Guidance

Clinical trials for medicines: guidance on quality and risk proportionality

Information on applying quality by design, risk-based quality management, and proportionate oversight in UK clinical trials.

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The amended Clinical Trials Regulations took full effect on 28 April 2026. As such, this guidance should now be considered effective and is

no longer in draft.

Part 2 of Schedule 1 to the amended Clinical Trials Regulations requires that the investigator and sponsor (https://www.hra.nhs.uk/planning-and-improving-research/research-planning/roles-and-responsibilities/) (and any individual or organisation that the sponsor or investigator delegates trial-related activities to) have regard to all relevant guidance with respect to commencing and conducting a clinical trial.

Investigators and sponsors must, therefore, ensure that they are fully aware of the information within this guidance and act accordingly to achieve and maintain regulatory compliance.

In addition, the following guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) are also considered relevant guidance and should be consulted:

- ICH E6 (R3) Guideline for Good Clinical Practice (https://www.ich.org/page/efficacy-guidelines#6)
- ICH E8 (R1) General Considerations for Clinical Trials (https://database.ich.org/sites/default/files/E8-R1_Guideline_Step4_2021_1006.pdf)

Scope

This guidance should be read in conjunction with ICH E8 (R1) General Considerations for Clinical Studies. ICH E8 (R1) establishes the overarching scientific and quality principles for clinical study design and conduct, including the application of quality by design approaches.

These principles form the basis for the more detailed operational expectations explained in ICH E6 (R3), and organisations are expected to apply ICH E8 (R1) and E6 (R3) together when planning, conducting and overseeing clinical trials.

ICH E6 (R3) provides principles and detailed guidance which are intended to support sponsors and investigators in delivering high-quality clinical trials.

This guidance serves to provide an explanation of the interconnected quality concepts embedded within ICH E6 (R3); quality by design (QbD), risk-based quality management (RBQM), and risk proportionality, and outlines the practical implications for trial conduct, oversight and compliance.

Schedule 1, Part 2 paragraph 1 of the Clinical Trials Regulations adopts the principles of good clinical practice as set out in ICH E6 making it a

requirement to implement these quality concepts when conducting clinical trials in the UK.

This guidance applies to all UK clinical trials of IMPs.

It is not the intention of this document to rewrite the guidance contained in ICH E6 (R3) or ICH E8 (R1) and it is expected that organisations are conversant with these documents.

Note that the concept of type A, B and C trials as introduced in the MRC/DH/MHRA joint project paper Risk-adapted Approached to the Management of Clinical Trials of Investigational Medicinal Products (Oct 2011) has been retired.

ICH GCP E6 R3 and ICH E8 core quality concepts

E8 (R1) introduces critical to quality (CTQ) factors in Section 3.2, describing them as trial attributes fundamental to participant safety and the reliability and interpretability of trial results.

ICH E6 (R3) Principle 6 reinforces the concept that ’quality should be built into the scientific and operational design and conduct of clinical trials’ and more specifically states:

“Factors critical to the quality of the trial should be identified prospectively.”

These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. Quality by design involves focusing on critical to quality factors of the trial in order to maximise the likelihood of the trial meeting its objectives.

QbD requires sponsors to identify the CTQ factors, which are the trial attributes essential to clinical trial participant protection and the reliability of the trial results, early in trial planning. Examples include (but are not limited to):

- validity of primary endpoint measurement
- integrity of randomisation and blinding
- fit-for-purpose decision-making (for example those which impact safety, dose-escalation and/or stopping criteria)
- correct application of eligibility criteria
- collection and management of relevant clinical data
- fit for purpose of validation of computerised systems that are used for clinical data or endpoints

- informed consent of trial participants

QbD also requires sponsors to:

- design trial processes intentionally to protect these essential factors
- ensure that scientific and operational feasibility (including investigator and participant burden) are assessed from the outset
- establish metrics or key risk indicators (KRI) related to the CTQ to proactively identify risk realisation, including the use of quality tolerance limits (QTL) of acceptable values of KRI and those that initiate defined escalation processes

ICH E6 (R3) Principle 7 states:

“Clinical trial processes, measures and approaches should be implemented in a way that is proportionate to the risks to participants and to the importance of the data collected and that avoids unnecessary burden on participants and investigators.”

This principle links the identified CTQ factors to the quality management activities undertaken to protect them. Risk-based quality management translates QbD into operational practice through:

- systematic hazard and risk identification, evaluation, and prioritisation
- focused risk mitigation/acceptance, control measures and monitoring aligned with CTQ factors and KRIs
- ongoing, dynamic risk review throughout the trial lifecycle

ICH E6 (R3) Principle 7.1 states:

“Trial processes should be proportionate to the risks inherent in the trial and the importance of the information collected. Risks in this context include risks to the rights, safety and well-being of trial participants as well as risks to the reliability of the trial results.”

This directly reflects the E8 (R1) concept that conduct and reporting of clinical studies should be tailored to what is critical.

These both emphasise that risk proportionality should be applied to ensure that:

- oversight, data controls, and monitoring reflect the likelihood, detectability and impact of identified risks
- effort and resources are allocated where they protect participant safety and the reliability of key data.

ICH E6 (R3) Principle 9 states that “Clinical trials should generate reliable results”.

This principle underlines the fundamental expectation that trial outcomes can be trusted, interpreted appropriately, and used confidently in regulatory and scientific decision making.

Principle 9.1 builds on this by stating:

“The quality and amount of the information generated in a clinical trial should be fit for purpose and sufficient to provide confidence in the trial’s results and support good decision making.”

This means the data collected should be sufficient, relevant, and proportionate to support robust conclusions about the safety and efficacy of the investigational product.

It encourages sponsors and investigators to focus on critical data and processes, those that directly support fit-for-purpose decision making during the trial, participant safety, data integrity, and the credibility of trial results.

ICH GCP E6 (R3) 3.10 states:

“The sponsor should adopt a proportionate and risk-based approach to quality management, which involves incorporating quality into the design of the clinical trial (i.e., quality by design) and identifying those factors that are likely to have a meaningful impact on participants’ rights, safety and well-being and the reliability of the results (i.e., critical to quality factors as described in ICH E8 (R1)).”

Sponsors should therefore move away from a “one size fits all” model of quality management as was previously common, and adopt trial-specific proportionate measures based on the intended design of the trial in order to:

- safeguard participant safety and rights
- maintain scientific validity and reliability of trial results
- avoid unnecessary complexity or burden

It is essential to recognise that the risks associated with a clinical trial may evolve as planned modifications are executed and as practical experience accumulates during the trial.

Therefore, systems and processes should allow for the continued assessment of CTQ factors and related risks with appropriate risk control and mitigation applied where indicated.

QbD and RBQM work together to ensure that clinical trials focus on what truly matters: protecting participants and generating reliable, fit for purpose results. By identifying and safeguarding CTQ factors from the outset and adapting controls as risks evolve, sponsors can direct oversight and resources to the areas that have the greatest impact on participant safety, data integrity and results reliability.

Risk proportionality is therefore not about reducing effort but about applying it intelligently, reducing oversight where risk is low and strengthening it where aspects of the trial are critical to trial success.

This approach replaces ’one size fits all’ quality models with a responsive, evidence driven framework that supports efficient, credible, and participant centred trial conduct.

The MHRA’s expectations

Critical to quality factors

These should be defined prior to/alongside protocol development.

These should be integrated into the trial protocol, risk assessments, quality plans, data management plans etc. so that they are transparent and considered cross-functionally.

A factor that is critical to quality rarely affects only a single area, so cross-functional involvement is essential to ensure broad input and holistic assessment. Establishing a common definition and consistent nomenclature for CTQ factors across functions helps ensure shared understanding, even when each department’s specific risks or level of interest may differ.

CTQ factors should be reconsidered routinely as part of the evolution of the trial as protocols are modified and changes are made to trial processes and learning from experience of conducting the trial are integrated.

Risks identified through the assessment of CTQ factors should be transparent and communicated as appropriate to Investigators and delegated service providers.

To ensure that CTQ factors are appropriately protected, sponsors should also establish meaningful metrics, including key risk indicators (KRIs) and quality tolerance limits (QTLs).

KRIs act as early warning indicators of emerging issues that may affect participant safety or the reliability of critical data, while QTLs define the acceptable boundaries of variation for critical parameters.

Exceeding a QTL should trigger predefined review and escalation processes. Together, KRIs and QTLs provide a measurable and proactive mechanism to detect risk realisation and ensure timely oversight of what matters most.

Quality management

ICH E6 (R3) provides guidance on the identification of risks generally, as well as on how sponsors should determine which risks significantly impact CTQ factors. The MHRA does not prescribe a specific methodology for risk management but expects the following:

- the establishment and maintenance of a transparent, documented risk management framework from protocol development through to trial close-out and reporting
- assurance that risk management remains dynamic and embedded within ongoing trial processes, recognising that risks may change as information accumulates. Previously identified risks may reduce in significance, new risks may emerge, and certain events, such as protocol amendments, accumulating data trends, deviations from expected recruitment or safety patterns, or a SUSAR that warrants reconsideration of study conduct, may require a re-evaluation of CTQ factors and associated controls. The risk management system should therefore support continuous review and timely adjustment of mitigation measures throughout the trial
- regular review and updating of risk assessments throughout the course of the trial.
- cross-functional engagement in both risk identification and review processes to ensure comprehensive input and holistic evaluation
- sponsor oversight of the trial, including quality management, should be clearly demonstrated

Finalisation of the protocol should only take place after all initial risk assessments involving relevant stakeholders are completed in order to encompass required risk control and mitigation.

For example, some risk mitigations may require inclusion in the clinical trial protocol such as how eligibility of trial participants is determined and confirmed.

These assessments should aim to minimise risks to participants and ensure data integrity, while also reducing burden and inefficiencies for Investigators and participants.

It is expected that sponsors utilise all relevant stakeholders to identify and manage risks to CTQ factors with an emphasis on cross-functional,

open, and proactive dialogue.

Stakeholders should also include representatives from quality assurance (QA) to facilitate exchange of knowledge from this function.

QA staff hold significant knowledge of issues associated with the conduct of clinical trials, often across many functional areas/teams, and this information should be considered during the identification and management of CTQ factors. Care, however, should be taken to ensure the independence of audit activities conducted by the QA function.

Differing incentives among trial team functions can pose significant challenges to conducting trials in a risk proportionate manner, with priorities often placed on speed or financial milestones, such as activation of the first site or enrolment of the first participant, rather than on quality objectives that support participant safety and scientific rigour.

It is suggested that sponsors implement performance goals that emphasise quality, thereby promoting cross-functional alignment, enhancing risk proportionality, safeguarding participant safety, and ensuring the reliability of trial outcomes.

It should be ensured that risk-based quality management which focuses on participant safety, data integrity and results reliability is not confused with operational risk assessments which often focus on trial milestones, timing, or cost.

Once CTQ factors and any risks to those are identified, it is important that sponsors employ a structured approach to management of those during the lifecycle of the trial ensuring continuous reassessment of the CTQ factors and RBQM.

Organisations should ensure that timely proactive actions are taken when issues associated with CTQ factors are identified.

Essential record requirements

Essential records should align with the essentiality criteria described in ICH E6 (R3) Appendix C3.1, and sponsors may use structured trial master file (TMF) content lists to prospectively identify essential records.

The TMF consists of repositories, usually with a principle or key repository that contains the majority of essential records. The TMF should be used to retain documentation to demonstrate proactive, prospective quality planning; QbD decision making, identification of CTQ factors and RBQM activities.

Documentation should describe the critical to quality (CTQ) factors identified for the trial, the associated risks, and the strategies implemented to mitigate those risks. This information should be readily accessible and may be documented within the protocol, or in the TMF as described in ICH GCP E6 (R3) B.12.1.

Retained evidence should enable effective evaluation of key discussions and decision making but avoid excessive or unnecessary record-keeping.

The focus should be on capturing what is necessary to demonstrate that the sponsor identified key risks in the trial and any processes put in place to control and mitigate those risks.

Certain decisions may be taken at the programme or product level rather than at the trial level. Appropriate consideration should be given to how these decisions are referenced, documented, and presented within the TMF.

Evidence should be retained to demonstrate the structured risk management process implemented:

- initial risk assessment identifying risks to CTQ factors
- risk evaluation outputs (likelihood, detectability, impact)
- rationale for prioritising or deprioritising risks considered as ‘important’
- version history of risk assessments (updated as needed during trial conduct)
- personnel and functions involved in the risk management process
- evidence that the risk controls developed are proportionate to risk severity

Evidence should also be retained to demonstrate that the risk controls were implemented and monitored, including:

- retained documentation that should clearly demonstrate completion of activities put in place to detected and mitigate risks. For example, evidence of central monitoring outputs and necessary escalations
- evidence to demonstrate continuous assessment of CTQ factors and RBQM activities
- use of meeting minutes, oversight logs, key risk indicator (KRI) review and quality tolerance limit (QTL) assessments to show continuous oversight and decision-making

It should be clear that risks highlighted are communicated to stakeholders, such as investigators or delegated service providers.

Records should allow a reader to clearly trace each CTQ factor to associated risks, corresponding controls, and evidence of lifecycle oversight thereby presenting a coherent narrative and demonstrating effective safeguarding of the CTQ factor.

For instance, a single CTQ factor can be exposed to several types of risk, each possibly requiring different controls. 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.

Regular reviews, audits, and oversight logs are essential, and sponsor oversight should be clear, especially when third parties are involved. The emphasis is on efficient, effective, and proportionate documentation that supports compliance throughout the trial lifecycle.

Records related to the risk management process may be requested and reviewed during inspections. Inspections are likely to include review of such records and interviews with relevant personnel related to, but not limited to:

- the process for identification of CTQ factors
- established risk management framework activities, such as the risk assessment process
- review of any mitigations or controls implemented to safeguard CTQs
- effectiveness of mitigations and controls
- review and updates to the above
- associated record-keeping

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