

The Evolution of an Enterprise Risk-Based Monitoring Process

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Objectives

- Describe the evolution of an enterprise Risk-Based Monitoring (RBM) process from the baseline problem across clinical trial conduct, the processes implemented and the data-backed outcomes achieved
- Share a comprehensive and differentiated approach to RBM as well as benefits achieved from previous implementations
- Demonstrate how to achieve measurable quality and cost-saving improvements in global clinical trials by applying RBM methodology throughout the study lifecycle

Methodology

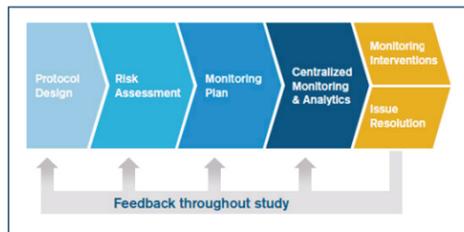
Over the past five years a global cross-functional group (including clinical study teams, functional leaders and expert working groups) has collaborated to define and implement an enterprise RBM process.

This enterprise approach is rooted in an operational platform based on predictive, proactive and preventive clinical trial management, leveraging clinical trial conduct expertise and experience across the enterprise.



Enterprise RBM Process – Three Key Characteristics

- End-to-end process from protocol design through to study reporting and ultimately NDA/MAA submission to ensure quality is built up-front for scientifically valid and ethical trials
- Comprehensive set of study and site risk assessments to ensure critical data is identified early on and monitored throughout the study lifecycle
- Ongoing management of risk to adapt monitoring plans and safeguard patient safety and data integrity



The enterprise RBM process is designed to transform risks into returns through a proactive, preventive, and systematic approach.

Core methodology principles include:

Focus Resources for Greatest Impact and Highest Value

- Resources are directed to high ROI areas such as risk prevention and primary data quality
- Flexibility to scale up or down, and adapt efforts as study and site risk profiles evolve
- A focus on fit-for-purpose quality prioritizes risks and errors that may impact patient safety, data quality, regulatory compliance and drug approval
- Realization of efficiency benefits focused on low-risk, non-critical data and processes

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Proactive Planning and Primary Quality Reduces Likelihood of Delays

- Operationally consistent implementation of RBM designs out risk. This helps to reduce the likelihood of delays, rework and threats to quality and investigator enthusiasm
- Enterprise experience and quantitative forecasting expertise leveraged to proactively identify and mitigate risks and optimize trial conduct
- Optimized site selection included to help better predict which clinical sites are likely to deliver the right patients

Clearly Document Risk-Driven Decisions and State of Control

- Regulatory compliance by design: effort is matched to the most important risks, preventing errors that would impact patient safety and study results
- Actions taken to address risk are clearly documented, as well as preventive plans
- Robust operational design and implementation focused on real-life pressure points support state of control: comprehensive team training, process design and optimization, technological enablement and communication plans combine to prevent variability and loss of control

Simple at the Point of Use

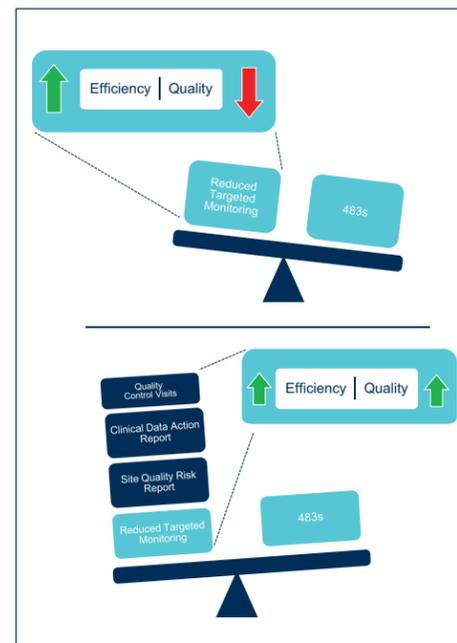
- The enterprise RBM approach is designed to be operationally robust, efficient and scalable. Ensuring compliance and taking the right actions at the right time needs to be simple. To that end, an end-to-end RBM road map for clinical trial staff is in place and this road map includes:
 - Training to promote adherence to the protocol and monitoring plan
 - Easily understandable data visualization and interpretation
 - Clearly defined operational steps to take to reduce or mitigate risk
 - Firm directions for documenting actions and prevention plans consistent with regulatory expectations
 - Targeting on-site monitoring on pre-identified key risks

Results

Background for the Enterprise RBM Solution

The drug industry was seeing high numbers of monitoring-related 483s; cross-study issues were not being adequately identified with traditional monitoring approaches. A trend toward larger and more complex studies was exacerbating the problem, and highlighting the need for a different approach

One approach followed was **reduced targeted monitoring**. Reduced targeted monitoring, however, focuses on efficiency and therefore raises concerns over quality. As a result, quality enhancing approaches were identified to help reduce quality concerns:



Site quality risk report

- This report represented a form of proto risk-based monitoring, introduced before the related regulatory guidance, using same principles associated with risk targeting, variable risk factors and risk points

Clinical data action report

- A clinical data action report follows same principles as risk-based monitoring i.e. identifying largest backlogs of data entry and queries at sites and SDV with monitors

Quality initiative supporting registration – site quality risk reports established across portfolio

Quality control visits

- Applying risk-based monitoring principles across an entire study portfolio
- Assessing general risk factors which apply across all studies and implementing additional on-site assessment at high-risk sites

Site Quality Risk Reports

- In one study the site quality risk report process helped identify more than 20 sites with high regulatory risk prior to database lock

These sites were investigated and an action plan was implemented based on outliers using site quality risk reports in a number of areas such as adverse events (AEs), PI oversight, data flow, etc.

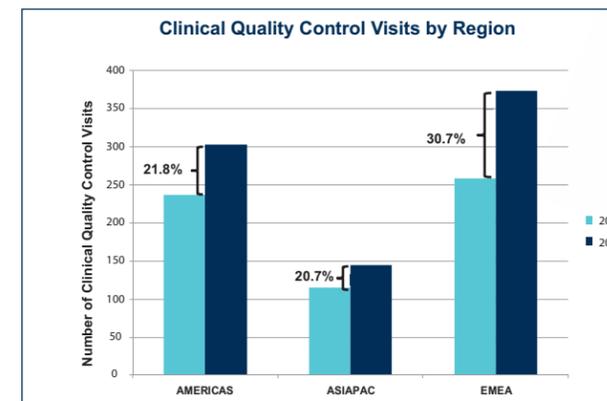


- Looking at AEs, supplementary training was performed, as well as additional SDV and in some cases audits

- This approach corrected significant under-reporting of events. Corrective actions were taken in time to secure approval from the FDA and EMA

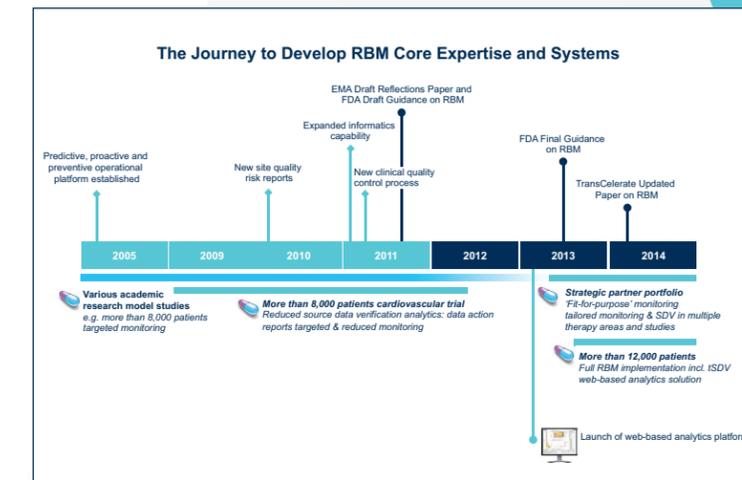
Clinical Quality Control Value Drivers

- Process rigor identifying sites at highest risk across entire portfolio
- Centrally managed issue management
- Improved transparency of performance
- Increased confidence



Increased Efficiency Resulting in Reduced Study Delivery Costs

- A mix of targeted Source Data Verification and RBM helped reduce the number of Routine Monitoring Visits needed by 30% and had a significant effect on travel costs. This translated in 63,606 hours saved on visits, based on 3,517 visits not needed and 18 hours per visit. This generated \$3,165,300 savings in travel costs



Conclusion

Five years ago, the industry relied heavily upon individual monitor capability to identify and resolve site issues in a find-and-fix paradigm. This process was prone to individual CRA failure and did not identify and manage cross study risks and trends effectively.

It was hypothesized that designing and implementing trial delivery processes to maximize up-front risk identification, design monitoring interventions, and track actual performance using data and risk indicators would simultaneously drive improvements in quality and deliver efficiency benefits.

A sequence of improvements was designed – implementation of a predictive, proactive and preventive study delivery paradigm, designing of site quality risk reports, an enhanced clinical quality control program and adaptive monitoring designs all drove improvements. These formed the cornerstone of an enterprise RBM approach which was validated with the release of the FDA Risk-Based Monitoring guidance.

Disclosure

The author of this presentation has the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:

- Ben Dudley: Nothing to disclose