Workstream 4: Trial Management and Monitoring:

C) Monitoring Procedures

1. Introduction

The purpose of trial monitoring as defined in ICH GCP[1] 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[2];
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)*

In addition, there is now an international consensus that a move towards more flexible and targeted monitoring activities is the most effective approach. For example, DRAFT guidance published by the Food and Drugs Administration (FDA) states: *"risk-based approaches to monitoring such as focusing on the most critical data elements, are more likely to ensure subject protection and overall study quality, and will permit sponsors to monitor the conduct of clinical investigations more effectively than routine visits to all sites and 100% data verification."*

The European Medicines Agency (EMA) has published a Reflection Paper on Risk Based Quality Management in Clinical Trials stating: *"Clinical research is about generating information to support decision making. The quality of information generated should therefore be sufficient to support good decision making. The adequacy of that quality can also be characterised by stating that it should be such that the decisions made would have been no different had the quality of data and information generated been perfect"*

MRC/DH/MHRA Joint Project: For UK trials, The Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products has been published to help sponsors undertake the process of risk assessment. This document outlines a scheme for defining the risks associated with each clinical trial by adopting a dual strategy:

1) Defining the risks of the IMP using a simple IMP risk categorisation (Type A,B and C) based on marketing status and standard medical care.
2) Defining the risks associated with trial conduct by examining the trial design, population and procedures to identify specific areas of vulnerability and to determine how any risks can be mitigated.

---

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guideline for Good Clinical Practice E6.

[2] In some trials, the case report form (CRF) may hold the source data (e.g. a subject questionnaire may form part of the CRF). In this example, the information is collected directly from the participant and is not recorded elsewhere. Where this is the case, the identity and location of source data should be defined in advance, usually in the protocol or other form of documentation.

Appendix 2 of the MRC/DH/MHRA document outlines the implications of the IMP risk category for the monitoring of participant safety and the clinical trial and gives further information on the types of monitoring and the documentation of all aspects of the monitoring process.

The remainder of this document expands on some of the aspects of monitoring that are outlined in MRC/DH/MHRA: The Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products.

2. Types of Monitoring

There are a number of approaches to trial monitoring available, and the procedures for each trial should be considered as the trial is being developed. Some of these approaches are outlined below.

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[3].

Commonly employed oversight committees for a phase III trial include:

i) Trial Management Group (TMG)
ii) Trial Steering Committee (TSC)
iii) Data Monitoring Committee (DMC)

Trial Management Group: Most trials should have a TMG, although in very small simple trials the Chief Investigator may perform the functions of the trial management group. 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 an NHS Trust/Health Board or university. In larger trials a Trial Steering Committee is recommended.

Trial Steering Committee: 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. Formalised procedures should be in place directing its formation and membership as well as its agreed responsibilities.
The TSC should agree the trial protocol and any protocol amendments and provide advice to 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 will usually have members who are independent of the investigators; an independent chairperson in particular can be very helpful, as well as two other independent members[4].
The documentation produced by the TSC will include details of key decisions made during the trial and should be archived in the Trial Master File.

[3] The MRC Guidelines for Good Clinical Practice in Clinical Trials (1998) give further information relating to oversight committees.

[4] Extract taken from Appendix 3 of MRC Guidelines for Good Clinical Practice in Clinical Trials (1998) which also provides information for the TSC Terms of Reference.

Data Monitoring Committee: 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 the attention of the TSC 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 as to whether or not a DMC would be useful should be based on the potential risks and benefits to subjects 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 participants, should also be considered. For example, in a placebo-controlled trial using a well characterised and commonly prescribed medicinal product (most unlikely to cause any unexpected adverse effects) being undertaken to assess long-term benefits (e.g. at three years) with recruitment taking place over one year, a DMC would provide no added value. Subject 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 subjects would have been recruited and treated.
However, if outcomes 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, subjects not yet recruited would not have to be subjected to the disadvantage of the placebo treatment.

A proposed charter for clinical trial Data Monitoring Committees has been developed by the DAMOCLES study group - *The Lancet* 365:711-722, 2005
The EMA have also published guidelines - *EMA Guidelines On Data Monitoring Committees*.
Terms of Reference can be found in Appendix 3 of the *MRC GCP Guidelines for Good Clinical Practice 1998*

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:

- the data collected are consistent, with adherence to the trial protocol
- the case report forms (CRFs) are only being completed by authorised persons
- no key data are missing
- data appear to be valid (for example, range and consistency checks)
- a 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, this would provide an additional level of security (see section 2.4).
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 subject eligibility (for example, collection of pathology reports to substantiate a diagnosis), to corroborate the existence of the subject (for example, through Office for National Statistics (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-site trials, central monitoring of data using statistical techniques is particularly useful for the *early* identification of:

- Unusual patterns or trends
- Issues with plausibility or consistency
- Safety signals
- Other deviation from protocol/trial requirements such as poor/late completion of CRFs

Where centralised monitoring indicates problems, it can be used to efficiently direct on-site monitoring activities to those sites requiring further investigation and/or additional training support.
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 different sites to identify sites that warrant investigation.

Basic central statistical monitoring checks include[5]:

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 trials 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.
2. Calendar checks; Examining the day of the week that subjects were randomised can be revealing (e.g. randomisation on Sunday in a trial of patients attending outpatient clinic). It is also helpful to compare the order of trial 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 sites.
5. Repeated measures; Where the same variable is measured on multiple occasions for each subject during the trial, 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.

When applying these checks 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.
Various complementary central statistical monitoring techniques can be adopted that focus on comparing sites using the concepts listed above. A key risk indicator approach based on examining the main aspects of trial performance that are likely to impact subject safety and trial reliability can be useful for identifying problem sites[6]. For example, compliance with trial treatment is generally a useful key risk indicator. An excess of non-compliance at a particular site has the potential to impact trial reliability and may indicate poor on-site performance. In addition, central statistical monitoring techniques based on examining all aspects of the trial data, rather than selected indicators, are potentially useful for identifying sites that may require further investigation[7].

Other Remote Monitoring Checks: It is common practice for the sponsors of small, non-commercial trials to utilise self-assessment checklists/progress updates to help confirm

[5]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.

[6] E Valdés-Márquez, JC Hopewell, M Landray, J Armitage. A key risk indicator approach to central statistical monitoring in multicentre clinical trials: method development in the context of an ongoing large-scale randomized trial. *Trials* 2011, 12(Suppl 1):A135.

[7] D Venet, E Doffagne, T Burzykowski, F Beckers, Y Tellier, E Genevois-Marlin, U Becker, V Bee, V Wilson, C Legrand, M Buyse. **A statistical approach to central monitoring of data quality in clinical trials.** *Clin Trials* (published online ahead of print, 8th June 2012)**.**

GCP/protocol compliance. For example, sites may be required to complete a checklist confirming the contents/versions of documents held in their investigator site file thereby giving assurance that the site file is up to date and being maintained.

Fraud: Data anomalies (e.g. fraud, including fabrication of data and other non-random data distributions) may be more readily detected by using central monitoring techniques compared with other methods of monitoring. For example; 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).

2.4 On-site Monitoring

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

- to educate staff about the trial and review their understanding of the protocol and trial procedures;
- to verify that the staff at the site have access to the necessary documents/trial materials 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 subject eligibility;
- to verify that all protocol required data (e.g. adverse event/concomitant medication) have been transcribed into the case report form (CRF) accurately (source data verification);
- to observe trial procedures (e.g. informed consent procedures, data collection, CRF completion) to ensure quality and consistency and to confirm all assessments are being made by appropriately qualified staff;
- to identify staff training needs.

Section 5.18.4 of the ICH GCP Guidelines gives a more comprehensive list of the responsibilities of a monitor.

Reciprocal Monitoring Arrangements: Non-commercial organisations sponsoring trials may consider developing in-house or collaborative *reciprocal monitoring arrangements* where clinical staff from different teams are trained as trial monitors, and then perform monitoring checks on trials run by a separate team.

3. The Monitoring Plan

Appropriate procedures to monitor each trial should be established during trial design.
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/Health Board) or funding body.
It is recommended that a monitoring plan is produced to formalise and define the strategy for each trial and that it is based on the trial design and the risk assessment performed. This plan should define the data to be reviewed as well as the types of checks that will be performed by outlining:

- the extent and nature of monitoring to be employed;
- the responsibilities of those involved (and any training required);
- the procedures for monitoring reports including dealing with any issues that arise from monitoring such as;
    - how issues identified are escalated when required
    - how findings may lead to the monitoring plan being adapted

4. Extent and Nature of Monitoring

The extent and nature of monitoring should be determined prior to the start of the trial, preferably at the grant application stage to allow additional monitoring costs to be included in the budget. 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 trial 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 also be important 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. When establishing procedures for trial monitoring, it is helpful to consider the following key areas.

4.1 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 trial subjects (e.g. incapacitated adults, minors).
In such cases, training and competency assessment 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[8]. 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 subjects participating in the trial (e.g. junior medical staff) should be included. It is also important to specify how staff, that subsequently join the trial team (e.g. rotational registrars), receive appropriate training.
For simple, low risk 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 provided to subjects.
Provided the subject has given consent for his/her name to be given to the trial co-ordinating centre (and appropriate confidentiality arrangements are in place), a copy of the signed consent form may be filed at the centre as well as at the site so that the centre can confirm that the correct version has been signed/dated by the subject. 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, or by implementing a reciprocal monitoring arrangement.
If a central randomisation process is being employed, it is good practice to include a question on consent in the eligibility check.

4.2 Training of Investigators and Site Staff

Before a trial begins, it is common practice for a start-up/initiation meeting to be held to confirm all site staff are adequately trained and ready to start the trial. For more complex trials (for example where requirements differ markedly from routine care or require the use of novel procedures/techniques or specialised equipment supplied for the trial) a site visit may help reassure the trial team that an adequate level of training/competence has been achieved. For more pragmatic trials, with a simple design using standard therapies, a telephone initiation may be sufficient to confirm the site is ready to begin.
The method of training (or any on-going knowledge assessment) may also be influenced by factors such as whether sites are geographically dispersed or whether a number of different professional groups require training. Regional meetings, discipline-specific meetings, webinars, videoconferences or teleconferences are all efficient ways of accomplishing these tasks.

[8] For an example of on-site monitoring using these techniques, see Lane JA et al, A peer review intervention for monitoring and evaluating sites (PRIME) that improved randomized controlled trial conduct and performance. J Clin Epi 2011;64:628-636.

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 is recorded and that care should be taken to ensure that all the relevant staff have been included.

Training Commensurate to Roles: Where possible, the training delivered to site staff should be commensurate to their role. For example, the Principal Investigator may benefit from training on the trial's IMP dose escalation procedures whereas those involved in data collection may benefit from training relating to case report form completion. Where possible, this proportionate approach should apply to GCP training. The MHRA strongly recommends training in relevant aspects of GCP for anyone involved in conducting CTIMPs, even if the activities are part of an individual's routine job but the GCP knowledge requirements of, for example, hospital laboratory staff analysing clinical trial samples will differ from those of the core trial team.
Training of site staff is often an on-going process and should be monitored appropriately. The trial team would also need to ensure any new staff that join the trial team receive training before they undertake trial specific activities. The monitoring process often identifies areas where staff may require further training (for example in response to GCP non-compliances).

4.3 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 subject recruited into the trial has met the eligibility criteria.
In other trials, for example those recruiting large numbers from a more general population, it might be appropriate to check eligibility criteria for only a sample of subjects. 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 subject's eligibility prior to recruitment (e.g. an eligibility check list). Examples are outlined below:

- Where fax based registration is used for a trial, it may be possible to request anonymised copies of key source documents (e.g. in a cancer trial, the histology report to confirm the subject's tumour type or a CT scan to confirm baseline requirements are met). The subject's registration will only be completed once a central review has taken place.
- Where a web-based randomisation system is used, the site may be required to complete fields requesting key eligibility data derived from a review of the source data, (e.g. baseline lab results) to positively confirm eligibility. The subject's registration will only be completed if all entries are acceptable.

For some trials, a central laboratory may play a key role in assessing eligibility (e.g. by directly reporting imaging results, ECGs, pathology specimens, or other investigations). In these circumstances, quality assurance methods are built in at the trial design stage.

4.4 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 subjects for adverse events, to check for both accuracy and completeness.
In contrast, in a trial of a well-established treatment with a known risk profile, detailed examination of a random sample of case records may be appropriate.

4.5 Capturing, Processing and Coding Trial Endpoints

The nature and design of the trial will determine the way in which trial endpoints are monitored. For example, in a trial in which subjects are followed-up by telephone or by using subject-administered web-based data entry forms it would be inappropriate to plan monitoring visits. However, if large amounts of data have been collected and need to be verified to ensure the reliability of key end point data and the trial publication could result in a major change in clinical

practice, a more intensive monitoring approach may need to be applied.
In pharmaceutical company sponsored trials, a high percentage of source data verification occurs but historically, this approach has not been utilised widely by non-commercial sponsors (on site monitoring with a high percentage of source data verification is very resource intensive) and may not be useful depending on the trial[9]. Use of central laboratories and blinded endpoint adjudication processes provide other opportunities for Quality Assurance.

4.5 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 IMPs are not being stored in a pharmacy, the storage conditions may need to be checked.
In trials where pharmacies are dispensing IMPs, the trial team may need to verify that the correct supplies are being used and staff understand the requirements of the trial. This is particularly important when site staff are involved in randomisation or unblinding procedures (or if, for example, IMP is unblinded to pharmacy staff).
The intensity of monitoring of IMP will again be determined by a risk based approach with a higher intensity employed where IMP storage or compliance are critical to the end points of the trial. For example, a vaccine may need to be stored within a narrow range of temperature or may lose its potency so specific checks to confirm that it has been transported/stored appropriately may be warranted.
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. Where central monitoring is employed, the case report form (CRF) may be designed to capture and positively confirm information relating to compliance, or that dosing or dispensing of IMP is in accordance with the protocol.

5. Responsibilities and Training of Monitoring Staff

Trial monitoring procedures should be described in such a way as to make clear the responsibilities of all staff involved. A site monitoring standard operating procedure (SOP) is recommended to specify any generic monitoring procedures.
To monitor a trial successfully requires both relevant scientific and/or clinical knowledge and a good working knowledge of Good Clinical Practice and the Clinical Trials Regulations. Appropriate training on all aspects of the trial protocol and the procedures/processes to be followed, is also required.
It is recommended that qualifications and training be documented (e.g. in the CV and/or training records held by the individual or Personnel department). In many cases, developing a mentoring system 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.

6. 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 and any recommended actions. Information relating to the resolution/outcome of any historical findings should be included.

7. Procedures for Dealing with the Issues Raised by Monitoring

The review/sign-off process for monitoring reports should be defined and documented.
The procedure for dealing with issues arising from monitoring visits and monitoring checks should be provided. As unanticipated risks may emerge in the course of a trial; it is recommended that the monitoring plan is kept under review and modified as necessary. It is

[9] Bakobaki J et al. The potential for central monitoring techniques to replace on-site monitoring: findings from an international multi-centre clinical trial. Clinical Trials 2012; 9: 257-264.

important therefore to include a defined **escalation process** for significant findings as this helps to ensure that:

- monitoring findings inform trial related decisions: for example, instigating substantial amendments, serious breach of GCP/protocol or communication with other trial bodies.
- all non-compliances are handled in such a way that any significant non-compliance can be included in the final trial report.
- any required corrective and preventative actions have been implemented in a timely fashion.
- clear triggers are in place to initiate on-site monitoring (or other monitoring activities) when issues arise from central monitoring procedures.

Updated November 2012 by:
T Symons (T Symons Associates Ltd.), R Macefield (MRC ConDuCT Hub) and J Hopewell (CTSU, University of Oxford).