

## **Monitoring of Clinical Trials: a summary of the outcome of the Trial Management and Monitoring Workstream of the MRC/DH Joint Project**

### **Introduction**

This paper is in response to the invitation on the European Commission website dated 28/7/2006 to comment on the monitoring of non-commercial trials as part of the consultation on 'Draft Guidance on 'specific modalities' for non-commercial clinical trials referred to in Commission Directive 2005/28/EC laying down the principles and detailed guidelines for good clinical practice'. The paper is based on work undertaken as part of the MRC/DH Joint Project. The aim of the Project was to document best practice in publicly and charitably-funded clinical trials of medicines. Further information can be found on the Clinical Trials Toolkit (<http://www.ct-toolkit.ac.uk>).

### **Definition of monitoring**

Monitoring is defined as 'the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, Standard Operating Procedures, Good Clinical Practice (GCP) and the applicable regulatory requirements'<sup>1</sup>.

The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. Although there may be a need for on-site monitoring, before, during and after the trial, central monitoring in conjunction with procedures such as investigators' training and meetings and extensive written guidance can assure appropriate conduct of the trial in accordance with the principles of GCP, particularly if the investigators are experienced and have collaborated in previous studies.

### **Risk assessment for the monitoring plan**

The quality assurance systems to be employed for a clinical trial should be based on the specificities of the individual trial. A risk assessment should be undertaken at the protocol development stage to plan the appropriate approach to, and extent of, monitoring in the trial. The plans should be documented, together with the risk assessment, so that the procedures for monitoring are both transparent and justified. It is recommended that the monitoring plan should be part of the trial proposal and therefore subjected to peer review. It is also recommended that the plans should be agreed by the sponsor and recorded in the trial protocol and submitted with the CTA application.

When conducting a risk assessment for a specific trial, it is recommended that the following be considered:

- Trial design, randomisation system and outcome measures
- Participating sites - the trial experience of the investigator and their team; experience of using the medicinal product; the sponsor's experience of the sites

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<sup>1</sup> Note for Guideline on Good Clinical Practice ([CPMP/ICH/135/95](http://www.emea.europa.eu/pdfs/clinical/CPMP/ICH/135/95.pdf)) published by the European Agency for the Evaluation of Medicinal Products in July 2002

- Study population - does the trial population have the same characteristics as those covered in the indication specified in the product's marketing authorisation? Are the patients from a vulnerable population (e.g. incapacitated adults)?
- Medicinal product – does the medicinal product have a marketing authorisation? If so, is this a new indication? How much clinical experience is there of the medicinal product?
- Trial supplies – how are the trial supplies being provided – from routine pharmacy supplies or from the manufacturer?
- Data management systems – does the trial involve paper or electronic CRFs?
- What oversight mechanisms are in place to monitor safety of the participants?

## **Types of monitoring in clinical trials**

Approaches to trial monitoring should be appropriate to the trial and should be proportionate to the size, complexity and risks (both to the participants and the results) associated with the trial. Some or all of the following approaches to monitoring may be employed to oversee the progress of a clinical trial and to ensure that it is conducted, recorded and reported in accordance with the protocol, Standard Operating Procedures, GCP and the applicable regulatory requirements:

### **1. Trial Oversight Committees**

For each trial appropriate oversight mechanisms should be put in place. Commonly employed oversight committees include:

#### *i) A Trial Management Group*

The Trial Management Group normally includes those individuals responsible for the day-to-day management of the trial, such as the chief investigator, statistician, trial manager, research nurse, data manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

#### *ii) Trial Steering Committee*

The role of a Trial Steering Committee is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The Trial Steering Committee should agree the trial protocol and any protocol amendments and provide advice to the investigators on all aspects of the trial. A Trial Steering Committee may have members who are independent of the investigators, in particular an independent chairperson. Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the Trial Steering Committee

#### *iii) Independent Data Monitoring Committee*

The role of an Data Monitoring Committee is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. The Data Monitoring Committee should be independent of both the investigators and the funder/sponsor and should be the only body that has access to unblinded data. It normally makes recommendations to the Trial Steering Committee (or Trial Management Group).

### **2. Coordinating centre day-to-day monitoring**

Day-to-day monitoring should be carried out by those responsible for running a trial. This typically would include the following checks:

- that data collected are consistent with adherence to the trial protocol
- that CRFs are only being completed by authorised persons
- that no key data are missing
- that data appear to be valid (for example, range and consistency checks)
- review of recruitment rates, withdrawals and losses to follow-up overall and by clinical site.

### **3. Central monitoring**

Central monitoring is defined as the centralised procedures for quality control of trial data. These may include within subject consistency checks over time and across different data items, statistical techniques to identify unusual data patterns within and across participating centres and external validation of selected data items.

The central collection of copies of radiographs, scans, or pathology reports, where applicable, may permit the study coordinators to verify independently key criteria for eligibility or outcome. With the participant's consent, national vital statistics services may be used for the corroboration of the existence of the subject or the verification of mortality outcomes. Disease registers, for example cancer registers may be used to confirm information on eligibility or outcomes. In large, multi-centre studies, central monitoring of data using statistical techniques is particularly useful for identification of unusual patterns of data, and can be used to identify sites or contributors that may be deviating from the protocol. Participant consent may be confirmed by the collection of a copy of the consent form at the co-ordinating centre, with the agreement of the participant and measures to ensure confidentiality.

### **4. On-site monitoring**

On-site visits provide the opportunity to:

- educate staff about the trial, review understanding of the protocol and trial procedures
- verify that the staff at the site have access to the necessary documents to conduct the trial
- confirm that the required pharmacy and laboratory resources are in place
- check adherence to the protocol and GCP
- verify selected data items and/or serious adverse events recorded on the CRFs compared with data in the clinical records to identify errors of omission as well as inaccuracies, and
- confirm that the participants have provided written consent (if copies of the form are not held in the co-ordinating centre).

Arrangements for site visiting may vary from routine visits to all sites, visits to a random selection of sites or visits targeted at less experienced sites or those for which the central monitoring procedures suggest possible problems.

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