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

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Introduction

The U.S. Food and Drug Administration's (FDA) release of the 2013 guidance document*, Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring*, coincided with the development of new approaches to the monitoring of clinical investigations.[1] Monitoring is an important part of the clinical investigation process and is a crucial component of human subjects protections and data quality management. Traditional monitoring includes frequent on-site visits and 100% source data verification (SDV), a process of examining case report form data and source data to correct transcription errors,[2] but, research has shown that such transcription errors are infrequent and rarely critical to the quality of data necessary for regulatory decision making. In one study, only 1.1% of "critical and noncritical data" required correction through SDV.[3] Given that SDV is also expensive—one calculation suggests it accounts for approximately 25% of the budget of phase 3 trials[4]—widespread interest exists in moving away from 100% SDV and focusing monitoring resources on high yield activities.

Unlike traditional monitoring, risk-based monitoring (RBM) "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 a significant impact on the overall quality of the investigation."[5] FDA is not alone in supporting the adoption of RBM as part of a risk-based quality management system. In 2013, the European Medicines Association (EMA) released a *Reflection Paper on Risk Based Quality Management in Clinical Trials,* which promotes risk-based approaches to quality management and encourages quality by design methodology in trial designs and monitoring plans.[6] The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) *E6 (R2) Good Clinical Practice* guidance, released in 2016, promotes the use of risk-based approaches in a trial's quality management system.[7] Additionally, the 2019 draft ICH *E8 (R1) General Considerations for Clinical Studies* guidance outlines a quality by design approach to clinical trials, which includes the important step of identifying critical to quality factors for each study, which can then drive an appropriate risk management strategy.[8] The FDA followed up on its 2013 guidance by releasing additional draft guidance *A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance to Industry* in 2019.[9]

Sponsors, contract research organizations (CROs), and clinical research sites have begun to adopt RBM with the goal of improving the quality of clinical trials and aligning with recent trends in regulatory guidance documents. On July 17, 2019, under a cooperative agreement with the FDA, the Duke University, Robert J. Margolis, MD, Center for Health Policy convened a public workshop to solicit stakeholder input on the challenges, barriers, and enablers that impact the successful implementation of RBM and what opportunities exist to improve RBM implementation. This paper summarizes the themes captured during the workshop sessions as well as conclusions and takeaways from the day as a whole.

Regulatory Foundations for Risk-Based Monitoring

To begin the meeting, FDA and EMA highlighted the conceptual foundations underlying RBM. Citing the draft of ICH E8 (R1), EMA defined the quality of a clinical trial as "fitness for purpose" where "[t]he purpose of a clinical study is to generate reliable information to answer key questions and support decision making while protecting study subjects."[8] FDA emphasized that RBM is best understood as a part of a risk-based quality management system that includes a prospective risk assessment, a well-designed and articulated protocol and investigational plan, and a risk-based monitoring plan. Achieving a common understanding of RBM concepts is crucial because confusion about terminology among stakeholders can hinder implementation.

Discussion also included ways to achieve a quality clinical trial, with both FDA and EMA referencing the use of quality by design methodology in conducting a prospective risk assessment. Quality by design involves identifying "critical to quality" factors in a study and developing strategies to manage risks related to those factors. The quality by design approach to promoting quality in clinical trials is driven by prospective work rather than by retrospective quality assurance checks. It follows that a study-specific risk assessment should occur during study design, before the start of a trial. Likewise, RBM does not end with a monitoring plan—it extends from preliminary study planning through execution of the clinical investigation.

When implementing RBM, many monitoring strategies can be employed including central statistical monitoring, remote monitoring, targeted SDV, and site visits. A comprehensive RBM plan can include some or all of these monitoring strategies. FDA noted, however, that these monitoring strategies are not inherently risk-based (e.g. a trial is not using RBM simply because it has remote monitoring). Furthermore, given that studies vary, a risk-based monitoring approach should not be one-size-fits-all. Monitoring strategies must be applied in a study-specific, risk-based manner.

During this session, FDA also highlighted the distinctions between the quality of the clinical investigation and regulatory compliance. FDA classifies inspections based on whether the inspected entity was in compliance with applicable laws and regulations. Inspections may also identify significant quality issues impacting data that are not addressed under current regulations; though not considered regulatory violations, these quality issues may still impact the acceptability of data to support regulatory decisions. An analysis of Clinical Inspection Summaries (CISs) was prepared by the Office of Scientific Investigations summarizing the findings from inspections conducted in support of marketing application review. Citing data from this analysis FDA noted that although 19% of CISs had "active recommendations" that required additional assessments related to data quality and human subject protection, these recommendations did not necessarily correlate with Official Action Indicated (OAI) inspection findings. Based on this analysis, FDA noted that industry should focus on improving clinical trial quality through effective risk-based management approaches to maintain data integrity and protect trial participants, rather than focusing on concerns of OAI inspectional findings.

Experiences with Implementation of Risk-Based Monitoring Approaches

The second session of the day contained a discussion of the challenges faced and lessons learned by clinical and academic research organizations, sponsors, and clinical research sites as they implemented RBM. One CRO shared that RBM did not initially prove as cost-effective, or as quality-enhancing, as their organization had expected. Challenges arose in the "order of operations" when implementing RBM. The CRO noted that reducing the amount of SDV would not improve data quality unless central statistical monitoring was first implemented. Similarly, it was difficult to create more cost-efficient processes simply by adding new monitoring tools on top of traditional monitoring approaches. Even as the CRO eventually found success in implementing RBM, the presenter reported challenges including difficulties with change management, concern within the organization about not adequately monitoring studies, and the need to create new metrics to measure success.

An academic research organization offered its perspective on the implementation of RBM. To create global monitoring plans for large multinational phase 3 and 4 trials, the organization drew on principles that included identifying the right patients, giving them the right treatments, collecting the right safety and efficacy data, and preventing Good Clinical Practice (GCP) concerns. The academic research organization found that these principles were the basis for an RBM plan that was well articulated but not overly complicated. The organization also sought input from the FDA on its global monitoring plans and suggested that consulting with the appropriate regulators may be one strategy to address CRO and sponsor concerns about varying international RBM standards.

Sponsors faced many of the same challenges as academic and clinical research organizations, including inconsistencies with how global regulatory authorities handled RBM and concerns that RBM would lead to decreased data quality. Sponsors also reported concerns around remote monitoring, specifically that it might lead to unblinding of data or violate data privacy standards. Confusion also was reported around how to apply RBM methodology to novel trial designs (e.g., basket trials or umbrella studies) and to trials with small sample sizes. In sharing lessons learned, sponsors emphasized that RBM is not a tool but rather is a process and part of a quality management system. To carry out RBM, sponsors found that they needed (near) real-time access to study data and to create new specialist roles to help with key risk and central statistical monitoring.

Much like CROs and sponsors, clinical research sites reported difficulties when implementing RBM. A 2016 survey of sites conducted by the Society for Clinical Research Sites reported that RBM increased site workload but did not increase site perceptions of trial quality. Sites noted an increase in regulatory obligations, workload, resources used, cost, and data monitoring; a decreased relationship with sponsors and CROs; and no changes in data quality, participant safety, regulatory findings, observations during audits, and number of patients seen. More broadly, sites expressed confusion about RBM's purpose and value as well as frustration that they are end-users of RBM but are not always involved in the creation of monitoring plans. Solutions suggested included more training to help sites understand the value of RBM, involving sites in the creation of monitoring plans, and increasing communication between sites, CROs, and sponsors to help sites obtain answers to questions that arise during the implementation of RBM.

A common theme throughout the session was the need for increased communication and collaboration between stakeholders. In the past, confusion has occurred because methods of implementing RBM vary between CROs and sponsors. While organizations, including TransCelerate Biopharma Inc., have worked to standardize RBM implementation (e.g., through the creation of the Risk Assessment and Categorization Tool), the industry is not fully aligned. Various stakeholders proposed solutions, such as the creation of a reference dataset that could improve the validation of monitoring methods. During the open discussion period, one audience member proposed that a certification program for RBM could help standardize understanding and implementation of RBM within the industry. The audience member believed a certification program could allow for flexibility in how RBM was implemented across organizations while allowing sponsors and CROs to feel confident in the validity of the varying methods. Regardless of the solutions employed, stakeholders agreed that addressing inconsistencies and inefficiencies is an important part of successfully implementing RBM going forward.

Analytical Tools and Methods to Support Risk-Based Monitoring

In the third session of the day, the workshop transitioned to a discussion of specific approaches to RBM. As one example, central statistical monitoring was endorsed as a versatile strategy that can support RBM by leveraging data analytics to examine trends across sites and patients, indicate potential fraud, data fabrication, and/or sloppiness in clinical trial conduct. Even in small trials, statistical tools can identify systematic errors (e.g. equipment calibration concerns). When information from central statistical monitoring is conveyed through analytic platforms it can promote the democratization of data by allowing team members without statistical training to identify data trends and visualize risk.

Although central statistical monitoring is a powerful monitoring strategy, it must be conducted in a risk-based manner and corresponding analyses must be designed to fit the protocol. Selecting, for example, too many Key Risk Indicators (KRIs) to include on an analytics dashboard does not necessarily promote the quality of a trial. A representative from a software company warned that analogous to discussions of "alert fatigue" in the medical world too many alerts or notifications on a monitoring dashboard may distract from the most important errors.

Once appropriate triggers or monitoring notifications have been identified, study teams should have appropriate plans for how to respond to them. Stakeholders noted that these triggers or notifications do not always require action; however, they do always require evaluation and decision-making regarding whether action is needed. Organizations should establish plans at the start of trials for how to handle dashboard alerts. When deciding whether or not to act on a trigger, teams should systematically document their decision-making processes. Similarly, when it is determined that an action is needed, teams should not always assume that a site visit is the appropriate action, as alternate forms of communication may be equally or more useful tools for addressing concerns.

Despite the benefits of RBM strategies and tools, including central statistical monitoring, meeting participants reported implementation challenges. CROs mentioned that they are not always involved in the study design process and are sometimes given a complete protocol, limiting their ability to collaborate on the data monitoring components of the risk management plan. Study-specific analytic

reports take time to program into a software system and they may not be ready when the clinical aspects of the trial commence. Similarly, sponsors noted that analytic tools are expensive and not all CROs use the same tools or software platforms, creating confusion between sponsors and CROs.

Additionally, the adoption of RBM practices and data monitoring strategies varies across companies. One informal survey conducted among data managers within the Society for Clinical Data Management noted that some large pharmaceutical companies had just started using risk-based approaches to data monitoring, whereas a small CRO had a more extensive and successful implementation. Others reported that change was slow because of concerns regarding change and regulations, as well as the belief that reviewing everything is the best way to minimize risk.

Later discussions turned to strategies to support the successful implementation of central statistical monitoring and other analytic methods that support RBM. For example, software companies suggested that the deployment of new analytics could be facilitated by standardizing data outputs so that data from different sources and software platforms could be easily integrated. Creating a set of common analytic rules that can be applied across studies also would assist in integration. As analytic tools evolve, they may further enable quality in clinical trials. Data managers speculated that, in the future, advanced analytics could predict risk through machine learning.

The current and future benefits of analytic strategies that support RBM, including central statistical monitoring, are not possible without rapid (ideally real-time) access to trial data. Gaining rapid access to data may pose a challenge, however, because it is not standard practice in more traditional trial monitoring practices. Stakeholders suggested that going forward sponsors and CROs may need to design contracts to require faster transmission of data.

Identifying Enablers to Support Implementation of Risk-Based Monitoring Approaches

During the course of this session, stakeholders identified enablers for successful implementation of RBM. Echoing the first session of the day, stakeholders emphasized the importance of a shared, clear understanding of RBM. Despite reports of initial confusion as to the goals of RBM—a view corroborated by FDA, who noted that companies may believe they have implemented RBM whereas, in the opinion of FDA, they have not—organizational understanding has since shifted. Speakers described RBM as part of a continuous improvement process, where upfront planning is critical to building quality into the research and optimizing the operational success of a trial.

Organizations, including TransCelerate, shared lessons learned when designing RBM processes. TransCelerate emphasized that the first step of RBM is conducting a risk assessment. During the risk assessment, a multidisciplinary team should identify risks, as well as the probability and magnitude of the risks. Other stakeholders noted that critical thinking is the most important tool when assessing risks and is more useful than an overly long, checklist-type process that does not account for variability between trials. RBM is not achieved by using certain tools but rather by applying them in a risk-based manner. Similarly, when implementing RBM, it is important to avoid “Christmas tree monitoring plans,”

where additional monitoring strategies ("ornaments") are appended to existing plans. Instead, traditional monitoring plans should be replaced with RBM plans.

Progress away from traditional monitoring practices and 100% SDV has occurred. TransCelerate presented a survey of its member companies, which found that only 1 of 18 still required 100% SDV. Some panelists felt that in some circumstances, 0% SDV might be acceptable. A software solutions organization suggested that when Source Data Review (SDR) occurs, SDV may be entirely duplicative and that 100% SDV may add risk. Others agreed, noting that SDV may only be useful to RBM when there is a high risk of transcription errors for a critical study endpoint.

Despite the general consensus on the panel that it is important to move beyond 100% SDV, obstacles remain. One audience member noted during the discussion period that 100% SDV is still commonly used among smaller sponsors. Another difficulty in moving away from SDV is its role as a metric used by sponsors and CROs to quantify work, evaluate sites, and drive contract bidding. For example, CRO bids traditionally include a set of services for a price, a process that is not well suited to the adaptive nature of RBM. The industry must establish new bidding practices, which might include assigning prices to given monitoring actions, rather than to the monitoring package as a whole.

Another challenge is evaluating site performance. An audience member wondered how new study teams would be trained and how their performance would be monitored without SDV. Panelists countered that the best way to improve a site's performance is not to increase SDV but rather to increase upfront training. One CRO proposed a strategy to consider risk at a site level might include assigning ratings or rankings to sites. These areas of tension suggest that in order for the industry to move away from 100% SDV, replacement metrics that address site performance and study readiness must be developed and adopted.

The differing industry positions concerning the value of SDV serve to highlight that while the adoption of RBM is at an inflection point, change is difficult. Despite the fact that much work has been conducted to develop RBM and support its implementation, barriers still exist. Some of these barriers are regulatory; although FDA and the EMA are generally aligned regarding RBM guidance, stakeholders expressed concerns that other regions of the world (e.g., Asia) have varying regulatory standards and requirements. Other barriers are cultural; stakeholders reported that organizations are afraid to be the first to adopt RBM due to fear of failure. Senior leadership in larger organizations generally accept the importance of RBM, but there has been more resistance among clinical teams. Small sponsors and small CROs were reported by meeting attendees to be likely to adopt RBM. Finally, procedural barriers exist. One CRO shared its experience implementing RBM and reported a large need for support and training—a need which did not, on average, diminish during 18 months of measurement.

Many stakeholders shared strategies for overcoming barriers. When training site and monitoring staff, suggestions included providing "just-in-time" training, following up with additional education, and offering multilingual training when conducting large multinational phase 3 and 4 trials. Pilot studies may have a role in establishing RBM processes within an organization and may assist in convincing leadership

that RBM is worth any potential infrastructure investments or study timeline delays (e.g., delayed first patient first visit).

Strategies for changing industry culture to support RBM include shifting discussion away from the amount of SDV and toward the avoidance of critical errors in trials. Attendees suggested that education is needed to help study teams understand that SDV alone does not drive quality and that RBM does not increase risk. It is similarly important to destigmatize the concept of risk: to describe a site as having risk is not to say that the site requires FDA inspection or is in violation of a regulation. TransCelerate proposed that the FDA may help address such concerns by emphasizing that the goal of RBM is to avoid systematic error, not all error.

To promote cultural change and reduce fear, many stakeholders called for more collaboration through the sharing of experiences, case studies, and data. Sponsors inquired whether FDA could provide data on how RBM alters regulatory decision-making timelines. Because RBM requires an upfront investment, this information could help make the case for RBM to companies. FDA emphasized it is not possible to isolate RBM's impact on time to approval of a drug from the rest of the regulatory process. Still, data sharing remains an important strategy for sponsors to consider as they continue to improve the implementation of RBM.

Measuring the Impact of Risk-Based Monitoring Approaches

In this session, discussion shifted to consider the strategies for measuring the impact of RBM approaches. In order to systematically implement RBM, stakeholders emphasized that organizations must be able to measure their performance. Traditional metrics, such as rates of transcription errors discovered during SDV, are not applicable to RBM. One sponsor suggested that while measuring the performance of RBM after the completion of a trial is useful, the implementation of RBM would be best served by identifying leading indicators of success. Finding such leading indicators is difficult given the study-specific nature of RBM, which makes comparing and quantifying the success between trials difficult. A 2019 survey conducted by TransCelerate, for example, found that eight RBM metrics[*] were largely reported to be "somewhat useful" by its member companies—no single metric was considered to be particularly useful across studies. One specific challenge within the survey was the difficulty of linking any changes in quality to RBM. TransCelerate shared that, according to the member companies, RBM metrics worked best when they were flexible and responsive to the different processes and monitoring strategies being used.

Scientifically assessing the impact of RBM has been the focus of several academic studies and one presentation during this session highlighted such research. The TEMPER trial studied the use of triggered

[*]The eight metrics used in the TransCelerate survey were average number of major/critical audit findings, percentage of unreported confirmed Serious Adverse Events (SAEs) as compared to total SAEs as discovered through any method, number of significant protocol deviations, average monitoring (all types) cost per site, average interval between on-site monitoring visits per site, median number of days from issue open to close, median number of days from patient visit to eCRF data entry, and median number of days from query open to close.

monitoring, using a prospective matched-pair design to compare the number of major or critical protocol and GCP findings identified during onsite visits to triggered sites and untriggered control sites.[2] When re-consent findings were excluded from analyses, 85.7% of triggered sites were found to have one or more major or critical findings compared to 59.5% of untriggered sites.[2] Other studies, including ADAMON found RBM to be non-inferior to traditional monitoring.[10] The MONITORING study compared 100% SDV to SDV of only key scientific and regulatory data and found little difference; other studies compared triggered SDV to 100% SDV and found minimal differences in the results of primary analyses.[11,12] Taken together, these studies provide evidence in support of the effectiveness of RBM; however, the presenter argued that more research is needed, particularly surrounding the utility of triggers.

During this session, stakeholders proposed various metrics to quantify the success of RBM, including assessing how well the monitoring is implemented, if the monitoring reduced risks, how long it takes to enroll the final patient, and how fast it takes to reach database lock. There is room for future research to determine the validity of these metrics, as well as to identify others. Both the analysis of existing data and the generation of new data can help with the identification of RBM metrics and with the exploration of the utility of triggers.

Sponsors emphasized that utilizing any of these metrics will require rapid access to data. Similarly, advances in monitoring that might allow prospectively predicting problems using machine-learning techniques will require large amounts of data delivered in near real-time. As with other elements of RBM, stakeholders cautioned that it is important to be deliberate when creating metrics and not just measure data points because they can be measured. Although metrics are a necessary tool for RBM implementation, the availability of metrics alone is not sufficient for improving the quality of clinical trials and must be paired with people who can utilize the metrics to make any necessary adjustments to monitoring strategies.

Discussion at the end of this session returned to the importance of RBM metrics in change management and the continuous improvement process. Measuring the impact of RBM is important both to ensure quality trials and to demonstrate to organizations the value of effectively implementing an RBM strategy as part of a risk-based quality management system. CROs noted that quantifying quality would help them better communicate with sponsors regarding the success of their monitoring activities. Metrics also could help organizations consider the “cost of poor quality,” thereby rewarding people who avoid problems rather than fix them after they have occurred.

Finally, although RBM is a relatively new concept, some organizations have been using RBM for several years. The Association of Clinical Research Organizations (ACRO), for example, reported an increase in the adoption of RBM by its members: 61% of trial starts in 2018 included RBM technology, compared to 18% in 2016.[13] Going forward, stakeholders suggested that an RBM maturity model may support implementation throughout the change management process.

Workshop Synthesis

The final session allowed stakeholders to present their perspectives on the workshop in its entirety. Many topics were revisited, including the need for common definitions and understandings of RBM and the importance of focusing on risk-based quality management rather than particular monitoring strategies. Stakeholders reemphasized that technology used in RBM has the potential to democratize data but that to achieve such a goal, analytic platforms require real-time access to data and teams must be trained to evaluate any resulting findings and determine when action is needed.

Another point of emphasis was that effective design and implementation of RBM requires input from a multidisciplinary team. While implementing RBM has led to challenges, stakeholders noted that the challenges are not unexpected. A large percentage of clinical trial funds are spent on data management and monitoring; it follows that changing a large portion of the industry requires a shift in organizational culture along with training and educating a large number of people.

The session also contained a discussion of how clinical research sites fit into the RBM ecosystem. Sites responded to the earlier recommendation of ranking or publicly rating sites and stated that they did not think ranking or rating sites would promote quality in trials. Instead, sites stressed that CROs and sponsors should recognize that not every site is the same and partner with sites to help address challenges. Similarly, sites want to be told what aspects of research are being monitored for a given study. Although other stakeholders worried that sites would then focus all their efforts on those elements, sites countered that if the items being monitored are truly essential to quality, then placing extra focus on them may promote quality.

Finally, stakeholders returned to the idea of an RBM maturity model. Although some organizations have been implementing RBM for years, others have not. There is room to learn from past experiences and share strategies for success. Such collaboration between stakeholders is even more valuable because RBM is not one size fits all—multiple paths to successful RBM implementation exist.

Conclusion and Next Steps

RBM offers a path to update clinical trial monitoring practices, improve data quality and integrity, protect human subjects, and make clinical trials more cost-efficient. Although many organizations have taken significant steps to implement RBM in recent years, challenges remain. Throughout this workshop, as stakeholders shared their efforts with the goal of improving the implementation of RBM, several themes arose as topics for discussion, challenges, and potential next steps.

The first theme involves the need for common standards and definitions of RBM. Stakeholders noted that confusion around what RBM is and how it differs from traditional monitoring has slowed its adoption. Various professional organizations shared frustrations that different companies implement RBM differently and stressed that RBM is not an addition to traditional monitoring but rather a replacement. Stakeholders, including FDA, suggested that some of these challenges in defining and understanding RBM occur because RBM is better understood as a part of a larger risk-based quality

management system. Without an accompanying understanding of risk management principles and the quality by design approach to clinical trials, confusion may persist.

Another takeaway is the importance of change management. Stakeholders across sessions emphasized that RBM is at an inflection point, and change may be difficult. Change management within all levels of an organization, from senior leadership to study teams, is necessary to effectively implement RBM. Meeting participants also shared that smaller CROs and sponsors are generally less likely to have adopted RBM—different stakeholders may be at different points in the change management process, and different educational strategies may need to be employed. The development of RBM metrics will be important to the change management process as metrics can assist in assessing the success of changes, quantifying the impact of RBM, and presenting leadership with a business case for RBM adoption.

Finally, stakeholders identified a need for increased collaboration and communication among sponsors, sites, and CROs. Sharing experiences, case studies, and data may alleviate some of the fears and confusion surrounding RBM implementation. In addition to the communication of existing data, a need exists for research on triggered site visits and how RBM compares to traditional monitoring, particularly as RBM is adopted for use in smaller trials and trials with complex designs. Such research can both help optimize RBM implementation and provide evidence to support a business case for RBM.

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