Duke | Robert J. Margolis, MD Center for Health Policy

Improving the Implementation of Risk-Based Monitoring Approaches of Clinical Investigations

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Discussion Guide

Introduction

Monitoring of clinical investigation conduct is necessary to help ensure overall study quality including human subject protections and data integrity. Traditionally, such monitoring is accomplished by sponsors conducting on-site monitoring visits every 4-8 weeks with 100% source data verification (SDV). This approach is highly resource intensive, costly, and has been found to have minimal impact on the quality of the clinical investigation when compared to less resource-intensive approaches.[1, 2] To improve the quality of clinical investigations, in 2013 the U.S. Food and Drug Administration (FDA) released the guidance to industry, *Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring*.[3] To further assist sponsors in planning and conducting risk-based monitoring, in 2019, the FDA released additional draft guidance on risk based monitoring, *A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance to Industry*.[4] (The recommendations from the two guidance documents are collectively referred to as the RBM Guidance hereafter.)

As stated in the RBM Guidance from 2013, "risk-based monitoring, including the appropriate use of centralized monitoring […] and reliance on technological advances (e.g., e-mail, webcasts, online training modules), can meet statutory and regulatory requirements under appropriate circumstances." As one option, the RBM Guidance encourages the development of monitoring plans that incorporate risk-based approaches for centralized and on-site monitoring of clinical investigations. Centralized monitoring is generally remote evaluation carried out at a location other than the site at which the clinical investigation is being conducted, whereas on-site monitoring is in-person evaluation carried out at the site of the clinical investigation. More broadly, risk-based approaches focus sponsor resources and oversight on important and likely risks to investigation quality, including risks to human subject protections and data integrity, and on risks that may be less likely to occur but that could have significant impact on the overall quality of the investigation. Once critical risks are identified, sponsors are encouraged to perform a risk assessment. The results of the risk assessment should then be used to determine how to mitigate important risks, when possible, prior to the start of the investigation, and to support the development of a monitoring plan that will describe how remaining important risks will be tracked and managed throughout the investigation. Significant issues identified through

monitoring should be communicated to appropriate parties and used, along with ongoing risk assessment evaluation, to adjust monitoring activities.

In the RBM Guidance, FDA encourages greater use of centralized monitoring practices than have been used historically, with correspondingly less emphasis on on-site monitoring, where appropriate, while recognizing that the two forms of monitoring complement each other. Centralized monitoring may assist in the identification of missing or unusual data, the evaluation of trends in data over time, the detection of errors in data collection processes, and the assessment of site performance. Results of centralized monitoring may then be used to guide allocation of sponsor resources to those clinical sites where concerning issues have been identified. On-site monitoring, whether or not it has been guided by centralized monitoring, may also be performed using risk-based approaches that permit monitors to focus on evaluation of critical data and study procedures during site visits, including investigational product accountability, the identification of important data entry errors and missing data, assurance that study documents exist, and the assessment of staff compliance with the protocol at each site.

To date, few studies have directly compared risk-based monitoring approaches to traditional monitoring approaches. Studies suggest, for example, that risk-based monitoring may be as or more effective than non-risk-based approaches involving on-site monitoring with accompanying 100% SDV. TEMPER, a prospective matched-pair study conducted by Stenning, et al., examined the ability of triggered monitoring, a risk-based monitoring approach, to identify sites with critical protocol or Good Clinical Practice (GCP) compliance issues that were not identified through centralized monitoring. [5] Excluding re-consent findings, which can often be identified through centralized monitoring, 85.7% of triggered sites had greater than 1 major or critical finding, compared to 59.5% of untriggered sites. ADAMON, a study conducted by Brosteanu, et al., cluster-randomized 213 sites between extensive on-site monitoring and risk-adapted monitoring and found risk-adapted monitoring to be non-inferior.[6] Several additional studies examined in the literature review conducted by Olsen et al. on the effect of trial monitoring approaches on data integrity and cost demonstrate that 100% SDV added little value to data integrity. This literature review further supports the incorporation of risk-based monitoring approaches into on-site and centralized monitoring. [7]

Risk-Based Quality Management Systems

Risk-based monitoring approaches can be integrated into an efficient clinical trial quality management system (QMS). The International Council for on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) *E6 (R2) Good Clinical Practice* guidance recommends integrating risk-based approaches into a quality management system to:

- Identify, during protocol development, data and processes critical to ensure human subject protections, the reliability of trial results, and the risks to such critical data and processes;

- Evaluate the likelihood, detectability, and impact of such risks;
- Determine if risks are acceptable or if they must be reduced based on prespecified limits;
- Document and report risks in the clinical investigation;
- Review risk control measures periodically, to ascertain effectiveness of risk control measures and to take into account emerging knowledge and experience.[8]

As a part of this QMS, E6 (R2) recommends sponsors develop a systematic, prioritized, risk-based approach to monitoring clinical trials.

Also under the QMS umbrella is quality by design (QbD), an approach to improve the quality of a clinical trial through prospective attention to preventing important errors that could undermine the ability to obtain meaningful information from the trial. When employing a quality by design approach as outlined in *ICH E8 (R1) General Considerations for Clinical Studies*[*] investigators should identify factors critical to study quality in order to protect human subjects, ensure reliability of results and the decisions made based on these results, and mitigate and control risks to these critical factors.[9] The Clinical Trials Transformation Initiative's Quality by Design project recommends quality be built into the scientific and operational design and conduct of clinical trials from the outset, and revisited throughout the conduct of the clinical trial, and that monitoring and other quality assurance efforts focus on ensuring that those "critical to quality factors" are appropriately tracked and managed throughout the trial. Likewise, the EMA, in its 2013 *Reflection Paper on Risk Based Quality Management in Clinical Trials*, encourages more systematic, prioritized, and risk-based approaches to quality management system-wide, and recommends the use of a quality by design approach across all aspects of trial design, including a trial's monitoring plan.[10]

Implementation of Risk-Based Monitoring

When deciding to implement RBM, organizations must consider several factors that may impact the clinical investigation conduct, including the integration of new technology, adjustments to organizational change management, and the creation of a system for evaluating RBM approaches.[11] Advanced technology and appropriate analytical platforms are essential for performing centralized monitoring as part of risk-based monitoring. The opportunities for centralized monitoring will increase as more clinical research data is captured in digital form, but challenges associated with reconciling data with differing formats and sources remain. Organizational change management is another important consideration when adopting risk-based monitoring given that skills of staff, training programs, and communication processes may impact the successful implementation of risk-based monitoring approaches. Finally, to

[*] This guideline is draft and is made available for the purpose of obtaining public comment

ensure quality of the clinical investigations, organizations should consider evaluating RBM approaches in terms of key measures, such as quality, timeliness, and efficiency.

Presently, risk-based monitoring approaches have been implemented by multiple sponsors and clinical research organizations. In 2013, TransCelerate BioPharma developed and piloted a methodology for implementing risk-based monitoring that was adopted in some form by a number of its member companies.[12] This methodology uses quality risk management, starting with building QbD into trials and including use of risk indicators and risk thresholds to trigger an action such as increased data scrutiny and site follow up. This methodology allows for on-site monitoring practices to be used, in part for activities and studies that are not conducive to remote monitoring. The Association of Clinical Research Organizations (ACRO) also encourages the implementation of risk-based monitoring approaches, and recently reported that among its members, 61% of trial starts in 2018 included RBM technology, compared to 18% in 2016.[13] As a result of conducting risk-based monitoring, some ACRO members report an error rate in critical data that is four times lower than when using a 100% SDV approach.[14] Growing implementation of risk-based monitoring is encouraging, but widespread use of risk-based monitoring has yet to be put into practice as part of all clinical studies and across development portfolios.

Workshop Goals

On July 17, 2019, under cooperative agreement with the FDA, the Duke-Robert J. Margolis, MD, Center for Health Policy at Duke University will convene a public workshop to solicit stakeholder input on the challenges, barriers, and enablers that impact the successful adoption of RBM, and what opportunities exist to improve RBM implementation. Discussion will focus on the extent of RBM implementation among organizations and opportunities to increase RBM adoption.

Terms of Reference

- **Centralized Monitoring**: Program of analytical evaluation carried out by sponsor personnel or representatives (e.g. clinical monitors, data management personnel, or statisticians) at a central location other than the site at which the clinical investigation is being conducted.
- **Monitoring**: The act of overseeing the process of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), and GCP, and the applicable regulatory requirements.[15]
- **Monitoring Plan:** Describes the monitoring methods, responsibilities, and requirements for the trial. Elements that may be included in the monitoring plan are described in section IV.D of the RBM Guidance.[16]
- **On-site Monitoring**: In person evaluation carried out by sponsor personnel or representatives at a clinical site at which the clinical investigation is being conducted.[17]

- **Remote Monitoring**: Monitoring of specific activities, as defined either within process documents or in the monitoring plan, performed by the monitor away from the site at which the clinical investigation is being conducted.
- **Risk-Based Monitoring**: Monitoring that focuses sponsor resources and oversight on important and likely risks to investigation quality, including risks to human subject protections and data integrity, and on risks that may be less likely to occur, but that could have significant impact on the overall quality of the investigation.
- **Source Data Verification:** Process of checking case report form data against source data.[18]
- **Quality by Design:** In the context of clinical research**,** prospective attention in the design of a clinical trial to minimize the risk of important errors that could undermine the ability to obtain meaningful information from the trial.
- **Risk Assessment**: A process used to identify and understand the nature, sources, likelihood of detection, and potential causes of risks that could affect the collection of critical data, performance of critical processes, and/or the rights, safety, and welfare of research subjects.[19]

Summary of Workshop Sessions

Session 1: Regulatory Foundation for Risk-Based Monitoring

This session will feature two presentations intended to build a solid foundation for the day's discussion based on common terminology, and general background on risk-based monitoring. Presentations from FDA and EMA will discuss risk-based monitoring in the context of a quality management approach to clinical trials and will highlight the value of risk-based monitoring approaches using examples of inspection findings.

Session 2: Experiences with Implementation of Risk-Based Monitoring Approaches

Risk-based monitoring involves many different stakeholders, including sponsors, clinical research organizations (CROs), academic researchers, and clinical trial sites. This session will highlight the experiences of these groups in their efforts to implement risk-based monitoring approaches. Representatives from three trade organizations, the Pharmaceutical Research and Manufacturers of America (PhRMA), the Association for Clinical Research Sites (ACRO), and the Society for Clinical Research Sites (SCRS), will share the experience of their member organizations. In addition, the Duke Clinical Research Institute will describe their experience with RBM in an academic setting. Together, these groups will share their experiences in diverse settings and with a range of monitoring techniques, including on-site, centralized, and remote RBM.

Discussion Questions:

- To what extent are sponsors, CROs, and researchers using RBM? Does the fraction of trials for which RBM is implemented differ across therapeutic areas?

- How are key stakeholders deploying RBM within their organizations?
- How are monitoring techniques such as on-site, centralized, and remote RBM being employed?
- How does the implementation of RBM affect practices at clinical trial sites?

Session 3: Analytical Tools and Methods to Support Risk-Based Monitoring

Effective implementation of risk-based monitoring requires the use of analytical tools and methods that can predict risks in clinical trials, suggest threshold triggers and appropriate mitigation and management of those risks during protocol development as well as throughout the conduct of the study, and measure the impact of these efforts. Effective application of these tools requires advanced technology and appropriate analytical platforms, as well as effective application of these tools by organizations. During this session, panelists will discuss analytic approaches being used to support risk-based monitoring, how they can be applied effectively, and how the benefit of risk-based approaches can be measured.

Discussion Questions:

- What analytic approaches are being applied to support and assess risk-based monitoring?
- What technology and tools exist that could support the implementation of RBM, and how can they be applied effectively?
- What are the strengths and limitations of such analytical tools and methods?

Session 4: Identifying Enablers to Support Implementation of Risk-Based Monitoring Approaches

Following the publication of the RBM Guidance in 2013, EMA Reflection paper on risk-based quality management in clinical trials in 2013, and the release of ICH E6 (R2) in 2016, the adoption of risk-based monitoring approaches has grown, yet effectively implementing RBM remains challenging. During this session, panelists will share their experiences adopting RBM and describe enablers that can help organizations overcome barriers to implementation. Panelists will highlight the importance of change management and a strong working relationship between sponsors, CROs, FDA, and other key stakeholders. Panelists will also discuss the role of tools and templates, such as TransCelerate's RBM methodology, in supporting the adoption and effective use of risk-based monitoring approaches.

Discussion Questions:

- What factors influence the successful uptake and implementation of RBM?
- How can organizations apply change management best practices when adopting RBM?
- How, and under what circumstances, might approaches to RBM vary? When is centralized monitoring as part of an RBM approach appropriate?

- What are the challenges of implementing risk-based monitoring in multi-national trials?
- What role could templates or tools play in supporting the development and implementation of risk-based monitoring plans?
- Are there remaining challenges to implementing RBM fully within organizations? If so, what resources are needed to overcome these challenges?
- What is FDA's role in supporting the implementation of RBM?

Session 5: Measuring the Impact of Risk-Based Monitoring Approaches

The adoption of RBM has been driven by a desire to improve the quality and efficiency of clinical investigations, but to date there has been limited research on the extent of RBM adoption and its impact. The session will begin with a presentation from TransCelerate BioPharma, which will share recent research it has conducted on the uptake and impact of risk-based monitoring across the pharmaceutical industry. Panelists will go on to discuss how organizations decide whether to adopt RBM, what benefits they hope to achieve, and how they measure whether their RBM programs are achieving their intended result. Finally, the panelists will discuss existing research on the impact of RBM, including efforts to compare risk-based monitoring to traditional monitoring approaches that are focused on 100% source-data verification.

Discussion Questions:

- What benefits do organizations hope to achieve when deciding whether to adopt RBM?
- What metrics do organizations use to assess the impact of using RBM?
- What has been the impact of using RBM?
    - How has the use of RBM improved efficiency in the trial process and reduced costs?
    - How has the use of RBM affected data quality?
    - Are there instances where 100% SDV and RBM may have been directly compared during the conduct of clinical trials, and what was learned?

Session 6: Synthesis and Next Steps

In this final session, panelists from each of the preceding sessions will come together to discuss lessons learned from across the day and identify key steps that can be taken to improve adoption and effective use of risk-based monitoring approaches in clinical trials.

Discussion Questions:

- What lessons were learned regarding RBM implementation, tools, enablers, and impact?
- What next steps can be taken to promote the adoption, effective use, and systematic measurement of risk-based monitoring?

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