Workstream 4: Trial Management and Monitoring: C) Monitoring Procedures

1. Introduction

Good Clinical Practice requires sponsors to ensure their trials are adequately monitored. The purpose of trial monitoring is to ensure that:

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

Over the last decade, there has been international recognition that a more flexible and efficient monitoring practices in clinical trials should be encouraged because current practices do not seem to be achieving their desired goals; namely, creating an environment that facilitates cost effective, high quality clinical trials. Both the European Medicines Agency (EMA) and the Food and Drugs Administration (FDA) have endorsed this approach. The recent Addendum to ICH GCP, known as ICH E6 R2, also includes new content that encourages sponsors to adopt a more systematic approach to trial conduct and oversight.

Trial monitoring can take multiple forms but can be categorised into two main types:

- **On-site monitoring** that involves visits to the site by the trial monitor to perform checks that include: verification that trial documents exist, assessment of the site's understanding of, and compliance with the protocol and trial procedures, accountability checks for investigational medicinal product and checks of data quality and completeness. This process may or may not include source data verification (SDV); a comparison of information recorded in the Case Report Form with the site's source documentation, in order to detect discrepancies due to transcription errors. In general, on-site visits can provide sponsor staff with a sense of the quality of the overall conduct of the trial at a site [1].

- **Central monitoring** that involves the review of central data, for example, by trial oversight committees*, data/trial management personnel and statisticians. This may include the central review of data from sites (e.g. a review of the completeness of Case Report Forms) or, for multicentre trials, the use of **statistical monitoring,** where patterns of accumulating data are examined using statistical approaches or modelling across the trial. The MRC Hubs for Trial Methodology and MHRA GCP Forum websites provide further information on central statistical monitoring. As part of the centralised monitoring of trials, the term **remote monitoring** is also used to capture monitoring activities that were previously conducted on-site by the trial monitor but can now be conducted centrally (e.g. web-enabled training, site initiation visits conducted via video conference, remote review of signed consents or laboratory reports[2]).

  It is now widely accepted [1-7] that central monitoring processes can provide many of the capabilities of on-site monitoring as well as additional capabilities[3]. More and more, central monitoring activities are being used to complement, prioritise and inform on-site monitoring and thereby also reduce (and in some instances replace) the need for, and improve the efficiency of, any such visits..

[1] With the exception of certain data where the case report form has been defined in the protocol as the source.

[2] The MHRA Good Clinical Practice Guide provides information on the formal systems that should be in place when remotely monitoring documents containing patient identifiers, particularly in relation to the Data Protection Act.

[3] For example, the more efficient detection of fraud [7].

***Note:** The MRC Guidelines for Management of Global Health Trials (2017) describes three oversight structures: the day-to-day Trial Management Group (TMG), the executive Trial Steering Committee (TSC) and the Data Monitoring Committee (DMC). The role and function the TSC is outlined in Appendix 3 and the DMC in Appendix 4. In addition, Guidance on DMCs is also provided by the European Medicines Agency and the Health Research Authority.*

2. Quality Management to Reduce Reliance on Trial Monitoring

Incorporation of quality management processes into the scientific and operational design of a trial can improve trial quality by helping to address important errors [6, 8, 9]. This process generally requires the input of a multidisciplinary team including clinicians, statisticians as well as experts in trial and data management. Features of a robust design include: a properly generated randomisation schedule, outcome measures that are objective and simple to assess accurately or, when objective outcome measures cannot be used, effective masking of the intervention when assessing outcomes. ICH E6 R2 also recommends that trials, '*avoid unnecessary complexity, procedures and data collection*'. The more robust (and less complex) the design, the less dependence there is on trial monitoring (and other quality control and assurance measures) to obtain reliable results.

The *Reflection paper on risk based quality management in clinical trials* published by the EMA underlines that the quality of a trial needs to be ensured through proper design and also describes the key principle of risk based quality management. Many groups, from both industry and academia, encourage the adoption of Quality by Design principles[4]. For example, the US Clinical Trials Transformation Initiative (CTTI), who define 'quality' as '*the absence of errors that matter',* provide a useful Principles Document that outlines a framework for the identification of issues during the protocol design process.

3. Risk based Monitoring

There is growing consensus that risk-based monitoring of non-commercial trials can facilitate efficient and cost effective trial delivery without compromising patient safety or data quality [4]. The term risk-based monitoring may be used to denote the reduced (but essentially fixed) monitoring of a trial (e.g. when deemed low risk) but more and more, risk-based monitoring is used to describe 'adaptive' or 'triggered' monitoring methods that focus monitoring activities on those sites that appear to need it most. A risk-based monitoring strategy addresses the question:

What are the critical processes and critical data for this trial and how best can any risks and/or vulnerabilities identified in these areas be managed or mitigated in order to avoid errors that matter?

To apply remote monitoring strategies effectively, a risk assessment must be performed. Risk assessment is the process of identifying the potential hazards associated with a clinical trial and evaluating the likelihood of those hazards occurring and resulting in harm to participants or to the validity of trial data. For UK trials, *The Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products* (MRC/DH/MHRA Joint Project) was published to help sponsors undertake the process of risk assessment and to clarify how monitoring strategies can be adapted.

Appendix 2 outlines a two-step process to help define trial-related risks:

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. (*See Table 1 below).
2) *Defining the risks associated with trial conduct, design and methods.*

[4] Quality by Design is a systematic approach to development that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management.

In addition to the trial-related risks described above, system level risks should be identified as part of the trial's overall risk assessment, for example, those risk associated with computerised systems, standard operating procedures and personnel. The MHRA GCP Forum provides further guidance in FAQs and also Examples of Risk Assessments.

4. Data driven decision-making: Key Risk Indicators

In addition to the identification of risk (through risk assessment), ICH E6 R2 provides guidance on a systematic approach to data driven *risk control* stating:

'Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results.

The identification of *key risk indicators* and the setting of guidance *thresholds* that may trigger particular actions, ranging from additional data checks to on-site visits, enable a more data-driven approach to monitoring that may be used to detect and correct issues while the study is ongoing. The definition and potential combination of key risk indicators, that each directly or indirectly represent potential hazards and are likely to be somewhat interdependent, as well as the setting of meaningful thresholds, require careful consideration by the trial team and will commonly vary between studies. Furthermore, although key risk indicators offer many advantages and uses for detection of some issues, this approach may be less able to detect subtle differences that can also affect trial quality. Several risk based monitoring initiatives are underway that describe these activities. For example, in their Position Paper, TransCelerate Biopharma Inc outlines a set of commonly adopted risk indicators and guidance on the determination of thresholds. In their publication, Tudur Smith et al provide additional examples specific to a non-commercial trial and Q22 of the MHRA GCP Forum Q&A's provides examples of key risk (performance) indicators and a discussion on their use to target on-site visits.

5. Monitoring Strategy and Monitoring Plan

In relation to trial monitoring, ICH E6 R2 recommends that sponsors document the rationale for their chosen monitoring strategy in a monitoring plan[5] stating:

"The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use."

5.18.7

An example of a monitoring plan for a non-commercial trial can be found in *Tudur Smith et al:* Additional file 2.

A trial's monitoring strategy should be considered at the protocol design stage as part of the overall trial management plans so that processes to proactively manage critical aspects of the trial can be put in place. In addition, the monitoring strategy may contain elements that span across all trials sponsored by the organisation.

Where monitoring activities are undertaken centrally, sufficient documentation to support compliance with the monitoring plan and monitoring strategy will need to be retained. Traditional

[5] A monitoring plan may be a stand-alone document or may be incorporated into other documents (e.g. the protocol).

monitoring reports from site visits usually provide clear evidence of what was checked; any non-compliance and a description of associated actions/resolution. Any monitoring activities conducted centrally would be required to provide similar evidence. The MHRA FAQs for monitoring: Q9 provide further detail and describe how the monitoring strategy may be documented.

Although a risk based monitoring plan will often build in flexibility for monitoring activities, ICH E6 R2 requires sponsors to periodically review their risk control measures to ascertain whether the quality management activities that have been implemented remain effective and relevant. The results of monitoring may direct changes to the monitoring plan/strategy; either moderation (downgrading of activities) or escalation of activities.

6. Extent and Nature of Monitoring

Chapter 7 of the MHRA Good Clinical Practice Guide and the MRC/DH/MHRA Joint Project provide comprehensive guidance on how the intensity and focus of monitoring may vary based on the vulnerabilities identified in the risk assessment. In addition, 'Recommendations of the expert group on clinical trials for the implementation of (EU) No 536/2014' outlines specific areas where risk adapted approaches have been incorporated into the Clinical Trials Regulations (536). The FDA have also published guidance, 'Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Post-approval Clinical Investigations' that includes useful advice on selective safety reporting practices including the types of clinical investigation that may be considered for selective safety data collection.

7. References

1. Food and Administration: Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring (Aug 2013)
2. European Medicines Agency: Reflection paper on risk based quality management in clinical trials
3. The Integrated Addendum to ICH E6 R1: *Guidelines for Good Clinical Practice* (ICH E6 R2) (effective Jun 2017)
4. Risk-proportionate clinical trial monitoring: an example approach from a non-commercial trials unit: Catrin Tudur Smith, Paula Williamson. Ashley Jones, Alan Smyth, Simon Langton Hewer and Carrol Gamble. Trials 2014 15:127
5. Position Paper: Risk-Based Monitoring Methodology (TransCelerate Biopharma Inc.)
6. CTTI Recommendations: Effective and Efficient Monitoring as a Component of Quality Assurance in the Conduct of Clinical Trials (Dec 2009)
7. A statistical approach to central monitoring of data quality in clinical trials: David Venet, Erik Doffagne, Tomasz Burzykowski, François Beckers Yves Tellier, Eric Genevois-Marlin, Ursula Becker, Valerie Bee, Veronique Wilson, Catherine Legrand and Marc Buyse (Clinical Trials published online 8 June 2012)
8. Enhancing clinical evidence by proactively building quality into clinical trials: Meeker-O'Connell A, Glessner C, Behm M, Mulinde J, Roach N, Sweeney F, Tenaerts P, Landray MJ. Clin Trials 2016; 13:439-444.
9. Clinical Trials: Rethinking how we ensure quality: Landray MJ, Grandinetti C, Kramer JM, Morrison BW, Ball L, Sherman RE. Drug Information Journal 2012; 46:657-660.

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