ICH E6(R3) – Good Clinical Practice Update

Training for Clinical Data & Technology Professionals

Agilis | July 2025

Learning Objectives

- Understand what is GCP and how it affects our work
- Understand why ICH Guidance on GCP (ICH E6) was revised and what E6(R3) introduces.
- Learn how E6(R3) differs from the previous version E6(R2).
- Identify how the changes specifically affect our roles in data management, stats, and systems.
- Gain awareness to support regulatory compliance in clinical operations.

What is Good Clinical Practice (GCP)?

- GCP is an international ethical and scientific quality standard.
- Ensures the rights, safety, and well-being of trial participants.
- Applies to clinical trial design, conduct, performance, monitoring, auditing, recording, analysis, and reporting.
- Promotes credibility and reliability of clinical trial data.
- Accepted and enforced by global regulatory authorities (e.g., FDA, EMA, PMDA).

ICH GCP: A Quick Refresher

- ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.
- GCP = Good Clinical Practice – standards for ethics, data quality, and trial conduct.
- Initial GCP guidance (E6 R1) published in 1996.
- E6(R2) released in 2016 added oversight and technology-specific controls.
- E6(R3) reflects modern trial practices, data environments, and risk-based approaches.

Why ICH E6(R3)?

- Clinical trials have become more complex, decentralized, and digital.
- E6(R2) did not provide enough flexibility for new trial designs and systems.
- Modernization was needed to stay relevant and efficient.
- E6(R3) promotes a principles-based, proportionate, and flexible approach.

What Is New in ICH E6(R3)?

- E6(R3) adopts a modular structure to enhance adaptability.
- It defines 10 flexible, high-level GCP principles for all types of trials.
- Strong emphasis on **critical-to-quality (CTQ) factors** in trial planning.
- Encourages **risk-based and proportionate quality management**.

Structure of ICH E6(R3)

- The main body outlines general GCP principles applicable to all trials.
- Annex 1: Focuses on traditional interventional trials with investigational drugs.
- Annex 2 (in development): Will address non-traditional and emerging designs like pragmatic or decentralized trials.

GCP Principles (Condensed)

- 1. Protect participants' rights, safety, and well-being.
- 2. Ensure scientifically sound **trial design** and conduct.
- 3. Apply a proportionate approach **to trial risks**.
- 4. Clearly define roles and responsibilities.
- 5. Focus on trial design and conduct that ensure quality.
- 6. Involve qualified, trained personnel in all activities.
- 7. Safeguard **integrity, completeness, and accuracy of data**.
- 8. Maintain transparency, **traceability**, and accountability.
- 9. Promote continual learning and improvement.
- 10. Use fit-for-purpose technologies with appropriate **validation**.

Critical-to-Quality (CTQ) Factors

- CTQ factors are trial elements that are essential to participant protection and **reliability of results**.
- They vary by trial and **must be identified early during protocol development**.
- Examples include key eligibility criteria, primary endpoints, safety assessments.
- CTQ focus allows teams to manage resources effectively and **avoid over-monitoring** non-essential data.

Quality by Design (QbD)

- QbD encourages teams to embed quality into trial design rather than relying on reactive corrections.
- Engage **cross-functional teams** (e.g., statisticians, data managers, clinicians) **to identify CTQ risks**.
- Plan mitigation strategies and streamline data collection for relevance.
- Outcome: reduced protocol deviations, better data, safer participants.

Risk-Proportionate Approaches

- Monitoring, documentation, and validation are tailored based **on risk to trial integrity** and subject safety.
- Not all processes require the same rigor — allows scaling efforts appropriately.
- Promotes efficiency and focuses effort where it matters most.

ICH E6(R3) Risk Evaluation Approach

- Risk evaluation is a proactive, cross-functional process initiated during trial planning.
- Focuses on **identifying risks that could affect CTQ factors** such as participant safety and data reliability.
- Risks are assessed based on **likelihood, impact, and detectability**.
- Each risk should be categorized and prioritized using predefined criteria.
- **Mitigation strategies** must be documented, justified, and proportionate to the level of risk.
- Residual risks should be monitored throughout the trial lifecycle.
- Risk evaluation must be updated if trial conditions or knowledge evolve.

New Expectations for Sponsors

- Must perform formal risk assessments to guide design and oversight decisions.
- Ensure oversight of vendors and third-party systems, even if outsourced.
- Demonstrate system validation and fitness for purpose, especially for CTQ data collection.

New Expectations for Investigators

- Maintain control of essential source data even in electronic or decentralized models.
- Clarify delegated responsibilities with documentation.
- Stay involved in oversight of digital tools (e.g., eCOA, eConsent) used in the trial.

Impact: Statisticians

- Expected to define estimands and key efficacy/safety outcomes.
- Provide input on CTQ elements and support protocol and monitoring planning.
- Participate in cross-functional quality risk assessments and decision-making.

Impact: Statistical Programmers

- Implement transparent, traceable derivations that reflect protocol objectives.
- Support validation of analysis datasets tied to CTQ outcomes.
- Maintain documentation suitable for regulatory inspection and reproducibility.

Impact: Clinical Data Managers

- Ensure CTQ-related data are well defined, prioritized, and clean.
- Reduce focus on over-verification of non-critical fields.
- Partner in system testing and validation for data collection tools.

Impact: EDC & Tool Developers

- Responsible for designing systems that meet trial-specific CTQ needs.
- Validation scope should be justified by risk and intended use.
- Enable compliant audit trails, traceability, and secure access management.

Documenting CTQ & QbD

- Documentation includes risk logs, CTQ rationale, and design decisions.
- Clearly trace how quality was built into the protocol, systems, and oversight.
- Use these documents to communicate during audits or inspections.

Monitoring Plan Requirements (ICH E6(R3))

- A monitoring plan is required for every clinical trial to ensure appropriate oversight.
- Must be tailored to the trial's design, complexity, and identified CTQ factors.
- Defines methods: on-site, remote, centralized, or a hybrid monitoring strategy.
- Includes rationale for chosen approach and description of monitoring activities.
- Should specify frequency, scope, responsibilities, and tools used for monitoring.
- Must be updated when risks change or protocol modifications occur.
- Should include triggers for escalation, follow-up, and issue resolution procedures.

System Validation Under E6(R3)

- Validation is not one-size-fits-all — it should reflect actual risks to data and subject safety.
- Ensure documentation supports decision-making and testing outcomes.
- Revalidation may be required when system changes affect CTQ functionality.

Audit and Inspection Readiness

- Demonstrate that quality was proactively managed throughout the trial.
- Be prepared to show CTQ decisions and system validation logic.
- Inspections may focus more on rationale than rigid checklists under E6(R3).

Common Pitfalls to Avoid

- Over-monitoring and over-collecting data that are not CTQ.
- Ignoring early involvement of key functional experts.
- Treating all system changes as equally risky — undermines proportionality.

Practical Scenario

- Scenario: Global vaccine trial with tight timelines and digital tools.
- Q: What are your CTQ data?
- Q: How do you align your EDC build and validation with risk?
- Q: How can statisticians and data managers collaborate effectively here?

Key Takeaways

- ICH E6(R3) = flexible, modern GCP
- Focus on what matters: CTQ, risk, participant safety
- All roles are responsible for implementation