Moving Beyond Risk-based Monitoring: Improving Quality and Performance with Real-time Management

Risk-based monitoring (RBM) in clinical trials has long been touted as a more proactive way to reduce risk and improve data quality. But the current generation of risk monitoring tools and processes lack the transparency and integration needed to support a level of proactive risk-based management necessary to drive real-time cost and quality benefits.

Part of the problem is the reactive and narrow application of this approach. Organizations that have pursued RBM generally limit their monitoring strategies to reduced source data verification (SDV) conducted by onsite monitors who are still physically visiting every site in the study at some pre-defined interval. This type of monitoring is considered the most capital-intensive aspect of a trial, comprising up to 25% to 30% of overall trial costs.

These steps have isolated benefits, but without implementing further quality oversight measures, such as centralized monitoring, or undergoing a thorough and comprehensive risk assessment and mitigation process, the impact is limited. The Clinical Trials Transformation Initiative (CTTI) has found this approach to be inefficient, pulling resources away from more trial critical activities without improving data quality.

The ICH E6 (R2) Addendum to Good Clinical Practice, which went into effect more than a year ago, takes the concept of RBM one step further. It encourages the adoption of a systematic, quality-by-design risk management process to be applied from protocol design through trial execution. Companies will be expected to document and defend their risk planning, oversight, and mitigation strategies to achieve compliance.

ICH specifically designed the addendum to help sponsors reduce various complexities that put patient safety, data quality, and trial integrity at risk — calling for sponsors to develop systems (process and technology) that support a more proactive risk-based study oversight approach that focuses on delivering quality data and streamlining risk response in real-time. The regulatory document also supports the use of RBM and centralized monitoring processes.

The growing complexity of today's clinical trial protocols has resulted in an ever-increasing volume of data being collected from more disparate sources than ever, making it even more challenging for sponsors and CROs to proactively identify and manage risk. The ICH addendum aims to rein in some of this complexity by calling for sponsors to "…identify those processes and data that are critical to assure human subject protection and the reliability of study results." This is a true paradigm shift from collecting as much data as possible, and it creates an opportunity for sponsors and CROs to rethink their risk-management culture as a way to improve data quality and achieve significant time and cost savings — a competitive advantage any organization would sign up for.

However, CROs and sponsors have been slow to embrace this change, in part because they aren't sure where to begin. A 2017 study by the Avoca Group found one-third of sponsors still lack good understanding about best practices for risk-based approaches.

Beyond RBM

Taking a risk-based approach to trial oversight and management and focusing on quality by design throughout the clinical trial really translates into Risk Based Quality Management (RBQM). RBQM promises to dramatically reduce site and data issues, and the most common causes for extended timelines and missed milestones: faulty patient enrollment projections and poor performing sites. From designing more focused protocols and using data analytics to predict site performance and automatically trigger alerts that centralized monitoring teams can act on in real time, organizations will ultimately be able to build on their experience and use benchmarking data to model resource allocation and adjust thresholds based on the specific risks such as working with a new site, in a new country, or within a new indication.

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However, this calls for a significant shift from today's resource-driven and reactionary mindset, to a proactive and data-driven mindset. While easier said than done, having the right technology in place can be the catalyst for an organization to make this change. An effective RBQM strategy has to integrate data from multiple sources into an easy-to-access platform for real-time decisions. With a technology platform that centralizes data, information, and related action items, trial stakeholders from both the sponsor and CRO can access the data they need to carry out risk-management activities with confidence and transparency.

Regulators Are on Board

For years, leading industry voices have been pushing for changes to investigator over-

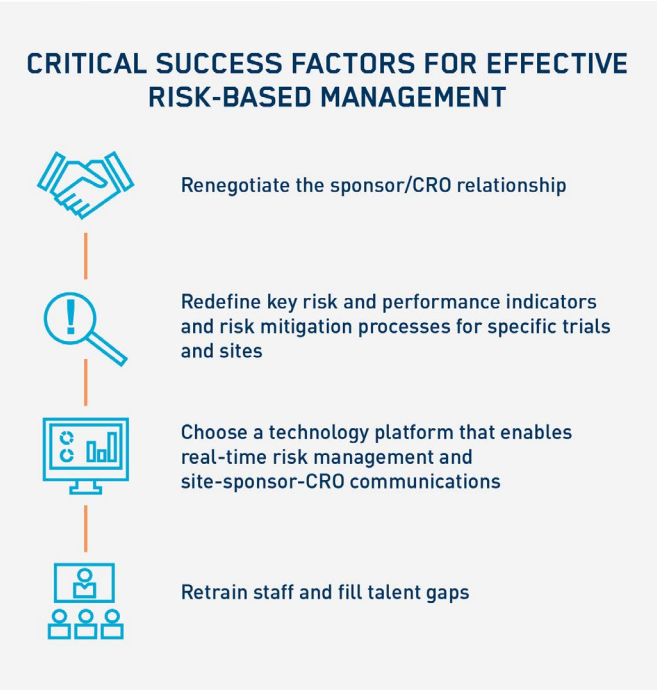

Figure 1: Key milestones for transitioning to RBQM

sight processes that better ensure patient safety and data integrity. In 2013, the FDA released a guidance titled "Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring." And while the primary focus was on monitoring, the guidance stated the "FDA considers monitoring to be just one component of a multi-factor approach to ensuring the quality of clinical investigations." Industry consortiums such as TransCelerate BioPharma have led the way in creating a standard framework and publishing tools for companies to integrate risk assessment and measurement into their oversight processes. The ICH Addendum's focus on sponsor obligations has moved the discussion from if to how soon companies will begin implementing these changes.

Common Hurdles

Where five years ago, organizations may have cited the lack of technology as their primary obstacle to adopting RBQM, this is no longer the case. In fact, the most common hurdle is that sponsors and CROs have to fundamentally change their approach to risk and how their partnership arrangements are defined. Moving toward a true RBQM environment will require a more collaborative approach where sponsors and CROs work together as a team to jointly redefine the risk management process with a focus on safety, quality, and efficiency. For example, jointly defining the processes, training, and technology requirements (including sponsor access to data) and the roles and responsibilities for oversight activities are challenging, but critical for success.

Roadmap for Success

To make the transition to RBQM, sponsors and CROs need to create a roadmap for transformation, with key milestones for adapting the people, processes, and technologies involved in risk-management strategies. Critical steps include:

1. Redefining the sponsor/CRO relationship.
The ICH addendum holds sponsors responsible for how risk is managed in a trial — even if the trial is fully outsourced. To achieve compliance, they should redefine how they will interact to share trial updates and response strategies, as well as the systems they will use to share data and monitor outcomes. To overcome challenges in budgeting and resource allocation in this more fluid RBQM environment, sponsors and CROs may want to consider building pay-for-performance criteria into the project plan.

2. Redefining key risk and performance indicators and risk mitigation processes for specific trials and sites.
Every trial faces a unique set of risks that evolve based on the phase of the research, biomarkers, protocols, and other criteria. An RBQM platform allows the CRO and sponsor to define KRIs and KPIs, and create weighted scorecards to more efficiently track outliers and risk signals.

3. Choosing the right technology platform.
An effective RBQM solution will provide the necessary integration, transparency, and analytics capabilities to drive real-time risk identification and mitigation, however many organizations cite the number of data sources required to centralize risk monitoring as a challenge. The Avoca Group survey found only one-third of sponsors were satisfied with the level of innovation and technology in the areas of RBM and risk-based quality management. Before choosing a system, sponsors and CROs should verify that it has the ability to integrate and aggregate data in real-time, and doesn't require an internal means of serving up the data to their RBM system. Otherwise they will be left with a data visualization tool that doesn't have the right data, or has it too late to be actionable.

4. Retraining staff and filling talent gaps.
Monitors and site staff will need training on how to operate in an RBQM environment, including how risk indicators are defined and configured and the expected mitigation responses when risks do occur. Data analytics play an important role in supporting these programs, so companies may also benefit from hiring new staff with data analytics and technical expertise to navigate the data-driven trial environment.

The Time Has Come

While taking the necessary steps to comply with the ICH addendum may be causing some anxiety in the industry, these best practices provide both sponsors and CROs with the potential to achieve significant cost savings and study performance improvements. When implemented effectively, this approach can help mitigate risks before they become costly problems, and ensure the best quality data are captured consistently throughout the trial lifecycle. In an industry where organizations invest millions of dollars over many years to get their products to market, hitting clinical development milestones can be the difference between success and failure in being first to market. With growing consolidation and increased competition in almost every therapeutic indication, companies can't afford to wait on making the move, and embracing RBQM as their "new normal." PV