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Highlights from MHRA Guidance Clinical Trials for Medicines: Guidance on Quality and Risk Proportionality

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On 27 March 2026, the MHRA released their guidance on Clinical trials for medicines: guidance on quality and risk proportionality. This guidance became effective on 28 April 2026 and applies to all UK clinical trials involving IMPs.

MHRA notes that the document assumes knowledge of ICH E8 (R1) and ICH E6 (R3). The intention of MHRA is not to rewrite ICH E8 (R1) or ICH E6 (R3), but instead to emphasize key principles of Quality by Design (QbD) and Quality Risk Management (QRM).

MHRA also provides practical advice and examples for implementing and documenting risk-proportionate approaches to quality management and provides insight into what inspectors will expect to see in regard to quality risk management activities. These include:

- Protocols should not be finalized until initial risk assessments are complete
- Risk and CTQ stakeholders should include quality assurance
- Teams should establish a "common definition and consistent nomenclature for CTQ factors across functions"
- Sponsors should develop trial goals that emphasize participant welfare and data integrity, not finances or milestones
- TMF documentation should demonstrate proactive quality planning, QbD decision making, identification and tracking of CTQ factors and Risk Based Quality Management (RBQM) activities
- TMF documentation should demonstrate that the sponsor identified key risks and the mitigations put in place for those risks
- TMF documentation should allow tracking of each CTQ factor throughout the trial lifecycle

Overall, the document signals MHRA's expectation that quality and risk management are proportionate to risk severity, that CTQ factors and risk mitigation should focus on participant safety and data integrity and that teams can provide evidence they conducted risk management activities.

The DMEG recommends that data managers review existing SOPs, TMF plans and document templates to ensure they align with MHRA expectations.

Additional details on these points and ACDM DMEG recommendations for implementation by data management are provided in the appendices.

Appendix 1 ICH GCP E6 (R3) and ICH E8 core quality concepts

In this section, MHRA highlights key quality concepts from both documents, such as ICH E8's guidance on identifying critical to quality factors (CTQ) (ICH E8) as well as ICH E6 (R3)'s Principles 3.10, 6, 7 and 9. MHRA uses this section to remind us that our design and conduct of trials should be based on an analysis of trial specific risks to participant safety and data integrity. The processes we put in place to oversee and manage the study should be proportionate to the risks.

In addition, MHRA reiterates the expectation that the quality of data should be fit for purpose to ensure the integrity of trial results and decision making. Because risks may evolve during trial conduct systems and processes should support continual assessment of risks to CTQ factors. Finally, MHRA notes that risk proportionality is not focused on reducing effort, but rather on applying resources, oversight, and quality management activities in proportion to the risks most likely to impact participant safety and data integrity.

Appendix 2 The MHRA's expectations

In this section, MHRA provides useful examples and clarifications on their expectations on implementing and documenting risk management.

Engaging stakeholders
Where ICH E8 simply states a broad range of stakeholders should be engaged, MHRA specifically states that the stakeholders should include representatives from Quality assurance (QA).

Differing incentives
MHRA also notes that trial teams often confuse operational risks (meeting site activation goals, costs, timing) with risks to participants and data. MHRA recommends that sponsors address this issue by implementing trial performance goals that focus on safety and quality.

Critical to Quality Factors
MHRA reminds us that CTQ factors typically affect multiple functional areas and therefore it is important to conduct cross functional reviews of risk. This also facilitates using a common definition and consistent nomenclature for CTQ factors across functions to ensure "shared understanding". The DMEG notes that data managers should ensure that the Data Management Plan (DMP) and other project documents use the definitions and nomenclature developed by the overall project team.

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Quality Management

MHRA states that the protocol should not be finalized until all relevant stakeholders participate in all initial risk assessments. This is particularly important as some risk mitigations may impact the design of the study.

The DMEG notes that while data managers may not be responsible for determining the status of the protocol, they must ensure that they have provided their input into risk assessment prior to finalization. MHRA also shares its expectations that we can demonstrate key risk management approaches including:

- Establishing a risk framework that covers the full life cycle from protocol development to close-out and reporting
- Risk is reviewed continuously and dynamically throughout the conduct of the trial
- Risk identification and review is cross-functional, not siloed, in order to ensure a holistic evaluation
- Sponsor oversight of risk management must be clearly demonstrated

MHRA specifically states that the stakeholders identifying and developing mitigations for CTQ should include quality assurance as this group has a broad, cross-functional understanding of trial conduct issues.

MHRA also recognizes that teams often prioritize operational priorities, such as financial objectives and milestones, before risks to participants and scientific integrity. Sponsors should implement performance goals that emphasize quality. This approach helps ensure cross-functional alignment on safety and quality.

Essential record requirements

MHRA notes that while essential records management should align with ICH E6 (R3), teams should also ensure that the TMF documentation provides evidence of "proactive, prospective quality planning; QbD decision making, identification of CTQ factors and RBQM activities".

MHRA expects to find documentation of the trial specific CTQ factors, risks to those factors, and mitigations for the risks. This can be documented in the protocol or in the TMF in alignment with ICH E6 (R3) B.12.1.

In addition to initial documentation of identification of CTQ, risk, and mitigation, the TMF should contain evidence of ongoing risk management processes. MHRA provides the following examples:

- Initial risk assessment
- Risk evaluation outputs
- Rationale for prioritising or deprioritising risks
- Version history of risk assessments

- Personnel and functions involved in the process
- Evidence that risk controls and mitigations are proportionate to risk severity

The DMEG notes that data managers need to ensure they are performing ongoing risk management activities, and that documentation of these activities and decisions is available in the TMF.

TMF records should provide a clear history of risk management activities for each CTQ factor, including those that might have multiple risks, requiring different controls. MHRA provides this example:

"Risks A, B, and C have been identified for CTQ factor 1; these are managed by processes X, Y, and Z, detected via KRIs i, ii, and ii and where a KRI exceeds the QTL, action α is taken."

The DMEG notes that data managers need to ensure that they are collaborating with the cross-functional team to provide clear documentation of the risk management process. This includes use of consistent nomenclature and clear traceability of risk identification, review and management of each CTQ factor.

Finally, MHRA provides examples of risk management records which are likely to be reviewed during inspections in conjunction with personnel interviews:

- Process of CTQ identification
- Risk management framework activities (ex: risk assessment process)
- Review of CTQ mitigations or controls
- Effectiveness of those mitigations and controls
- Evidence of review and updates to the above
- Associated records

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