White Paper

Transformational Risk-Based Monitoring: Running Faster, Smarter Trials

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Introduction

The need for virtual trials has never been greater than it is now, in the time of COVID-19.

It is critical for clinical teams to harness the most advanced technological innovations in order to keep clinical trials on track and to respond to the growing need for decentralized trials and the accompanying technological developments to ensure safety and compliance.

Today's clinical trials are light-years away from the paper-heavy models in the past and have improved dramatically even since the first "virtual" trial run by Pfizer in 2012. As the life science industry seeks to transform clinical trials, it is embracing new technology using a multitude of data sources, from sensors to electronic reported outcomes to telehealth interactions, in search of ways to propel clinical studies to a higher level of efficiency, enhanced patient safety, quality and superior outcomes.

The cornerstone of ensuring the viability of cloud-based decentralized trials is the ability to assess and monitor risk. Risk assessment needs to be holistic in its approach—from molecule to market—so that all potential risks can be considered as part of the management of the whole study. Risk-Based Monitoring (RBM) contributes to better quality control and data accuracy and is considered the premier strategy for upfront trial planning, risk indicator identification, and the implementation of efficient approaches to trial monitoring.

How to reduce protocol risk

It is impossible to consider monitoring risk without first assessing it. The evaluation of risks will inform the monitoring strategy and have a direct impact on ensuring patient safety and trial data reliability.

As the processes and data that are essential to the study are identified, careful consideration needs to be given to the probability of errors, how they might adversely affect the study, and how they could be identified and managed throughout the course of the trial.

DOCUMENT ACTIVITIES

In developing an organized approach to monitoring clinical trials, a project-specific risk plan is created, building in configurable, Key Monitoring Points such as threshold, milestone, or event-based Key Risk Indicators (KRIs), Critical Data/Processes (CD/Ps), and Quality Tolerance Limits (QTLs). For each such Key Monitoring Point identified, monitoring and mitigation plans are created, with appropriate justification, documenting the need for choosing specific strategies for risk management and mitigation.

Considering the role of central monitoring teams and taking into account the perspective of data managers, site monitors, medical monitors, etc. will help expand insight into their distinct areas of concern, and overall help structure a complete trial risk assessment plan, conveying the full spectrum of potential trial risk. Leveraging the services of a CRO with a depth of expertise in the specific therapeutic area being studied also minimizes risk.

TRIAL COMPLEXITIES

Considerations should include:

- Determining if the investigational product itself requires specific temperature control or other special handling requirements and whether the supply chain is nimble and robust
- Assessing clinical endpoints as to whether they are a composite of lab/safety data along with clinical outcomes assessments and determining how the monitoring functions will detect and address any missing data
- Management of a large number of 3rd party vendors

Considerations before conducting a risk assessment

- Assess and utilize current resources
- Identify and train multifunctional lead roles within the organization who already assess risk
- Choose clinical operations professionals, or those with a clinical background, who understand the reasons why certain topics may be of concern
- Select senior-level study managers with the discernment skills to parse critical from non-critical topics

The right technology partner can help fill in the gaps with solutions designed to assist in decentralized risk assessment and detection efforts, and in every aspect of risk monitoring activities throughout the clinical trial.

Begin in advance

It is wise to start the risk assessment while still in the early stages of the investigational product formulation, before the protocol is finalized. In the development stage, begin to devise ideas about the potential for error and identify areas that may represent risk.

As studies become more complex and protocols may have multiple endpoints, trial enrollments grow increasingly difficult. Implementing a risk plan early on in the trial enables guidance through the steps necessary for determining study-specific thresholds.

Catching up on risk assessment

If for some reason a risk plan is not established at the beginning of a trial, study teams and trial data quality would still benefit from completing the risk assessment and establishing a risk mitigation plan when the study is underway. Predictive analytics integration can help anticipate issues, such as which sites are likely to exhibit high levels of protocol non-compliance, and which subjects are likely to experience adverse events.

Re-visiting risk assessment is important too. Proactively applying the lessons learned while conducting the critical trial to update risk assessment and mitigation strategies can enhance trial outcomes.

Risk documentation

FDA regulations require that companies document what is important. This includes information and risk potential related to trial endpoints, patient safety, informed consent and the reliability and validity of the data. Documenting these cross-functional risks in one central place is of key importance as the trial progresses in order to remain in compliance.

Gone are the days when monitoring data via source data verification (SDV) was the only mitigation strategy. Much of our data comes directly from the source via laboratory integration, ePRO and sensors. Determining a complete, near real-time risk landscape requires effective aggregation of the data to allow for early signal detection and the propagation of risk-mitigation efforts via an integrated management system. Now machine learning (ML) is assuming the role of effective anomaly detection, due to its ability to scan enormous amounts of data and organize it in a meaningful way.

HOW AND WHAT TO DOCUMENT

- **Document the risk:** what it is and how it is being measured
- **Document how the risk** will be tracked and mitigated
- **Utilize a fully electronic risk assessment tool** with the ability to trace and audit monitoring plans to be compliant with regulatory guidance

Challenges in traditional monitoring

Traditional monitoring, composed of 100% SDV, is time- and labor-intensive and represents as much as 30% of overall trial costs. Siloed and unstructured data from disparate sources make it difficult to identify trends, risks and outliers early on, causing concerns regarding patient safety and presenting integration challenges for data management.

These liabilities lead to increased costs, poor data quality, and a dearth of actionable data that contributes to trial delays.

Former approaches to centralized monitoring presented challenges due to “islands” of expertise, such as data management and site monitoring, preventing the ability to see the full picture from a data, subject or operational control perspective, throughout the trial.

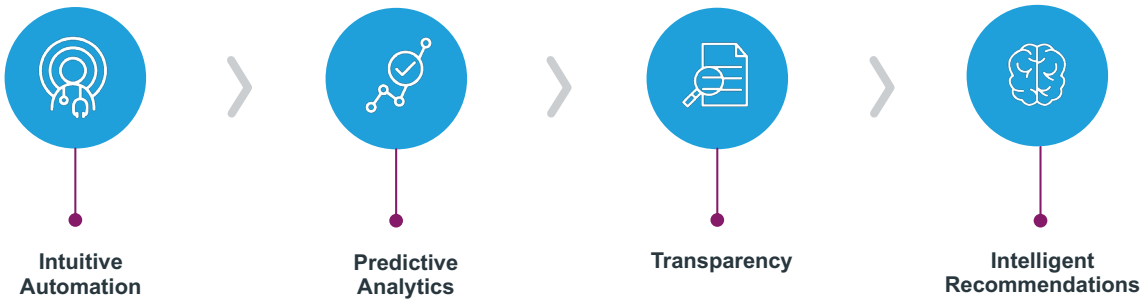
BARRIERS TO RBM ADOPTION

Many life science companies are implementing RBM solutions, but many do not have the experience and/or technology necessary to do so effectively. Change management is critical to realizing the benefits of RBM, in order to develop new workflows supported by integrating innovative technologies and multiple data sources.

Centralized monitoring: a dynamic model for trial execution

Today's centralized monitoring is at the heart of every RBM strategy, but RBM also requires the elements of planning and risk assessment, project-specific monitoring, and a centralized, risk-based, data-driven review of all data.

Centralized monitoring and RBM streamline efficiencies and create a holistic view to reduce the silos that prevented a full picture of the trial risks. Well-executed centralized monitoring can manage the dynamic codependence within a risk-based trial, enabling responses to signals from any of these vertical areas of expertise.



Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

Reviews that may include statistical analyses of accumulating data from centralized monitoring can be used to:

(a) Identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations

(b) Examine data trends such as the range, consistency, and variability of data within and across sites

(c) Evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems

(d) Analyze site characteristics and performance metrics

(e) Select sites and/or processes for targeted on-site monitoring

This excludes traditional data management activities and traditional medical safety monitoring reviews.

A highly adaptive approach

In order to prove effective and remain in compliance, the RBM solution needs to embrace the entirety of the organization's unique clinical operations requirements, and utilize a technology platform that brings key data and processes together in innovative ways that help mitigate overall trial risks.

Powerful algorithms enable central monitors to drill down into site-level, subject-level, and study-level risks and empower them to take optimum preventive and corrective actions. Carefully designed RBM technology can help Central Monitors to propagate issues from the subject level to site/region/study as a broader mitigating action may be called for. This type of innovative platform provides a quick view of outstanding alerts, helps with optimal management of monitor workflows, and provides an audit trail of actions to facilitate regulatory reviews.

Technological transformation

IMPLEMENTING CENTRALIZED MONITORING ANALYTICS

The use of advanced analytics through artificial intelligence and machine learning models can help identify site risks and patient outliers across multiple attributes to help monitors make more informed decisions. Used with purpose-built technology, these tools can help identify issues with study quality and patient safety earlier, so they can be prevented or mitigated.

Advanced Analytics provide a composite site ranking for holistic risk assessment at sites

Predictive Analytics identify which sites are at high risk of protocol and performance non-compliance

Machine Learning identifies which subjects are at potential safety risk with high outliers in lab analytes

The four essential components of RBM

1) RISK ASSESSMENT PLAN

The sponsor/CRO performs the protocol risk assessment, which includes the identification of critical data and processes and produces an optimal monitoring strategy using:

- Protocol-specific risk plans
- CD/Ps
- Monitoring and mitigation plans
- Therapeutic area/indication risk plan templates
- Configurable KRIs and Thresholds, and QTLs

2) DATA INGESTION AND SURVEILLANCE

A site- and patient-level review is performed, using advanced and predictive analytics to identify trends and outliers. This includes continuous review of data, sites and risks. The four pillars of data surveillance are:

Subject-level data review and early signal surveillance

A holistic subject review improves patient safety, identifying issues earlier

Key risk indicators (KRIs) and alert management

Identifying and managing site performance issues enables reduction of risk throughout the study

Targeted site support

Improves site-level data flow and assists with visit preparation by CRAs for increased study compliance

Predictive and advanced analytics

Provides statistically driven insights for site, study and project management to proactively identify risks and mitigate issues

3) DYNAMIC MONITORING

Onsite monitoring: Source data review, source data verification, informed consent process review, investigational product and file review

Remote monitoring: Site process review of how assessments are obtained for critical data, data entry, data cleaning, enrollment discussion, event capture and documentation

Centralized monitoring: Covering end-to-end, real-time patient case report forms and critical data

4) METRICS AND ANALYTICS

Configurable outcome and operational reports

Configurable dashboards for high-level insights across studies, sites, and subjects

Analytics and trend analysis for more precise, transparent reviews

Audit trails to track all system transactions

Case study in centralized monitoring

This case study in monitoring patient data used machine learning to identify duplicate subjects and outlier patients through lab tests and vital signs. New algorithms were built to help with day-to-day monitoring of subjects.

Analyzed records	*10,008 records were analyzed in 37 seconds; 1,230 duplicates discovered*	Machine learning was used to arrive at best rules to automatically find similar records in dataset
Identification of outliers	*> 85% accuracy in lab test identification of outliers (small sample); with scale the expectation is ~ 95%*	Proposed a dissimilarity measure to quantify the differences between subject records for flagging as outliers
Detection of vital signs	*88.9% accuracy to detect the vital signs outliers effectively*	Identified subjects with large or small variations from baseline

How does RBM impact site monitoring teams?

The key emphasis in clinical trials is on upholding the highest quality standards. With this focus, technology that provides greater efficiency and enhanced data quality can certainly improve outcomes and transparency.

When properly implemented, technology also frees up monitoring teams to use their expertise:

- Engaging in deeper, more analytical thinking
- Having more time to devote to developing relationships with sites
- Focusing on how to further improve productivity

Technology designed for monitors can help empower CRAs to perform high-value tasks while streamlining workflow, eliminating technology burden and improving efficiency. An optimal RBM tool should also allow seamless data integration across mobile devices and help ensure compliance of site visits and reporting, as defined by the protocol.

Defining the ideal RBM technology

A comprehensive RBM solution would offer an end-to-end, patient-centric platform with an all-inclusive data infrastructure, seamless connectivity and intuitive design that can serve to drive faster, more efficient trials.

The solution should be configurable and scalable—to accommodate all studies from emerging BioPharmas to large, global trials in one integrated application. Ideally it would be interoperable, to allow seamless connectivity with legacy systems. The inclusion of AI and ML facilitate flexible business models and allow for predictive intelligence to proactively assess and prevent risks.

Transparency is key, so the model technology would have intuitive automation and provide intelligent recommendations and insights so sponsors can improve their data quality and integrity. Automated planning, intelligent alert management, and real-time analytics increase productivity and further enhance efficiency.

How the ideal RBM technology benefits stakeholders

REDUCES RISK AND COST

- AI/ML-enhanced applications provide better data analysis
- Intuitive workflows allow for faster, more informed decisions
- Interoperable technologies work together and with 3rd party applications

RBM IMPROVES STUDY QUALITY

- Lowers error rate
- Reduces aged queries and missing pages
- Allows near real-time data visibility and site communication
- Drives timely actions with real-time predictive/prescriptive analytics
- Leverages current and historical data, identifying risk triggers and suggesting "next best action"

RBM ENHANCES PATIENT SAFETY

- Identifies and resolves issues immediately at the site and patient level
- Places focus on higher risk sites, data, events and patients with timely site communication and compliance
- Performs patient-level data reviews to identify trends and ensure medical accuracy and congruence

Conclusion

Today's clinical trial landscape demands an ideal RBM solution; one that is robust enough to meet the requirements of today's complex clinical trials. An effective RBM solution is built upon a **modern system** architecture that accommodates multiple sources of data capture and different operational solutions like CTMS and eTMF.

Discover how IQVIA Technologies Risk-based Monitoring helps planners and monitors reduce costs, improve workflows, and increase accuracy for safer and more efficient trials.

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