

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

Workstream 4: Trial Management and Monitoring

C) Monitoring Procedures

1. Introduction

The purpose of trial monitoring as defined in ICH GCP is to ensure that:

1. the rights and well-being of trial participants are protected,
2. the reported trial data are accurate, complete, and verifiable* from source documents, and
3. the conduct of the trial is in compliance with the currently approved protocol/amendments, with GCP, and with the applicable regulatory requirements.

Compliance with ICH GCP is often interpreted as requiring intensive site monitoring, but the following paragraph should be noted:

“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. In general there is a need for on-site monitoring, before, during and after the trial; however ...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 GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.” (ICH GCP 5.18.3)

2. Types of monitoring in clinical trials

There are a number of approaches to trial monitoring available, and the procedures appropriate for monitoring an individual trial should be considered as the trial is being developed.

Some or all of these different approaches to monitoring may be employed.

* This does not imply that every item of data recorded must be supported by a source document or checked. Where there are original documents the trial data should be in agreement with the information they contain. Where the CRF is the source document (e.g. information collected directly from the participant and not recorded elsewhere) then the training of the persons collecting and recording those data and clearly documented procedures are crucial.

2.1 Trial Oversight Committees

The funding body or sponsor may specify particular oversight arrangements, but even if they do not, some form of oversight is strongly recommended for all trials, although the appropriate structures will vary according to the size, complexity and risks associated with the trial.

Commonly employed oversight committees include:

- i) a Trial Management Group
- ii) a Trial Steering Committee
- iii) a Data Monitoring Committee

i) Trial Management Group (TMG)

Every trial should have a TMG, although in very small simple studies this may comprise only one individual, the chief investigator.

The TMG should include those individuals responsible for the day-to-day management of the trial, such as the chief investigator, statistician, trial co-ordinator, research nurse, data manager, as relevant.

The group should keep a close eye on all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take speedy action as necessary to safeguard participants and the trial itself.

As a trial increases in size and complexity more formal structures become appropriate.

In single-centre trials oversight may be provided through the research governance arrangements made by a hospital trust or university, in larger trials a formal Trial Steering Committee is recommended.

ii) Trial Steering Committee (TSC)

The role of a TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of Good Clinical Practice and the relevant regulations.

The TSC should agree the trial protocol and any protocol amendments and provide advice to the investigators on all aspects of the trial.

The TSC monitors the progress of a trial, including the recruitment, data completeness, and losses to follow-up and ensures that there are no major deviations from the trial protocol.

A TSC may have members who are independent of the investigators; an independent chairperson in particular can be very helpful.

iii) Data Monitoring Committee (DMC)

A Data Monitoring Committee should be considered for every trial, although one may not always be necessary.

The role of a DMC 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 ethical reasons why the trial should not continue.

In the course of a blinded trial, it is the only body that has access to unblinded data.

The DMC should be independent of both the investigators and the funder/sponsor. It should report to the TSC (or TMG if there is no TSC).

The decision of whether or not a DMC would be useful should be based on the potential risks and benefits to participants associated with the trial and the trial design.

The time-frame for recruitment and administration of the intervention relative to the timing of the outcome assessment and whether these provide an opportunity to act to protect current or future participants should be considered.

For example, in a placebo-controlled trial of a well characterised and commonly used intervention that is most unlikely to cause any unexpected adverse effects that is being undertaken to assess long-term benefits (e.g at three years) and recruitment will take place over one year, it could be argued that a DMC may not only be unnecessary it would be pointless.

Patient safety is most unlikely to be threatened, and even if a benefit were observed before all the participants had been followed for 3 years, there would be no opportunity to intervene because by the time the effect had been observed all the patients would have been recruited and treated.

However, if the outcome were being assessed at one year and recruitment was likely to take several years to reach the projected sample size, a DMC would be desirable because if an unexpectedly large benefit were detected early, patients not yet recruited would not have to be subjected to the disadvantage of the placebo treatment.

2.2 Coordinating centre 'good housekeeping'

This is the day-to-day monitoring that is carried out by those responsible for running a trial. This typically includes 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

If it is feasible for another team within the institution to undertake some aspects of the review (e.g. internal audit) that provides an additional level of security.

Any problems identified should be reviewed by the TMG and remedial action taken as necessary.

2.3 Central monitoring

Centralised procedures can be used to confirm patient eligibility (for example, collection of pathology reports to substantiate a diagnosis), to corroborate the existence of the patient (for example, through ONS flagging or collection of an imaging investigation) and to determine the outcome (for example, ONS flagging for survival end-points or central assessment of the results of an investigation, such as a X-ray or scan).

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 detect sites or individuals where there may be deviation from the protocol.

This may be due to a misunderstanding, but could indicate falsification of data. In either case, further investigation is required; a site visit, and additional training and support may be needed.

Although omissions (e.g. failure to report a serious adverse event) or data entry errors cannot be detected directly, it may be possible to compare data from the different sites to identify sites that warrant investigation.

Examples of central statistical monitoring techniques include¹:

1. **Missing or invalid data**
Range checks can be used to identify unlikely or implausible values, such as extreme values for weight, or diastolic greater than systolic blood pressure. For studies using electronic data capture methods, these checks can usefully be built into the data collection form; any such automatic safeguards should be validated to ensure that they function correctly.

¹ M Buyse, SL George, S Evans, et al. for the International Society for Clinical Biostatistics Subcommittee on Fraud. The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. *Statist Med* 1999;18:3435-51.

2. **Calendar checks**
Examining the day of the week that patients were randomized can be revealing (e.g. randomization on Sunday in a study of patients attending outpatient clinic). It is also helpful to compare the order of study forms (particularly if they have an ordered numbering system) with the dates they were completed.
3. **Unusual data patterns**
Data from one site can be compared with data for the trial as a whole to identify patterns such as digit preference, rounding, or unusual frequency distribution (e.g. mean, variance, skewness). Such checks can be applied both to a single variable (e.g. systolic blood pressure) and to the joint distribution of several variables (e.g. systolic blood pressure and weight).
4. **Rates of reporting**
The frequency of reported adverse events and of missing data can be compared between centres.
5. **Repeated measures**
Where the same variable is measured on multiple occasions for each participant during the study, it is possible to check that the variability and within individual changes of such repeated measurements is broadly consistent with the pattern seen for the trial as a whole.
6. **Comparison with external sources**
Checks with birth and death registries or with disease-specific registries (e.g. cancer registry) can be used to identify that particular patients exist and that particular events have (or have not) occurred.

In applying all these check it is important to recognise that some variability is to be expected. Data that are too good should raise suspicion in the same way as data that are unusually poor.

2.4 On-site monitoring

On-site monitoring visits may be used in a variety of different ways:

- to educate staff about the trial; review understanding of the protocol and trial procedures;
- to verify that the staff at the site have access to the necessary documents to conduct the trial;
- to ensure that the required pharmacy and laboratory resources are adequate;
- to check adherence to the protocol and GCP by reviewing such things as signed consent forms and patient eligibility, and
- to 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.

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.

3. Monitoring of clinical sites

Appropriate procedures to monitor each particular trial should be established.

These may need to refer to or incorporate the relevant policies or procedures required by other bodies involved in the trial, such as those of the host institution (university or NHS Trust) or funding body.

However, it is helpful to consider the particular monitoring requirements of each trial based on the trial design and methodology and the Clinical Trial Risk Assessment.

It is recommended that planned monitoring procedures for a particular trial be documented. This would typically include:

- the extent and nature of monitoring to be employed;
- the responsibilities of those involved; and
- procedures for monitoring reports and for dealing with issues raised

3.1 Extent and nature of monitoring

The extent and nature of monitoring should be determined prior to the start of the trial. The clinical trial risk assessment may be used to determine the **intensity** and the **focus** of the monitoring activity, whilst the trial design would inform the **methods** used for monitoring.

In many trials, procedures can be established in the design stage that will greatly facilitate the monitoring process, focussing resources on the key areas of potential risk.

The focus should be on developing, checking and adjusting these procedures, and on providing training, mentoring and support to study staff in response to the issues identified.

There is often a tendency to over-emphasise routine processes rather than identifying the most appropriate means of addressing the underlying concerns.

For example, one of the principles of GCP is that each individual involved in a clinical trial should be qualified by education, training and experience to perform his/her respective tasks.

The ICH guidelines suggest that this is verified by collecting curriculum vitae from each investigator.

In many trials it might be more appropriate to ensure that an investigator has an appropriate appointment in the care organisation or is on the relevant specialist register and that appropriate training sessions on the trial procedures have been undertaken.

In establishing procedures for monitoring appropriate to a particular trial, it is helpful to consider the following key areas.

3.1.1 Consent

Ensuring that the consent procedures result in freely given and appropriately informed consent is imperative.

There may be particular challenges in trials with complex interventions, potentially toxic or hazardous treatments, invasive assessment methods (e.g. liver biopsy, coronary angiography) or vulnerable study participants.

In such cases, training including role play, observation or recording of investigators obtaining informed consent may be helpful in ensuring that the trial is presented in a clear, comprehensive and balanced manner.

These techniques may reveal deficiencies in the level of understanding, style of presentation, or extent of discussion in the consent process.

If training is required, all those who may request consent from patients in the study (e.g. junior medical staff) should be included.

In other trials, it may be sufficient simply to check that the consent form has been signed and dated and that there is a record of the information to participants that should be covered during the consent process.

Provided the participant has given consent for his/her name to be given to the trial co-ordinating centre, a copy of the signed consent form may be filed at the centre as well as at the site.

If not, confirmation that the consent form has been signed can be undertaken either in the course of a site visit or by the care organisation R&D staff, if they agree.

If a central randomisation process is being employed, it is good practice to include a question on consent in the eligibility check.

3.1.2 Eligibility

For some trials, particularly those recruiting a precisely defined population because of concerns about the safety of the intervention (e.g. early phase trials), it may be necessary to confirm that every patient recruited into the study met the eligibility criteria.

In other studies, for example those recruiting large numbers from a more general population, it might be appropriate to check eligibility criteria for only a sample of the participants.

Indeed, in some very pragmatic trials, eligibility may be based on self-reported characteristics which cannot be checked against some other source.

If randomisation is being managed centrally, it is good practice to review each patient's eligibility prior to recruitment (e.g. an eligibility check list).

For some trials, a central laboratory may play a key role in assessing eligibility (e.g. by reporting imaging results, ECGs, pathology specimens, or other investigations).

In these circumstances, Quality Assurance methods can be built in at the trial design stage.

Central monitoring may be helpful in identifying suspicious patterns of recruitment (e.g. abnormal clustering of blood pressure just above the cut-off for inclusion in a hypertension trial).

Use of such methods allows the monitoring effort to focus on those sites or investigators where there is the greatest concern about data accuracy and possible falsification of data.

3.1.3 Capturing and reporting information on Serious Adverse Events

In an early phase trial where the safety profile of the intervention is not well established, it might be appropriate to examine the clinical records of all participants for adverse events, to check for both accuracy and completeness.

In contrast, in a study of a well-established treatment with a known risk profile, detailed examination of a random sample of case records may be appropriate.

3.1.4 Capturing, processing and coding study endpoints

The nature and design of the trial will determine the way in which study endpoints are monitored.

For example, in a study in which patients are followed-up by telephone or by using participant-administered web-based data entry forms it would be inappropriate to plan monitoring visits.

Use of central laboratories and blinded endpoint adjudication processes provide other opportunities for Quality Assurance.

3.1.5 Training of investigators and study personnel

Investigator meetings, both before and during a trial, play a valuable role both in providing trial-specific training and reviewing knowledge and understanding of trial procedures.

Where investigator meetings are being used as part of the training or monitoring process, it is recommended that attendance be recorded and that care should be taken to ensure that all the relevant staff have been included.

Trials with sites that are geographically dispersed or that require the training of a number of different professional groups may find that regional meetings, discipline-specific meetings or teleconferences are an efficient way of accomplishing the task.

3.1.6 *Investigational medicinal product (IMP) storage, dispensing and accountability*

It is important to ensure that appropriate storage, dispensing, accountability and destruction arrangements are in place. If investigational medicines are not being stored in a pharmacy, the storage conditions may need to be checked.

In trials in which pharmacies are dispensing IMPs, the trial team may need to verify that pharmacy staff understand the requirements of the trial and that the correct supplies are being used.

If IMPs are coming from routine stocks it may be advisable to confirm that what is being dispensed is the product specified in the protocol.

4 Responsibilities and training of monitoring staff

Trial monitoring procedures should be described in such a way as to make clear the responsibilities of the staff involved, including their organisation training and relationship to other trial staff, the arrangements for central monitoring, the frequency and nature of site visits (if required) and how the results of monitoring inform other activities such as the training of personnel at study sites.

To monitor a trial successfully requires both relevant scientific and/or clinical knowledge, and appropriate training.

It is recommended that these be documented (e.g. in the CV and/or training records held by the individual or Personnel department).

In many cases a system of mentoring, with more senior staff supporting junior colleagues is recommended.

Such an approach not only provides an appropriate environment for Continuing Professional Development but also enables a consistent approach to monitoring within a team.

It is recommended that on-the-job training of this sort is documented in staff training records.

5 Monitoring reports

Monitoring visits and other monitoring procedures should be recorded.

Visit reports would typically include the date, site, name of the monitor, and name of the investigator(s) or other individuals contacted, as well as a summary of what was reviewed.

The monitor should record significant findings, any deficiencies detected, conclusions and any recommended actions.

6 Procedures for dealing with the issues raised by monitoring

It should be clear by whom monitoring reports are to be reviewed.

In many cases the monitoring process can provide valuable information that can be used to improve trial methods and to focus further training.

The procedure for dealing with actions arising from monitoring visits and monitoring checks should be provided.