MEDIDATA

WHITE PAPER

The Evolution of Source Data Verification (SDV), Source Data Review (SDR), and Risk-Based Quality Management (RBQM) in Driving Clinical Trial Data Quality

Table of Contents

Introduction

Clinical trial complexity has escalated exponentially with the increased adoption of complex trial methodologies over recent years–adaptive trials (basket, dose-ranging, platform, umbrella), real-world, targeted or stratified, and Bayesian methods. These have significant benefits, for example, broadening the scope of the data collected for potential use in other research, flexibility to make structural changes to the study mid-way, or running multiple studies in parallel. These methodologies also increase the levels of operational complexity, volumes of data, and burdens for clinical research sites.

A significant portion of time and cost from clinical trials are attributed to manual monitoring–an industry paper from the *Journal of Clinical and Translational Science* (2024) estimated that 46% to 50% of the time is attributed to Source Data Verification (SDV) and an average of 25-40% of clinical trial costs.[1]

TransCelerate BioPharma's landmark risk-based monitoring (RBM) position paper (2013), determined that only 2.4% of the queries in critical data were driven by 100% SDV.[2] Other sources concur and make similar observations, demonstrating that this approach is unsustainable–up to 3% of all Case Report Forms (CRFs) are attributed to data changes due to 100% SDV, allocating over 50% of site monitoring budgets, and spending up to 50% of time carrying out 100% SDV on-site.[3]

The conclusion is that SDV has a negligible effect on overall data quality. Additionally, the impact of SDV on a study is wide-reaching–reducing SDV would positively impact data quality, data integrity, compliance, and costs while increasing operational efficiency, improving assessments for risks and critical quality factors, and improving data management and trial outcomes.

DEFINING SOURCE DATA VERIFICATION (SDV) AND SOURCE DATA REVIEW (SDR)

Source Data Verification is the process of ensuring that the data reported for analysis accurately reflects the source data at the clinical trial site–a comparison of source data against the Case Report Form (CRF) data (transcription errors). SDV predominantly detects random errors.

Source Data Review (also referred to as Source Document Review) is the review of source data in relation to the clinical conduct of the protocol. SDR focuses on areas that may not have an associated data field in the CRF or a system. Historically, SDV has been conducted for most of the CRF data; however, SDV of 100% does not guarantee error-free results, and concentration on transcription accuracy does not guarantee data quality. SDR instead focuses on the quality of data collection and compliance against the protocol and standard of care. SDR tends to be more strategic, resulting in a focus on present and future proactive activities to maintain data quality.

Designing Quality into Study Protocols & Processes

In the European Medicines Agency's (EMA) International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) "Guideline for Good Clinical Practice" (GCP), one of the key themes is alignment with quality-by-design (QbD) principles in clinical trial planning.

As the original ICH guideline, ICH E6 (R1), was published in 1996 and corrected in 2002, it was largely based on paper-based manual processes.[4] The 2016 ICH E6 (R2) and 2023 ICH E6 (R3) amendments included changes that reflected the evolution in technology and processes.[5]

ICH E6 (R2) stated that it had been "*amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.*" The ICH E6 (R3), published in 2023, further built on this guidance and ICH E8 (R1) **"**General Considerations for Clinical Studies" was published in 2021.[6] It was made clear that the overall quality of a trial is driven proactively by designing quality into the study protocol and processes, which in turn impacts the choice and implementation of appropriate and fit-for-purpose technology.

The most accessible and most significant value gain is from a targeted and focused approach to reduced SDV and SDR.

The Shift from 100% SDV and SDR to Risk Based Monitoring (RBM)

Despite evidence of its ineffectiveness and the strong encouragement from regulators that the industry should develop and adopt better strategic monitoring processes such as RBM, SDV has remained the primary monitoring activity.

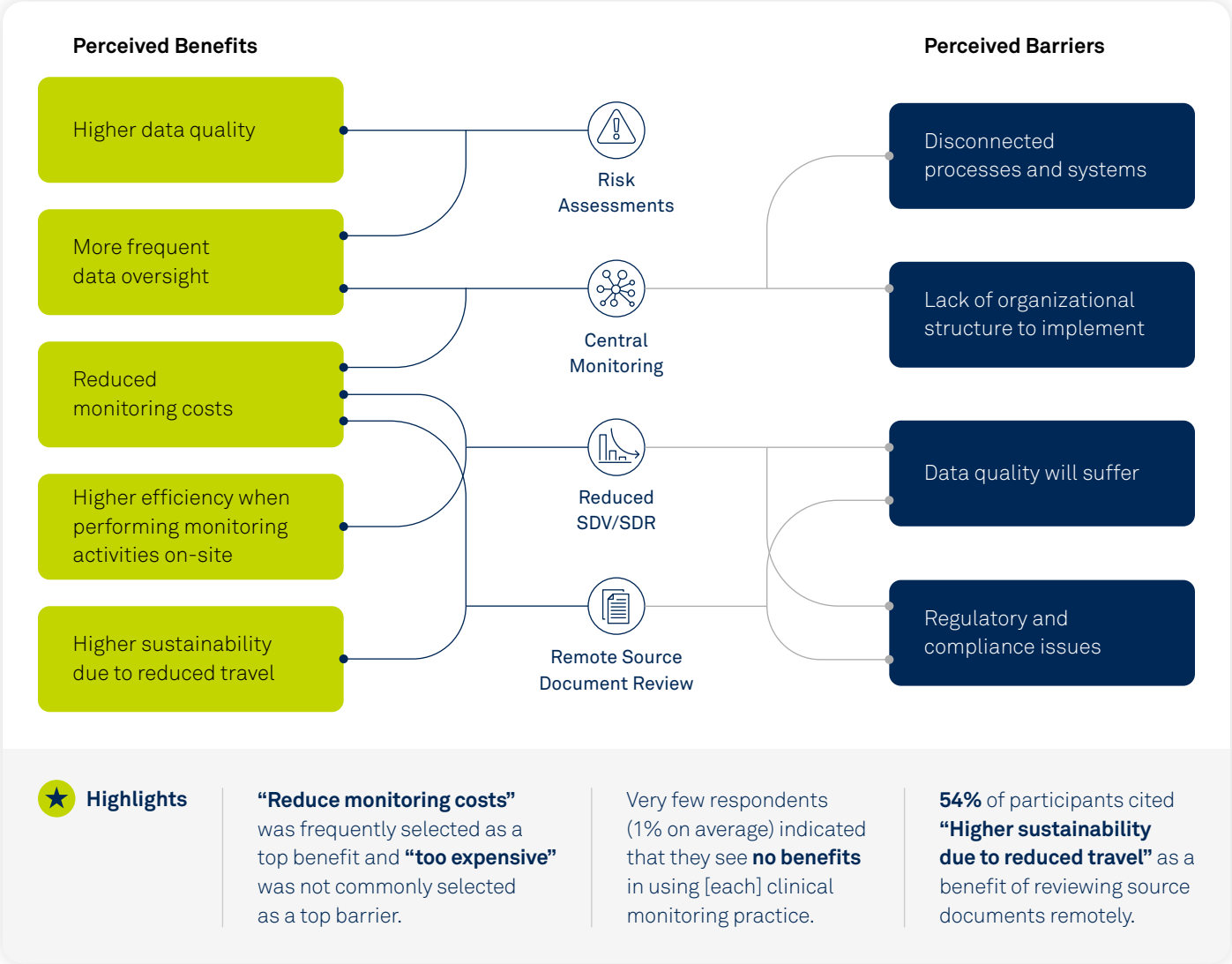
TransCelerate's paper also supported a shift from traditional 100% on-site monitoring source data verification–an almost premonitory view. Years later, the global impact of the COVID-19 pandemic changed the world, and the clinical trials industry saw a significant shift from on-site monitoring to the widespread adoption of hybrid and remote decentralized trials (DCT), driving remote monitoring to the forefront.

> … prior to the pandemic, only 22% of trials included at least one RBM component, with each individual component being implemented in just 8–19% of trials. There was, however, a **rapid shift from 82% of trials using on-site monitoring in February 2020 to 93% of trials using remote monitoring in April 2020**, corresponding with the first wave of the pandemic.[7]

The variability in global regulations, standards of care, and technological infrastructure across different countries adds additional layers of complexity that cannot be addressed by a one-size-fits-all approach, requiring instead strategies, technologies, and services that are highly flexible and able to mirror the nature of complex studies.

While attitudes to adopting RBQM are predominantly positive and implementation of RBQM technology solutions has increased since 2020, there are still barriers to industry-wide adoption. From industry surveys commissioned by Medidata, feedback showed those barriers are mainly due to uncertainty over potential disconnected processes and systems, a lack of internal organizational structures to implement systems, perceived decreases in data quality, and regulatory and compliance concerns. (Figure 1)

Figure 1: Perceptions around adopting clinical monitoring elements



Highlights

"Reduce monitoring costs" was frequently selected as a top benefit and **"too expensive"** was not commonly selected as a top barrier.

Very few respondents (1% on average) indicated that they see **no benefits** in using [each] clinical monitoring practice.

54% of participants cited **"Higher sustainability due to reduced travel"** as a benefit of reviewing source documents remotely.

Respondents acknowledged that the benefits of RBQM were reduced monitoring costs, higher clinical trial data quality, more frequent data oversight, higher efficiency for on-site monitoring activities, and higher sustainability due to reduced travel. Nearly two-thirds of respondents expected their companies to increase adoption of remote SDR in the next 36 months.

Respondents stated that risk assessments (determining critical quality factors, risks, and associated mitigation strategies) and central monitoring were very or extremely important in DCT trials.

Evolving Regulatory Recommendations for RBM Adoption

Guidance to adopt RBM practices was given by regulatory authorities in 2011, and there have been updates and new guidance published since 2013 (Figure 2), with notable excerpts shown here:

"Oversight of Clinical Investigations–A Risk-Based Approach to Monitoring" from the FDA (2013) states that a "*risk-based approach to monitoring does not suggest any less vigilance in oversight of clinical investigations. Rather, it focuses sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical to human subject protection and trial integrity.*"[8] This was expanded on within their 2023 guidance, "A Risk-Based Approach to Monitoring of Clinical Investigations, Questions and Answers."[9]

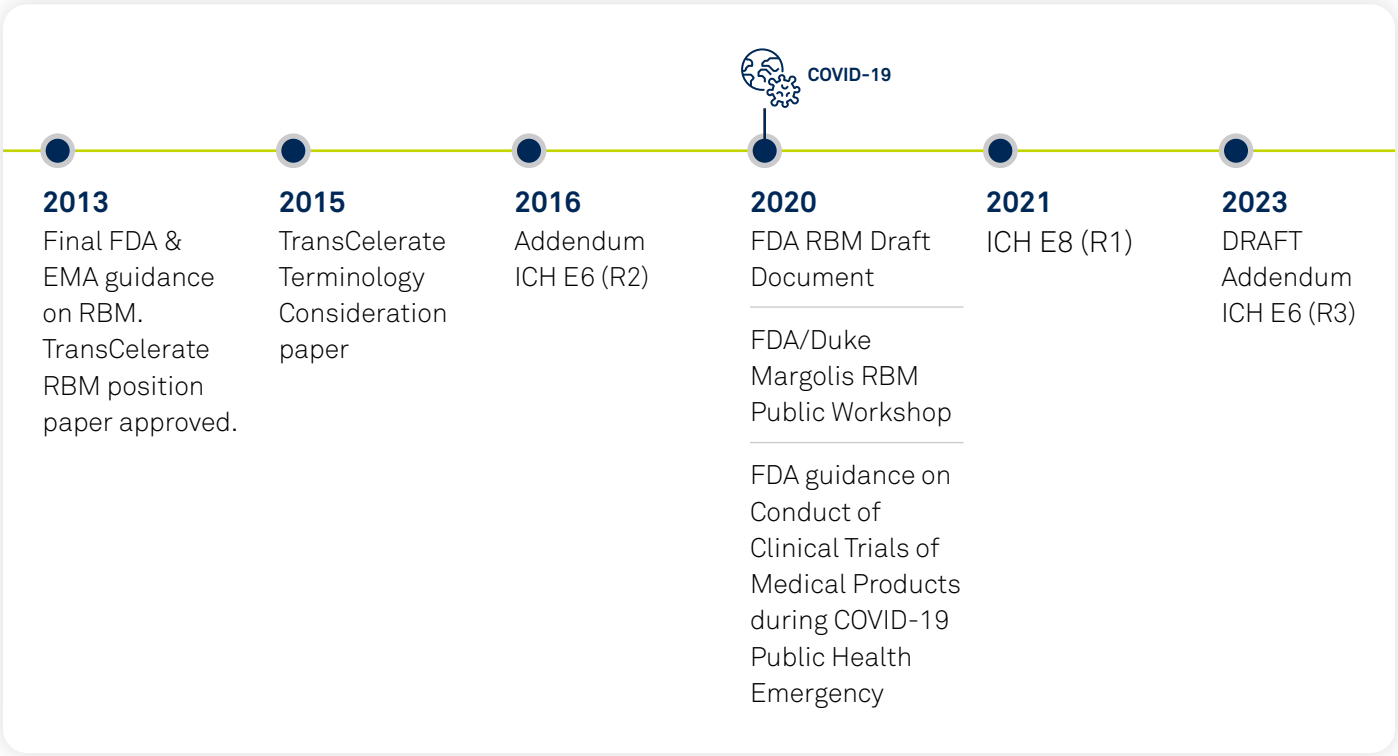
The EMA's guidance, "Reflection paper on risk-based quality management in clinical trials" (2011) sought to "*facilitate the development of a more systematic, prioritized, risk-based approach to quality management of clinical trials, to support the principles of Good Clinical Practice and to complement existing quality practices, requirements and standards*."[10]

The ICH has released multiple guidance papers related to RBM:

ICH E6 (R3) "*encourages innovation, focuses on quality, and establishes proportionate and risk-based approaches for conducting clinical trials while minimizing unnecessary complexities.*"

ICH E6 (R2) states that "*Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities," and "Advances in the use of electronic data recording and reporting facilitate implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested in the original text. Therefore, this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting while continuing to ensure human subject protection and reliability of trial results,*" and ICH E8 (R1) states that "Quality by design in clinical research sets out to ensure that the quality of a study is driven proactively by designing quality into the study protocol and processes."

Figure 2: Regulator timeline



The United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) stated that "*GCP Inspectors will review risk assessments*" and "*Organizations are not recommended to undertake 100% SDV.*"[11]

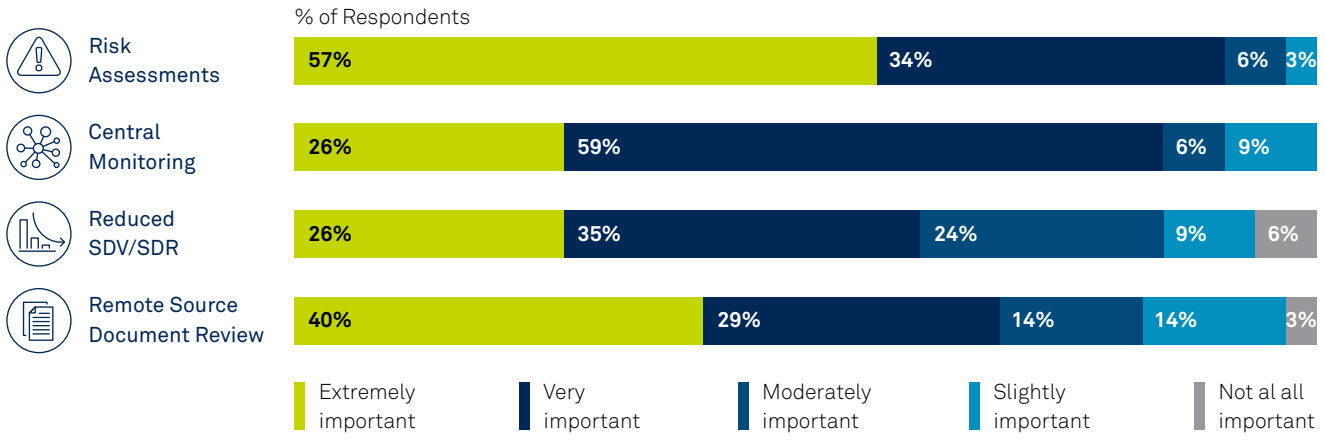
Despite early guidance from regulators, RBM practices had a low adoption rate until COVID-19 triggered the industry shift in 2020, leading to sponsors and CROs adopting RBM in a provisional but not formalized way.

Risk-based Quality Management (RBQM) is a methodology and strategy that has a more expansive approach than RBM, involving a continuous cycle that consists of planning and initiation, identification and assessment, management and control, and implementation and adapting. A significant component of RBQM is reduced SDV and SDR.

The methodology and deployment of advanced RBQM technologies provide a targeted, strategic approach that supports clinical trial project teams, reducing burdens while enabling them to focus on placing resources in the areas that bring the most significant value. The aim is to focus monitoring and oversight activities on those trial processes most likely to affect participant safety and data quality, to enable clinical operations teams to mitigate risks or address errors quickly and effectively before they compromise trial outcomes.

RBQM has played an increasing role as the industry continues to focus more on DCT. 73% of respondents to the Society for Clinical Research Sites' survey stated that they had been approached to run a hybrid study by sponsors or CROs in 2023.[12] In a Medidata-commissioned industry survey, the elements that sponsors stated are most needed for operationalizing monitoring in DCTs are risk assessments (57%), remote source document review (40%), central monitoring (26%), and Reduced SDV/SDR (26%). (Figure 3)

Figure 3: Impact of Clinical Monitoring Elements on Operationalizing DCTs



Highlights

Among the survey participants that are currently running decentralized/hybrid trials (50%), **risk assessments** and **central monitoring** were valued by most as very or extremely important in running this type of trial.

Another key area of consideration that must be considered is the question of ethics.

Study methodologies have evolved, and it is usually the case that data collection now exceeds the needs and scope of any given clinical trial–that data could significantly benefit further research.

Whilst this has potentially exciting implications and benefits, it also raises ethical issues related to data privacy and informed consent that need to be addressed.

Effective Alternatives or Additions to 100% SDV

While 100% SDV is considered one of many quality control mechanisms used to determine whether an acceptable level of accuracy has been achieved in the transcription of critical data, a heavy reliance on SDV should not be taken as a mechanism to ensure study quality oversight. To determine the proper volume and targets for reduced SDV & SDR, a critical first step is a protocol-based risk assessment to inform an intelligent monitoring strategy.

Additionally, as SDVs and SDRs are so time, resource, and cost-intensive, the natural step is to leverage RBQM methodologies, software tools, platforms, and artificial intelligence (AI) assisted technologies that have been specifically developed to automate and streamline monitoring, enable accurate tracking and reporting, improve data quality, and reduce monitoring time and costs with risk-based practices.

Key areas of focus are strategic quality management methods: risk assessment, Reduced or Targeted SDV, remote SDR, and centralized statistical and data monitoring.

Risk assessments involve the determination of critical quality factors, risks, and associated mitigation strategies and are done in the planning stage and throughout the trial.

Remote Source Data Review is defined as the completion of SDR activities outside of a traditional investigation site.

Reduced or Targeted SDV (TSDV) is defined as performing less than 100% review of all data and documents focusing on Critical-to-Quality components.

Centralized statistical monitoring and central data monitoring are defined as monitoring processes, happening outside of a traditional investigative site, that provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring.

CASE STUDY

The Transformational Impact of RBQM

RBQM methods and a unified technology platform can positively impact a study almost immediately, as evidenced by our customers.

One such example is a world-leading biotech that was burdened by highly manual processes and facing challenges in transitioning from reduced monitoring to true RBQM.

They adopted Medidata Rave TSDV to streamline reduced SDV in a global study involving over 40 sites and spanning Eastern Europe, Asia, Latin America, and the United States.

Centralized monitoring identified emerging trends and potential high-risk areas, allowing them to make real-time adjustments to SDV requirements, prospectively or retrospectively, at the geography, site, or subject level.

The biotech's Head of Clinical Development stated that within one week of having Rave TSDV up and running, they immediately saw the benefits of replacing spreadsheets in their monitoring practices, eliminating manual comparison, tracking, and reporting in SDV execution. In addition to improving the efficiencies of both data managers and monitors, human errors inherent in manual processes were eliminated.

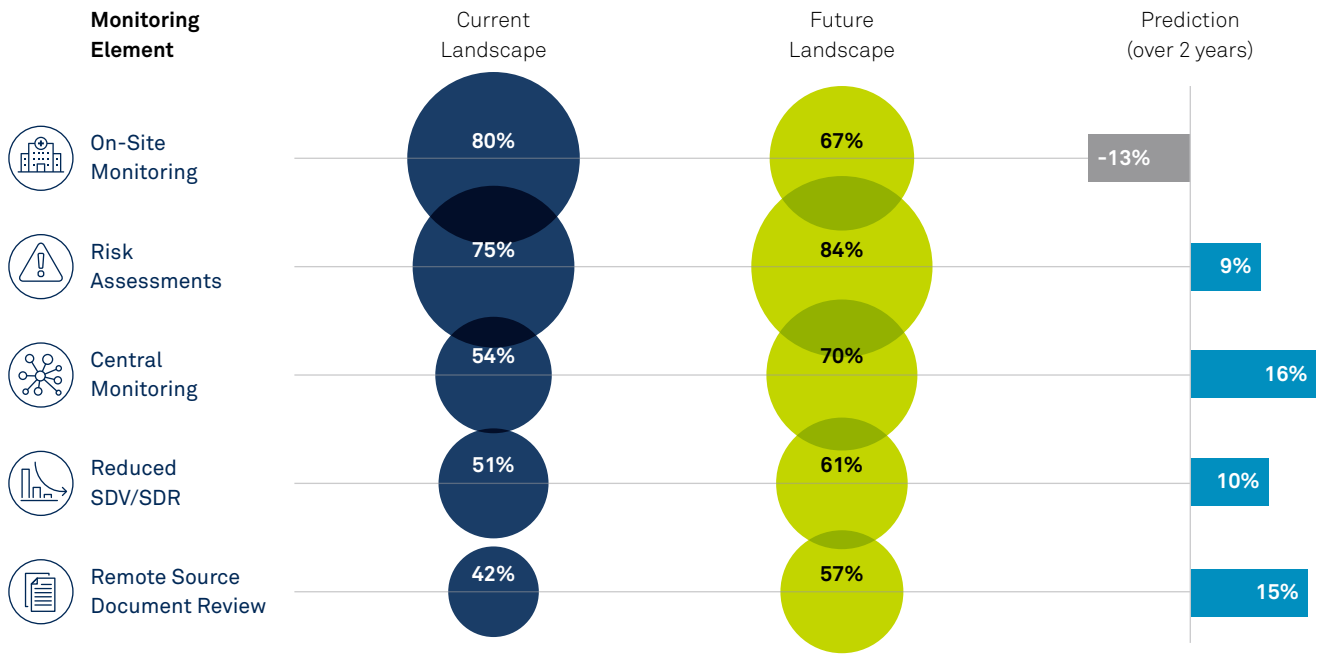
The biotech expects to reduce its SDV coverage from today's 50 percent to its target of 15–20 percent by fully leveraging risk-based SDV. This has the potential to realize millions of dollars in cost savings per study while improving data quality and enabling monitors to focus on data elements that are truly critical to the overall quality of the study. They can now dynamically adjust SDV requirements mid-study based on identified risks–the heart of risk-based monitoring–which was nearly impossible in their previous spreadsheet-based practices.

The Future of Source Data Verification, Source Document Review, and Risk-based Quality Management

Assessing RBQM technology in line with current and future needs can be complex.

The Medidata survey highlighted expected trends in monitoring component utilization, showing a shift to central monitoring, remote source document review, and risk assessments in particular. (Figure 4)

Figure 4: Monitoring component utilization



Highlights

Respondents reported their companies still use **on-site monitoring** in a majority of trials, 8 out of 10 on average, but expect this proportion to decrease over the next two years being replaced with central and remote monitoring elements.

Usage of **central monitoring** and **remote source document review** are predicted to increase the most, by 16 and 15 percentage points, respectively, over the next two years.

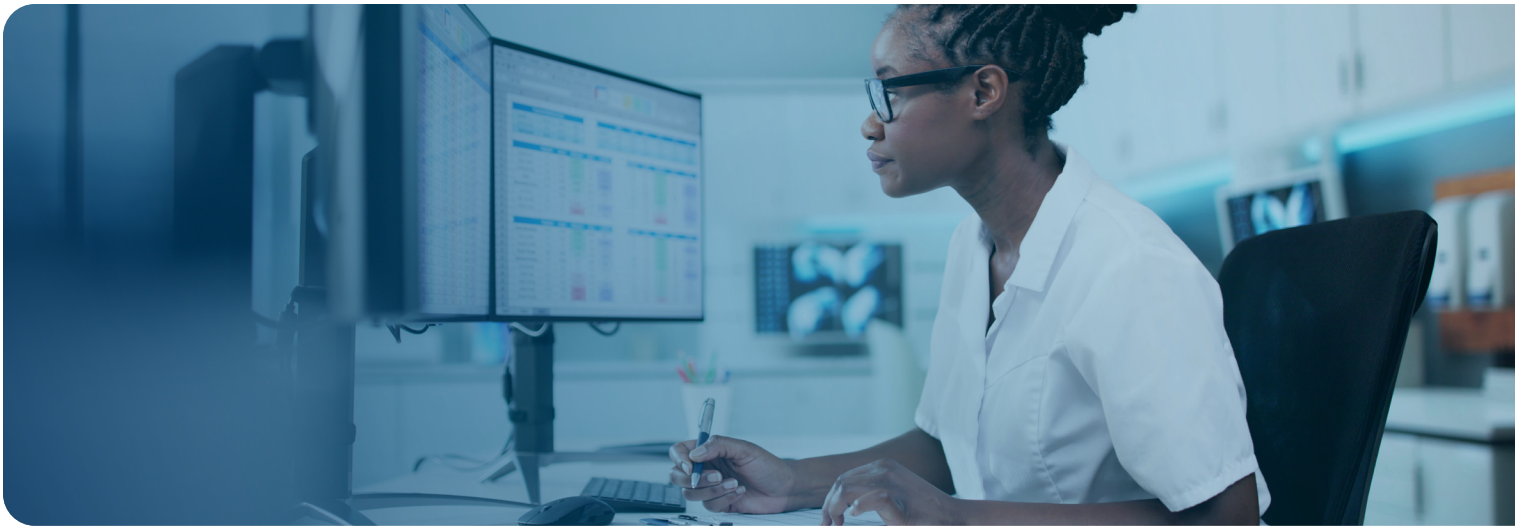
Respondents noted reasons for not using some of these clinical monitoring elements including they felt more confident with **100% SDV/SDR** or that their organizations were slower to adopt remote and centralized monitoring practices.

Identifying technology solutions for these components can be complex, depending on the scope of the study–complexity, therapeutic area, diversity of the patient population, global challenges, etc.

One possible solution is the piecing together of disparate technical solutions to fulfill the different elements of an overall RBQM ecosystem, but industry feedback shows that integration and interoperability are two of the most prominent issues faced when that approach is taken. This is because the different systems used often have difficulty interfacing with at least one other system seamlessly. This leads to delays, inconsistent user experiences, burdens on sites and patients, costs, and inefficiencies.

The better option is to use fit-for-purpose solutions that sit on a unified, advanced technology platform designed to enable seamless cross-communication internally and with third-party systems and data sources.

The future is clear–an appropriate RBQM technology platform empowers clinical trial teams to overcome the many challenges they face today and tomorrow.



About Medidata

As the industry leader, Medidata has supported 35,000+ clinical trials, 10 million+ patients, and 2,300+ customers, and supported 65% of 2023 FDA novel drug approvals and 60% since 2015 (excluding vaccines and biologics).

The Medidata platform is an intuitive, integrated, unified platform with a single log-in, and a consistent patient, site, and sponsor experience that is supported by local time zone and multi-language support.

Underpinning our clinical solutions and data management is Medidata Clinical Data Studio which provides seamless access to integrated data from Medidata and non-Medidata sources. Built with a user-friendly, no/low code environment, it leverages AI and human-in-the-loop capabilities to streamline data aggregation, standardization, and management workflows so that multiple users can act on real-time data in ways that reduce burden, shorten review timelines, increase quality, reduce risk, and improve patient safety. Clinical Data Studio unlocks efficiencies and accelerates clinical discovery by supporting a wide variety of use cases for clinical data managers, clinical operations, medical monitors, clinical programming, and other data stakeholders.

Medidata's award-winning RBQM solutions leverage the power of the Clinical Data Studio's Data Quality Management offering with its data surveillance and risk surveillance capabilities, supporting a holistic RBQM approach to data quality.

References

1. Hamidi M, Eisenstein EL, Garza MY, et al. Source Data Verification (SDV) Quality in Clinical Research: A Scoping Review. *Journal of Clinical and Translational Science*. Published online 2024:1-33. doi:10.1017/cts.2024.551.
2. TransCelerate BioPharma, Position Paper: Risk-Based Monitoring Methodology, 2013.
3. E. Eisenstein, P. Lemons II, B. Tardiff, K. Schulman, M. Jolly, R. Califf, "Reducing the costs of phase III cardiovascular clinical trials" American Heart Journal 149, 3 (2005): 482-8.
4. EMA, GCP ICH E6 (R1), 2002.
5. EMA, GCP ICH E6 (R2), 2016; EMA, GCP ICH E6 (R3), 2023.
6. EMA, ICH E8 (R1), 2021.
7. Stansbury N, Barnes B, Adams A, et al. "Risk-Based Monitoring in Clinical Trials: Increased Adoption Throughout 2020". Ther Innov Regul Sci. May 2022;56(3):415-422. doi:10.1007/s43441-022-00387-z.
8. Food and Drug Administration, "Oversight of Clinical Investigations–A Risk-Based Approach to Monitoring", 2013.
9. Food and Drug Administration, "A Risk-Based Approach to Monitoring of Clinical Investigations, Questions and Answers", 2023.
10. EMA, "Reflection paper on risk based quality management in clinical trials", 2011.
11. Medicines and Healthcare products Regulatory Agency guidance. January 2022. "Risk-Adapted Approach to clinical trials and Risk Assessments".
12. Society for Clinical Research Sites, "2023 Site Landscape Survey", January 2024.