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THE EVOLUTION OF GOOD CLINICAL PRACTICE: A COMPARATIVE REVIEW OF ICH GCP E6 (R2) AND E6 (R3)

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Abstract: Good Clinical Practice (GCP) provides the ethical and scientific foundation for conducting clinical trials and safeguarding participant welfare. The transition from ICH GCP E6 (R2) to E6 (R3) represents a significant evolution in response to increasingly complex study designs, digital technologies, and decentralized trial models. These developments require regulatory guidance that remains robust while allowing sufficient flexibility to support innovation. In addition, the globalization of clinical research and the growing involvement of multiple stakeholders have further emphasized the need for harmonized yet adaptable regulatory standards. The aim of this review is to compare ICH GCP E6 (R2) and E6 (R3) and evaluate the practical impact of the updated framework on investigators, sponsors, and other research stakeholders. Specific attention was given to how the revised guidance supports operational efficiency without compromising ethical safeguards or scientific validity. A structured qualitative analysis of both versions was conducted. Key aspects examined included trial design, quality management, data governance, investigator and sponsor responsibilities, monitoring strategies, and participant protection. The review focused on identifying major conceptual shifts and evaluating their significance for contemporary clinical research practice. The analysis demonstrates that ICH GCP E6 (R3) adopts a principle-based, risk-proportionate approach, moving beyond the more prescriptive structure of R2. It prioritizes the identification and management of factors critical to participant safety and data integrity, encouraging sponsors and investigators to tailor processes according to study-specific risks. This approach supports innovative methodologies, including decentralized and hybrid trials, facilitates the integration of digital health technologies, and promotes proactive quality management systems embedded throughout the trial lifecycle rather than relying primarily on retrospective corrective actions. For example, in multicenter oncology trials, monitoring activities may focus on critical safety endpoints and high-risk procedures rather than exhaustive source data verification. Such targeted oversight reduces administrative burden while maintaining scientific rigor and regulatory compliance. Furthermore, R3 provides clearer expectations regarding the validation and oversight of digital systems, the management of diverse data sources, and the maintenance of continuous ethical oversight throughout the trial lifecycle. Overall, ICH GCP E6 (R3) aligns regulatory standards with contemporary clinical research realities, enhancing efficiency, flexibility, and sustained participant protection while advancing innovation in global clinical development

Keywords: *ICH-GCP, clinical trials, participant safety, risk-based monitoring*
Field: Medical Sciences and Health

1. INTRODUCTION

The International Council for Harmonization (ICH) guideline for Good Clinical Practice (GCP) is a globally recognized standard for the design, conduct, recording, and reporting of clinical trials involving human participants, ensuring participant safety, well-being, and data integrity.[1] First introduced over two decades ago, the guideline underwent its second major revision, E6(R2), in 2016.[2]

Since then, the clinical research landscape has evolved considerably. The growing adoption of decentralized and hybrid trial models, patient-centered approaches, and digital health technologies (DHTs) has reshaped traditional trial conduct. These developments have exposed certain operational and structural limitations of E6(R2), particularly in addressing technological innovation and enabling risk-proportionate oversight across diverse trial settings.

The European Medicines Agency (EMA) announced the effective date of ICH GCP E6(R3) as 23 July 2025, marking a shorter revision interval compared with the previous update.[3,4] The transition from E6(R2) to E6(R3) reflects a broader shift toward a principles-based, flexible regulatory framework while maintaining established standards for participant protection and data integrity.

This review compares the key components of ICH GCP E6(R2) and E6(R3), highlighting conceptual and structural changes and evaluating their implications for investigators, sponsors, and other stakeholders within the clinical research ecosystem. Specifically, it aims to: (1) analyze the major differences between E6(R2) and E6(R3) in trial design, quality management, monitoring, and data governance; (2) assess how the updated guidance facilitates innovative methodologies while preserving ethical and scientific standards; and (3) examine the operational impact of E6(R3) adoption on contemporary clinical trial conduct.

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2. MATERIALS AND METHODS

A structured comparative qualitative analysis of the ICH Good Clinical Practice (GCP) guidelines E6(R2) and E6(R3) was conducted. The full texts of both versions were reviewed in detail, focusing on investigator and sponsor responsibilities, trial design and execution, quality management systems, data governance, monitoring approaches, and participant protection. The principal differences between the two guidelines were identified and analyzed.

The review examined significant structural and conceptual changes, emphasizing how E6(R3) transitions from a prescriptive framework to a principles-based, risk-proportionate approach. The potential impact of these changes across the trial lifecycle, from planning to reporting, was explored. Special attention was given to elements relevant to contemporary clinical research, including decentralized and hybrid trial models, the adoption of digital technologies, and risk-based monitoring strategies.

Beyond listing differences, the analysis interpreted the practical implications of these changes for trial operations. To illustrate real-world relevance, examples from recent multicenter oncology trials were used to demonstrate the application of E6(R3) principles in practice. [5,6] This approach provides a structured, practice-oriented assessment of the evolution from E6(R2) to E6(R3) and its implications for modern clinical research across disciplines.

3. RESULTS

The findings highlight major changes from E6(R2) to E6(R3), including developments in risk management, monitoring strategies, and ethical oversight, reflecting a broader evolution in how Good Clinical Practice is conceptualized and implemented.

Principle-Based Approach: E6(R3) adopts a flexible, risk-proportionate framework, allowing trial processes to be tailored to study-specific risks. Rather than prescribing a fixed set of procedures for all trials, the guideline emphasizes prioritizing factors critical to participant safety, data integrity, and scientific validity, and designing trial processes accordingly. [7]

Risk-Based Monitoring: While E6(R2) introduced risk-based monitoring, E6(R3) expands this into an integrated risk-based quality management (RBQM) approach. Monitoring focuses on the most critical aspects of a study, embedding quality proactively throughout trial design and conduct. Key trial activities, including monitoring and data management, are recognized as essential quality control functions. This approach enables trial teams to allocate resources strategically while maintaining high standards for participant safety and data integrity. [5] Under E6(R3), monitoring strategies prioritize critical safety endpoints and high-risk procedures rather than exhaustive source data verification, reducing administrative burden without compromising study quality. [7]

Digital and Decentralized Trials: ICH GCP E6(R3) explicitly acknowledges the growing role of decentralized and hybrid clinical trial models. It recognizes that trial-related activities may occur outside traditional investigative sites, including participants' homes or local healthcare facilities. This reflects the integration of telemedicine, electronic informed consent (eConsent), wearable sensors, and remote data capture platforms into contemporary clinical research. Data originating from multiple digital sources must remain traceable, attributable, contemporaneous, original, and accurate (ALCOA principles), with clear documentation of data flows and system interfaces.

Examples from oncology trials demonstrate that decentralized studies may incorporate remote symptom monitoring through wearable devices while limiting on-site visits to critical assessments such as imaging or complex procedures. Monitoring efforts can thus focus on high-risk data streams and key safety endpoints rather than uniformly verifying all remotely collected data. This risk-proportionate approach reduces logistical burden while preserving scientific rigor. [8]

Ethical Oversight: Whereas E6(R2) emphasized ethics committee approval at study initiation and during major protocol amendments, E6(R3) promotes continuous ethical oversight integrated within quality management systems.[9] Ethical responsibilities are treated as ongoing commitments, systematically incorporated into risk assessment, monitoring strategies, and data governance. The guideline further requires that technological tools enhance, rather than compromise, participant comprehension, confidentiality, and data protection. The framework underscores the need to protect vulnerable populations, safeguard privacy in the context of increasingly large and diverse datasets and maintain transparent communication with participants. Through continuous safety evaluation and adaptive mitigation strategies, E6(R3) shifts from reactive corrective action toward proactive, risk-informed participant protection.

4. DISCUSSIONS

The transition from ICH GCP E6(R2) to E6(R3) represents a conceptual evolution rather than a purely structural revision. While R2 reinforced quality management and introduced risk-based monitoring, it remained largely procedural. In contrast, R3 establishes a principle-driven framework emphasizing critical-to-quality factors, proportionality, and integrated quality across the trial lifecycle.

By prioritizing participant safety and data integrity over standardized procedures, R3 facilitates decentralized trials, adaptive designs, and the use of digital data systems. This approach is particularly valuable in oncology and rare disease research, where remote participation can improve patient access, recruitment, and retention.

For sponsors, R3 requires a cultural shift toward proactive risk identification and integrated quality systems. Quality considerations must be embedded during protocol design, moving beyond a retrospective audit mindset. Investigators may benefit from reduced administrative burden through targeted monitoring, allowing greater focus on clinical oversight and participant care. At the same time, they must actively engage in risk assessment and ensure appropriate supervision of delegated activities, particularly in decentralized settings.

The effectiveness of R3 ultimately depends on meaningful implementation. Organizations that integrate risk-based thinking and cultivate a strong quality culture are more likely to achieve operational efficiency without compromising ethical or scientific standards. By translating principles into practice, E6(R3) provides a flexible yet rigorous framework capable of supporting innovation in trial design and execution.

5. CONCLUSIONS

ICH GCP E6(R3) introduces an updated paradigm for the conduct of clinical trials. While it does not fundamentally alter the structural framework established in E6(R2), it represents a clear shift from a prescriptive model toward a principles-based, risk-proportionate approach aligned with contemporary clinical research practices.

By integrating quality management systems, prioritizing critical-to-quality factors, and supporting decentralized and digitally enabled methodologies, E6(R3) enhances operational flexibility while maintaining rigorous standards for participant safety, welfare, and data integrity. Ethical oversight and robust data governance are further strengthened within this framework.

When effectively implemented, E6(R3) has the potential to improve operational efficiency, foster innovation, and sustain high standards of participant protection in global clinical development.

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