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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 ef□ciencies and improvements in trial execution as a result of the risk-based approaches they took in 2020, and these bene□ts 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 veri□cation (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 veri□cation (SDV) and source data review (SDR) without conducting a comprehensive risk assessment □rst. 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-speci□c 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 □ve 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

- 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].

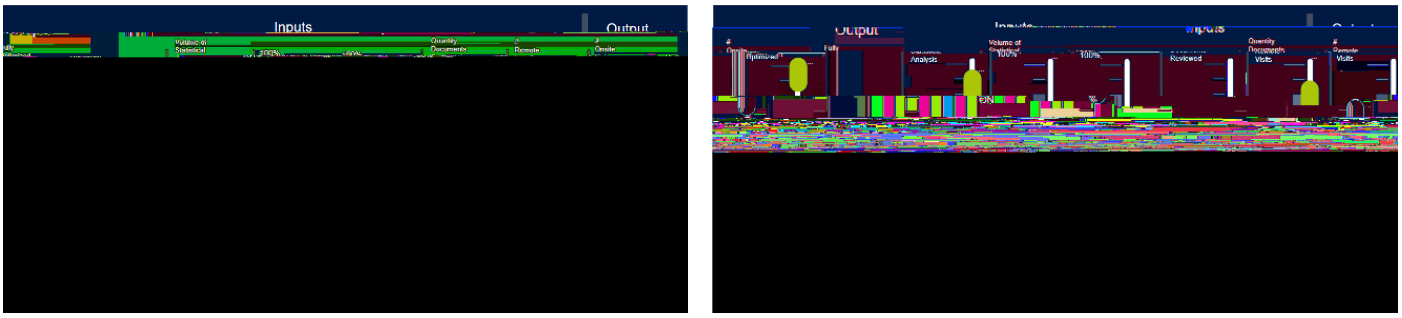
In contrast, the organizations that already had implemented robust processes using RBQM practices including centralized monitoring, flexible on-site interactions and remote data collection and document review were agile in adjusting to the complex new environment brought on by the pandemic. They reported 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.

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 ef□ciencies in drug development timeless 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 bene□ts 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 □ne-tuned resulting in improved ef□ciency, better site satisfaction, and increased overall trial quality.

# RBQM - The Foundation for Clinical Operations Excellence

The fundamental □rst 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 identi□cation of critical data and processes, known as Critical to Quality (CtQ) factors. As these factors are determined the risks associated with successful collection are identi□ed and evaluated. For those risks with greatest impact, risk control mechanisms, also known as mitigations, are identi□ed. Metrics, such as Key Risk Indicators (KRIs) and Quality Tolerance Limits (QTLs) are identi□ed 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 □nal component is ongoing risk oversight and communication to ensure continual improvement throughout the lifecycle of the study.

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 ef□cient 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 Digital Oversight provides a set of integrated capabilities on top of a uni□ed 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.

# References

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