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Commentary

E6(R3) is here: what it means for the future of clinical trials

Anuja Deo*, Kirti Chadha, Vishal Wadhwa, Varsha Birla, Ankit Gupta, Shibani Ramchandran, Raj Jatale

Metropolis Healthcare Ltd., Mumbai, Maharashtra, India

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***Correspondence:**
Dr. Anuja Deo,
E-mail: anuja.deo@metropolisindia.com

ABSTRACT

The ICH E6 Good Clinical Practice (GCP) guideline provides internationally harmonized ethical and scientific standards for the conduct of clinical trials involving human participants. While the E6(R2) revision introduced risk-based monitoring and strengthened sponsor oversight, rapid advances in trial complexity, digital technologies, and patient-centric and decentralized research models necessitated further modernization. The recently revised ICH E6(R3) guideline builds on the principles of ICH E8(R1) and emphasizes quality-by-design, proportionate risk-based approaches, and identification of factors critical to trial quality. It expands guidance on data governance, innovative trial designs, use of digital tools, and inclusive participant recruitment, while clarifying stakeholder roles and responsibilities. This article reviews the evolution of ICH E6 and discusses the key changes and practical implications of E6(R3) for the conduct of efficient, ethical, and globally acceptable clinical trials.

Keywords: ICH GCP, ICH E6(R3), Good Clinical Practice, Clinical trial quality, Risk-based approach

INTRODUCTION

ICH GCP E6 (International council for harmonisation of technical requirements for pharmaceuticals for human use good clinical practices efficacy guideline 6) is a set of International ethical and scientific quality standards for designing, conducting, recording and reporting clinical trials involving human subjects. ICH GCP aims to provide a unified standard for conducting clinical trials across different countries, facilitating the mutual acceptance of clinical trial data by regulatory authorities.

Clinical trials conducted in accordance with this standard are intended to ensure the protection of participants' rights, safety, and well-being. They also support the generation of reliable clinical trial results and promote adherence to ethical principles originating from the declaration of Helsinki. In this guideline, “trial conduct” refers to the full range of processes involved in a clinical trial-from planning and initiation through execution, oversight, evaluation, analysis, and reporting.

The primary objective of this ICH GCP Guideline is to establish a harmonized standard that facilitates the mutual acceptance of clinical trial data by regulatory authorities across ICH member countries and regions.

This guideline builds upon foundational concepts introduced in ICH E8(R1) general considerations for clinical studies, emphasizing the importance of fostering a culture of quality. It encourages proactive integration of quality principles into clinical trial design and drug development planning, identification of critical-to-quality factors, engagement with relevant stakeholders as appropriate, and application of a proportionate, risk-based approach.

Recognizing the wide variation in clinical trials in terms of scale, complexity, and cost, this guideline highlights

the need for thoughtful assessment of critical-to-quality factors and associated risks. Such evaluations support efficient trial conduct by prioritizing activities essential to meeting the trial's objectives.

The revision of ICH E6 (R2) was driven by the growing scale and complexity of clinical trials, along with advancements in technology and evolving approaches to risk management. The E6 (R3) revision influences every aspect of clinical trial conduct-including planning, initiation, execution, documentation, oversight, evaluation, analysis, and reporting. This article examines the key amendments to the GCP guidelines and explores their implications for the conduct of clinical trials.

HISTORY AND OVERVIEW OF ICH GCP E6

In 1996, ICH published the ICH E6 GCP guideline. It became the global standard for good clinical practice. It was adopted by regulatory authorities worldwide (e. g., FDA, EMA).

Revised ICH E6 (R2) focused on risk-based approaches to trial monitoring, better documentation, improved sponsor oversight and electronic data integrity.

ICH E6 (R3) aims to modernize GCP further by emphasizing on flexibility, proportionality and efficiency. It incorporates advances in trial designs, technology and data handling.

INITIAL TAKEAWAYS FROM FEEDBACK AND COMMENTS ON ICH E6 (R2)

Concerns about the following:

The clinical trial ecosystem is rapidly evolving and this was not reflected in the guideline

The evolving clinical trial ecosystem is characterized by the increased adoption of decentralized clinical trials (DCTs), driven by technological advancements like AI, a focus on patient-centricity, and new regulatory adaptations and economic trends.

Key shifts include hybrid trial models, greater emphasis on data management and security, evolving stakeholder relationships (especially with patients and sponsors), and the growth of global research hubs in emerging markets.

The academic community were concerned about a lack of proportionality

A lack of diversity in the study population that doesn't reflect the general population the drug is intended for.

The R2 guidance was seen as a "one-size-fits-all" approach to clinical trials

A "one-size-fits-all" approach in clinical trials applies a single treatment or protocol to a diverse group of patients, often leading to varied outcomes where some may benefit while others do not.

This traditional strategy, though sometimes followed due to compliance with general guidelines, contrasts with the modern precision medicine approach, which uses genotypic and phenotypic data to tailor treatments to individuals, improving efficacy and reducing side effects. The limitations of the one-size-fits-all model contribute to health inequities.

The ability of clinical trials to meet all GCP requirements in different situations (e.g., during public health emergencies)

Challenges regarding informed consent procedures and trial site access, maintaining rigorous data quality, subject protection and ethical standards.

GCP requirements were being applied where they were not applicable

Rigid application of GCP made it difficult to have innovative trial designs and the implementation of new technologies. It increased costs and complexity for sponsors, investigators, and other stakeholders, especially in less complex research or public health scenarios.

WHAT IS NEW ABOUT E6(R3) STRUCTURE AND CONTENT?

Provides additional clarity on the scope

This guideline applies to interventional clinical trials of investigational products that are intended to be submitted to regulatory authorities. The principles of GCP in this guideline may also be applicable to other interventional clinical trials of investigational products that are not intended to support marketing authorization applications in accordance with local requirements.

This guideline builds on key concepts outlined in ICH E8(R1) general considerations for clinical studies

This includes fostering a quality culture and proactively designing quality into clinical trials and drug development planning, identifying factors critical to trial quality, and engaging interested parties, as appropriate, using a proportionate risk-based approach.

Focus on fit for purpose clinical trial quality (QbD and proportionate, risk-based approaches)

Thoughtfulness in trial design and conduct.

QbD should be implemented to identify the factors (i.e., data and processes) that are critical to ensuring trial

quality and the risks that threaten the integrity of those factors and ultimately the reliability of the trial results.

Clinical trial processes and risk mitigation strategies implemented to support the conduct of the trial should be proportionate to the importance of the data being collected, the risks to trial participant safety and the reliability of trial results.

Trial designs should be operationally feasible and avoid unnecessary complexity.

Table 1: ICH E6(R2) to ICH E6(R3) comparison.

Topic/section	E6 (R2)	E6 (R3)
Scope	Not defined	Applies to interventional trials for regulatory submission; may apply to others per local rules
Terminology changes	a. Subjects b. CRO	a. Trial participants b. Service provider
Principles of GCP	13 principles focused on ethics, safety, integrity	11 enhanced principles with sub-points; includes risk proportionality and role responsibility
IRB/IECs	3-year record retention; no reimbursement guidance	Record retention per regulations; allows reasonable reimbursements without coercion
Investigator	General responsibilities; training; safety reporting	Expanded roles, safety reporting, consent updates, investigational product management, data oversight, confidentiality, digital tools, and records
Sponsor	Covered trial design, management, monitoring, agreements	Expanded to include quality assurance, risk management, safety reporting, data handling, decentralized trials, and diversity
Data governance	Not addressed	New section: covers data systems, privacy, access control, and computerized systems
Clinical trial protocol and amendments	Structural guidance	Emphasizes quality-by-design, operational feasibility, and fit-for-purpose materials
Risk-based approach	Introduced limited risk-based monitoring	Broader scope-applies to design, conduct; emphasizes proportionality and mitigation
Risk management	Introduced QTLs (Quality tolerance limits)	Focus on critical-to-quality (CtQ) risks; proactive risk mitigation
Critical data/processes	Introduced	Embedded into CtQ-based risk planning
Innovative designs	Focus on traditional RCTs (Randomized control trials)	Supports adaptive designs, real-world data, and digital integration
Technology	Focused on e-documents and systems	Includes digital health tools, eConsent, decentralized trial support
Diversity and inclusion	Brief mention	Strong focus on diverse populations; strategies for inclusive recruitment/retention
Quality management	SOP-driven	Lifecycle quality integration, risk-based focus, detailed documentation
Patient-centric focus	Process- and data-focused	Prioritizes patient safety, burden reduction, and engagement
Essential records	Section 8 focused on evaluation and TMF (Trial master file)	Considers blinding, data protection, and records across multiple systems

LOOKING FORWARD

It is essential for all clinical research stakeholders-including sponsors, investigators, service providers, regulators, and ethics committees-to thoroughly understand these changes. Embracing the new guidelines enables us to collaboratively advance clinical trials that are more effective, efficient, and patient-focused.

The transition to E6 (R3) represents more than regulatory compliance; it's an opportunity to raise the bar for clinical research. It calls for deeper critical thinking in trial design, smarter use of technology, and a renewed commitment to placing patients at the heart of every decision.

For countries like the USA and EU nations, the focus will be on refining existing frameworks, integrating AI-driven monitoring and ensuring seamless adoption of decentralized trial methodologies.[6,7] In contrast, nations like India must address regulatory alignment, workforce

training, infrastructure gaps, and digital transformation to fully leverage the benefits of E6 (R3).[8]

CONCLUSION

The updated ICH GCP E6 marks a major step forward in advancing knowledge and understanding of clinical trial practices by aligning ethical and regulatory standards with the evolving landscape of modern research. Through its focus on risk-based approaches, quality management, data integrity, and the integration of innovative digital tools, the revision enhances the reliability, efficiency, and transparency of clinical studies. It further reinforces participant protection and data integrity while encouraging global consistency across regulatory frameworks. Ultimately, the revised guideline fortifies the scientific and ethical basis of clinical research, promoting more resilient, patient-focused, and adaptable trials in today's dynamic healthcare environment.

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