Paper **RM01**

Reducing Rate of False Positives Risk Signals with Risk Management Strategy

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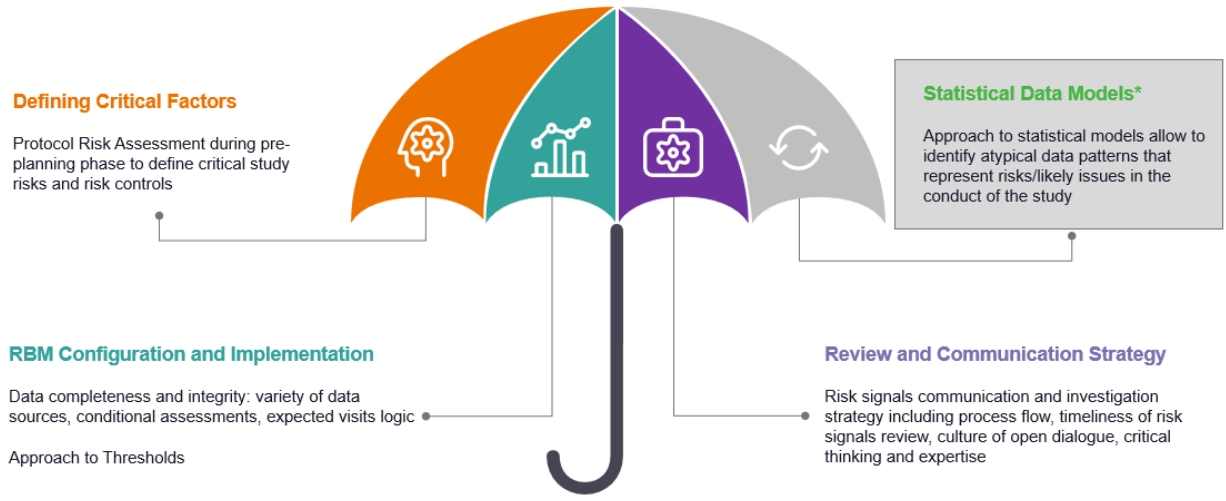
This article covers various aspects of the risk management strategy design aiming to reduce the rate of false positive signals in centralized monitoring. Risk-based monitoring (RBM) is a widely adopted approach in clinical trials that uses statistical algorithms to identify potential risks and issues in real-time. However, one of the challenges with RBM is the high rate of false positive signals, where risk signals are triggered but do not actually represent real issues. Companies estimate that the rate of false positives in RBM can range from 50% up to 90%, with an average of 70%. While analytics and statistical data models are often blamed for false positives, there are other factors that contribute to this issue, such as critical study factors, RBM configuration and implementation, and review and communication strategies. In this article, we will explore strategies to reduce the rate of false positives in centralized monitoring that are not directly related to statistical data models.

There are multiple factors including but not limited to analytics contributing to the rate:

- Critical Study Factors
- RBM Configuration and Implementation
- Statistical Data Models
- Review and communication Strategy

The focus of this work is to explore strategies to reduce rate of false positives which is not directly related to the statistical data models:



DEFINITIONS AND FACTORS IMPACTING THE RATE OF FALSE POSITIVES OVER THE COURSE OF RISK MANAGEMENT

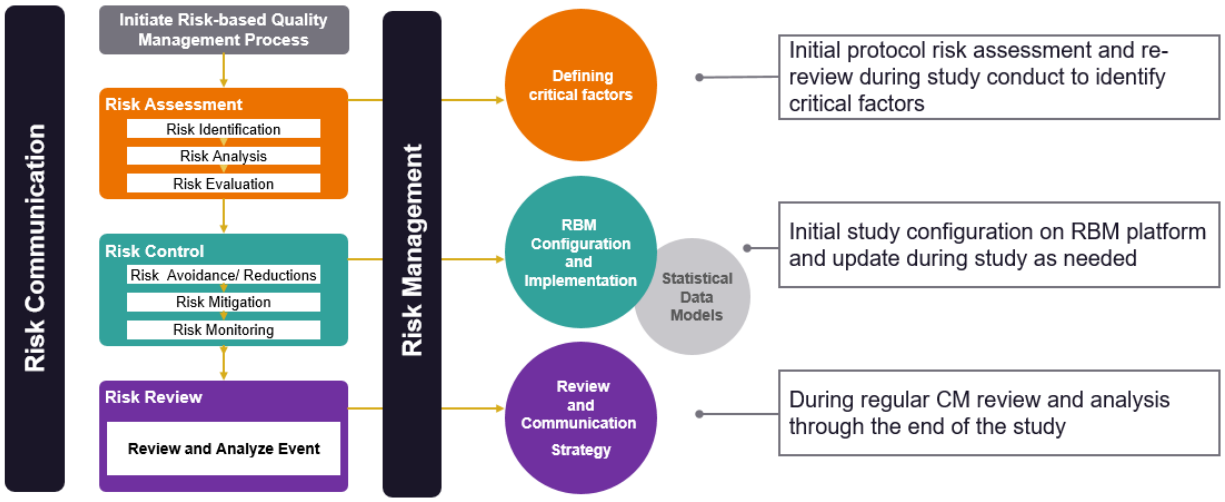
One of the foundational steps in reducing the rate of false positives is to define critical factors in the risk management strategy. Critical factors are the data and processes that are most important for the study and require focused attention. Over-engineering the approach to data collection without scientific justification can result in triggering meaningless signals and contribute to false positives. Therefore, a Quality-by-Design (QbD) approach should be followed, which emphasizes focusing on critical factors, simplifying processes, and being proactive in risk management. This can be achieved by optimizing study design, reducing burdens, and evaluating the approach to data collection during the protocol risk assessment and throughout the course of the study

	Example 1	Example 2
Risk Signal	"Abnormally low rate of AE at site 1010"	"High rate of Race reported as 'Unknown' in France compared to the other countries."
Actions	"SDV is conducted, no records were missed. Patients on the site have very few AE. Not an issue" False Positive	"Collection of race is not allowed per local regulation. Not an issue" False Positive
Reality	Same site consistently had lower AE rates across other studies Investigation was very limited (SDV only). No additional actions taken, e.g., signs of potentially missing AEs, conversation with PI etc.	Risk Indicator is not critical Neither KRI algorithm nor data collection modules reflect the regulation constrain, local requirements

Common scenarios of risk signals deemed false positive in RBM are:

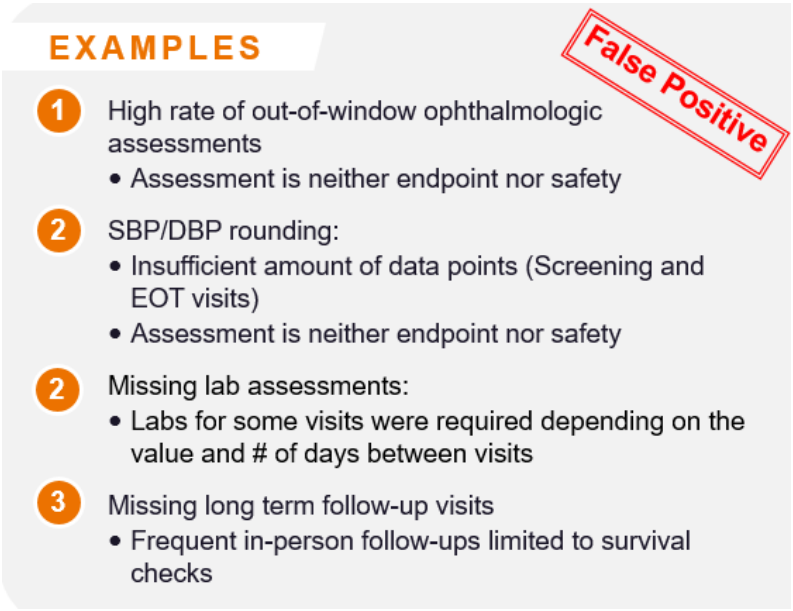
- Lack of understanding of a risk signal message, mitigation actions or root cause analysis
- Risks are neither critical nor timely. For example, risk for the high rate of screen failures should be treated during screening and beginning of treatment phase, but would not be useful for the study entering long term follow up
- Risk owner wants to avoid difficult conversation, for example with PI/Site
- Ambiguous configuration of KRIs or Thresholds

Major factors contributing to the false positive rates are correlated with the ability to define critical factors during protocol risk assessment, RBM configuration and implementation based on the study and data collection modules design, and risk review and communication strategy. Activities for each of the factors should be aligned with the risk management process:



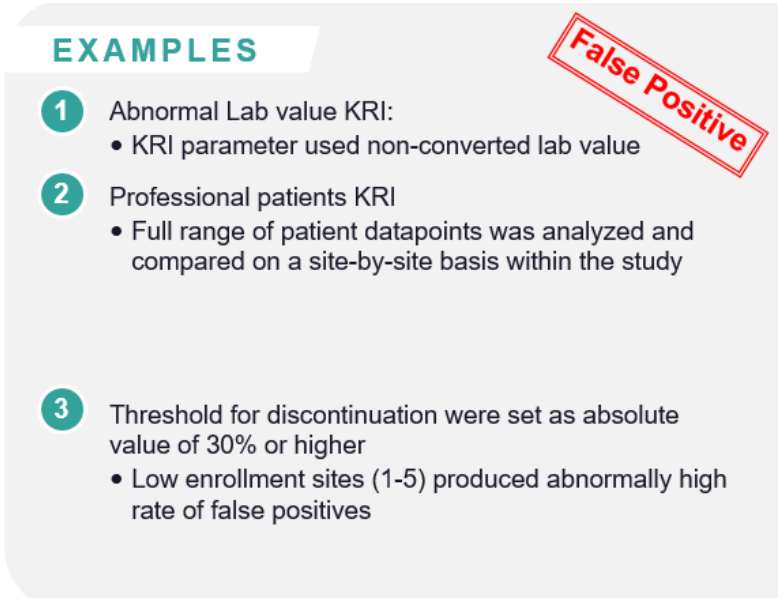
RISK MANAGEMENT STRATEGY TO REDUCE THE RATES

The RBM configuration and implementation should accurately reflect the study design and data collection approach to avoid false positives.



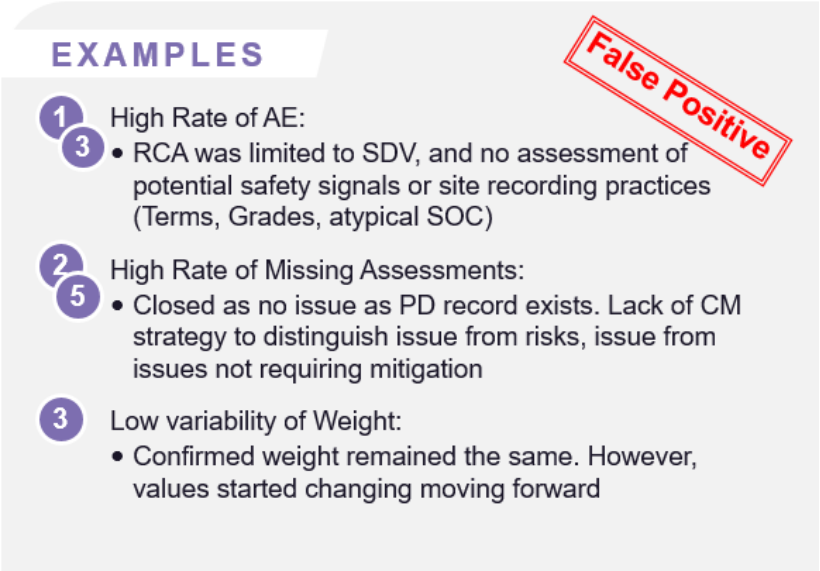
This can be achieved by evaluating the completeness of data collection, ensuring appropriate parameters are used in key risk indicators (KRIs), assessing whether KRIs reflect the complexity of study/data design (e.g., conditional assessments, visit windows), and evaluating the flexibility of the approach to thresholds.

Discussions and assessments of the data sources, data modules, and parameters should be conducted during study configuration on the RBM platform to ensure that they align with the study design and data collection approach.



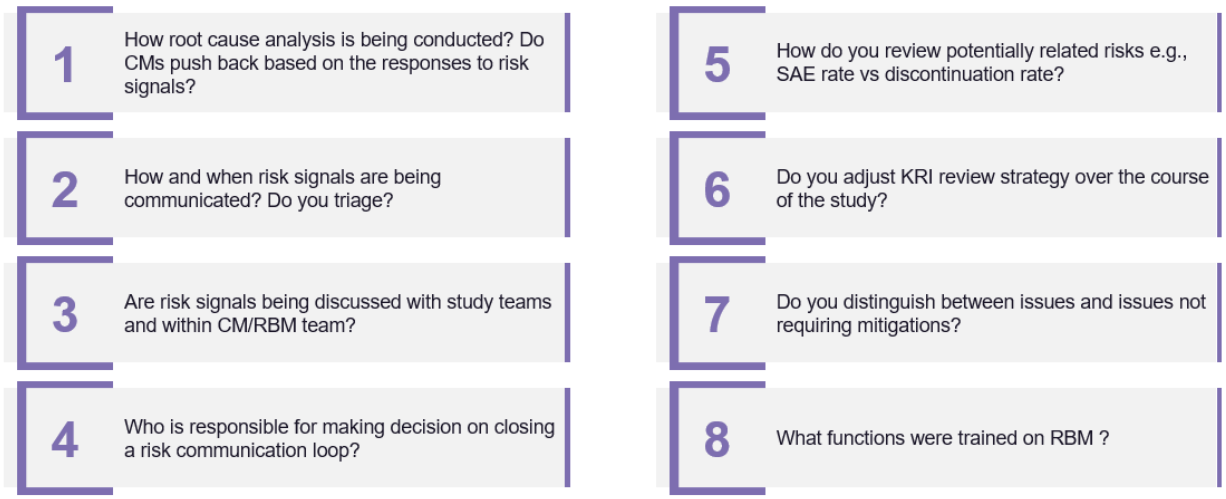
RISK REVIEW AND COMMUNICATION PRACTICES

Risk signal review and communication practices play a crucial role in reducing false positives. It requires a combination of company best practices and various skills of the centralized monitoring team, including knowledge of the clinical trial, ability to analyze data and identify root causes, good communication skills, persistence, and critical thinking. Some common challenges in risk signal review and communication include insufficient root cause analysis, lack of review analyzing the combination of multiple relevant KRIs, communication challenges such as resistance to acknowledge an issue, lack of open discussion, unclear risk messages and mitigations, timeliness of risk signals, and lack of consistent strategy in defining and following up on risk signals.



Risk review and communication is a big chunk of the risk management activities occurring over the full course of the study risk-based monitoring. To improve risk signal review and communication practices, RBM good practices should be continuously discussed and developed within the organization.

This may involve establishing clear guidelines and procedures for risk signal review and communication, providing training to the centralized monitoring team on effective risk management techniques, and fostering a culture of open communication and collaboration among team members. Regular discussions on how risk review should be conducted and communicated can help ensure that risks are properly identified and addressed, and false positives are minimized.



CONCLUSION

Reducing the rate of false positives in centralized monitoring requires a multi-faceted approach that goes beyond statistical data models:

- Identified risks are not critical to data and processes
- Configuration does not fully reflect study design and/or data collection
- Risk signals and/or mitigations are misunderstood or misinterpreted
- Responsibilities and risk communication processes are not defined
- RBM methodology is not mature and expertise is low in the organization

By taking these steps, companies can enhance the effectiveness of their risk management strategies and improve the overall quality of their clinical trials:

- Implementing thorough protocol assessment process to reduce potential risks due to flows in the protocol design

- Evaluating study RBM configuration to ensure completeness of the source data
- Ensuring both RBM configuration and review strategy if flexible enough to reflect study milestones and design
- Establishing framework and internal best practices for risk signals management, including but not limited to risk signals handling, communication and mitigation
- Building culture of open dialogue, continuous learnings and improvements

CONTACT INFORMATION

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