WHAT EFFECT Does ICH E6 R2 Have on Risk-Based Monitoring and Overall Quality Risk Management?

A Bioclinica White Paper
Author: Kristin Mauri, Global Head Risk-Based Monitoring, Bioclinica
Regulators are encouraging the industry to take a new quality risk management (QRM) approach to clinical trial execution. The latest International Council for Harmonisation (ICH) Good Clinical Practice (GCP) E6 R2 guidelines represent the first update to the guidelines in over 19 years. As part of these updates, recommendations on ensuring quality management in clinical trials are at the forefront of this addendum. As companies start to review and interpret these draft guidelines before they are finalized, they are looking not only to reduce their clinical development risk but also to ensure their data quality is such that it continues to meet the standards expected by regulators. To reduce their risk, companies are paying increasingly more attention to risk management practices and are using risk-based monitoring approaches, or RBM, (including central monitoring) to support their compliance with regulations. Moving forward, additional methods to be proactive in their approach to quality management, including expansion of risk reduction, will be expected and possibly required.

Revision of ICH Good Clinical Practice (GCP) guidelines (E6 R2)
The revision of the ICH GCP guidelines takes advantage of advances in technology and risk management. It encourages the implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting. In addition, to increase clinical trial quality and efficiency, there are updated standards regarding electronic records and the essential 26 documents as well as updated requirements for sponsor oversight of investigators and CROs.

The draft guidelines were released for consultation in June 2015, and the regulatory consultation and discussion period ended in March 2016. The guidelines are now in the final stages of the process, which is the adoption of the ICH Harmonized Guideline and Implementation, after which time they will be finalized and companies will be expected to show compliance.

History of quality management
As an industry, we lag behind many other industries such as aerospace, nuclear energy and finance in the use of QRM to manage our business. The pharmaceutical industry is just now starting to recognize that a holistic approach to quality management is needed to drive forward a level of quality that will allow us to be more effective and efficient in achieving desired outcomes.

As far back as 2004, regulators such as Janet Woodcock were promoting the adoption of quality management approaches. As a concept, Woodcock defined quality by design (QbD) as “product and process performance characteristics that are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches.” With QbD, drug development begins with the end in mind and includes a structured risk assessment process. The QbD process uses the following steps:

1. Define the target product quality profile, including the performance needed to achieve a clinical benefit and meet consumer expectation
2. Design and develop the product and manufacturing process to meet the target product quality profile
3. Identify and control critical material attributes, process parameters and sources of variability
4. Monitor and adapt the process to produce consistent quality over time

Then, as early as 2007, regulators started talking about approaching clinical trial design and execution from a quality perspective. In 2009, the Clinical Trials Transformation Initiative (CTTI) was formed by the US Food and Drug Administration and Duke University based on QbD principles being applied to clinical trials. The CTTI is a public-private partnership to develop and drive the adoption of practices that will increase the quality and efficiency of clinical trials. This partnership was founded on the belief that QbD should be built into clinical trials, starting with protocol development and extending across all aspects of a trial; quality is defined as the ability to effectively and efficiently answer the intended question about benefits and risks, while ensuring subject safety. While QbD was talked about at industry conferences and at higher levels within organizations, very few companies were actually standardizing their practices to include this as part of their processes and procedures. Next, the idea of QRM for clinical trials surfaced, but early adopters trying to implement QRM principles into their trials had only the guidelines intended for drug manufacturing—ICH Q9. While the ICH E9 guidelines describe quality management for product development, the specific application examples are related with drug material attributes and manufacturing controls. Because these guidelines were not specifically defined for the quality management oversight of clinical trials, they were hard to apply. Furthermore, not all of the sections were applicable, resulting in companies struggling to find guidance about how to integrate QM into the execution of clinical trials. Thankfully, ICH E6 R2 provides more guidance for this integration.

As a result of the previous difficulties, the rate of introducing concepts such as QbD, QM and QRM into trials remains slow. Instead, companies running trials from a quality risk-based approach have done so under the umbrella of implementing RBM; however, the early adoption of RBM had an early focus on reducing source data verification (SDV), with only a handful of companies looking at this from a more structured approach that includes an upfront and ongoing assessment of risk review, control and mitigation.

**Risk-based management**

Fast forward to 2012, when TransCelerate formed and made RBM one of their first key initiatives, increasing the awareness around RBM. TransCelerate is a “non-profit organization comprised of pharmaceutical and biotechnology companies collaborating to create transformational process improvements that will help ensure safe and effective therapies are brought to market more efficiently.” RBM is defined as an “adaptive approach to clinical trial monitoring that directs monitoring focus and activities to the evolving areas of greatest need, which have the most potential to impact subject safety and data quality.” This focus on RBM shifted the concentration from SDV to comprehensive risk-driven monitoring. Although the first movers in this area were mainly TransCelerate member companies, not even all of the TransCelerate member companies are fully adopting an RBM approach. Some of the challenges that have prevented companies from moving to RBM include the level of change management required to adopt an RBM approach, lack of experience with and ability to feel confident in data quality if not performing 100% SDV, and lack of industry experience with approval of new drug applications that moved away from the old 100% SDV model.

![Image](image.png)

**Figure 2.** TransCelerate methodology for risk-based monitoring—high-level process and associated tools. Image source: TransCelerate Biopharma Inc. (2013) Position paper: risk-based monitoring methodology.
Content of the ICH E6 R2

Now a time of change has come—with the anticipated release of the revised ICH E6 R2 guidelines in November 2016, companies are no longer going to have a choice; regardless of the challenges they may face, they are going to have to move away from their old ways of working and evolve their operations to conform to these new guidelines. There is a wide range of topics covered in the updated guidelines; however, the broad theme of these revisions is “to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting while continuing to ensure human subject protection and data integrity” (p. 1). While the updates impact investigators, sponsors and CROs alike, the biggest impact will be felt by the sponsor companies, and the updates span across many different areas. One goal of the revised guidelines is to align current recommendations on clinical trial execution from different global regulatory bodies into a common set of guidelines to help drive innovative risk-based approaches to clinical trial execution. Therefore, the changes are particularly impactful around Quality Management and are outlined in the entirely new section 5.0 (Figure 3).

5. SPONSOR

5.0 Quality Management

The sponsor should implement a system to manage quality throughout the entire lifecycle of a clinical trial. Furthermore, the guidelines recommend that the quality management system should use a risk-based approach and cover the following areas:

- Critical Process and Data Identification
- Risk Identification
- Risk Evaluation
- Risk Control
- Risk Communication
- Risk Review
- Risk Reporting

Regardless of whether or not companies deploy an RBM strategy, with the issuance of these guidelines, they are going to have to show that they have followed a systematic process for these areas. Although the future focus will still likely be nested under the RBM title, these guidelines have a far-reaching impact on all clinical trials and how they will be executed that goes way beyond the traditional view of RBM.

Another significant change to the guidelines can be found in section 5.18.3 (Figure 4), which recommends sponsors “develop a systematic, prioritized, risk-based approach to monitoring clinical trials... A combination of on-site and centralized monitoring activities may be appropriate. The sponsor should document the rationale for the chosen monitoring strategy” (p. 30). In order to show compliance with this new guidance, companies are going to face a significant amount of process change and will need to devise a plan to defend the chosen monitoring strategy. With the recommendation to include a variety of different approaches to monitoring, including central monitoring, sponsors will also need to ensure that central monitoring activities are clearly documented. Technology will support the ability to ensure a data-driven approach to centralized monitoring but the critical piece will be to ensure auditable documentation of findings, decisions and actions resulting from centralized monitoring. Also worth noting is the addendum to section 5.18.7: the Monitoring Plan. Of significant note in this section is the recommendation that the...
monitoring plan should outline a plan for monitoring critical data and processes. This ties back to the need for companies to implement a QRM approach that includes upfront identification of critical data and processes with a clear plan on how these will be monitored throughout the trial lifecycle.

RBM Goes Mainstream

**Suggestions to move forward:**

1. Take a systematic approach to interpreting the guidelines.
2. Sketch out, plan for and take steps toward implementing a quality management framework based on your organization’s structure and culture.
3. Ensure that methods for overall risk management, including monitoring strategies, are proportionate to identified trial risks.
4. Be consistent with your methodology for assessment and implementation across the organization.
5. **Document, document, document**

**Document your approach**

Once you interpret the guidelines, you need to be able to clearly defend your interpretation and show that you have implemented a quality management system and monitoring strategy that align with your defendable interpretation. Throughout the process, documentation is key. In the revised guidelines, the word “documentation” is mentioned approximately 216 times, indicating that however you choose to interpret and implement quality management, you better document it throughout the entire process.

**Be consistent, but evolve with experience**

Once processes and systems have been chosen (and documented) for these new guidelines, stick with them throughout the entire trial. Don’t deviate from your overall approach and position, but do make sure to continuously reevaluate your chosen risk activities and tolerance levels (mitigation and acceptance) to ensure they remain effective and relevant. Evolve the thought process as more experience is gained with risk identification, management, mitigation and control; you will begin to have a better handle on how to identify and manage the most relevant risks. Until that experience is gained, documentation of why you selected the risks and parameters will show the regulators you are following a consistent process.
Consider the level of risk

Make sure that methods used to ensure quality management throughout the trial are proportionate to the risks identified in the trial. Not all risk is created equal; therefore, be careful to choose quality risk management strategies that are consummate with the level of risk of the overall trial. In addition, recognize that your risk models run on data and they are only as good as the quality of the inputs that fuel them—good data in, good data out; bad data in, bad data out. Also, recognize that you cannot necessarily identify or predict all risks; you will improve with time, but there are some risks for which you cannot plan.

One strategy for assessing and mitigating risks is to use the TransCelerate Risk-Assessment Categorization Tool (RACT) for guidance on risk assessment. This tool can be used for any study type, phase and stage and facilitates, and includes the following three steps:

1. Identification of risks that could affect patient safety, data integrity or regulatory compliance
2. Categorization of the risks that will be managed with the Monitoring Plan (and data review)
3. Determination of the baseline level of monitoring activities
   - The overall risk level score will determine the baseline level of monitoring activities as defined in the Risk-Based Monitoring Position Paper

In addition, completing an overall Risk Statement for the study will help your teams gain a better understanding of trial level risk and allow them to design mitigation strategies that align to risk level.

Develop required assessment and mitigation plans

Risk assessment and mitigation plans appear not to be optional and need to be in place even if you are not using an RBM strategy for data review. At this stage of awareness, many organizations mistakenly think that QRM = RBM; instead, RBM is an action and one way to ensure and support QRM but is not QRM itself. Absent of a targeted or reduced SDV/SDR strategy and flexible monitoring visit schedule, the new guidelines suggest that a process for risk assessment and mitigation needs to be in place.

It could be mistakenly believed that the guidance is not relevant if you are not using an RBM approach or that implementing RBM is enough to comply with the guidelines.

Consider using centralized monitoring

The definition of “monitoring” is re-defined by these guidelines and expands beyond the traditional method of on-site monitoring activities. In the RBM section, centralized monitoring is specifically called out in the regulations, leading us to believe that regulators are expecting to see its use (or a justification for not using) in studies moving forward. Therefore, you are going to have to think about how to enable centralized monitoring within your organization. A centralized review of critical data and processes ensures risk is assessed and managed holistically.

While some form of centralized monitoring is likely to already be in use at most companies, the guidance suggests that a more formalized approach to this activity is expected, and documentation of processes to enable central monitoring should be clearly outlined in the appropriate study management plans. Additionally, the completion of central monitoring reports will be expected, and regulators will expect to see formal documentation of central monitoring activities—the most common interpretation of this will be in the form of a “central monitoring report.” However, this may also be achieved through the combination of technology and process, providing a documentation trail showing when a risk is surfaced, confirmation that the risk required action, triaging of the risk to the right individual, the mitigation strategy that was put in place and closure of the outstanding item.

To provide an aggregated view of data across the study, it is reasonable to assume that the only way to achieve this is through the use of technology. Manual methods for aggregating and reviewing data, such as the use of spreadsheets, might still be effective, but are slow and inefficient for gathering and analyzing data; therefore, they are not going to be manageable over the long term. Furthermore, the use of technology that allows for tracking specific risks based on predefined risk tolerances and thresholds will ensure that the intent and benefit of the various different types of monitoring, including central monitoring, is realized.
Implementing the guidelines

These guidances bring about a fundamental shift in the way we run clinical trials and will require a combination of people, process and technology. The cohesive design of technology and process working together to provide people with the support they need to implement QRM will be critical to achieving success (Figure 5).

What should you consider as you think about how to implement these new guidances?

What is the impact of moving from your old way of working, which involved systems and processes that may not have been integrated, to this new way of working?

To help understand what needs to be addressed, perform a gap analysis and outline the gaps from both technology and process perspectives.

Do you have the right people, with the right skill sets, in place?

Some examples include deep analytical skills, experience with data monitoring and critical-thinking skills.

Think about whether you need new roles within your organization or if you can achieve this new model by adding other responsibilities to current roles.

What is your organizational culture and how will that impact your approach to complying with these new guidelines?

Every company will approach these new guidelines a bit differently; to be successful, your new processes and procedures need to fit your culture. As with the old adage, you can’t fit a square peg into a round hole. Although it can be helpful to see how other companies approach and implement QRM, it is not helpful to copy what others are doing because the implementation needs to be purpose-fit to your organization.

Do you have the right technologies in place?

In the current landscape, disparate systems that aren’t integrated are commonly used; these systems provide views into the data for a single purpose or to answer a specific question. Instead, moving to a QRM approach will require technologies that speak to one another, aggregate disparate datasets and can deal with both unstructured and structured data to provide actionable information. In addition, technologies should be able to apply sophisticated algorithms to the data that help roles, such as central monitors, more easily identify outliers, data anomalies, patterns and trends in the data and surface patient-level and site risk based on pre-set tolerances and thresholds. It will also be key for technology to help filter out the noise and present only the true risks. Because workflows will now be more integrated across departments and functions, technologies will need to support and enable workflows designed to support quality risk management processes.

Are your partners ready and able to embrace this change with you?

From your CRO to your technology partners, your team needs to be on board to help support this change.
Conclusion

The revised guidelines are moving forward, and there is no other option than to make sure that you are ready to implement them. While there is some flexibility in how the guidelines are implemented, the implementation must be justifiable. Make sure to document all of your decisions and be consistent with the implementation. Moreover, the right combination of people, process and technology is required; now is the time to review your specific needs in each of these areas to determine what changes are required within your organization.

Figure 6. Moving to a QRM approach will require technologies that speak to one another, aggregate disparate datasets and can deal with both unstructured and structured data to provide actionable information.

References


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**About Bioclinica**

Bioclinica is a specialty services provider that utilizes expertise and technology to create clarity in the clinical trial process. Bioclinica is divided into three business segments to deliver focused service supporting multifaceted technologies. The Medical Imaging and Biomarkers segment provides medical imaging and cardiac safety services and includes a molecular marker laboratory. The eHealth Solutions segment comprises an eClinical technology platform and professional services along with safety and regulatory solutions. Under the Global Clinical Research segment, Bioclinica offers a network of research sites, patient recruitment/retention services, and a post-approval research division. The company serves more than 400 pharmaceutical, biotechnology, and device organizations – including all of the top 20 – through a network of offices in the U.S., Europe, and Asia.

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