Executive summary

Clinical development is at a crossroads — it costs too much and takes too long to develop and bring new therapies to market. With support from the Food and Drug Administration, other global regulatory bodies and industry consortia, risk-based monitoring (RBM) is transforming how clinical studies are being executed and managed.

RBM can produce faster, more efficient trials and reduce risks associated with clinical trials by identifying and focusing on the higher risk areas of a study, at both the scientific and operational levels, and utilizes resources accordingly to mitigate those risks. Risk assessment and mitigation drives the strategic and operational plans for the life of the study.
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RBM is Driving Clinical Development Changes

According to a 2014 study by the Tufts Center for the Study of Drug Development, clinical studies can take up to 10 years and cost up to $2.6B to deliver a new medicine to market. Clinical trials, including monitoring costs, account for a significant portion of that cost.* Risk-based monitoring (RBM) is transforming how clinical studies are being monitored, executed and managed.

RBM focuses on the higher risk areas of a study, at both the scientific and operational levels, and utilizes technology and resources accordingly to mitigate those risks. RBM also emphasizes more accurate and timely data collection and analysis for faster, near real-time decision making, allowing for improvements in patient safety, study quality and operational efficiencies.

Sponsors using RBM are experiencing not only cost savings, but increased study quality and patient safety, as a byproduct of improved resource utilization and efficiencies. These enhancements are a direct result of the upfront planning and identification of potential risks for more targeted and more efficient monitoring. A key step in this process is the identification of key risk indicators (KRIs) and associated protocols to guide efficient responses to alerts and triggers. Focusing on KRIs and utilizing alerts and triggers drives more efficient monitoring and initiates most appropriate response to potential risks.

A key to successfully implementing RBM is defining the high risk elements of the study protocol with the study team, including leaders from project management, biostatistics, data management, medical review, therapeutic experts and more from both the CRO and sponsor. Buy-in begins with the agreement of these risks and the development of the associated plans, which sets the tone for the entire project.

The project manager oversees risk assessment, risk mitigation and management strategies. RBM project leads operate much as they do in traditional studies, reviewing study performance data and making high-level decisions. A key difference is the use of technology and enhanced data management and review processes that enable ongoing and earlier data review by the right resources for faster decisions. Process enhancements also include more direct integration into data collection, analysis and management.

With ongoing data surveillance, teams can expect faster access to more complete data, including patient, site and study insights. Improved data analysis tools allow them to visualize timely, holistic data in new ways to complete reviews more quickly and more accurately, improving patient safety.

Clinical research associates (CRAs) visit sites as needed, with visits being dictated by the results, triggers and alerts generated by the RBM process and technology, rather than by a timed schedule. The goal is to visit a site at the right time, focused on doing the right things, using the right resources.

Research suggests that some sponsors and site staff worry that RBM may mean more work for the site. Done right, RBM should mean less work at the site, not more. While the CRA may spend less time onsite, a central support team identifies needs and prepares action plans for the site. The CRA can therefore assist with more critical site tasks such as enhancing enrollment or patient engagement, rather than spending time verifying data. As much of the interaction with the site is performed centrally, queries are reduced and can be resolved faster, by phone or email rather than by waiting for the CRA to appear onsite.

Do the Right Thing, At the Right Time, With the Right Resource

Centralized monitoring lies at the heart of RBM. Centralized monitoring is the hub that integrates clinical operations, clinical monitoring, data management, analytics with subject-level data review and early signal detection. It uses Quintiles Infosario® technology platform to provide global insights into patient, site and study performance to enable faster, more informed decisions throughout the trial. It also provides full transparency with the study team, reducing the oversight burden. Utilizing a global delivery network provides standardized processes for consistent delivery for global scale with local touch for sites.

* Innovation in the pharmaceutical industry: New estimates of R&D costs, DiMasi, Grabowski and Hansen, 2016
Centralized monitoring operates in four key areas to mitigate trial risks.

1. **Predictive and advanced analytics** provide statistically-driven insights that proactively identify risks and potential problems before they can affect operations. Improved analytics are enabled by faster data collection and integration with more efficient data visualization.

2. **Targeted site support** allows the central hub to support CRAs and sites directly and ensure sites get all the support they need. Support may be a proactive, informative telephone call or a response to site queries. These additional resources replace and enhance the support provided by CRAs. The central team also supports the CRA during site visits, identifying key areas of focus and preparing materials for the visit. The goal is create a more standardized site support structure to optimize the right action, at the right time, using the right resource.

3. **Subject-level data review** and early signal surveillance is a holistic subject review that improves patient safety by seeking out issues earlier and ensuring medical congruency. Medically-trained staff review patient data in near real-time, following patients through the life of the study. This provides earlier trend detection and earlier identification of potential issues, greatly enhancing patient safety.

4. **KRI and trigger management** are unique to each study because every study has its own universe of risks and triggers. Central monitoring triages KRI alerts to help site and project personnel take the right action at the right time using the right resource.

**Understand Risk to Mitigate Risk**

The RBM initial risk assessment leads directly to a Risk Assessment Mitigation Plan, or RAMP. The RAMP is developed early in the study planning process, typically in parallel with the development of the protocol, electronic case report form (eCRF) and other guidance documents.

The RAMP identifies the core risk assessment and management approach for the lifecycle of the study. It identifies the essential data or processes to be monitored and how they will be monitored, remotely, onsite, by centralized monitoring or some combination.

The RAMP is created by a cross functional core group with representatives from each operational team that has a role in the study, including project management, biostatistics, data management, medical review and more. Each team brings its own perspectives, skill set and knowledge. This is the team that identifies the different scientific and operational risks that drive planning and execution for the entire project.

Key data points and processes typically include primary and secondary efficacy endpoints, serious adverse event recording and reporting, informed consent, key inclusion and exclusion variables, events leading to discontinuation of treatment, variables for visit schedules, treatment windows, dosing, intellectual property management, laboratory values and other study-specific variables and data streams.

The RAMP is a dynamic document. Events such as protocol and eCRF amendments, risk reevaluation and...
adjusts to monitoring triggers should all generate a RAMP review and update it accordingly throughout the trial.

The goal is to build data monitoring and operational plans that mitigate risks while maximizing patient safety, data quality and study outcomes. Risk assessment and mitigation are a roadmap extending from study concept and design through execution to analysis of data and interpretation of outcomes. The RAMP delineates the core guiding principles that ensure every step of the study applies the right action at the right time using the right resource.

**Use Triggers and Analytics to Manage Site Risks**

The RAMP defines risks as high, medium or low, depending on the type of risk and its potential to affect the trial. High risk activities such as informed consent, IP, onsite relationships and source documents must be reviewed and monitored onsite to maximize visibility, expedite response and minimize the potential negative impacts on patients and study.

Lower risk areas such as site progression can be monitored remotely by the central monitoring team. Protocol questions can almost always be answered by phone or email.

Centralized monitoring can initiate different types of site visits in response to trigger alerts. The most serious alerts trigger an ad hoc site visit by the CRA. Less serious alerts trigger a remote visit, typically in the form of a structured phone call or email from the central monitoring team. Sites are encouraged to query central monitoring team for advice or assistance.

The RAMP also creates rules and operational procedures for defining and managing triggers. Most triggers are automatic, but subject level reviews can trigger manual alerts.

All alerts, automated and manual, are displayed on a Quintiles Infosario dashboard created for the study. Triggers are triaged by a clinical analyst. Reconciling the trigger may require an ad hoc site visit by the CRA, it may be resolved remotely by the analyst or it may be an event that requires no action.

Trigger analytics give the project manager and central monitoring team broad insight into the status and progress of the study. Analytics are performed in near real-time, giving study teams an opportunity to spot early trends and preempt problems before they become serious. Analytics transform traditional reactive monitoring that attempts to isolate and repair problems into a proactive and preactive process that identifies and resolves problems in the earliest stages. Analytics identify the highest risk sites and the highest risks at each site, allowing the team to focus attention, time and resources. This focused response improves study safety and quality.

**Employ Risk-Based Monitoring to Improve Investigator Satisfaction**

Performance measures based on investigator feedback from a broad range of Quintiles studies show that RBM-run studies score consistently higher on each of 12 measures sampled. Notable gains included, more effective communications and better working relationships in RBM versus conventional studies.

Survey results also showed that substituting remote visits for regularly-scheduled site CRA visits is highly effective. Investigators commented that fewer CRA visits translate into more efficient and effective site operations, in part because the central monitoring team is always available for questions and support.

**Apply Risk-Based Monitoring to Improve Study Quality**

An analysis of RBM versus traditional studies shows improved quality outcomes:

- 45% reduction in the number of missing pages in RBM studies vs. traditional studies in 2015
- 5x as many RBM study sites enter data within 7 days vs. traditional study sites in 2015
- 28% improvement of aged queries (>10 days) in RBM studies vs. traditional studies in 2015
- 47% higher action item closure on RBM vs. non-RBM in 2015
- 4x lower error rate in critical data in a head to head comparison of RBM to traditional 100% SDV from 2014 to 2015

Analytics give the project manager and central monitoring team broad insight into the status and progress of the study.
Improved analytics and subject-level data review improve patient safety while early signal detection helps sites identify and act on problems before they affect patient safety or site operations. The end result is improved safety with improved study quality, which results in lower risks.

**Mitigate Risk with more Efficient Study Execution and Stronger Outcomes Using Risk-Based Monitoring**

RBM is transforming clinical development. Connecting new insights in monitoring with improved operations improves safety and outcomes. Risk can never be eliminated from clinical studies, but risk-based monitoring helps to reduce and mitigate those risks.

Implementing an up-front risk assessment and a team-based, cross-functional risk assessment mitigation plan that guides the entire lifecycle of the study enhances safety, helps to improve quality results, encourage faster and better-informed decisions, boost site effectiveness and expand operational efficiency while reducing risks.

RBM can improve study outcomes by redefining the roles of CRAs and redesigning the entire monitoring process with a focus on safety, quality and performance. The result is a targeted, focused monitoring mindset designed to do the right thing, at the right time, using the right resource. This enhanced focus on the most critical elements of the trial improves data entry speed and accuracy, reduces the need for in-person site visits, improves operational efficiency at study sites, provides more effective site support and improves patient safety while reducing risks.

RBM

The result is a targeted, focused monitoring mindset designed to do the right thing, at the right time, using the right resource.