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Practical Considerations of a Successful RBM Implementation

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Introduction to ICH E6(R2) and Its Relevance to Industry

Clinical trial professionals are likely aware of significant changes in Good Clinical Practice (GCP) standards since the initial release of ICH E6 GCP guidance. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) recently finalized their addendum to the original E6 guidance for Good Clinical Practice (GCP).[1] This was spurred by the move away from paper-based source documents toward electronic data capture (EDC) technology. The purpose of this update was to expound upon ways to modernize clinical trial conduct—based on recognition of the growing cost and complexity of clinical trials and the increased capability of modern technology. This modern approach is referred to as risk-based monitoring (RBM).[2] As studies become more complex and expensive, utilizing emerging technology should benefit sponsors and contract research organizations (CROs).

At a basic level, the addendum increases the responsibilities of accountable parties within the clinical trial process to improve safety for the subjects and improve the reliability of the trial itself while ensuring that resources are used for the highest risks within a trial.

- The **Investigator** has increased responsibilities to supervise trial functions and to ensure that source data is accurate and complete. "Certified copy" is now clearly defined, and it is expected that sites will provide certified copies of source documents generated using validated systems.

- The **Sponsor** has increased responsibilities on the implementation and maintenance of a quality management system, as well as the oversight of all trial-related duties and functions (including those performed by a CRO). The sponsor should develop and use a systematic, prioritized, risk-based approach to clinical trial monitoring.

ICH GCP E6(R2) has been adopted by multiple regulatory bodies to date, and it is expected that more will adopt it in the future:

ICH GCP E6(R2) Adoption by Regulatory Authorities

Country/Standards Organization	Date of Adoption/ Notes
ICH	Adopted November 9, 2016.
Canada	Published the ICH guidance on the Health Canada Website with an effective date of May 25, 2017. Published draft "Drugs for Clinical Trials Involving Human Subjects," GUI-0100 and opened consultation from December 15, 2017 through April 15, 2018.
Europe	Published "Guideline for good clinical practice E6(R2)," EMA/CHMP/ICH/135/1995 guidance, dated December 1, 2016.
Japan	Per ICH Efficacy Guidelines webpage, no update yet.
Switzerland	Published "Ordinance on Clinical Trials in Human Research," 810.305, dated May 01, 2017.
U.S.	Published "E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)," UCM464506, dated March 2018.

1 FDA (2018). E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), Guidance for Industry.
2 FDA (2013) Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring.

Advances in technology, such as electronic capture and storage of study data and documentation, have accommodated the growing reliance on RBM for clinical trials.

With any new technology, there are questions about implementation and best practices. To address the technological aspects of RBM, TransCelerate Biopharma Inc. identified four areas critical for technology-based RBM[3]:

1. Risk and issue management;
2. Data integration so that data is available for efficient monitoring;
3. Adaptive monitoring process; and
4. Risk assessment, reporting and analysis so that knowledge is accessible for learning.[4]

Overview of the Benefits of RBM to Trial Sponsors and CROs

RBM CHANGES HOW WE CONDUCT CLINICAL TRIALS

RBM is an innovative approach to clinical trial monitoring that should be "tailored to the specific human subject protection and data integrity risk of the trial."[4] Identifying and allocating resources to the most critical aspects of the study can result in improved quality and compliance. Improved resource allocation can also enable cost optimization and/or application of clinical experts to higher value complex activities of the trial. The risk-based philosophy is a holistic approach that can be incorporated into all important study activities, including protocol development, patient recruitment, data management, site monitoring, and inspection readiness.

Monitoring is one of the top-three cost drivers of studies conducted in the United States.[5] In the real world, it is common for some sites or investigators to require more attention than others, yet traditional monitoring plans typically allocate similar resources across sites. With RBM, *the purpose of site visits becomes proactive issue prevention, not reactive issue detection and information collection*. This profound shift in how the industry views study monitoring is made possible by advances in data technology.

3 Transcelerate Biopharma (2015). Risk-based monitoring technology considerations: Part 2. US Food and Drug Administration (2013). Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring.

4 FDA (2013) Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring.

5 Sertkaya A, Wong H, Jessup A, Beleche T (2016). Key cost drivers of pharmaceutical clinical trials in the United States. *Clinical Trials*. Vol 3(2): 117-126.

TECHNOLOGY DRIVES THE PARADIGM SHIFT TOWARD RBM

EDC, cloud-based storage platforms, and centralized analytics have enabled risk-based approaches to monitoring. Some of the most critical areas for technology-based RBM plans include risk and issue management; effective data integration to aid onsite monitoring visits; an adaptive monitoring process; and risk assessment, reporting, and analysis so that knowledge is accessible for learning and auditing.[6]

Centralized monitoring provides real-time capture and analysis of trial data, which changes the concept of trial monitoring. When a holistic view of real-time data is available with a cloud-based platform, a study team can identify sites in need of corrective action as deviations occur, a much more efficient process than using site visits to discover issues.

Some of the questions that can be answered with centralized monitoring and analytics include:

- Are sites enrolling participants quickly enough?
- Are sites enrolling participants who violate inclusion/exclusion criteria?
- Are sites experiencing a greater-than-average number of protocol deviations?
- Are sites conducting activity in ways that may correlate to potential compliance or performance concerns?

In the past, answers to these questions may have been discovered during monitoring visits, perhaps weeks after issues occurred. High-level analytics provide centralized monitoring with an effective tool to rapidly identify deviations in a trial. In a retrospective analysis based on anonymized site data from studies used in four recent new drug applications (NDAs), centralized analytics detected (with 83 percent accuracy) sites that had been recommended for data rejection by the FDA, and detected (with 87 percent accuracy) the sites that had been found by the FDA to have one or more regulatory deviations during inspection.[7] From a prospective viewpoint, RBM allows trial sponsors to establish quality tolerance limits (QTLs) according to the specific needs of a given trial. By establishing QTLs prior to starting enrollment, sponsors can enhance data validity as well as participant safety.[8]

RBM provides constant communication between study team members and allows a tailored, customized approach to allocate study resources. It seems likely that RBM, in conjunction with centralized monitoring and analytics, will continue to play an ever greater role in clinical trials.

Given the many advantages of RBM, it is easy to see why there is so much interest in adapting RBM to new clinical trials. However, the paradigm shift from a one-size-fits-all monitoring and full source document verification to the RBM approach is not without challenges. Modifying clinical trials in accordance with regulatory guidance can be a difficult process that requires the use of change management principles.

6 Transcelerate Biopharma (2015). Risk-based monitoring technology considerations: Part 2.

7 Lindblad AS, Manukyan Z, Purohit-Sheth T, Gensler G, Okwesili P, Meeker-O'Connell A, Ball L, Marler JR (2014). Central site monitoring: results from a test of accuracy in identifying trials and sites failing Food and Drug Administration inspection. Clin Trials. Vol. 11(2):205-17.

8 Zink RC, Dmitrienko A, Dmitrienko A (2018). Rethinking the Clinically Based Thresholds of TransCelerate BioPharma for Risk-Based Monitoring. Ther Innov Regul Sci. doi: 10.1177/2168479017738981

Organizational Impact of RBM and Ways to Mitigate

The biopharma industry is known to be risk averse, with well-entrenched processes following sometimes decades-old regulations. This is to be expected in an industry that must test its products on patients as part of the process for getting medicines approved. The last thing any biopharma company wants is to subject patients to unnecessary risks during a clinical trial. Thus, once processes and monitoring checks are seen as safe, they quickly become institutionalized.

Institutionalizing significant changes included in ICH E6(R2) in this atmosphere requires a thoughtful change management plan and implementation. There's no doubt that clinical trial management is well overdue for change to bring it into the 21st century. However, due to the significance of the changes, organizations must spend time identifying who is affected, what changes are needed, how change is communicated and so on.

It's important to spend time identifying process, culture, and strategic changes necessary for successful adherence to ICH E6(R2). Change management can be optimized through a focused implementation team that will identify affected people, processes, and the long-term approach.

PROCESS CHANGE

ICH E6(R2) is first and foremost a major process change for clinical trial management within a biopharma organization. The new and updated requirements described in the addendum must be pulled apart and matched to current processes, or the lack thereof.

As discussed earlier in this paper, it is likely that new or updated technology may be the best solution to address aspects of ICH E6(R2). Sponsors and CROs have extensive access to process experts who can analyze existing state, design future-state processes that maximize value from the technologies chosen, and create robust implementation plans to ensure organizational alignment.

EXAMPLE: PROCESS CHANGE RELATED TO TIMING OF STUDY RISK MANAGEMENT

A sponsor had historically delayed structured risk identification and mitigation discussions until the conduct phase of their studies when subjects were already enrolled. This sponsor found that when they shifted the timing of their study risk assessments to take place prior to final protocol approval, they realized both quality and cost savings. The risks identified during protocol design allowed study teams to "de-risk" the draft protocol, thus decreasing the number of avoidable protocol amendments. For example, one study team included an additional third-party lab to track an important KRI that was brought up during the risk assessment.

Takeaway: Conduct risk assessments as early as possible to influence protocol design and avoid amendments downstream.

CULTURAL CHANGE

Cultural change is the second type of change that must be managed. Teams need to adjust their thinking and priorities on their role in the clinical trial. Although it can be tempting to merely state that the regulation must be followed, it is better to communicate the positive results that come from adhering to the new guidance, such as:

- Early access to trial insights for mitigation
- Improved identification of safety issues
- Reduced regulatory review times
- Faster time to market
- Decreased mundane manual activity through access to technology

The cultural change management needs for ICH E6(R2) are comparable to what was needed to implement the eCTD v3 submission format where sponsors were tasked with transitioning to the electronic Common Technical Document format. The regulatory requirement clearly called for process change; however, implementations were most successful when regulatory departments convinced upstream departments that their everyday reality would improve after they implemented the changes. Authoring teams and data teams faced significant change in their processes and deliverables to adhere to a new standard that meant little to them. Once these departments began to understand the new format brought increased automation, improved quality, and reduced mundane tasks, they were better able to optimize performance.

Communication and education are core components to cultural change management—both of which benefit from sharing the "why" behind the change. In the eCTD example, regulatory teams had to use both communication and education to convince the rest of the organization to embrace the new electronic format. While an author could no longer switch out a revised page in a paper document hours before a submission date, the payoff was a submission more easily reviewed and maintained by the regulatory authority and by a cross-functional global team. The larger goal was important enough to the company for authors to accept that last-minute page switches were no longer an option. As minor as this example may seem now, this was a significant pain point when eCTD and electronic formats were first being adopted.

Communication and education must serve as ongoing initiatives during the change management process. The more that teams understand why a change is being made and how it will benefit patients and the company, the easier it will be to adopt that change.

EXAMPLE: CULTURAL CHANGE RELATED TO TARGETED SOURCE DOCUMENT VERIFICATION (TSDV) IMPLEMENTATION

It is still common to come across sponsors who perform 100 percent source data verification across all studies. One sponsor implemented **Medidata Edge Targeted SDV** and rolled out a targeted approach of verifying only critical data points as defined by the study team. This sponsor tracked value metrics to look at time and cost savings derived from clinical research associates (CRAs). While they verified only a subset of source data in the targeted, risk-based approach, they were surprised to see virtually no change in SDV levels across their studies.

When they looked further, they found that even though their CRAs were instructed to verify only the subset of critical data points, they were still performing 100 percent SDV out of habit. The CRAs did not trust the targeted approach and felt uncomfortable leaving data unchecked since they assumed accountability for data accuracy. The sponsor put in additional effort to educate CRAs on the rationale for TSDV to build trust and confidence in the process. Studies show that less than three percent of source data is changed as a result of 100 percent SDV. A risk-based, targeted SDV approach can deliver trial quality equal to or better than the 100% approach.

Takeaway: Invest time to educate impacted stakeholders on the rationale for RBM. Training isn't always sufficient to make change happen.

TWO EXAMPLES OF PROCESS AND CULTURAL CHANGE RELATED TO RISK ASSESSMENT

For sponsors adopting a RBM approach, it can be challenging to justify the amount of effort across stakeholders to hold an effective risk discussion and gain buy-in from leadership to prioritize these discussions.

Some sponsors have used multi-day workshops to handle study risk assessments. Sponsors have seen success in collaborative and interactive cross-functional risk discussions that result in more productive risk mitigation compared to those that take a more siloed approach. It's important to think beyond the traditional data operations, trial management, and site monitoring study teams and include representation from clinical science, manufacturing and supply chain, drug metabolism and pharmacokinetics, medical writing, etc.

At the same time, some sponsors find the process can feel onerous and be difficult for team buy-in. It is important in these cases to learn from industry best practice on the ways that risk assessment discussions can be made as efficient as possible. Start with predefined, general risks and have a focused conversation on the study. These techniques make the risk-assessment discussions as lean as possible, but also make it easier for team members to see value in taking the time for these discussions.

Recently, a study clinical research scientist raised a risk on third-party data availability. It was critical to have timely and in-sync data sets to review across labs immediately following First Subject First Visit. The study manager and study programmer were both present in the discussion and quickly came up with an approach to alter their vendor startup agreements and data transfer specifications to meet the study needs. Having an early risk assessment with the right cross-functional representation in the room made this possible.

Takeaway: Invest time in risk assessment discussions, and include members across all functions. Prior to rolling out RBM, spend time on leadership alignment across all functions to make sure everyone understands the importance of risk assessment. Leaders can reinforce the message that people need to show up and take risk assessment seriously. Leverage the advice of experienced providers in making the time investment as focused and valuable as possible.

Elsewhere, a sponsor's study resourcing process did not align with the timing of their risk assessment process. The sponsor filled the risk assessment with temporary study team members, which eventually turned over to new staff. The sponsor saw a decrease in the new study team members' ability to mitigate the risks identified by their predecessors. In addition to having the full context from the initial risk assessments, the working relationships established in the cross-functional session broke down barriers and allowed study team members to communicate more openly with one another.

Takeaway: Identify study team members as early as possible, and avoid turnover to have continuity in risk mitigation plans.

STRATEGIC CHANGE

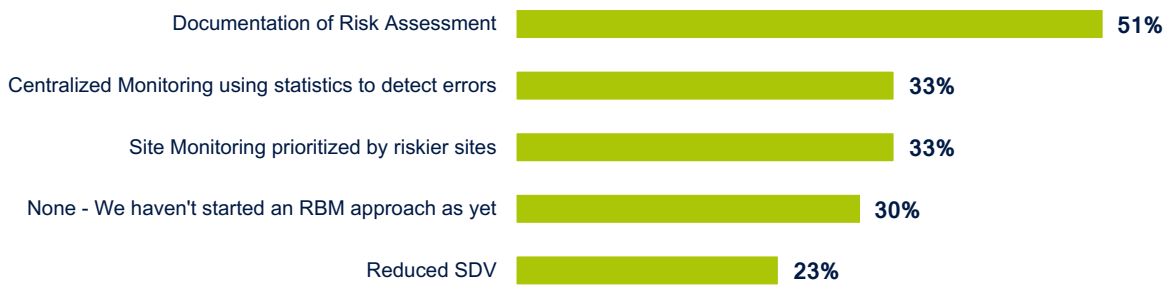
Finally, strategic change is an important consideration for sponsors as it relates to how RBM will be used and what strategic goals it will help achieve. Strategic goals may vary from sponsor to sponsor. Some sponsors may have deficits in quality or compliance, and an RBM implementation will be tuned to address these gaps. Other sponsors may be satisfied with their current quality but spend unsustainable resources to do so. In either case, the sponsor's overall RBM goals will drive strategic organizational change to align the implementation with the desired outcomes. These may also lead to discussions and changes to the organization's core definition of what a successful clinical trial is and how to achieve it. Change management principles used here are similar to those used for cultural change in that communication and education on RBM are required.

A Technology Roadmap to RBM

"A journey of a thousand miles begins with a single step." As discussed earlier, one of the barriers to implementing RBM is being unsure where to start. Many companies recognize that their processes and technology stacks are complex, inefficient, or outdated and ripe for change, but are often stuck on where or how to start.

In a recent survey, we asked respondents to tell us their starting point when they followed an RBM approach. More than half reported risk assessment as their starting point, a third of respondents equally chose to start by taking a centralized monitoring approach or a site monitoring approach prioritized by risk, and a quarter of respondents said they began by reducing SDV efforts. These survey results validate the idea that there can be multiple starting points, and that it's less important where you start. The optimal starting point depends on a sponsor's current processes, technologies, culture, and long-term goals. It is important that sponsors begin their RBM journey by leveraging industry experience to determine the optimal starting point and implementation path.

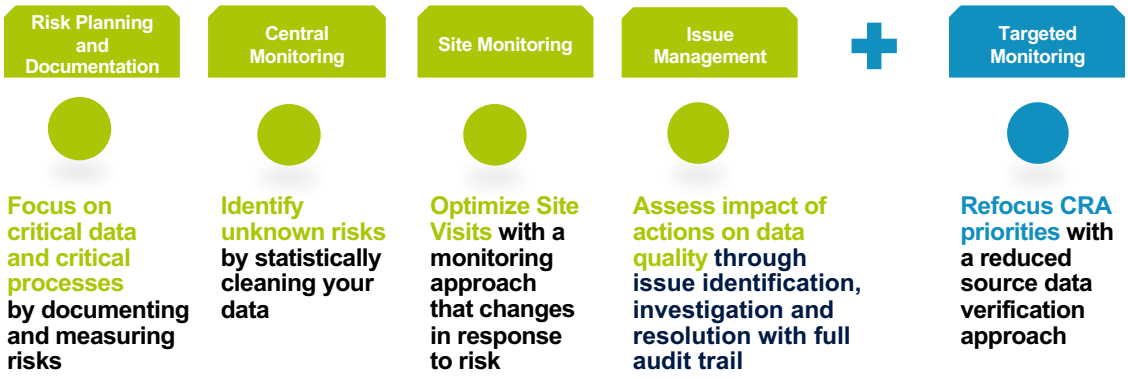
If you followed an RBM approach in one of more of your studies, which of the following did you choose as a starting point? [Select all that apply]



Survey of clinical trial professionals who attended Medidata RBM webinar on May 23, 2018 N=72

The technology roadmap to RBM at Medidata is a collection of capabilities that life science companies need to execute their RBM strategy. They may have some or all of these capabilities or may just want to improve one of more of these capabilities. The roadmap provides a simple, easy to follow, start-anywhere approach that stresses that the best starting point depends on each individual sponsor. After implementing a starting point, the roadmap offers flexibility to move in any direction depending on organizational priorities.

Medidata's Roadmap to RBM



STARTING POINT: FOCUS ON CRITICAL DATA AND CRITICAL PROCESSES BY DOCUMENTING AND MEASURING RISKS

This step captures components of a holistic and system-bound integrated quality risk management plan (IQRMP) through centralized documentation of risk assessment and categorization (RACT), key risk indicators (KRIs), configuration, source data review (SDR), and source data verification (SDV) strategies. This helps to assess impact, probability and detectability of study risks—a key step in the RBM approach.

Impact: Comply with regulation and lay the risk-based groundwork for subsequent improvements.

STARTING POINT: ANALYZE MILLIONS OF DATA POINTS TO IDENTIFY KNOWN AND UNKNOWN RISKS, ANOMALIES, OUTLIERS AND PATTERNS USING MACHINE LEARNING

This step applies sophisticated machine-learning algorithms to interrogate the clinical data in a trial for outliers, data anomalies, and trends. It identifies areas of risk quickly and accurately by providing immediate insight into clinical trial performance and data quality. In addition, KRIs configured in Edge Risk Management display in a centralized dashboard to identify risks and launch a series of corrective action workflows. Central monitoring is specifically designed for centralized statistical monitoring across functional areas.

Impact: Maintain or improve data quality with greater efficiency and insight.

STARTING POINT: OPTIMIZE SITE VISITS WITH A SITE MONITORING APPROACH THAT CHANGES IN RESPONSE TO RISK

This step provides CRAs an advanced user experience and proactive decision-making to reduce risk and costs while increasing study and site performance, patient safety, and time to market. These efficiencies are made possible by leading-edge technologies that support multi-tiered monitoring visits driven by risk category, optimal workload management, and a structured data approach to monitoring visit reports. The reduction in redundant data entry saves a tremendous amount of time, whether on-site or remote.

Impact: Increase CRA efficiency and output, reduce CRA attrition, and reduce site monitoring costs

STARTING POINT: ASSESS IMPACT ON DATA QUALITY THROUGH END-TO-END ISSUE MANAGEMENT THAT ENABLES ISSUE IDENTIFICATION, INVESTIGATION, AND RESOLUTION WITH FULL AUDIT TRAIL

This step ensures a centralized, cross-functional approach for all issues and action items throughout the clinical study. It ensures maximum collaboration across the clinical team and gives the ability to re-assign, copy stakeholders, and add ongoing comments as the issue moves through mitigation strategies.

Impact: Improve cross-functional collaboration and inspection-ready risk management documentation.

STARTING POINT: REFOCUS CRA PRIORITIES WITH A REDUCED SOURCE DOCUMENT VERIFICATION APPROACH

This step helps companies reduce SDV without sacrificing regulatory compliance or data quality strategies. Patients are assigned to pre-configured SDV regimens—focused on critical data—as they are enrolled, enabling study teams to achieve desired coverage levels. As the trial progresses, the team can make modifications at any level, without disrupting existing monitoring processes.

Impact: Save time and focus CRAs on what matters—patient enrollment and improved site performance.

ICH E6(R2) represents a sea change for the industry in its embrace of risk-based clinical development methodology. The process, technology, and cultural changes can be complex, confusing, and challenging to implement. However, done properly and with care to consider needs and goals, RBM can produce essential quality, efficiency and cost improvements over current monitoring methods. These benefits not only improve specific trial execution, but create strategic, enduring advantages for the sponsor that have sustainable impact throughout the clinical development lifecycle.

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info@mdsol.com | mdsol.com | +1 866 515 6044