Preparing for a Risk-Based Future: What ICH Revisions Mean for Clinical Trial Design and Conduct

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Risk-Based Quality Management (RBQM) will be the operational foundation of next-generation clinical research. RBQM mandates new ways of thinking and operating that will change the clinical development process, from the concept and design of clinical trials to the infrastructure and methodologies used to conduct them. A broad constellation of regulatory guidance is in progress to inform sponsors as industry implements this far-reaching revolution. In a two-part series, this first paper outlines the quality and regulatory thinking that underpins RBQM, and details essential points of compliance for emerging ICH core guidances on RBQM—including ICH E8 (R1) and ICH GCP E6 (R3)—and offers further discussion of RBQM implications for sponsors, clinical sites and patients. The second paper discusses risk-based competencies and behaviors required to truly embed RBQM into an organization.

Reinventing clinical development

Clinical trial innovation is moving fast, and global regulators are working hard to keep pace. The healthcare enterprise is advancing on a tidal wave of data, characterized by unprecedented volume and variety of sources. To harness these critical data, the biopharmaceutical industry is adopting a burgeoning array of information technologies, from social media to mobile devices and wearable sensors. Together, they are driving novel trial designs—collecting data remotely, reducing patient burden, and bridging controlled clinical trials and real-world therapeutic evaluation.

Regulators and industry are working to ensure patient safety, data quality and security, and the validity of study results. New regulatory standards are emerging as ICH working groups complete their reviews of all existing guidelines—across safety, efficacy and quality. The goal is to develop quality standards that incorporate patient perspectives, agile practices, and a diversity of research approaches to accommodate evolving clinical trial designs and technologies.

These guiding principles are formulated in the practice of RBQM. RBQM will be the operational foundation of the next generation of clinical research. RBQM will inform how we operationalize trial delivery through core staff competencies and how we collaborate across a broad community of intermediaries and stakeholders. Sponsors and CROs must prepare now for this seismic shift— in how to think about and prioritize risk, and in how to design and conduct clinical studies.

This paper outlines the fundamentals of RBQM from a regulatory perspective. We present overviews and essential points of compliance for core RBQM guidances —ICH E8 (R1) General Considerations for Clinical Studies, and ICH E6 (R3), the revision of ICH E6 (R2) Good Clinical Practice. We discuss implications for sponsors, clinical sites and the expanding role of patients as collaborators in the research process.

Foundational thinking: The ICH E6 (R2) addendum

In the 2010s, sponsors set a course toward risk-based practice as they implemented risk-based monitoring (RBM) strategies, which focused attention on critical risks to subject safety and data quality and reduced reliance on 100 percent source document verification. Evolving regulation has incorporated and expanded risk-based practice across clinical development, beginning with ICH E6 (R2).

ICH E6 (R2). The 2016 addendum to the guideline on good clinical practices, ICH E6 (R2), focused on subject protection and reliable trial results. Significant changes were introduced in Section 5.0 Quality Management, which identified processes and data critical to reliable research findings. E6 (R2) required sponsors to conduct risk management activities at the system level and clinical trial level, and included the introduction of Quality Tolerance Limits (QTL).

E6 (R2) mandated a systematic, prioritized and risk-based approach to clinical trial monitoring, with the intent to permit varied approaches that would improve monitoring effectiveness and efficiency (section 5.18.3). Approaches could include utilization of centralized and remote monitoring to reduce the burden of on-site monitoring. Monitoring plans were required to document the methods used, with appropriate justification, and present a clear focus on critical data and processes tailored to protect subject safety and potential risks to data integrity (section 5.18.7).

Risk-based practice has come into renewed focus as industry has worked to apply new data sources and technologies amid the myriad challenges and societal demands of the COVID-19 pandemic. In the post-COVID research environment, regulations are trending toward more comprehensive adoption of Risk-Based Quality Management (RBQM).

The key components of RBQM are:

- Initial risk assessment
- Ongoing risk assessment
- Quality Tolerance Limits (QTL)
- Key Risk Indicators (KRI)
- Central monitoring
- Remote monitoring
- Reduced Source Document Verification (SDV)
- Reduced Source Document Review (SDR)

The 2021 ACRO paper, "Risk-Based Monitoring in Clinical Trials: Past, Present and Future," reports that only a small percentage of clinical trials has adopted more than one RBQM component. The authors conclude that despite E6 (R2) expectations, sponsors have delayed further implementation of RBQM due to the industry's conservative approach to change and to a lack of consistent regulatory guidance.

ICH revisions on the horizon: RBQM-enhanced trial design and conduct

In the post-COVID research landscape, industry is preparing for much-needed revisions and alignment of ICH guidelines. The starting point for this general overhaul is ICH E8 (R1) General Considerations for Clinical Trials. The draft guidance has been reviewed and approved, with expected publication in the fall of 2021.

ICH E8 (R1): A Masterplan. E8 (R1), will guide revisions and alignments for the suite of ICH efficacy guidelines, including Revision 3 of ICH E6 (R2). The E8 (R1) blueprint delineates three overarching principles:

- Protection of clinical study participants
- Scientific approach to trial design, conduct, and analysis, including:
  - Quality by Design (QBD)
  - Identification and review of Critical to Quality (CTQ) factors
- Patient input into study design

Quality by Design. QBD is not new to clinical trials but is now being recognized in the E8 (R1) guidance, which considers clinical trial quality in terms of fitness for purpose. The intention of a study is to generate reliable information to answer key research questions and support decision-making while protecting study subjects. The quality of the information generated should be sufficient therefore to support good decision-making. E8 (R1) views quality as a primary consideration in the design, planning, conduct and analysis of clinical studies, within the protocol and associated functional processes (for example, the Risk Management Plan and Data Surveillance Plan). Quality will be a necessary component of all clinical development programs.

Critical to Quality factors. CTQ factors comprise a basic set of factors relevant to ensuring study quality. Factors are deemed "critical" if they have—by error of design or conduct—potential to undermine the ethics or reliability of study results and results-based decision-making. CTQ factors will be identified for each study and should be fundamental to subject protection, to reliability and interpretability of results, and to decisions made based on study results.

In detailing key elements of study design, E8 (R1) allows for flexibility in how these elements may be combined. Elements such as population, intervention, control group, response variable, methods to reduce or assess bias, and statistical analysis are expected to be relevant not only to trial designs and data sources in use now, but also to innovations developed in the future.

ICH E6 (R3): Enhanced Expectations. A May 2021 public webinar hosted by the ICH Expert Working Group characterized the E8 and E6 guidances as a quality continuum for study design and conduct. Based on principles set out in E8 (R1), Revision 3 of ICH E6 will call for a more proactive risk-management approach and address patient input in study design. According to ICH E6 (R3) concept paper, the current E6 (R2) will be re-written and re-organized with intent to align GCP principles to today's clinical trial environment and to provide flexibility to address future research technologies and methodologies.

Eleven Principles. The existing 13 principles of E6 (R2) have been incorporated into a revised set of 11 principles in E6 (R3) and are publicly available for review. The Expert Working Group advises that industry begin working now to implement them.

Compared to the more general guidelines in E6 (R2), the revised principles detail higher levels of expectation for RBQM in the study conduct. For example:

- Principle 7: Quality should be built into the scientific and operational design and conduct of clinical trials.
- Principle 8: Clinical trial processes, measures, and approaches should be proportionate to the risks to participants and to the reliability of trial results.
- Principle 10: Clinical trials should generate reliable results.

Language and intent clearly set expectations for Quality by Design, Critical to Quality factors, risk management and reliable results.

Patient focus. Patient safety is again the primary concern of E6, but Revision 3 further directs sponsors to include patients in the research process. Inclusion of patient insights is expected on issues that may range from burdens in study participation to meaningful trial endpoints. Sponsors must actively engage with patients and patient organizations and incorporate their views in both clinical trial design and conduct.

The E6 (R3) concept document further prepares industry to overcome the inflexibilities of our current operating environment by addressing broad issues related to the adaptability of trial design and conduct; Annex 1 and Annex 2 outline regulatory views on adoption of innovative research models, technologies and data sources.

Annex 1: Traditional Interventional Trials. In addition to revised principles and objectives, E6 (R3) Annex 1 aims facilitate innovation while protecting study subjects in traditional trials. It will address the use of unapproved or approved drugs in a controlled setting with prospective allocation of treatment to participants, and varied approaches for the collection of trial data. The expected publication date is November 2022.

Annex 2: Non-traditional Interventional Trials. With expected publication 12 to 18 months after Annex 1, Annex 2 will focus on non-traditional designs such as decentralized clinical trials, pragmatic clinical trials, and a host of emerging models that incorporate real-world data sources.

E6 (R3) revisions point to the collaboration of regulators and industry, working to identify promising trends in technology and methodology. The goal is to put the research enterprise in a position of preparedness. Regulation must move faster to enable the use of technology advances and new data sources—for example, decentralized clinical trials, a trend accelerated by the urgent needs of vaccine development during the COVID-19 pandemic.

Future vision. As clinical research expands from the traditional, clinic-based controlled trial to hybrid trial designs and real-world therapeutic evaluation, the Expert Working Group's vision for E6 (R3) is to:

- Allow for and encourage innovation.
- Focus on what matters the most (CTQ) to protect subjects and reliability of results.
- Allow for many ways to achieve GCP objectives.
- Enable principles to remain relevant as the industry evolves.
- Leverage and facilitate an increasingly digital environment.
- Encourage thoughtful end-to-end processes from concept to analysis.

Looking ahead: The RBQM road map

While there is a great deal of work ahead, revised guidelines are clearly moving toward more comprehensive and specific applications of RBQM. The extended family of ICH efficacy guidelines is expected to be integrated with the risk-based management principles of E6 (R3), and sponsors should watch evolving E-guidelines closely to prepare for impact on research methodologies and operations. As one indicator, an ICH Expert Working Group has been formed to create a new guideline for adaptive clinical trials, ICH E20.

Guidelines belonging to other categories, including efficacy and quality, are also under revision. A number of them will be relevant to trial design and conduct.

Spurred by the imminent ICH guidances, accelerating adoption of RBQM will test sponsors' ability to reinvent both the traditional clinical trial and their organizational mindset and processes.

The changes driven by RBQM will be pervasive and daunting. Part two of this paper discusses how sponsors and CROs can prepare now through the adoption of organizational competencies and behaviors focused on risk-based thinking and best practices.

Additional resources:

Risk-Based Quality Management & Risk-Based Monitoring | Parexel

Decentralized Clinical Trials: The Future of Clinical Trials | Parexel

Patient Innovation Center: Patient Centricity in Clinical Trials | Parexel

References

1. ICH E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), March 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1
2. Barnes B, Stansbury N, Brown D, et al., 2021. Risk-based monitoring in clinical trials: Past, present and future. *Therapeutic innovation & Regulatory Science*, 55, 899-906.
3. ICH E8(R1) General Considerations for Clinical Studies, August 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e8r1-general-considerations-clinical-studies
4. ICH Public Web Conference on ICH E6 Guideline for Good Clinical Practice—Update on Progress, April 27. https://www.pmda.go.jp/english/symposia/0205.html?print
5. ICH E6(R3) EWG, May 18-19, 2021. Current draft of GCP principles as a work in progress. https://www.ich.org/page/efficacy-guidelines
6. ICH E20 EWG Adaptive Clinical Trials, Topic endorsed June 2018. https://www.ich.org/page/efficacy-guidelines

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