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WHITE PAPER

Modernizing Clinical Trial Oversight: The Path to Clinical Operations Excellence

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The rising complexity of clinical trials, combined with pressures resulting from the COVID-19 pandemic, have forced sites, sponsors, and clinical research organizations (CROs) to adopt remote and risk-based approaches for clinical trial execution to ensure the safety of trial participants, maintain compliance with good clinical practice, and minimize risks to trial integrity. With the increasing prevalence of decentralized clinical trials (DCTs), the industry is now poised to fully embrace and implement risk-based quality management approaches to trial execution and oversight.

Summary

Despite a decade's worth of industry dialogue and widespread regulatory acceptance, Risk-Based Monitoring (RBM) and Risk-Based Quality Management (RBQM) have not been widely adopted by clinical trial sponsors and CROs. But the rising complexity of clinical trial protocols, the increase in the types and volume of patient-centric data, and the challenges of the COVID-19 pandemic - limits to on-site activities, in particular - have brought renewed attention and interest to these approaches. Now that risk-based approaches to clinical trial oversight are of greater importance, it is time to renew the conversation around RBQM. Many sponsors and CROs recognized operational efficiencies and improvements in trial execution as a result of the risk-based approaches they took in 2020, and these benefits could continue to accrue long after the pandemic is over. In this paper, Medidata outlines the current state of RBQM approaches to virtualizing clinical oversight, and the value that adopting these approaches brings to sponsors, CROs, sites, and ultimately patients.

RBQM: An Evolution

A decade ago, Risk-Based Quality Management, or RBQM, was still a relatively new concept. The initial regulatory support was introduced in 2013, when the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) published guidelines that promoted the practice[1,2]. RBQM is a proactive method to design quality into the study design rather than taking the reactionary approach of monitoring for quality issues in clinical trials. RBQM is rooted in Quality by Design (QbD) principals while applying RBM control mechanisms which offer ongoing clinical trial oversight.

In 2013, the quality control systems in use by most research organizations were not only time consuming and costly, they were outmoded - built for a time before technology made paper-based systems largely obsolete. Even worse, they focused excess energy on areas that were low-risk and failed to catch avoidable quality problems. For example, most organizations continued to conduct very costly 100% source data verification (SDV) on site, even though the practice typically uncovered few errors that meaningfully impacted data quality or patient safety.

RBQM supports the historical misallocation of limited resources. Rather than try to cover all risks and monitor all data, sponsors and CROs would instead focus on areas of top priority, such as likely risks to human subject safety and data integrity, as well as unlikely but potentially outsized risks to overall study quality. But due to confusion around terminology and scope, early adopters took a haphazard approach, focusing only on source data verification (SDV) and source data review (SDR) without conducting a comprehensive risk assessment first. To the rest of the industry watching from the sidelines, this seemed more like "risky" monitoring than risk-based monitoring. There were other barriers to adoption, too. Many sponsors and CROs worried that regulators would not accept risk-based data, expected pushback from inspectors at the site level, or ran into country-specific regulatory limitations. Logistical barriers, a lack of metrics for quantifying value and the need for potentially complex and unfamiliar technology also impeded full adoption.

As of a result, by late 2019, most clinical research professionals remained cautious about the new ways of thinking about risk-based monitoring and quality management. In fact, a survey of member companies of the Association of Clinical Research Organizations (ACRO) across 6,513 clinical trials ongoing at the end of 2019 found that only 22% of these trials included at least one of the five major components of RBQM: identifying key risk indicators (KRIs); practicing centralized and off-site/ remote site monitoring; and conducting reduced SDV and SDR. Implementation rates for individual components of RBQM, meanwhile, ranged from 8%–19%, with the most frequently implemented component being centralized monitoring and the least frequent being reduced SDR[3].

A Common Vocabulary

From the beginning, differences over the meaning of key terminology have been a sticking point, a source of confusion, and an obstacle to more widespread adoption of risk-based quality management protocols. Therefore, it is critical to clarify our terms and establish a common vocabulary.

- Decentralized clinical trials: The term "decentralized" (aka "virtual") has been widely applied to clinical trials when referring to patient participation outside of a traditional trial site using virtual solutions such as remote data capture or virtual video visits. Trial virtualization also applies to clinical trial oversight, which includes all the monitoring and oversight activities required to ensure patient safety and protect data quality during trial execution.

- Risk-Based Quality Management (RBQM): As noted in the introduction, RBQM is a holistic systems-based approach to trial management, that focuses sponsor/CRO resources and oversight on the biggest risks to a clinical study.

- Risk assessment / Risk management : The practice of designing quality into a clinical study by identifying the Critical to Quality factors (CtQ) - those that protect study subjects and the reliability of data collection - utilizing the historical state of knowledge and their experience with the drug and therapeutic area.

- Central Monitoring: The remote review of aggregated electronic data, including data analysis. These activities complement those taking place on-site, and can be used to reduce the frequency of on-site monitoring activities.

- Risk-based monitoring (RBM): Focused monitoring activities on trial processes most likely to affect patient safety and data quality, often in real time using advanced data analytics.

- Triggered or Targeted On-site Monitoring: In-person evaluation of research programs, data and protocols carried out by sponsor/CRO personnel at the clinical trial site where a research investigation is being conducted.

- Remote Monitoring: Monitoring of specific and often high-risk clinical trial activities performed by the monitor at a location that is removed from the investigative site. Remote monitoring is often used in combination with reduced source data verification (SDV) and reduced source document review (SDR).

- Source Data Verification (SDV), commonly known as "transcription checking", is the process by which data within the case report form (CRF) or other data collection systems are compared to the original source of information (and vice versa) to confirm that the data were transcribed accurately. Targeted SDV (TSDV) refers to strategies which involve less than 100% SDV.

- Source Data Review (SDR) (sometimes referred to as "Source Document Review") is the review of source documentation to check quality of the data source, review protocol compliance, and ensure the critical processes are documented. SDR is not a comparison of source data against CRF data.

- Remote Source Document Review: The act of performing focused SDR or SDV remotely.

A New Normal For Clinical Operations

When the pandemic hit, it reshaped almost every sector of the global economy in a matter of months. Clinical trials were particularly sensitive to the disruption. As travel restrictions took effect and vulnerable patients skipped site visits for fear of infection, thousands of life-saving investigations were placed on hold. Many trial sites were forced to close. In less than a month, from mid March 2020 to early April 2020, one life sciences organization reported that the percentage of institutions where patient or site monitoring visits for the company's trials were disrupted jumped from 18-93%[6]. A second company reported that 33% of planned trial visits were disrupted in March 2020, and by the end of March, approximately 70% of sites were inaccessible. New subject enrollment in trials managed by a third company was reduced by 65% in March 2020 compared with March 2019[3]. A recent report by Medidata on the impact of COVID-19 on clinical trials found that even as of August 2020, there was a global decline of 20% in new patients entering trials per study-site as compared to pre-COVID baselines[4].

In contrast, the organizations that already had implemented robust processes using RBQM practices including centralized monitoring, flexible on-site interactions and remote data collection and document review were agile in adjusting to the complex new environment brought on by the pandemic. They reported enhanced effectiveness of monitoring, increased overall trial quality, greater efficiency, improved patient safety, and better overall value[3]. Meanwhile, regulatory authorities responded to the clinical trials quagmire by amping up their calls for implementation of risk-based approaches to data monitoring and quality control. In March of last year, for example, the FDA issued nonbinding recommendations that supported risk-based approaches to clinical trial oversight activities[5].

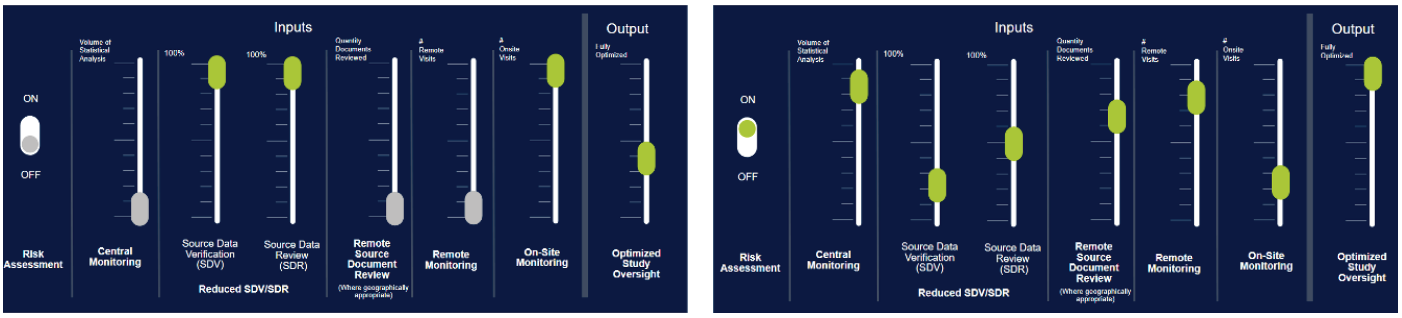
The COVID-19 vaccines currently finding their way to patients are a perfect and highly visible example. Remote monitoring, including central monitoring and virtualizing tools, enabled the development and manufacture of these drugs in record time without compromising quality, patient safety, or overall value. This rapid realization of benefits during the pandemic is the strongest argument yet in favor of full implementation of RBQM industry-wide. But while many clinical trial sponsors and CROs adopted remote monitoring in a provisional way in 2020, most have not formalized risk-based protocols or processes for clinical trial quality management. They have not taken the next step to unlock all of the value potential that rose to the surface last year, to fully transform their systems of quality control.

However, in a recent survey conducted by Medidata in 2022, the adoption of central and remote monitoring is on the rise and expected to increase by 15%+ in the next two years, while traditional on-site monitoring is expected to decrease by 13% over the next two years. This shows the industry is starting to move toward the benefits of these practices. In fact 2/3 of respondents expected increased adoption of remote source document review as a practice they expect their organization to adopt in the next 3 years. Another benefit sited by respondents in this research was the expected reduction in monitoring costs, showcasing the the on-going benefits of remote monitoring and the reduction of SDV/SDR beyond the initial COVID-19 need[6].

Even without the disruptions of a global pandemic, the benefits of RBQM and RBM are clear and far reaching for patients, sites, sponsors, and CROs. Because so many activities can be conducted off-site, monitoring is ongoing, allowing for the detection of potential adverse events sooner. This in turn improves patient safety.

Risk-based monitoring also creates massive efficiencies in drug development timelines and improves clinical research site satisfaction. Historically, on-site monitoring visits occurred every 8-12 weeks, while remote monitoring enables many of the core pivotal processes to be completed within 6 days. Additionally, in this approach data is reviewed in real time, which improves overall quality by preventing the same site-level mistakes from happening repeatedly. This accelerates the delivery of life saving medicines to patients, frees up time to focus on more high value activities such as patient care, and cuts cost for sponsors. Reduced travel to research sites for clinical research associates further cuts costs and timelines and even lightens a clinical trial's ecological footprint. When applied thoughtfully and holistically **(Figure 1)**, the cumulative benefits of taking an RBQM approach to clinical operations are enormous.

Figure 1: Medidata's perspective on optimizing clinical trial oversight virtualization.



Clinical trial oversight can be viewed as an equalizer, with the component activities as dials which can be tuned to achieve an optimized oversight strategy. The left panel represents the historical approach to clinical oversight, which included 100% SDV and SDR and on-site monitoring visits. The right panel shows a virtualization strategy driven by an end-to-end risk assessment which supports a central monitoring strategy, reduced SDV/SDR, and remote source document review, resulting in increased remote monitoring activities and reduced on-site monitoring visits. The output of optimized study oversight is achieved when the activities are fine-tuned resulting in improved efficiency, better site satisfaction, and increased overall trial quality.

RBQM - The Foundation for Clinical Operations Excellence

The fundamental first step in RBQM is development of a risk management plan through an end-to-end risk assessment. This risk-assessment should: 1) support protocol development, 2) prioritize trial participant safety and data validity, 3) take into account key stakeholder input and mitigation strategies, and 4) be reviewed and adjusted on an ongoing basis.

The risk assessment is implemented as part of a risk management approach to clinical operations. Risk management begins with identification of critical data and processes, known as Critical to Quality (CtQ) factors. As these factors are determined the risks associated with successful collection are identified and evaluated. For those risks with greatest impact, risk control mechanisms, also known as mitigations, are identified. Metrics, such as Key Risk Indicators (KRIs) and Quality Tolerance Limits (QTLs) are identified to support oversight of risks and performance of the control mechanisms. Within clinical operations the risk control mechanisms are most commonly evidenced as monitoring strategies such as RBM. The final component is ongoing risk oversight and communication to ensure continual improvement throughout the lifecycle of the study.

As noted above, the clinical operations risk mitigations are RBM activities such as on-site monitoring and remote monitoring, including central monitoring. Central monitoring is performed at a remote location and used to proactively identify and then report on issues in the conduct of a given clinical trial.

Centralized monitoring personnel examine data trends such as the range, consistency, and variability of data within and across sites. These trends are reviewed for systematic or significant errors in collection and reporting as well as potential data manipulation or data integrity problems across all sites. Site characteristics and performance metrics should likewise be tracked and certain sites or processes targeted for on-site monitoring.

In addition to central monitoring, remote monitoring extends beyond the evaluation of data trends to the acquisition and review of critical source documents off-site. Technologies supporting remote source data verification (rSDV) should be accessible to both sites and CRAs, yet be consistent with global regulatory guidelines for remote monitoring. These technologies should facilitate rSDV workflows with easy upload of source documents and redaction of protected health information, and should alleviate the burden on both the site and the monitor. Data types which may be included in rSDV include: concomitant medications, adverse events, serious adverse events, select medical history, general case history notes, informed consent, EMR records, radiography reports, laboratory reports, ECG reports and investigational product reports/logs.

Though in-person data review will be much reduced, person-to-person communications remain essential to quality control, so live video conferencing should be used to perform remote activities previously unavailable due to technology limitations. These activities include IP reconciliation, visiting site facilities, preselection visits, site initiation visits and close out visits.

It is worth noting that quality management systems will never be fully remote. Remote monitoring is a mechanism to reduce the frequency of on-site monitoring activities, not eliminate them. Certain trial procedures are often only possible on-site, such as storage of blood samples and handling of trial medication. On-site SDV will never be completely replaced by remote SDV. And in principle, granting access to the electronic health record (EHR) is only possible when a monitor has previously identified him or herself on site. Therefore this requires a visit to the research site. These details should be clarified in the study protocol and RBM plan.

Looking Forward

To support industry-wide adoption of RBQM principals, and move toward RBQM as a standard business process, some challenges remain. These include evolving regulatory guidelines, which could impact global trials, the burden of digitizing documents by hand, as well as the lack of metrics for measuring the value of remote monitoring and risk-based quality management.

Supporting RBQM as standard business practice begins with educating key internal and external stakeholders on RBQM implementation and the regulatory landscape, as well as managing expectations about compliant and efficient monitoring. For companies that do not have quality management systems already in place, Medidata can provide professional support. Our in-house implementation and consulting expertise and experience covers the full range of clinical trial execution lifecycle, from design to close out. A proven industry leader for over a decade in high quality data, data technology, regulatory compliance, solution mapping and the processes and workflow required to support change management, we can help you make the transition to value-driven risk-based quality management systems with confidence and ease.

For example, Medidata's strategic consulting team can train organizations on how to remain compliant in this new landscape, along with educating on the processes and tools needed for efficient monitoring. This team can also assist in developing formalized risk-based protocols and processes for clinical trial quality management. And, Medidata is working with industry partners and regulators to develop value metrics through industry-wide surveys. In cases where it's needed, having experts come in to perform the risk assessment, and help determine the Critical to Quality (CtQ) Factors, KRIs and QTLs, can also greatly accelerate adoption of RBQM.

Technology can help as well, particularly modular and scalable applications that meet life science companies where there are at from both a product and implementation perspective. Medidata provides a set of integrated capabilities on top of a unified data platform for companies to address the maturity of their clinical operations processes following risk-based quality management (RBQM) principles.

The result is continuous data monitoring from anywhere, allowing sponsors and CROs to innovate and optimize their approach to trial design, physical and virtual interactions with sites, and holistic portfolio strategy. Medidata's experience in data acquisition and aggregation leverages contextually surfaced real-time insights at the patient, study, and industry benchmark level, improving Clinical Operations decision making.

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