Introduction

Clinical trials play a critical role in the development and delivery of breakthrough medical treatments. They evaluate which drugs, devices and treatments are safe and effective for humans, and which therapies work best for certain illnesses or patient populations. Successful trials require quality data, protection of patient safety, affordability and speed.

This guide focuses on a modernized, proactive method of clinical trial monitoring called risk-based monitoring (RBM), an adaptive approach that directs monitoring focus and activities to the evolving areas of greatest need which have the most potential to impact patient safety and data quality.

Section 1: What is Risk-Based Monitoring (RBM)?
Backdrop: Challenges and Opportunities for Clinical Trials

Table of Contents
1. What Is Risk-Based Monitoring (RBM)?
2. How Does Clinical Trial Site Monitoring Work Under a Risk Based Monitoring approach?
3. Best Practices for Implementation
4. Research Milestones
5. The Next Frontier of RBM
Section 1

What is Risk-Based Monitoring (RBM)?

Backdrop: Challenges and Opportunities for Clinical Trials

Research conducted by biopharmaceutical companies is moving the needle on scientific discovery and helping patients to live healthier lives. But the clinical trial process is burdened by complexity and administrative costs, so to reduce risk of errors and to ensure faster time to market, more flexible monitoring approaches can be implemented.

On complexity...

Clinical trials are up against a number of modern challenges that make the development of a drug and its delivery to patients more complex than ever. Chief among them:

1. Trial design may make the conduct resource intensive to ensure quality data
2. Complex trial landscape may make it difficult to recruit patients into trials leading to low enrollment rates
3. Strain in balancing randomization across treatment arms
4. Low volume of data as a result of the size of the trial and timeliness of data entry

Quality data is critical to the success of a clinical trial. Poor data quality can result from a number of behaviors:

- Lack of understanding of the protocol (unintentional) or intentional non-compliance
- Carelessness on the part of investigators or sponsors
- Intentional misconduct – frequently motivated by personal gain

These behaviors can produce errors that may impact patient welfare or interpretation of trial results, which can then jeopardize the understanding of the risk-benefit profile, as well as the development of a drug that is eventually marketed to the public.

In other words, reliable trial results mandate quality data.

1 USE FDA

Section 1: What is Risk-Based Monitoring (RBM)?
The Discussion: On-site, Off-site and Centralized Monitoring in Clinical Trials
The Discussion: On-site, Off-site and Centralized Monitoring in Clinical Trials

Traditionally, the pharmaceutical industry has assessed site performance and addressed site risk using On-site monitoring. This approach is carried out by an individual who visits the trial site at regular intervals, e.g., every four to six weeks to ensure everything is running smoothly.

The approach has relied heavily on significant amounts of Source Data Verification (SDV) to provide a certain level of generalized quality control to ensure subject safety and reliable data entry.

But, due to the lack of real-time reporting and the timeliness of data entry, there can be perpetual backlog and delay in the review of site data.

Research indicates that 100% SDV is not effective at identifying material risk.

It’s applied uniformly throughout a trial rather than proportionate to risks.

AND

It’s resource-intensive.

AND

It is a reactive approach, limited in its ability to identify issues quickly and prevent them from recurring.

Advances in risk-based approaches and technology made room for a more rational, adaptive and proactive approach. As a result, there is a movement in the biopharma industry, being advocated by the FDA and, as a result, championed by TransCelerate BioPharma and other leaders, to transition to risk-based monitoring (RBM).

This philosophical shift in monitoring processes primarily uses Off-site and Centralized mechanisms to monitor important study parameters through a holistic lens, and uses adaptive Onsite monitoring to further support site process, subject safety and data quality.

Off-site and Centralized monitoring activities rely on the skills of people, well-defined processes and smart technologies that enable the transition of data into automation, and enable critical actions and decisions. The role of quality by design and robust risk assessment and planning are also essential to the approach.
Benefits of RBM

The principles of centralized analytics are used extensively in other industries to achieve multiple benefits, including improved quality of operations and product, with an associated lower cost. These principles can be effectively applied to pharmaceutical development and clinical trial monitoring through risk-based monitoring (RBM).

While paper-based data collection is a practice that still occurs in clinical trials, the industry is increasingly shifting towards processes that digitize clinical data.

Digitization specifically impacts the earlier detection of data quality issues, making possible a string of actions that weren’t feasible in a paper-based paradigm, most notably, a comprehensive risk-based monitoring (RBM) approach. RBM can involve the entry and storage of digital data, which improves quality by bringing data collection and tracking in real-time, and trends and analytics capabilities to the forefront. Digitization contributes to RBM’s core goals:

1. Ensuring that clinical data is accurate, complete, and verifiable
2. Ensuring the safety of patients in a clinical trial, ensuring the rights and well-being of human subjects are protected

Adoption of an RBM methodology can lead to increases in Quality Data, Patient Safety and Efficiency. Specifically, it can enable:

- **Reduction in Efforts**
- **Focus**
- **Cost Reductions**
- **Data Visibility**
- **Collaborative Approach**

Through centralization and data analysis triggered by risk-based monitoring, clinical trial operations can unleash specific improvements for stakeholders.

What are the specific and important benefits that RBM enables for investigator sites, regulators, sponsor companies and patients?

**SITES**

RBM benefits sites by providing a next generation of services, which in the past were limited to being generated months or years after the site was generated. The sites are provided with automated functions by reducing time spent on administrative tasks, and improves inspection readiness.

**REGULATORS**

RBM benefits regulators by enabling efficient review of data, ensuring alignment with respective guidance documents.

**SPONSOR COMPANIES**

Sponsor companies enjoy more efficient allocation of resources, and patient safety, data integrity and GCP compliance.

**PATIENTS**

RBM helps patients participating in trials by clarifying the focus to critical data points. This improves patient safety, and reduces the time to focus on the patients, since certain administrative issues will be streamlined.

RBM reduces burdens associated with trial monitoring to sharpen the focus on what matters most: the patients, the science and industry innovation.

The TransCelerate Model Approach

The TransCelerate RBM Initiative was one of the first five initiatives established in 2012 for creating more efficient and effective solutions in research and development (R&D). What sets it apart from other efforts, lies in its development of a modular RBM framework that can be successfully deployed and scaled to a collective manner.

TransCelerate’s methodology shifts away from dependence on on-sitemonitoring to instead prioritize and track outcomes through an emphasis on centralized monitoring. This initiative is unique in its approach that focuses on the changing needs of clinical research, which have been the most important to impact patient safety and data quality, and implements Quality By Design (QbD) as a foundational principle.

TransCelerate’s RBM methodology can be adopted by any site organization, and any type or phase of clinical trial. It incorporates risk management as a foundation for ensuring subject safety and data quality. TransCelerate’s RBM methodology promotes several key practices and values that have been defined by TransCelerate and include:

- Building Quality by Design (QbD) into trials
- Early and ongoing Risk Assessment
- A focus on Critical Processes and Critical Data
- Use of Risk Indicators and Thresholds
- Ongoing adjustment of monitoring activities based on the issues and risks that may arise throughout the study

What are the steps a sponsor might take to adopt an RBM model to a clinical trial?

1. **Implement Risk Assessment**

   Trans can conduct a cross-functional risk assessment at the program level, which means identifying the relevant risks that could impact subject safety and/or data quality.

   Trans can also assess risk at the protocol level, which involves evaluating the initial list of risks to assess those that are associated with the protocol level assessment typically relevant in more detailed examination.

   Researchers can use TransCelerate’s Risk and Control Plan (RCP) tool which provides categories and levels of risk by function and considerations specific to risk categories. The RCP helps determine risks that could affect subject safety, data quality, and regulatory commitments, and provides guidance on how and why the risks may be managed.

   Studies are assigned a high, medium or low Overall Risk Level, which may vary across the different stages of the study, the site and the protocol. The Overall Risk Level is based on the determined Overall Risk Level.

2. **Define Critical Data and Processes**

   Monitoring activities can be increased in response to issues and data identified, but increases should be done on a temporary targeted manner with the goal of returning to the standard level of monitoring assigned in the monitoring plan.

3. **Create a Quality and Risk Plan**

   Additional Considerations:

   - Investigations are responsible for their site’s data quality and must partner with Sponsors to address, resolve and prevent issues.

   - Monitoring activities are increased in response to issues and data identified, but increases should be done on a temporary targeted manner with the goal of returning to the standard level of monitoring assigned in the monitoring plan.

   - Channels of communication should be tailored to what is most effective for that particular study.

   1. "We Value Transparency: Clinical Quality Risk Management"
Section 2

How Does Clinical Trial Site Monitoring Work Under a Risk-Based Monitoring Approach?

People, Process and Technology

People & Process

In developing a risk-based monitoring plan, it’s important for teams to consider resource capabilities, as well as the organizational change management required to implement the plan successfully.

Training, coaching and ongoing communication are necessary at all levels of the sponsor organization, associated third-party providers and at the investigational sites. Transitioning to a model which empowers more Off-site and Centralized monitoring activities might require a different set of skills than traditional On-site monitoring activities. Off-site/Centralized monitoring might, for example, require data-focused, analytical skills to help manage risks and identify issues across a site and/or study.

As discussed, the TransCelerate RMM methodology centers on Off-site and Centralized monitoring, with On-site monitoring supplementing where necessary.

KEY ELEMENTS IMPORTANT TO PROCESS:

- Off-site and Centralized monitoring is dependent on the timely entry of data and quality validation.
- Functional oversight and associated quality assurance nuclei within or external to the ABM can be monitored at any point in the study to compensate for changing site or locale.
- Monitoring reports should serve as tools for the team to evaluate the consistency, high level summary of monitoring activities, issues and associated actions.

Enabling Technology and Preferred Attributes

Technology — and by extension, data integration and analytics — are key enablers for efficient implementation of the TransCelerate methodology.

While functional plans are tailored to the available technology in that trial, there are several criteria that hinge on technology in order to efficiently implement TransCelerate’s methodology.

What are those enabling technologies?

In order to improve the risk function efficiency of trials, TransCelerate recommends several preferred system attributes.

What are those preferred attributes?

Section 2: How Does Clinical Trial Site Monitoring Work Under a Risk-Based Monitoring Approach?

RBM Stakeholders: Research Sites and Regulatory Authorities
Section 2

How Does Clinical Trial Site Monitoring Work Under a Risk Based Monitoring Approach?

RBM Stakeholders: Research Sites and Regulatory Authorities

How do the key stakeholders interact with RBM?

Research Sites

One of TransCelerate's primary strategic priorities is to improve the site investigator experience. While Monitoring Plans are enacted by the pharmaceutical company or Clinical Research Organization running the trial, the site plays a critical role in enabling the plan and process.

Both On-site and Off-site monitoring are important to RBM – but with the TransCelerate model relying more heavily on remote activities, it's crucial that sites have solid relationships and communication with the sponsor company throughout the trial lifecycle.

Research sites have varying levels of experience, quality and technology available to them. Previously, sponsors used a "one-size-fits-all" approach to monitoring. Now, those varying levels are taken into consideration when developing a Monitoring Plan – which benefits the site by being tailored to its attributes, performance and needs.

As RBM evolves and industry knowledge and experience deepens, sites' use of technology, training and data-collection will also likely evolve. This will benefit the industry at large by modernizing investigator site capabilities in a clinical trial.

Regulatory Authorities

In 2011, the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the United Kingdom's Medicines and Health Products Regulatory Agency (MHRA) released guidance papers on RBM, showing their support of the practice, and recognizing some of the mounting concerns attached to clinical trials.

In 2013, the FDA issued additional guidance on RBM, this time declaring its ability to better ensure subject safety and study quality compared with On-site and SDV approaches. The FDA wrote that the volume of challenges to clinical trial oversight – particularly increased variability in clinical investigator experiences – combined with new technologies, present opportunities for new monitoring approaches.

By endorsing new monitoring approaches, the FDA is helping propel more widespread adoption of the RBM methodology.

TransCelerate cites ensuring regulatory compliance as a critical part of the IQRMP. In aligning quality management plans across identified risks and defined Critical Data and Processes, cross-functional study teams are able to ensure appropriate plans are in place to effectively monitor, manage and mitigate key risks as outlined by the regulatory authorities.

Section 3: Best Practices for Implementation

Responsibilities Within a RBM Plan
Responsibilities Within a RBM Plan

A comprehensive risk-based monitoring (RBM) plan has the potential to predict, control and prevent where possible areas of risk that can derail a clinical trial. Successful adoption requires that each member of the clinical trial team has a clear understanding of their roles and expectations from the outset of the trial.

Development and implementation of a strong RBM plan requires expertise from multiple functions; moreover, the shift toward On-site, Off-site and Centralized monitoring relies on the skills of team members and the well-defined roles that they must work within. In this section, we’ll look at specific responsibilities associated with each type of monitoring.

How do certain responsibilities and activities contribute to RBM?

RBM requires the cohesion of multiple roles, working together toward the common goal of proactive risk assessment. Functional roles involved, beyond the monitors, are data managers, statisticians and medical staff. The below are typical activities falling under each category. When conducting RBM activities, sponsor companies should consider how these new responsibilities may either call for new roles or tie into existing ones.

CENTRALIZED MONITORING

» Monitoring data quality and critical data reporting
» Ensuring proactive and early identification of quality, safety and operational risks based on the continuous monitoring of data and the risk indicators
» Tracking site performance metrics
» Triggering proposed site contacts and on-site visits based on issues that are identified

In the various monitoring activities, individuals must make sure that sites are adhering to the protocol, improving the likelihood that a sponsor company is going to have interpretable results from a study.¹

Additional Findings on Responsibilities

In the second quarter of 2015, TransCelerate conducted a blinded survey of its participating Member Companies to ascertain best practices associated with Centralized monitoring and feedback on people and processes.¹

Responses uncovered skills and competencies considered essential to the Centralized monitor role.¹ Those include:

1. Clear communication
2. Leadership
3. Knowledge and experience of site operations and data management
4. Keen comprehension of the assessment and management of risks, including the ability to analyze aggregated data and interpret risk indicators to evaluate site performance and data quality

In most instances, individuals performing Centralized monitoring activities were recruited from internal departments of the sponsor company, and included people with experience in clinical operations, data management, statistics, quality or systems support. Some Member Companies reported having created a new role specifically for the Centralized monitor, while others assign the key responsibilities among existing roles.

Overall, the survey results suggest that sponsor companies feel that clinical science/medical, data management, statistics, clinical operations and pharmacovigilance functions all must work collaboratively to establish a cohesive process for managing clinical trial risk effectively.

Section 3
Best Practices for Implementation

Risk Indicators and Thresholds

Risk Indicators and Thresholds are critical elements to the successful implementation of risk-based monitoring methodology into a clinical trial. So, what is a Risk Indicator?

A Risk Indicator can be qualitative (for example, a site monitor’s assessment of site quality) or quantitative (information that is used to monitor identified risk exposures over time, and are in many cases determined by comparing across programs, protocols, countries or sites, and are predominately used at the patient level).

TransCelerate created a collection of Risk Indicators that it contemplated would be monitored Centrally or Off-site on an ongoing basis – which would allow for more rapid detection of possible issues to either further investigate or mitigate.

TransCelerate highlights multiple Risk Indicator categories to help site personnel develop an optimal RIM plan.

TransCelerate conducted a blinded survey in the fourth quarter of 2016 on Risk indicators and associated benefits, which informed a Risk Indicator Library composed of more than 500 Risk Indicators. From this library, clinical trial operators can choose and adjust Risk Indicators specific to the above categories, and apply them to their clinical studies.

As technologies and methodologies evolve, new Risk Indicators will be identified in accordance with those advancements. Moreover, in the RIM model becomes more commonplace, the potential to test new Risk Indicators and determine their utility compared to established Risk Indicators will grow.

How do Thresholds play into this?

Thresholds are the level, point, or value associated with a Risk Indicator that will trigger an action. Thresholds can aid in decision-making, data quality, and GCP compliance.

Thresholds can be adjusted depending on the needs of the study to be either more or less stringent in how they report that study.

When establishing a value for a Threshold, consider whether to assign a relative weighting to each Risk Indicator – as certain risk, and Risk Indicators, could be deemed more important than others. This can be useful in determining the types of actions that need to be taken in response to a Threshold being exceeded.

**EXAMPLE:** In one study, the subject recruitment and discontinuation Risk Indicator could carry greater importance (greater weight value) than issues related to data quality. Subject recruitment and discontinuation Thresholds therefore can be given greater weighting and require more immediate attention than data quality Thresholds.

Actions after a Threshold is reached:

When a given Threshold is reached, a decision needs to be made regarding the appropriate action to take. The choice could be as simple as continuing Centralized or Off-site monitoring for potential trends. If the event is more serious, immediate investigation may be warranted. Actions are predominantly on the site level, and not on the trial level. Examples of actions for Thresholds include:

- Assessing other types of data trends
- Contacting the site to gather additional information
- Visiting the site to assess documentation on-site that cannot be made available remotely

Once it is determined, via the Threshold, that a risk requires some form of mitigation, a decision should be made as to whether the solution may be accomplished remotely or require an on-site visit. If possible a remote mitigation is preferable because it can be done right away, as opposed to waiting for an On-site visit to resolve. The sooner it is addressed, the higher chance of preventing recurrences.
Technology Guidance

Technology – and its ability to support data integration and analytics – is a key enabler for efficient implementation of the TransCelerate RBM methodology. The availability of a technology solution would be foundational in allowing an organization to fully implement the RBM concept to scale.

Before jumping into a new technology, however, companies need to know how it will be used in practice. Sponsor companies must understand the technology available and how it will integrate with the roles and processes set out by their RBM plan. Once organizations understand the impact that technology will have on their operations, they will be better prepared to move forward in adoption.

According to the results of a blinded survey, TransCelerate Member Companies that have implemented RBM have introduced a broad range of technical solutions – some introducing advanced technologies, others utilizing more basic software solutions that leverage their existing systems.

What is key is that technology used for RBM is designed to support a directed, data-driven, risk-based approach that provides data from multiple sources, so that users can access the information when there is a need to adjust the related monitoring activities.

What are some values and elements ideal to RBM technology?

What are some specific types of technology systems that a RBM methodology may integrate?

Future technology solutions would need to combine clinical trial data sources and operational systems such as clinical trial management systems, to supply the necessary data for predictive analytics.

Since RBM is evolving, successful technology solutions selected and implemented now should also be able to evolve.
Data Integrity

According to the World Health Organization’s Guidance on Good Data and Record Management Practices, data integrity is the degree to which a collection of data is complete, consistent, and accurate throughout the data lifecycle. Collected data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices.

The effectiveness of Off-site or Centralized monitoring requires data to be entered in a timely manner and be remotely accessible. In other words, **timely quality data is at the heart of a successful RBM strategy.**

To facilitate RBM and generate Risk Indicators, data from multiple sources would need to be integrated into a common platform. Moreover, to enable data integration and include data from other data providers – such as CROs – as well as reflect ongoing changes to RBM strategies, the RBM plan should allow for a flexible data model.

What are some key capabilities that will support data integrity and risk assessment success?

1. **A source agnostic data model that can be mapped to a source system data model**
2. **Ability to map data into a format that enables efficient generation and management of Risk Indicators and metadata management**
3. **Features that enable the defining and monitoring of data validation – which will help support data consistency and integrity**
4. **Contains mechanisms for mapping and aligning key data as part of its integration components, namely the ability to harmonize the data to a common target**
5. **Extensive data sourcing capabilities, with a scalable infrastructure that supports multiple integration formats and can integrate with internal systems within a corporate firewall**
6. **Maintained with a full data lineage that traces each data point from its origin through data integration to its usage in the user interface and Risk indicators**

Additional information on technology capabilities can be found in the TransCelerate paper, “RBM Update – Technology Considerations Part 2.”

RBM solutions offer companies a level of data visibility that didn’t previously exist – an aggregated, organized view of data that can help trials reach their clinical endpoints fast and safely.
Section 3

Best Practices for Implementation

Metrics

In implementing a RBM plan, it's important to define metrics in order to measure success. According to the TransCelerate model, key metrics measure changes in quality, timeliness of data collection and query resolution, and efficiency of trial operations affected by RBM, on an ongoing basis and after the closure of a study.

**QUALITY**

The number and classification of major/critical audit/inspection findings per audited site, number of significant protocol deviations per site

**TIMELINESS**

Average number of days from data entry to initial monitoring, median number of days from visit to CRF data entry, median number of days from query open to close

**EFFICIENCY**

Average monitoring (all types) cost per site and average interval between on-site monitoring visits per site

According to a blinded survey, TransCelerate sponsor companies that have implemented RBM have reported using several additional metrics to evaluate Centralized monitoring success, including data quality, frequency of On-Site visits, protocol deviations, serious adverse event (SAE) reporting rates, and site audit findings.

Centralized monitoring, as proposed by TransCelerate, is still new. A great deal of insight has been gleaned thus far – but there are many more insights and lessons to come. As the industry further adopts RBM practices into clinical trials, results and metrics will continue to inform a movement towards RBM.
Section 3

Best Practices for Implementation

Pace of Adoption

While this is a year of critical inflection and important evolution for the biopharma companies leading the charge on risk-based monitoring, it will be several more years until RBM is considered “business as usual” for other organizations. If the industry is to see a widespread uptake in Centralized monitoring, the following areas will likely need action and change:

- Advanced tools and technology to catch up with the needs of companies
- Budget to purchase the new tools and technology, as well as to provide for the installation timelines
- Training for internal auditors and agency inspectors
Section 4

Research Milestones

Member Research

Since the launch of the Risk-Based Monitoring (RBM) initiative, TransCelerate Member Companies have conducted extensive research to determine the efficacy of its model RBM methodology, as well as uncover new findings and implications. These publications and updates represent the learnings and evolution of the RBM methodology over time.

In the interactive graphic below, scroll over each icon and hold your mouse there to read a summary of the research paper; clicking on the icons will take you to the original publications.

- Risk-Based Monitoring Methodology Position Paper, May 2013
- TransCelerate RBM Update – Volume I, January 2014
- TransCelerate RBM Update – Volume II, July 2014
- TransCelerate RBM Update – Volume III, November 2014
- TransCelerate RBM Update – Volume IV, June 2015
- TransCelerate RBM Update – Volume V, January 2016

Section 4: Research Milestones

Member Pilots
Section 4

Research Milestones

Member Pilots

Through TransCelerate’s research on the RBM methodology since the release of the Position Paper in 2003, TransCelerate Member Companies have voluntarily piloted several programs aimed at testing the efficacy of certain elements of RBM. Below, we outline several key pilots and their high-level findings.

FDA Pilot Review

The FDA signaled interest in receiving data that would show if the methodology was effective. TransCelerate arranged for submission, review and feedback on RBM/Monitoring pilots for up to nine studies with the FDA. For the pilot study monitoring plans that were submitted, common areas of feedback received from FDA include:

- Ensuring cross-functional participation
- Providing rationale for overall risk determination of study
- In addition to areas sponsors had already focused on (e.g., subject eligibility, endpoint ascertainment, etc.), ensuring there is focus on:
  - Discontinuation/interruptions/Termination
  - Study drug compliance with dosing regimen
  - Adjudication process/identification of events

Quantitative Performance Metrics

TransCelerate piloted a program to study quantitative feedback to better understand how RBM is working. As published by the TransCelerate RBM team, TransCelerate used a core group of eight metrics focused on quality, efficiency and cycle time, and on a quarterly basis a third party collected metrics from Member Companies where RBM was implemented and disseminated aggregated results on a blinded basis. At least ten companies have implemented RBM methods in order to evaluate the methodology. The eight specific metrics used are outlined below:

1. Average number of major / critical audit findings per enrolled site (qualify)
2. Percentage per site of unreported, confirmed severe adverse events (SAEs) compared to total SAEs (qualify)
3. Significant protocol deviations only per treated subject / total number of deviations / total number of subjects for the amendment (quality)
4. Median number of days from query open to close (cycle time)
5. Median number of days from query open to close (cycle time)
6. Average number of days from data acceptance to final data transfer
7. Average number of days from data acceptance to final data transfer
8. Average number of days from query close to close (cycle time)
Section 4

Research Milestones

External Literature Search

Risk-based monitoring has been extensively examined by leaders and organizations throughout the pharmaceutical industry. In this section, we’ll provide links to some key literature that is helpful in understanding RBM and its impact on clinical development.

U.S. Food and Drug Administration (FDA)

Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring

European Medicines Agency (EMA)

Reflection Paper on Risk Based Quality Management in Clinical Trials

Medicines and Healthcare Products Regulatory Agency (MHRA)

Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products

Clinical Trials Transformation Initiative (CTTI)

Clinical Trials: Rethinking How We Ensure Quality
Section 4
Research Milestones

Publications

Several RBM studies conducted by TransCelerate leadership have appeared in industry publications since the launch of the initiative. Those publications are detailed below.

1. **Defining a Central Monitoring Capability: Sharing the Experience of TransCelerate BioPharma, Part 1**
   - DAIA Therapeutic Innovation & Regulatory Science (TIRS), September 2014, vol. 48 no. 5

2. **Technology Considerations to Enable the Risk-Based Monitoring Methodology, Part 1**
   - DAIA Therapeutic Innovation & Regulatory Science (TIRS), September 2014, vol. 48 no. 5

3. **Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials**
   - DAIA Therapeutic Innovation & Regulatory Science (TIRS), September 2014, vol. 48 no. 6

4. **TransCelerate Risk-Based Monitoring Technology Considerations Part 2**
   - December 2015

5. **Defining a Central Monitoring Capability: Sharing the Experience of TransCelerate BioPharma’s Approach, Part 2**
   - DAIA Therapeutic Innovation & Regulatory Science (TIRS), 2015

   - DAIA Therapeutic Innovation & Regulatory Science (TIRS), 2015

7. **Statistical Monitoring in Clinical Trials: Best Practices for Detecting Data Anomalies Suggestive of Fabrication of Misconduct**
   - DAIA Therapeutic Innovation & Regulatory Science (TIRS), February 2016

Section 5: The Next Frontier of RBM
Category 1: Management of Technology Solutions
Section 5
The Next Frontier of RBM

Category 1: Management of Technology Solutions

Sponsor companies implementing TransCelerate’s RBM methodology have observed that success of RBM is predicated on a combination of the right people, processes and technology. Since RBM technology is still relatively new and rapidly changing, successful technology solutions will likely adapt and evolve to meet the needs for future clinical trial environments. In other words, it’s important for the players enacting RBM plans to consider what technology products can offer right now, as well as what they can offer in the long-term.

Moreover, cost/benefit considerations of new technologies will undoubtedly affect companies’ evaluations of new solutions that will enable efficient delivery of the right information to the right person.

Right now, RBM relies on technology to support activities related to:

1. Risk assessment and cross-functional risk mitigation planning
2. Risk indicator data review
3. Data integration
4. Risk and issue tracking; management and analysis

Ideally, optimal RBM systems in the future will excel at each of these areas. But as the needs around these activities evolve, companies will need to support scalable implementation. Therefore, multiple technologies may be needed now and in the near future to achieve a holistic system solution. This means that it will be important for RBM systems to be able to integrate with independent systems that complement it.

What are some capabilities and processes that may change due to new technology?

As RBM continues to evolve, and as the industry more widely recognizes and adopts proactive risk assessment, technological support will also almost certainly evolve.

Section 5: The Next Frontier of RBM
Category 2: Integrating Change Management
Category 2: Integrating Change Management

Change management is the practice of aligning values, culture, people and behaviors to new modes of operation that will reshape an organization. A practice that’s applied to corporations across all industries and disciplines, successfully integrating change management into RBM adoption will be critical.

Addressing challenges and deviations from the outset of a RBM plan is important to efficiently manage roles and expectations throughout a trial’s lifecycle. This includes educating and involving new and potential adopters about the nuances of RBM, debunking myths surrounding RBM, and creating awareness campaigns and comprehensive training tailored to key stakeholders. Essential to efficient adoption of RBM is a shared understanding of terminology, scope of tasks, and roles and responsibilities across the entire stakeholder ecosystem.¹

Let’s explore what change management could look like for key trial players.

¹ Meeker-O’Connell. Update on clinical trials transformation initiative (CTTI) quality-by-design project. DA Quality Risk Management Conference 2012, Philadelphia, PA.
Category 3: Managing Guidance and Requirements from Health Authorities

Globally, inspectors within health authorities have differing opinions on RBM and may set different expectations during inspections. We hope to see alignment across agencies in order to prevent the creation of complex and country-specific RBM processes. Further, cross-agency alignment will increase compliance while reducing fears around inspection findings and rejection of application, since interaction with RBM will be more systemized.

Further, there is an International Council for Harmonisation of Technical Requirements for Human Use (ICH) E6 guide that will be published in the future and which may encourage companies to implement RBM over time.

More clarity is needed on RBM documentation requirements; right now it is unclear which RBM activities and information (e.g., issues, actions, remote data reviews) should be documented where (e.g., in reports, Trial Master File). We predict that in coming years, as RBM implementation becomes more commonplace, we’ll see external communication and accessible knowledge banks when filing with health authorities.

RBM focuses on errors that matter, not error-free research. We hope to see this key differentiator emphasized and supported by agencies. Some agencies, such as the US Food & Drug Administration (FDA) and the UK’s Medicines and Healthcare Products Regulatory Agency (MHRA), have released guidance on RBM – reflecting that they actively support the model and are taking actions to establish RBM training for inspectors. Still, there is ample work needed to get additional health authorities on board, as well as establish a more RBM-friendly and consistent training.

As regulatory guidance evolves and becomes increasingly prescriptive around RBM, a natural outcome will be the adoption and increased use of RBM and Centralized monitoring activities.

Section 5: The Next Frontier of RBM
Category 4: Identifying the Right Metrics
Category 4: Identifying the Right Metrics

A robust set of metrics would greatly help to properly assess the benefits of RBM implementation in the long-term. The definition of an RBM output considered “acceptable” needs to be defined by each sponsor company and the sites with which it works based on their experiences implementing RBM plans, combined with input from health authorities. The value of Centralized monitoring and the pathway to predictability of RBM will be enabled by this definition of, and agreement within the organization, on critical success factors.

In its RBM Position Paper, the TransCelerate team developed and published eight core metrics in the categories of quality, timeliness and efficiency, but whether these will become widely accepted within the industry or if there will be improved ways to measure RBM impact remains to be seen.

Metrics can be complex and need to be carefully developed, particularly when being compared to baseline data. Sponsor companies obviously may consider additional measurements such as:

- **Increased Data Quality**
- **Reduction in Compliance Risk or Increased Fraud Detection**
- **Better Relationships with Sites**
- **Cost Efficiencies**

With expanding implementation of RBM to broader reaches of the industry, organizations will have the ability to measure these and other performance metrics in a macro rather than anecdotal way, and make adjustments to RBM methodologies as appropriate.

Key to this is encouraging sponsor companies, investigative sites, CROs and technology companies to openly publish and share success and failure of various RBM models and technological solutions. By sharing results, we will move the needle on RBM metrics. And by utilizing metrics, we will improve our understanding of, and success with, a holistic and proactive RBM system.

TransCelerate’s RBM Initiative is continually evolving, so additional content and materials may be added to this guide in the future. Please stay tuned and stay connected for future updates!
Section 5

The Next Frontier of RBM

GLOSSARY: Key Terms Defined

- Centralized Monitoring
- Critical Data
- Critical Processes
- Integrated Quality and Risk Management Plan (IQRMP)
- Monitors
- Off-site Monitoring
- On-site Monitoring
- Overall Risk Level
- Quality
- Quality by Design (QbD)
- Quality Data
- Quality Risk Management
- Risk
- Risk Assessment
- Risk-Based Monitoring
- Risk Indicators
- Source Data Review (SDR)
- Source Data Verification (SDV)
- Thresholds

2. US FDA
3. US FDA, Guidance for Industry – Quality Risk Management
Section 6

RBM Toolbox

Initiative Resources

Overview Materials

This top "Overview" section contains materials that will provide a reader who is not acquainted with RBM Methodology an overview. The best place to start is to read The Original Position Paper or the Informational Materials. The Updates will provide the reader with additional updates about the Transcelerate RBM Initiative over a few years.

- Original Position Paper
- Informational Materials
- Updates I
- Updates II
- Updates III
- Updates IV

More Detailed Materials

Once you've familiarized yourself with the RBM Overview materials above, the "More Detailed Materials" section below will provide additional details on the topics specified.

Risk Planning and Assessment

Monitoring

Data Quality

Technology

Metrics