator questionnaire to check appropriate training and skills**

*Optimal*

- **Most also considered a site visit to review setup and trial supply arrangements desirable, particularly for inexperienced sites**

# Monitoring 2 - During recruitment

## Without site visiting

- Regular investigator meetings
- Verification of pt existence
  - Collect signed consent form at coordinating centre
  - Collect ECG/lab results
  - Flagging
- Collect signed consent at coordinating centre (patient consent required)
- Review of eligibility prior to randomisation
- ECG/blood test results
- Collect death certificates, discharge summaries and lab reports
- Monitor data consistency and site differences

## With site visiting

- Regular site visits
- Patient existence from clinic records
- Check consent forms in patient's clinical records
- Check eligibility against clinic records
- Check completeness and accuracy of AE reports against clinic records in a sample

# Monitoring 3 - End of trial

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

# Example 2: RCT of prescribing strategies for sore throat in $1^0$ care

**Interventions:** 1. No prescription; 2. Immediate prescription
3. Prescription to be filled if no improvement

**Outcome:** patient-assessed symptom duration

**Randomisation:** sealed envelopes in GP surgeries

*- most vulnerable aspect*

- **Oversight:** Trial management group; no DMC
- **Essential to ensure randomisation not compromised**
  - Pre-trial meeting/site visit to train all staff involved
  - During trial site visits to check where envelopes kept & patients allocated in order of presentation
  - Patient treatment corresponded to allocated treatment
- **Patient existence & consent check**
  - possible centrally but efficient to do during site visits

# Example 3: International RCT of pre-operative chemotherapy for a cancer

**Open trial**: pre-operative chemotherapy or not
**Intervention:** standard chemotherapy regimen
**Eligibility:** histology & staging (investigation results)
**Randomisation:** centralised, telephone / fax
**Main outcome:** death
**Sites:** 8 countries / 42 sites

- Main concern: effect on peri-operative complications
- Independent DMC essential
- Trial details very amenable to central monitoring with targeted visits if required

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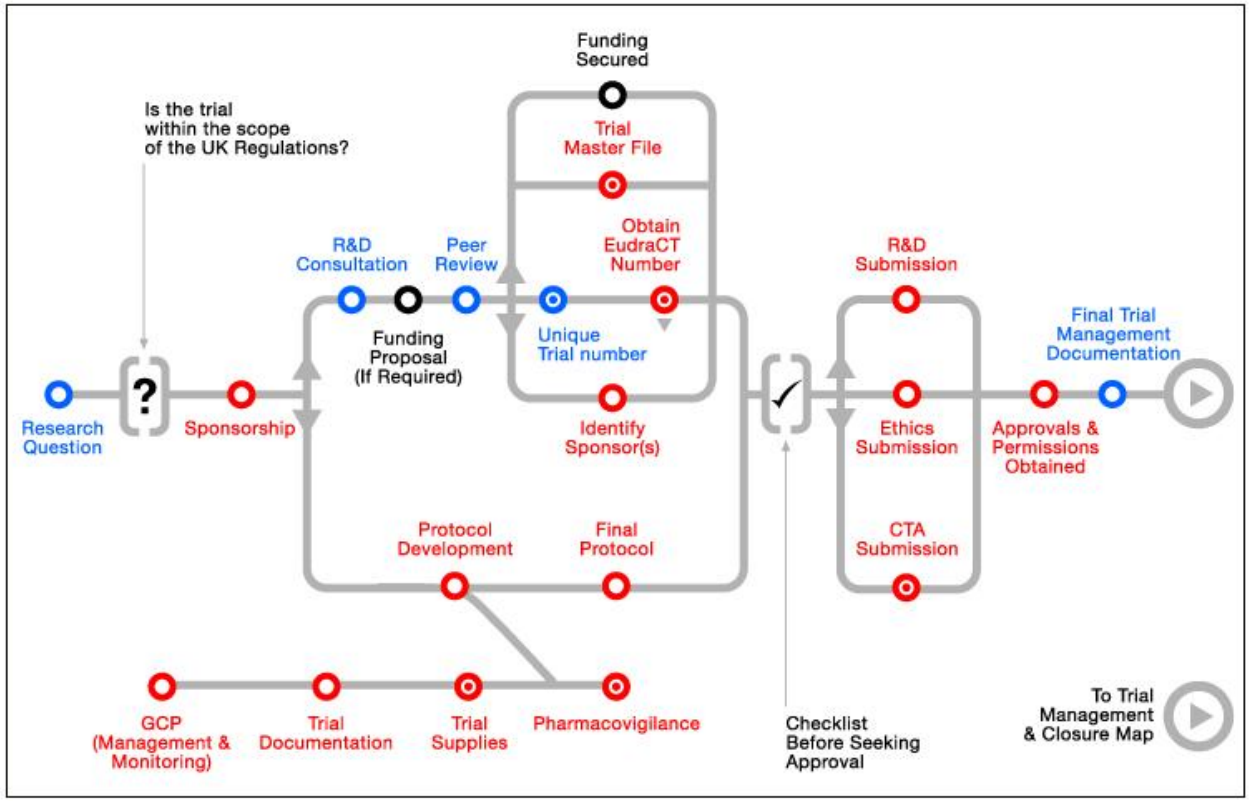
Map View | List View

## Planning a New Trial

Click on any station on the map below to go to the associated resource page.

| Key to Symbols | Standard Process | Legal Requirement | Good Practice |
|---|---|---|---|
| Specific for trials fall under scope of Directive | ○ | ○ | ○ |
| Wider relevance to other trials not covered by Directive | ○ | ○ | ○ |

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# Achievement of Joint Project: Proportionate approach accepted

- **Commercial *v.* non-commercial**
- **Medicinal product *v.* other interventions**

} **unimportant**

- **Systems should depend on risks to patients and trial:**
  - **intervention - type, status, danger and clinical experience**
  - **vulnerability of the population**
  - **sites - number, distance, team experience**
  - **trial design - eligibility, outcomes, data collection methods**