TRANSFORMING RISKS INTO RESULTS WITH XCELLERATE® MONITORING

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As the complexity of clinical trials grows, sponsors are increasingly revisiting their monitoring methods to uncover new efficiencies while ensuring ongoing patient safety and data quality. Risk-based monitoring (RBM), which employs statistical approaches and centralized monitoring practices to focus on critical risks, is often compared with traditional reviews that require source data verification (SDV) during frequent on-site visits.

At Covance, we recognized the opportunity to develop a more advanced monitoring strategy into an integrated data visualization and insight platform: Xcellerate® Monitoring. By centralizing and consolidating key clinical trial data into a single world-class technology platform, Xcellerate Monitoring delivers a risk-directed and trigger-driven approach to clinical monitoring and trial conduct.

If you’re ready to enhance patient safety, data quality and cost efficiency in your clinical trials by redirecting monitoring efforts, learn how our customized approach to RBM can transform your risks into results. Let’s discuss:

▶ Benefits realized from integrated regulatory guidance
▶ The foundation for efficiently employing risk-based monitoring
▶ Measures of success for an integrated monitoring approach
▶ Evolving approaches for ongoing improvements in monitoring across your portfolio of trials
Tailoring Regulatory Guidance to Realize New Benefits in Clinical Monitoring

Our industry’s shifting approach to managing risk has been explored and evaluated by many regulatory agencies. The FDA Guidance to Industry titled “Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring” in August 2013 made several recommendations to guide development of Risk-Based Monitoring (RBM) methodology. This guidance signaled further movement toward RBM from a regulatory authority, following the lead of other health authorities including the European Medical Agency (EMA) and the United Kingdom’s Medicines and Healthcare products Regulatory Agency (MHRA). Industry-generated guidelines were also released by TransCelerate Biopharma Inc., a consortium of pharmaceutical and biotechnology companies.

As a whole, the guidance documents encourage pharma, biotech, CRO and ARO groups to adopt risk-based approaches in clinical trial execution. The documents also include the redefinition of Source Data Verification (SDV), introduce the concept of Source Data Review (SDR) and encourage the industry to focus on high-risk study sites and high-value activities.

At Covance, we integrated these practices into a risk-based approach to clinical monitoring to focus on four key benefits:

- Reduced effort on non value-added SDV transcription checks
- Sharper focus on value-added SDR compliance and documentation checks
- Potential reduction in effort and time for on-site monitoring visits
- Increased use of remote monitoring

With a widespread and growing industry view that traditional monitoring is unsustainable from a cost and outcome perspective, implementing these monitoring practices marks the first steps toward “intelligent monitoring.”

Employing Risk-Based Monitoring to Proactively Mitigate Risk and Drive Better Outcomes

Based on the framework developed by TransCelerate along with guidance from industry regulators, we developed a robust monitoring strategy to build three pillars for Xcellerate Monitoring and help sponsors improve outcomes.

1. **Quality by Design** – Builds quality in and designs risk out of studies during the planning phase to proactively reduce complexity
2. **Adaptive and Triggered Monitoring** – Identifies issues and focuses on critical data and processes through remote monitoring and risk-triggered on-site monitoring
3. **Central Monitoring** – Holistically reviews a wide spectrum of risk with specialized central reviewers, spanning global trends to site-specific outliers across multiple clinical data sources

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<th>Xcellerate® Monitoring: 3 Foundations</th>
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<td>QUALITY BY DESIGN</td>
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<td>Protocol review</td>
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<td>Critical data &amp; process definition</td>
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<td>ADAPTIVE AND TRIGGERED MONITORING</td>
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<td>Central review of risk</td>
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Quality by Design begins as early as the pre-award, study planning stage and involves protocol review, critical data and process definition and careful evaluation of risk at the study, site and operational levels. The risk assessments are supported by a customizable Xcellerate Monitoring tool containing multiple risk indicators, including complexity of the study and quality of the sites involved based on staff experience and prior site performance, among other factors, to help identify critical data and shape the monitoring approach.

Adaptive and Triggered Monitoring includes a review of the Xcellerate Monitoring Operational Risk Dashboard based on integrated and incoming data streams. Here, the team identifies new site risks and adapts the monitoring plan with targeted actions for each site based on the level of observed risk. The review can include remote monitoring of site data, increased or decreased SDV/SDR, risk-driven site visits and targeted training.

Central Monitoring further enhances the benefit of RBM for clinical monitoring teams by supporting site-focused clinical research associates (CRAs). RBM experts or central monitors use the Operational Risk Dashboard, Central Medical Review, Central Statistical Monitoring and Central Data Review tools to enhance their visibility into safety, study performance and statistical processes. The centralized platform is optimized to identify outliers and trends at protocol, country or site level, extending the capability of CRAs reviewing data at individual study sites. Then CRAs can focus on critical data and processes while developing strong relationships with the chosen investigative sites.

Profiling Risk with a Three-Tier Approach

Risks can emerge in many different areas of a clinical trial. That’s why we identify and profile risks through a comprehensive, unique three-tier approach. Employed consistently across Xcellerate Monitoring studies, this approach has built-in flexibility to accommodate study-specific risks at the protocol, site and operational levels.

Level 1: Study Risk Assessment – A cross-functional team of experts assigns the study risk profile and details study risks and mitigations in line with the TransCelerate proposed Risk Assessment and Categorization Tool (RACT). Before a study begins, new studies are tiered based on risk and internal teams are alerted to follow high-risk studies and drive mitigating actions earlier.

![Risk & Intervention Level Chart](image-url)
Developing a Risk-Based Monitoring Plan

Studies are supported by both Xcellerate Monitoring and a study-specific RBM plan that guides monitoring staff to accurately and consistently evaluate site performance in such key areas as:

- Quality of source documentation
- Protocol compliance
- Adequacy of critical processes
- Confirming appropriate investigator involvement and appropriate delegation
- Compliance to other areas (e.g., SOPs, ICH GCP guidelines) through focused SDR

The plan carefully defines specific monitoring interventions based on the assessment of study risk level, including the definitions of SDV and SDR requirements during the initiation and monitoring of the study. Accurate and timely assessments of site performance are critical to the success of RBM methodology. These assessments allow the monitor to make immediate adjustments to the site-monitoring strategy by evaluating risk indicators while on-site along with feedback from the centralized review process and with appropriate guidance from a clinical team lead, when needed.

Supporting proactive risk identification and management requires extensive up-front planning and continual reliance on accurate and timely information. The Xcellerate Monitoring methodology has been designed from the ground up by a cross-functional team of experienced experts, guidance from industry regulators and the TransCelerate RBM working group. At Covance, we remain focused on developing a holistic process to continually improve in-patient safety, data integrity and regulatory compliance.
Measuring Success of an Integrated Approach

As with any approach, performance must be measured and compared to determine its impact on results and the bottom line. Yet there is no single measurement to confirm the success of a holistic and integrated approach to clinical monitoring. We can, however, observe success based on indicators in patient safety, data quality, regulatory compliance and cost efficiency. Results with Xcellerate Monitoring show positive returns in overall quality, timeliness of data handling and cost efficiency. These measurable benefits include:

### Xcellerate Monitoring

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<th>Success Measure</th>
<th>Description</th>
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<td><strong>Quality</strong></td>
<td>Covance Xcellerate Monitoring studies average 20% fewer critical/major findings per CQC (clinical quality control) visit when compared with traditional studies over the period January 2013 – November 2015 (p &lt; 0.001)</td>
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<td><strong>Cost Efficiency</strong></td>
<td>When compared with traditional studies in our portfolio, Xcellerate Monitoring studies average (based on average % of clinical monitoring spend over the period January 2013 – July 2015): - 30% lower site management spending - 18% lower travel spending</td>
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<td><strong>Timeliness</strong></td>
<td>When compared with traditional studies in our portfolio, sites involved with Xcellerate Monitoring studies average (as of October 2015): - 66% fewer missing eCRF pages - 50% less SDV backlog at sites</td>
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These initial measures reflect the quantifiable benefits of an integrated and adaptive clinical monitoring approach that focuses on the areas of highest risk.

### Ongoing Improvements in Risk-Based Monitoring

While we've covered straightforward ways to implement an RBM methodology, multiple challenges still exist. TransCelerate recommends additional consideration in the following areas:

- **Creating Ongoing Success Measures.** As RBM becomes more widely used in the industry, we must continually evaluate methods to assess quality, timeliness and efficiency and build findings back into the development process.

- **Maximizing Digital Technology Use.** Clinical trial data is increasingly digitized, stressing the need for robust analytics, technology and data integration to enable efficient and effective monitoring. In the near term, we will see further integration of cross-functional data streams and increased sharing of informatics platforms between interdependent operational teams such as clinical monitoring, pharmacovigilance, clinical data management, statistics and risk-based or central monitoring groups. The next steps are underway to include expanded access to informatics platforms among a sponsor, its CRAs, and possibly, investigator sites. In the long term, we may even see the demand for on-site SDV eliminated and the movement to adaptive and focused SDR, as our industry increasingly embraces electronic health records and adopts “eSource” online document repositories to conduct clinical trials.
Improving Resourcing Capabilities. Data-driven resourcing decisions will help CRAs focus on the sites of highest risk and reduce their efforts at lower-risk, well-performing sites. Our informatics platforms also can support physicians, statisticians and data managers as they redirect their resources to the areas of highest risk. As this holistic approach to study and site management evolves to include a wider range of centralized and specialized roles, we’ll witness new roles and opportunities to collect and integrate data, identify issues and mitigate risks across the program, trial, country, site, patient and critical data point levels.

Driven by a global, cross-functional team of experts, the Covance Xcellerate® Monitoring team is working to continually refine our methodology to align with industry guidance. Through the comprehensive state-of-the-art data integration and analytics platform Xcellerate Informatics, we are helping sponsors turn clinical trial risks into measurable results. Learn more about how our robust approach to clinical trial monitoring delivers greater improvements in data quality, patient safety and cost efficiency across the clinical research industry.

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Adam has spent 26 years in clinical research and has been with Covance for over eight years. With job roles in pharma and with an EDC vendor and several major CROs, he is experienced in RBM, process excellence, project management, clinical data management and clinical monitoring. Adam leads Covance’s full-service RBM and central monitoring team, which implements RBM tools and processes on client studies. Until October 2015, Adam led the cross-functional transformational project team responsible for the implementation of RBM at Covance. Most recently, the transformational team launched Xcellerate® Monitoring version 2.1, which includes expanded RBM services and capabilities such as medical review, protocol deviation reporting, study data warehouse and client access.

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Chris has been with Covance five years, after starting in the clinical research industry with Quintiles in 2006. With broad experience in clinical operations and line management in the Asia Pacific region, Chris is now applying RBM into clinical monitoring and other functions. Chris is the process lead for RBM at Covance, and a senior manager within the Monitoring & Data Flow Optimization team (Covance’s RBM function). In this role, Chris coordinates the design of RBM tools and processes across interdependent functional groups and supports the implementation of new components as part of Covance’s full-service RBM and central monitoring offerings.
References:


2. DIA – Therapeutic Innovation & Regulatory Science: Evaluating SDV as a Quality Control Measure in Clinical Trials. 30 October 2014.


