

# INSPECTION FOCUS IN CLINICAL TRIALS USING A RISK-BASED MONITORING APPROACH

Current regulatory guidance explains how risk-based monitoring (RBM) should be implemented within a quality management system; however, a key question is left unanswered: *“how will clinical trials that adopt an RBM approach be inspected by regulatory agencies?”*

This is a topic the regulatory agencies are still considering; however, we have received some indications of how RBM trials will be inspected, based on recent conference presentations by US and European regulatory agency staff. We also have received some indications based on discussions with the agencies. These indications may help to start answering the question “how will clinical trials that adopt an RBM approach be inspected by regulatory agencies?” and are summarized in this paper.

It is well documented that clinical trials have become increasingly complex and costly. Driven by these factors, the biopharmaceutical industry and regulators have recognized that applying a Quality by Design (QbD) approach and using quality risk management techniques in clinical trials can potentially reduce complexity and cost, while at the same time improving quality. To achieve these goals, **a key first step is to identify potential risks that could impact the delivery of robust data.** These can then be relied upon for developing conclusions about the study endpoints. **The next step is to focus resources on managing and mitigating these risks, while also ensuring that the safety and rights of trial subjects are protected.** A quality risk management system applied to clinical trials includes the elements of risk identification, risk analysis/evaluation, risk control/mitigation, risk review, continuous improvement and communication.

## Good Clinical Practice compliance is key – also when applying RBM approaches

Just as in clinical trials conducted with a conventional monitoring approach, the purpose of inspection in a risk-based environment is to verify that the clinical trial was conducted in accordance with good clinical practice (GCP) principles and applicable regulations. The objective is to provide assurance that the rights, safety and well-being of clinical trial subjects are protected and the results of the clinical trial are credible and accurate.

## So what is likely to be different?

When an RBM approach is used, we believe there will be an emphasis during inspection to verify that **all parties involved in managing the clinical trial demonstrate they established a state of control** to safeguard the clinical trial subjects and maintain data integrity throughout the life of the trial.



It is our current view that a regulatory inspection of a clinical trial using RBM approaches will pay particular attention to the following questions:

- ▶ How were critical data and processes in the clinical trial identified and what was the extent of cross-functional participation in this process?
- ▶ To what extent was the risk analysis incorporated into the protocol design to eliminate or mitigate identified risks to the critical data and processes?
- ▶ To what extent was the output of the risk analysis aligned with the risk mitigation and monitoring strategies described in the monitoring and other study plans to eliminate or mitigate identified risks to the critical data and processes?
- ▶ Were clearly defined responsibilities captured in study plans for monitoring the clinical trial, including required activities that must be performed on-site, off-site (remote) and central?
- ▶ Was meaningful consideration given to the impact of RBM on other study oversight processes (e.g. vendor oversight, investigational product supply chain, independent monitoring board)?
- ▶ Were risk indicators and associated thresholds clearly identified and quantified so that they were measurable and informative, and how were these metrics monitored throughout the trial?
- ▶ What is the evidence and rationale to justify tolerance levels and the acceptable ranges of variability built into the protocol and study plans?
- ▶ How were the actions defined to be taken when a threshold is exceeded?
- ▶ To what extent was sponsor/CRO staff and investigational site staff trained on the application of RBM?
- ▶ What was the extent of compliance with the protocol and study plans?
- ▶ What is the evidence that processes, including definition of roles and responsibilities, were in place and used effectively throughout the clinical trial to allow for emerging issues and risks to be identified, communicated and resolved satisfactorily in a timely manner?

## Closed-loop feedback vital to document state of control

We consider this last point to be especially important. This is because any quality management system must provide for an effective feedback mechanism to maintain control of clinical trial quality when events or metrics fall outside the established tolerance limits, and to apply “lessons learned” throughout the remainder of the clinical trial. We believe regulatory inspections of clinical trials using RBM are likely to ***focus on confirming that the critical data and processes were identified and managed appropriately.***

Regulatory guidance points to the need to identify and prioritize risks to the critical data and processes, recognizing that identification and mitigation of all potential risks is not practicable. ***Instead, the importance of having systems in place to deal swiftly and effectively with emerging issues and risks is emphasized as a key component of the RBM approach.***

## What stays the same and what may change?

We believe that it is unlikely for there to be any fundamental change in the underlying approach to regulatory inspections in response to the use of RBM techniques. While single issues that are not managed appropriately in the clinical trial may be raised as findings during a regulatory inspection, ***the focus in RBM trials, just as in non-RBM trials, will be on identifying systemic issues that cast doubt on the protection of clinical trial subjects and/or the integrity of the data generated in the clinical trial.*** The difference, in an RBM environment, is that additional activities related to the identification, assessment and mitigation of risks and the timely resolution of issues will likely be of increasing importance during regulatory inspections.

We will continue to monitor and analyze developments on this topic in order to maintain alignment of our approach to RBM with regulatory agency expectations.

## More RBM Information

More information about our approach to risk-based monitoring is available at [www.covance.com/RBM](http://www.covance.com/RBM).

### Effective RBM Implementation: the basics of “how to”

There is great interest in the use of RBM as an important component of an effective overarching quality risk management system for clinical trials. For instance, consider recent regulatory guidance from the US Food and Drug Administration (FDA)<sup>1</sup>, the European Medicines Agency (EMA)<sup>2</sup>, the Ministry of Health in Japan<sup>3</sup> and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK<sup>4</sup>. Additionally, industry initiatives by the Clinical Trials Transformation Initiative (CTTI)<sup>5</sup> and the TransCelerate BioPharma Inc. consortium<sup>6,7</sup> have provided recommendations on how to incorporate RBM techniques within a quality risk management system.

The papers published by these organizations establish the case for RBM and the advantages of using multiple and flexible monitoring techniques within a single clinical trial. Also, recommendations are provided on the elements required to implement RBM effectively. Key elements include:

- ▶ Prospective identification of critical data and processes which, if inaccurate or not performed properly, would threaten data integrity or the protection of clinical trial subjects
- ▶ Risk assessment to identify and understand the nature, sources and potential causes of risks that could affect the collection of critical data or the performance of critical processes and to prioritize these potential risks
- ▶ Use of the risk assessment analysis to determine the important risks that can be addressed through monitoring (rather than by other means, such as modifying the clinical trial protocol to remove the source of the risk) and the types and intensity of monitoring best suited to address these risks
- ▶ Effective escalation processes to identify and manage emerging issues and risks rapidly and appropriately
- ▶ A monitoring plan that includes details of the critical data and study procedures, the specific risks to be addressed by monitoring, how monitors will be provided with adequate information to effectively perform their duties, monitoring activities, criteria for determining the timing, frequency and extent of the planned monitoring activities, definition of events or findings that trigger planned changes in monitoring activities, processes for appropriate communication of monitoring results, processes for management of issues of unresolved or significant noncompliance identified by monitoring, specific training required for personnel conducting internal data monitoring and specific training required by investigational site staff
- ▶ Specific areas of focus in developing the monitoring plan and appropriate risk mitigations should include subject eligibility, endpoint assessment, safety assessment, event adjudication process, compliance with the dosing regimen and arrangements for discontinuation, retention and follow-up of trial subjects

<sup>1</sup> US Department of Health and Human Services Food and Drug Administration. Guidance for Industry: Oversight of Clinical Investigations – A Risk-based Approach to Monitoring, August 2013.

<sup>2</sup> European Medicines Agency. Reflection paper on risk based quality management in clinical trials. 18 November 2013.

<sup>3</sup> Ministry of Health, Labour and Welfare, Pharmaceutical and Food Safety Bureau, Evaluation and Licensing Division Notice: Basic rules of the risk-based approach to monitoring clinical trials. 1 July 2013.

<sup>4</sup> Medical Research Council/Department of Health/Medicines and Healthcare products Regulatory Agency Joint Project. Risk adapted approaches to the management of clinical trials of investigational medicinal products. 10 October 2011.

<sup>5</sup> Clinical Trials Transformation Initiative. Results and Recommendations: Effective and efficient monitoring as a component of quality assurance in the conduct of clinical trials. August 2011.

<sup>6</sup> TransCelerate Biopharma Inc. Position Paper: Risk-based monitoring methodology. 30 May 2013.

<sup>7</sup> TransCelerate Biopharma Inc. Risk-based monitoring update – Volume I. 27 January 2014.

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