# Trial Management and Monitoring: Monitoring Procedures Workstream Document C

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

### Introduction

Good Clinical Practice (GCP) 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
- the trial complies with the protocol, GCP, and all relevant regulatory requirements

There is increasing international recognition that more flexible and efficient monitoring practices should be encouraged for clinical trials, because traditional monitoring practices do not always facilitate cost-effective, high-quality trials. Both the European Medicines Agency (EMA) (pdf) (.PDF) and the Food and Drugs Administration (FDA) and the Addendum to ICH GCP (pdf) (.PDF) have endorsed a flexible approach to trial conduct and oversight.

Trial monitoring can be conducted in several ways.

**On-site monitoring** involves site visits by trial monitors who carry out checks that include: verifying that trial documents exist, assessing 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 to detect discrepancies due to transcription errors. In general, on-site visits can give sponsor staff a sense of the quality of the overall conduct of the trial at a site.

**Remote monitoring** includes monitoring activities previously carried out on site, which are now carried out centrally, such as web-enabled training, site initiation visits conducted via video conference, remote review of signed consents or laboratory reports. The MHRA Good Clinical Practice Guide provides information on the formal systems that should be in place when remotely monitoring documents containing patient identifiers, especially in relation to data protection. Since the pandemic, remote access and review of source documents is increasingly becoming standard practice.

**Central (statistical) monitoring** involves the review of central data, for example by trial oversight committees*, data/trial management personnel and statisticians. This may include aspects of remote monitoring such as the central review of data from sites or for multi-centre 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.

Central monitoring processes can provide many of the capabilities of on-site monitoring, including the detection of fraud. Increasingly, central monitoring activities are used to complement, prioritise, and inform on-site monitoring, thereby reducing (and in some instances replacing) the need for such visits, thus improving the efficiency of trials.

***** *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).*

## 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. This process generally requires the input of a multidisciplinary team, including clinicians, statisticians and experts in trial and data management. Features of a robust design include: a properly generated randomisation schedule, outcome measures that are objective and easy 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 (.PDF) (2013) published by the EMA, underlines that the quality of a trial must be ensured through proper design and also describes the key principle of risk-based quality management. Many groupski from both industry and academia, encourage the adoption of Quality by Design principles. 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.

## 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. The term risk-based monitoring may be used to denote the reduced, but essentially fixed monitoring of a trial. Increasingly, risk-based monitoring is used to describe 'adaptive' or 'triggered' monitoring methods that focus monitoring activities on 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 (.PDF)) was

published to help sponsors undertake the process of risk assessment and to clarify how monitoring strategies can be adapted.

The document outlines a two-step process:

1. Defining the risks of the IMP using a simple risk categorisation (Type A, B and C) based on marketing status and standard medical care.
2. Defining the risks associated with trial conduct, design and methods.

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.

## Data driven decision-making: Quality tolerance limits and key risk indicators

ICH E6 R2 recommends that sponsors decide which trial risks to reduce and which to tolerate, and suggests that **quality tolerance limits** are set. A quality tolerance limit is a level, threshold or value associated with a parameter that triggers an evaluation when a deviation is detected to determine whether a systematic issue has occurred. Predefined quality tolerance limits are established, taking into account the medical and statistical characteristics of the variables, as well as the statistical design of the trial.

**Key risk indicators** are metrics that predict potential risks that can have a negative impact on the quality or safety of a trial. The identification of key risk indicators and the setting of guidance thresholds that trigger certain actions (such as additional data checks or on-site visits) enable a more data-driven approach to monitoring. This may be used to detect and correct issues while the study is ongoing. In its Position Paper (pdf), TransCelerate Biopharma Inc outlines a number of commonly adopted risk indicators and guidance for determining thresholds. In their publication, Tudur Smith et al (pdf) provide additional examples specific to a non-commercial trial and Q22 of the MHRA GCP Forum Q&A's provides an example of a monitoring plan for a non-commercial trial and examples of key risk (performance) indicators, as well as a discussion on their use to target on-site visits.

## Monitoring Strategy and Monitoring Plan

ICH E6 R2 recommends that sponsors document the rationale for their chosen monitoring strategy in a monitoring plan:

*"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."*

A monitoring plan can be a stand-alone document or be incorporated into other documents, such as the protocol.

For clinical trials, the development of a monitoring strategy should be considered in the protocol design phase as part of the overall trial management plan, so that processes to proactively manage critical aspects of the trial can be implemented.

Where monitoring activities are carried out centrally, sponsors should maintain sufficient documentation to support compliance with the monitoring plan and monitoring strategy. Traditional monitoring reports from site visits usually provide clear evidence of what was checked, any non-compliance and a description of associated actions and resolutions. Any monitoring activities carried out centrally should provide similar evidence. The MHRA FAQs for monitoring: Q9 provide further details and describe how the monitoring strategy may be documented.

A risk-based monitoring plan will often build in flexibility for monitoring activities, and ICH E6 R2 requires sponsors to periodically review their risk control measures to determine whether the quality management activities 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.

## Extent and Nature of Monitoring

Chapter 7 of the MHRA Good Clinical Practice Guide and the MRC/DH/MHRA Joint Project (.PDF) provide comprehensive guidance on how the intensity and focus of monitoring can vary based on the vulnerabilities identified in the risk assessment. The Clinical Trials Transformation Initiative has published recommendations (.PDF) on the effective and efficient monitoring of clinical trials. For safety monitoring, FDA guidance (.PDF), provides advice on selective safety reporting and data collection practices for late stage trials.

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