

Risk-Based Monitoring Goes Mainstream with ICH GCP E6 Revision 2



ABSTRACT

With the recent update to the ICH Good Clinical Practice (GCP) guidelines, risk-based approaches to clinical trials and risk-based monitoring are now requirements, not just recommendations. Now, sponsors and CROs alike face the challenge of adopting a formal approach to quality management which embraces technology and leverages access to real-time information to drive a more structured approach to risk.

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Introduction

In 2016, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP) was updated for the first time in 20 years by means of an addendum. Originally produced in June 1996, ICH GCP serves as an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.¹ While the original ICH GCP still provides an excellent standard for the conduct of clinical trials in humans, the clinical trial landscape has fundamentally changed.

The drug development process is now a truly global enterprise. The complexity and cost of clinical trials has grown, and ethical and quality standards have increased in rigor. Conduct of global clinical trials requires progressively greater division of tasks across multiple functional teams, organizations, and locations. Thus, the current research environment is creating pressure on sponsors and contract research organizations (CROs) alike, as they strive to control costs and manage risk, while ensuring patient safety and data quality.

Part of the rationale behind the ICH GCP update – commonly referred to as ICH E6 (R2) – was the need to keep pace with the scale and complexity of clinical trials today and to

ensure appropriate use of technology. An ICH concept paper emphasized the need to modernize the approach to GCP to enable implementation of innovative approaches to clinical trial design, management, oversight, conduct, documentation, and reporting that would better ensure human subject protection and data quality.² In addition, the concept paper suggested that the previous ICH guidelines had been implemented in ways that impeded innovation by focusing too heavily on the completeness and accuracy of every piece of data at the expense of carefully managing risks to the integrity of key outcome data, underscoring a push toward risk-based, rather than traditional, monitoring.

As a result, it is not surprising that the most significant change brought about by ICH E6 (R2) is the introduction of guidance on a new risk-based approach to the management of quality in clinical research. The updated guideline calls for more measures and a formal approach to quality management, which now includes the efficient design of a trial, thus delivering a strong message that many clinical trials are overly complicated in design and reduced in efficiency.

In this white paper, we explore the revised guideline as it pertains to risk-based approaches to clinical trials and risk-based monitoring.



A call to action: increased emphasis on risk

With the introduction of ICH E6 (R2), sponsors are encouraged to pursue innovative approaches for conducting clinical trials, and quality by design and risk-based quality management are now the approaches of choice.³

Quality management

The quality management section of the updated guideline has eight contemporary items, and in most cases, what was once a recommendation for GCP has now become compulsory as a direct result of this addendum. Everything is now risk-based, and the methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected.

The updated guidance states that the sponsor should implement and document a system to manage quality throughout the design, conduct, reporting, evaluation, and archiving of clinical trials. It also states that the sponsor should focus on those trial activities that are essential to ensuring patient safety and the reliability of trial results.

Monitoring

ICH E6 (R2) more clearly defines the nature of monitoring, stating that sponsors should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. This can be a combination of both on-site and central monitoring, but the sponsor

must clearly define the rationale and justification for the strategies chosen. While ICH E6 (R2) states that a combination of on-site and central monitoring may be appropriate, it does not provide specific guidance regarding to what extent this combination is right or if this combination is needed at all. This underscores that in fact a risk-based approach is not one-size-fits-all and must be tailored to the unique requirements of a particular clinical trial.

ICH E6 (R2) contains an extensive section on trial monitoring which includes the requirement of documentation in the form of a monitoring plan. A monitoring plan is a document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial. It should focus on:

- Risks to human subject protection and data integrity
- The monitoring strategy, including roles, responsibilities, monitoring methods, and the rationale behind their selection
- Critical data and processes, e.g., non-routine clinical practices that require additional training

Sponsors should keep in mind that risk management is a prerequisite to a risk-based monitoring strategy. Regulators will not accept a reduction in on-site monitoring under the pretext of risk-based monitoring without a fully justified, adequate demonstration of how oversight is exercised.



Moving toward risk-based quality management

Risk-based quality management is a systematic process put in place to identify, assess, control, communicate, and review the risks associated with a clinical trial. The primary objective of risk-based quality management is the identification of risks on a continuous basis throughout the lifecycle of a clinical trial, from design and conduct to evaluation and reporting. Application of risk-based quality management approaches can facilitate better, more informed decision-making and more efficient utilization of available resources. The process should begin at the time of protocol design so mitigation can be built into the protocol and other trial-related documents.⁴

Key elements of a QMS

According to the EMA reflection paper on risk-based quality management in clinical trials, the key elements of a quality management system (QMS) include:⁴

- Documented procedures and validated methods being developed, implemented, and kept up-to-date
- Documentation systems that preserve and allow for the retrieval of any information or documentation to show actions taken, decisions made, and results
- Appropriate training of sponsor personnel, as well as of the personnel of affiliates, vendors, or other service providers at trial sites

- Validation of computerized systems
- Quality control, e.g., monitoring of trial sites and central technical facilities on site and/or by using centralized monitoring techniques
- Quality assurance including internal and external audits performed by independent auditors

In practice, it is also important to create a culture of quality at every level of the organization, from senior management to site staff. This culture should be driven by a clearly articulated vision and values, as well as well-defined quality goals that are linked to performance expectations.

Implementing a QMS

The critical first step in designing and developing a QMS is for sponsors to assess the current state of their QMS and then perform a gap analysis to evaluate their risk and quality needs in the context of the evolving regulatory landscape, including the new ICH E6 (R2) guideline, and industry best practices.

ICH E6 (R2) goes into detail on the process of implementing a system of quality management, which can be broken down into seven steps:³

1. **Critical process and data identification.** Critical processes and data identification start at the protocol development stage. If a CRO is being used, but is not contracted to participate in protocol development, then it is critical for the sponsor to share this assessment with the CRO.



Figure 1. Seven steps to quality management



2. **Risk identification.** The sponsor should identify risks to critical trial processes and data. Risk needs to be considered at both the system level (e.g., SOPs, vendor oversight, resourcing) and the clinical trial level (e.g., trial design and data collection).
3. **Risk evaluation.** Risk evaluation is a three-step process that begins with an assessment of the probability of errors occurring, given the existing risk controls that are in place. The second step is an evaluation of the impact of such errors on patient safety, patient rights, and data integrity and quality. The final step involves detectability, or the extent to which errors or threats are detectable.
4. **Risk control and mitigation.** The sponsor must decide which risks to reduce, and which to accept. These decisions – as well as the process and criteria used to reach these decisions – need to be documented. Sponsors must determine what minimum information is required to make an informed decision based on objective, verifiable data. Key decisions will depend on the level of risk that the sponsor is willing to tolerate. Such

limits will determine how and when alerts of risk communication must be triggered.

Predefined quality tolerance limits should be established – taking into consideration the medical and statistical characteristics of the variables, as well as the statistical design for the trial – in order to identify systematic issues that may have an impact on patient safety or data integrity. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

Risk mitigation activities may be incorporated into protocol design and implementation, or in:

- Monitoring plans
- Agreements between parties, defining roles and responsibilities
- Systematic safeguards to ensure adherence to standard operating procedures
- Training
- Processes and procedures

Sponsors and CROs should keep in mind that risk assessment is not a one-time event; it should



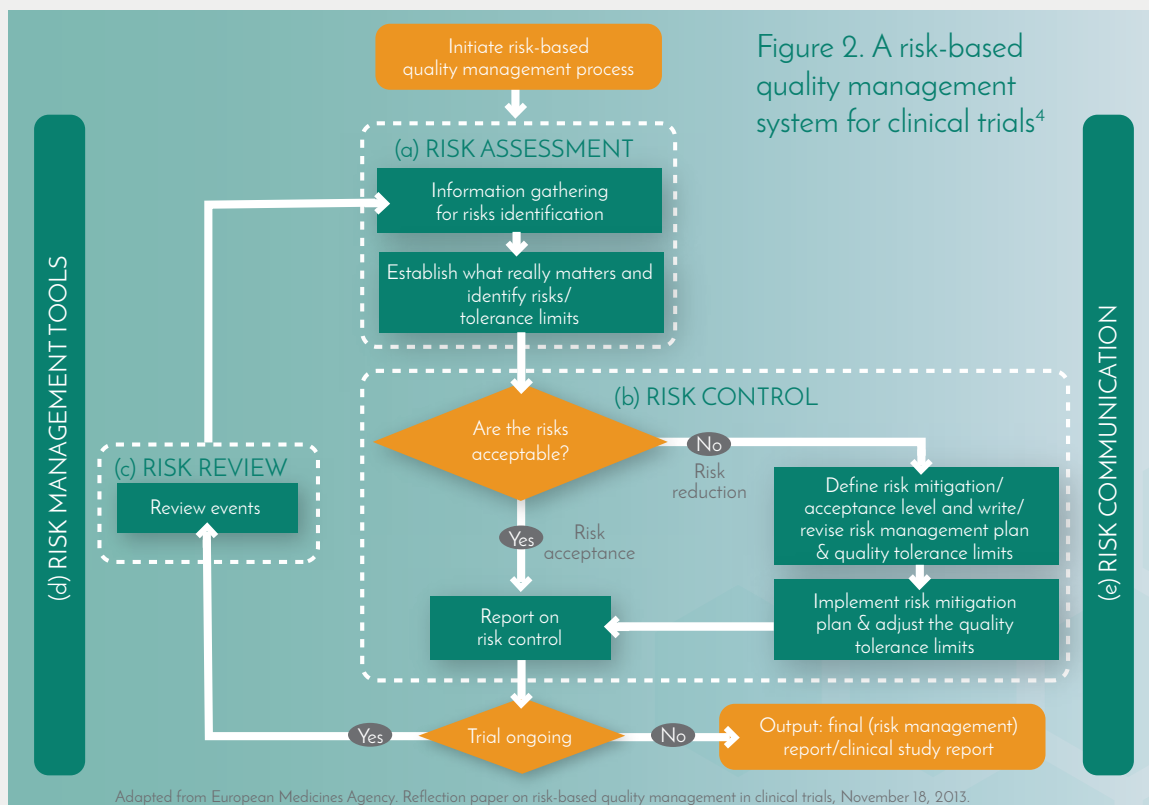
be reviewed on an ongoing basis. It should be emphasized that risk assessment and mitigation plans are required, regardless of whether the sponsor is utilizing risk-based monitoring. The quality of a trial needs to be ensured by fact-driven planning and a quality-by-design concept. Efficient and effective trials must be supported by tools, processes, and technology that leverage real-life data, as well as past experiences, to ensure that a study is set up well from the beginning.

- 5. Risk communication.** It is important for the sponsor to document quality management activities and communicate these activities to those who are involved in or affected by such activities to facilitate risk review and continual improvement during clinical trial execution. It is important for sponsors and CROs to share information

regarding emerging risks, particularly when only select services are contracted to the CRO.

- 6. Risk review.** Like risk assessment, risk review is not a static event. The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain efficient and relevant, taking into account emerging knowledge and experience.
- 7. Risk reporting.** The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report.

The EMA reflection paper on risk-based quality management in clinical trials includes an algorithm that illustrates how risk-based quality management can be applied to, and integrated within, existing quality systems (see Figure 2).





Integrating risk-based monitoring technology into clinical trials

Risk-based monitoring (RBM) has long been a topic of discussion, but implementation has been challenging and adoption has been slow. With ICH E6 (R2), RBM is again at the forefront of conversation as sponsors are now required to take a more structured approach to risk.

While traditional monitoring focuses on achieving 100 percent source document verification (SDV), RBM utilizes a combination of monitoring strategies and a greater reliance on centralized monitoring and statistical assessments to guide monitoring visits. With RBM, clinical trial operations and advanced technology are designed to bring together the metrics and information necessary to increase efficiency, safety, and quality and to enable data-driven decision-making. Targeted monitoring replaces calendar-based visits with data-triggered ones. Centralized monitoring and risk-based SDV helps reduce the number of data points clinical research associates (CRAs) must verify against source data, reducing workload, time, and cost.

Comprehensive RBM technology solutions address risk in all layers, including:

- **Risk identification and assessment.** The system should allow the ability to identify and log critical processes and data, as well as to assess and characterize risks throughout the course of a study through a built-in risk register.
- **Risk control and mitigation.** For each risk, the system should have the ability to mitigate and control the risk through a variety of risk mitigation strategies. These strategies may be a combination of automated and manual methods. For example, an automated alert is issued when an established threshold is reached, triggering an in-person visit to an investigative site. More advanced RBM software may utilize machine learning to report potential risks that were not pre-identified by analyzing prospective data to find patterns and anomalies.
- **Risk communication and actioning.** Risk detection is only one part of the risk management continuum. A robust RBM system should allow for the ability to review signals generated in a streamlined manner through a combination of drill-down capabilities, statistical models, and intuitive data visualization. It should also allow for the ability to act on, close, and prevent risks through built-in workflows and ticketing functionality.
- **Risk review and updating.** To comply with ICH E6 (R2), RBM software should also allow for regular, ongoing review and modification of risks to ensure that the implemented risk-management activities remain effective and relevant throughout the course of a study.

Implementing RBM in a comprehensive manner can bring clear, measurable returns for patient safety, data quality, and trial timelines, costs, and compliance.



Conclusion

With the introduction of ICH E6 (R2), the momentum behind risk-based approaches to clinical trial design and management and risk-based monitoring has never been stronger. Keeping pace with the evolving regulatory landscape will require innovative thinking and intelligent integration of technologies such as RBM systems that help automate and improve clinical trial efficiency, patient safety, and data quality.



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Mike Arlotto is the president of Remarque Systems, Inc. – a software development company formed in 2015 and dedicated to improving clinical trial safety and efficiency. Our first product is Remarque RBM, a comprehensive, purpose-built SaaS platform to design, deploy, and manage risk-based monitoring clinical trials.

Prior to founding Remarque Systems, Mike was the global vice president for Quintiles Corporate Development responsible for transformational partnerships and strategic relationships. Earlier in his career with Quintiles, he led the project management group in North American Clinical Development Services. Mike also managed the proposals, pricing, and contracts groups.

Prior to joining Quintiles in 1997, Mr. Arlotto was a research scientist with Bayer Corp. where he implemented an in vitro metabolism laboratory. He also held the position of Director of Scientific Planning and Development at Dallas Biomedical, a venture capital-backed company that commercialized novel technologies from universities. He was also a founder of OXYgene Dallas, a venture-backed molecular reagent company. Previously, as a research scientist, Mike worked on the application of recombinant enzymes for in vitro drug metabolism and toxicology testing, among other projects. Mike has published dozens of abstracts and articles in research journals and patented a generation of radioactive oxidation products.

Mike earned his Bachelor of Sciences degree in Toxicology at the Philadelphia College of Pharmacy and Science, and a Ph.D. in Toxicology at Kansas University. He completed a post-doctoral fellowship in genetic toxicology at the National Center for Toxicology Research.



Remarque Systems is a provider of risk-based monitoring (RBM) software solutions. Headquartered in Chapel Hill, NC, with a development center in Indianapolis, IN, Remarque Systems has developed the first fully integrated workflow system to design, deploy, and manage RBM clinical trials.

For more information about Remarque's RBM solution, visit the website RemarqueSystems.com or email info@RemarqueSystems.com. Also, follow Remarque on Twitter [@RemarqueSystems](https://twitter.com/RemarqueSystems) and join our LinkedIn group, [RBM Industry Dynamics](#).