

**MRC/DH joint project to codify good practice in publicly-funded UK clinical trials with medicines**

**Workstream 4: Trial Management and Monitoring**

**A) Clinical Trial Risk Assessment**

**1. Introduction**

The Research Governance Framework (RGF) specifies the separate responsibilities of the sponsor, main funder, chief investigator (CI), his/her employer and the Trust (or care organisation).

In practice, the dividing lines are often blurred in non-commercial trials because one organisation may take on more than one role. The sponsor is not usually a separate entity, but one or more of the other individuals or organisations listed.

The employer of the CI is commonly a university, but may be a Trust or the funder. In some large trials, for example some of those funded by MRC or CRUK, there may be a clinical CI employed by a Trust or university, but the trial is managed from an independent trials unit.

Although the hazards of a trial may be defined, the risks to any one individual or organisation will depend on their role(s) and responsibilities in relation to the trial and their ability to control the hazards.

All of the various individuals and organisations involved in a clinical trial need to assess their risks in relation to their responsibilities. This guidance is written from the perspective of the Chief Investigator, who is directly responsible for the conduct of the research.

**2. Definitions**

**Hazard:** anything that could cause harm

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

The CI should consider the list of potential hazards, their relevance to the specific trial and specify how they propose to minimise them.

This could then be reviewed by the various organisations with responsibility for aspects of the trial to provide a basis for their individual risk assessment and plans to control the risks.

### 3.0 What are the potential hazards inherent in the trial?

For each hazard, the following should be considered:

- a) the associated risks to the particular trial;
- b) the potential consequences;
- c) reasonable steps to reduce the risks by (1) reducing the probability of the hazard occurring or (2) minimising its adverse consequences

### 3.1 Hazards for the participants

#### 3.1.1. For the participants' rights

##### a) *Entry to trial without fully informed consent*

**Consider:**

- *vulnerability of the patient/study group and capacity to give consent*
- *consent process*
- *participant information*
- *training of those providing participant information and obtaining consent*

##### b) *Failure to act on patient's request to withdraw from the trial*

**Consider:**

- *communication and recording systems*

##### c) *Failure to protect the privacy of participants*

**Consider:**

- *data protection and security systems*
- *anonymisation*

#### 3.1.2. For the participants' safety

##### a) *Hazards of the intervention*

- Expected adverse effects
- Unexpected adverse effects
- Clinical management of adverse effects
- Clinical management of patients' underlying medical condition

**Consider:**

- *nature of the intervention*
- *treating clinician's previous experience of intervention*
- *if medicinal product*
  - *development phase, licensing status, indications, clinical experience, pharmacology*
  - *pharmacy/drug handling requirements, training and competence*
- *staff training*
- *susceptibility of the population– disease, genetic, age, sex*

##### b) *Likely risk/benefit ratio of the intervention(s) in the study population*

**Consider: -**

- *systems to monitor and review adverse effects*
- *systems to maintain awareness of and to act on new knowledge*
- *ability of participants to report adverse events and study outcomes reliably*

**c) Hazards of assessment methods (e.g. biopsy, X-ray)**

**3.2 Hazards of the trial**

**3.2.1 To the completion of the trial – recruitment and follow-up**

**Consider:**

- *feasibility, study population, numbers of subjects required*
- *staff competence and experience at sites,*
- *length of F/U*
- *frequency of F/U*
- *alternative means of F/U (ONS flagging, GP, relatives)*

**3.2.2 To the reliability of the results**

**a) Study power**

**Consider:**

- *Plausible treatment effects*
- *Patient numbers*

**b) Major violation of eligibility criteria**

**Consider:**

- *importance to the trial,*
- *need for checking and possible procedures*
- *unduly restrictive/prescriptive eligibility criteria*

**c) Fraud**

**Consider:**

- *potential,*
- *incentives – financial and non-financial*
- *consequences -size and severity of threat to trial results,*
- *options for checking*

**d) Randomisation procedure**

**Consider:**

- *robustness of procedure*
- *potential for loss of allocation concealment / unblinding*

**e) Outcome assessment**

**Consider:**

- *blinding (single, double)*
- *objectivity of measure*
- *standardisation of assessment*
- *potential for independent review*
- *potential for simple external verification e.g. death certificate, laboratory investigation result*

**f) Other data – completeness and accuracy**

**Consider:**

- *data type and complexity (CRF design)*
- *collection method (paper, electronic)*
- *data entry method,*
- *key data items*
- *staff training*
- *need for and options for verification*

**g) Adherence to the protocol**

**Consider:**

- *complexity*
- *staff training and trials experience*
- *barriers to compliance with intervention (for trial personnel and participants)*