



Reducing The Rate of False Positive Risk Signals With A Risk Management Strategy

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PHUSE, March 2023

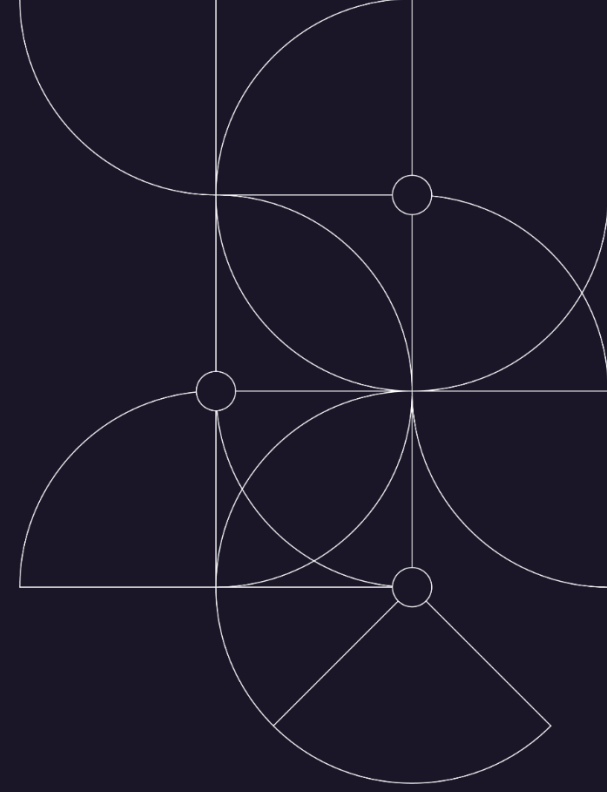
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Impact where it matters.



Content

- False positives in RBM:
 - Definitions and Examples
 - Factors and alignment with process
- Challenges and strategy to reduce false positive rate
- Summary
- Contacts



False positives in RBM

Definitions and application to RBM



Definitions

1

True Positives - Risk signals that correctly identify actual issues

2

True Negatives - The appropriate absence of risk signals where no issues

3

False Positives - Risk signals that do NOT identify issues

4

False Negatives - The inappropriate absence of risk signals where actual issues DO exist

Some companies estimate rate of false positives from 50% up to 90% with the average of 70%. Typically, the highest rates are Early Termination and AE/SAE, lowest - CRF entry delay and off-schedule visits

Operations vs Statistics: Any Differences?

Examples of ‘false positive’ RBM signals

	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” 	“Collection of race is not allowed per local regulation. Not an issue” 
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



Factors contributing to the high rate of false positives

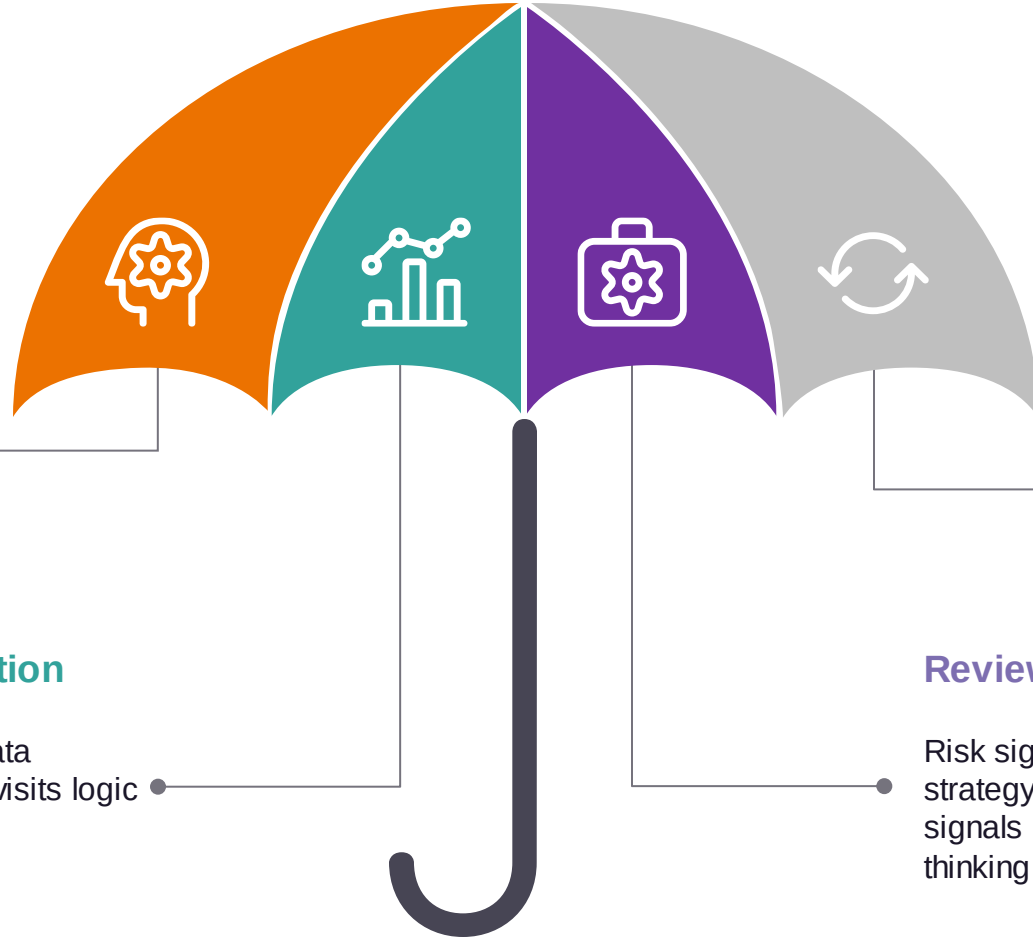
Defining Critical Factors

Protocol Risk Assessment during pre-planning phase to define critical study risks and risk controls

RBM Configuration and Implementation

Data completeness and integrity: variety of data sources, conditional assessments, expected visits logic

Approach to Thresholds



Statistical Data Models*

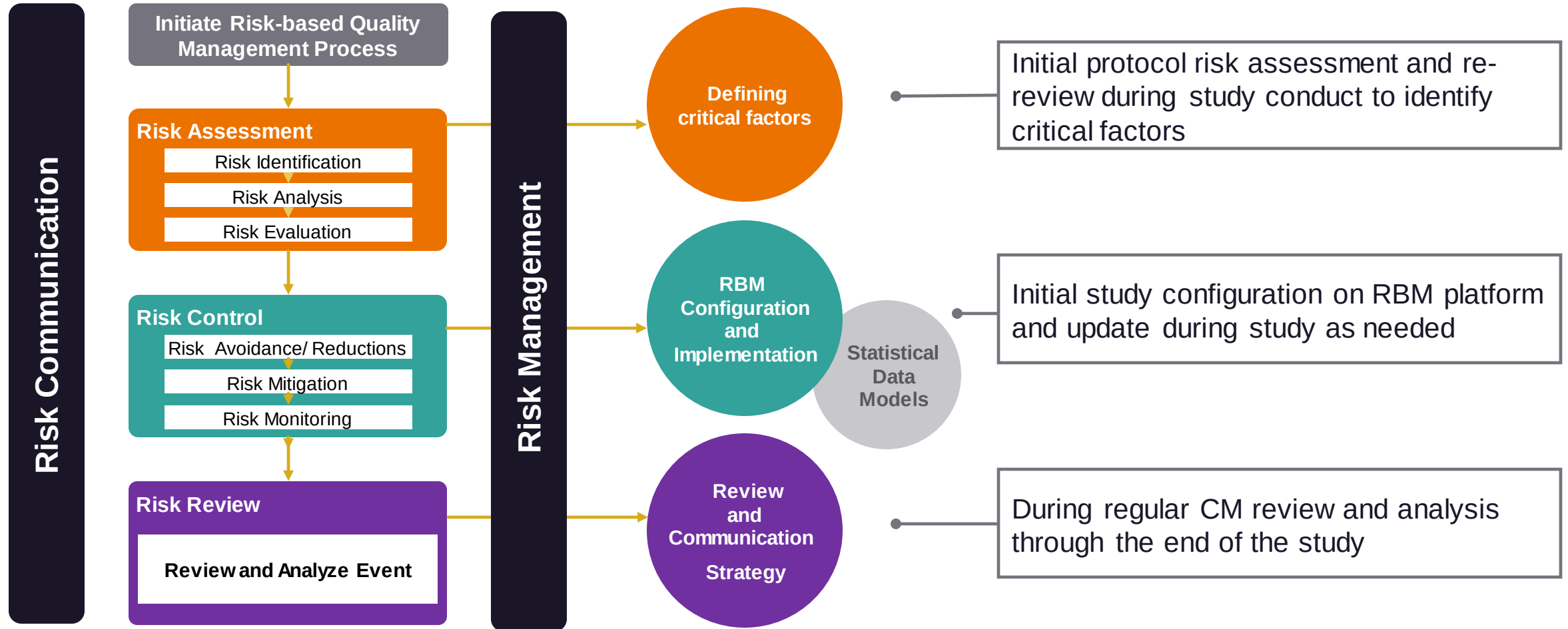
Approach to statistical models allow to identify atypical data patterns that represent risks/likely issues in the conduct of the study

Review and Communication Strategy

Risk signals communication and investigation strategy including process flow, timeliness of risk signals review, culture of open dialogue, critical thinking and expertise

* While Statistical Data Models are extremely important, they are out of scope for this presentation

Aligning factors with the RBM process



Challenges and strategy to reduce false positive rate



Defining Critical Factors: Challenges and Examples

CHALLENGES

- 1 KRIs for non-critical data/ processes
- 2 Overengineered approach to data collection which can limit analytical capabilities
- 3 Burdens due to poor study design
Note: can boost 'false positives' risks which cannot be mitigated and could be avoided with robust protocol risk assessment

EXAMPLES

- 1 High rate of out-of-window ophthalmologic assessments
 - Assessment is neither endpoint nor safety
- 2 SBP/DBP rounding:
 - Insufficient amount of data points (Screening and EOT visits)
 - Assessment is neither endpoint nor safety
- 2 Missing lab assessments:
 - Labs for some visits were required depending on the value and # of days between visits
- 3 Missing long term follow-up visits
 - Frequent in-person follow-ups limited to survival checks

False Positive



Defining Critical Factors: Points to Consider

STRATEGY

- 1 Think QbD:**
 - Optimize Study Design
 - Reduce burdens
- 2 Optimize set of KRIs to focus on critical factors**
- 3 Evaluate approach to the data collection:**
 - Assess complexity
 - Simplify whenever possible

WHEN

During Protocol Risk Assessment and prior to protocol finalization

Be proactive
Focus on critical
Simplify: reduce unnecessary burdens and risks



RBM Configuration and Implementation: Challenges and Examples

CHALLENGES

- 1 Data collection via multiple sources
(Local and Central labs, Questionnaires, General AE/AE of Special Interests)
- 2 Erroneous configuration of KRIs
 - Conditional assessments schedule
 - Incorrect Values/Parameter (conversion, coding)
 - Algorithms are not fit for purpose
- 3 Ambiguous KRI thresholds

EXAMPLES

- 1 Abnormal Lab value KRI:
 - KRI parameter used non-converted lab value
- 2 Professional patients KRI
 - Full range of patient datapoints was analyzed and compared on a site-by-site basis within the study
- 3 Threshold for discontinuation were set as absolute value of 30% or higher
 - Low enrollment sites (1-5) produced abnormally high rate of false positives

False Positive

RBM Configuration and Implementation: Points to consider



STRATEGY

- 1 Evaluate **completeness** of the **data collection**
- 2 Ensure appropriate **parameter** used in KRI
- 3 Assess **KRIs reflect study design** (e.g., conditional assessments, visit windows etc.)
- 4 Evaluate the flexibility of **thresholds approach**, e.g. different thresholds may be used for low vs high enrolling sites

WHEN

During RBM study configuration and throughout the course of the study based on feedback and/or changes

Flexible design
Data completeness
Fit for purpose algorithm design



Review and Communication: Challenges and Examples

CHALLENGES

- 1 Insufficient RCA (Root Cause Analysis)
- 2 Lack of review analyzing combination of multiple relevant KRIs
- 3 Communication challenges:
 - resistance to acknowledge an issue
 - lack of open discussion
 - unclear risk message and mitigations
- 4 Timeliness of risk signal
- 5 Lack of consistent strategy in defining and following up on risk signals

EXAMPLES

- 1 High Rate of AE:
 - 3
 - RCA was limited to SDV, and no assessment of potential safety signals or site recording practices (Terms, Grades, atypical SOC)
- 2 High Rate of Missing Assessments:
 - 5
 - Closed as no issue as PD record exists. Lack of CM strategy to distinguish issue from risks, issue from issues not requiring mitigation
- 3 Low variability of Weight:
 - Confirmed weight remained the same. However, values started changing moving forward

False Positive



Risk Review and Communication: Points to Consider

STRATEGY

- 1 **RBM expertise** across different functions
- 2 Culture of **open dialogues** and **continuous learning**
- 3 Established **processes** and **best practices** for managing risk signals, risk messages and defining risks/issue/issue with no mitigations
- 4 Awareness of **interconnections between** different **risks** and **KRIs**
- 5 **Flexible** risk monitoring model across study **phases**, sites etc.

WHEN

During risk signals review, communication, and discussions

Reactive
Repetitive and Consistent
Interconnected
Critically Thought Through Cross Functional
Communicated broadly



Building Risk Review and Communication

Think Of:

1

How root cause analysis is being conducted? Do CMs push back based on the responses to risk signals?

2

How and when risk signals are being communicated? Do you triage?

3

Are risk signals being discussed with study teams and within CM/RBM team?

4

Who is responsible for making decision on closing a risk communication loop?

5

How do you review potentially related risks e.g., SAE rate vs discontinuation rate?

6

Do you adjust KRI review strategy over the course of the study?

7

Do you distinguish between issues and issues not requiring mitigations?

8

What functions were trained on RBM ?

Summary

Risk signals can be considered as False Positives in RBM when:

- 1 Irrelevant to critical data and processes
- 2 Data is incomplete, or configuration does not reflect study design and/or collection
- 3 Risk signals and/or mitigations are misunderstood or misinterpreted
- 4 Responsibilities and risk communication processes are not defined
- 5 Low expertise in RBM methodology across the organization

Optimize your RBM strategy by:

- 1 Focusing on **critical data** and **processes**
- 2 Evaluating study **RBM configuration** for data completeness and flexibility
- 3 Building culture of **open dialogue** among CM and across other functions
- 4 Ensuring study strategy fits the design and phase - **No one-size-fits-all**
- 5 Establishing frameworks and internal **best practices** for risk management, including but not limited to risk and mitigation statements
- 6 **Learn continuously and implement**



Thank you!

CONTACTS



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