RBM, Why It Matters

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ICH E6 R2 Sponsor Oversight

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"The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s)."

ICH E6 R2 – Risk-based QMS

"The quality management system should use a risk-based approach."

"The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process)."

ICH E6 R2 – Risk-based QMS

Cross-functional Taskforce:

- Quality Management
- Project Management
- Medical Monitoring
- Clinical Operations
- Vendor Management
- Data Management
- Statistics

Risk Assessment

Critical Processes

CTTI Critical to Quality Factors

Risk Response Planning

Gap Analysis

Risk Control

Issue Management

ICH E6 R2 Risk-based Monitoring

"The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring … is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring."

What is Risk?

Risk - combination of the probability of occurrence of harm, the severity of that harm and how easy that harm can be detected.

Key questions:

- What might go wrong?
- What is the likelihood it will go wrong?
- What are the consequences?
- How easy it is to detect?

What is Monitoring?

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

What is Risk-Based Monitoring?

An adaptive approach to clinical trial monitoring that directs monitoring focus and activities to the evolving areas of greatest need which have the most potential to impact subject safety and data quality.

Key Assumptions: RBM Methodology

- Methodology applies to all types and phases of trials
- Risk assessments should take place prior to protocol/CRF finalization
- Monitoring activities are responsive to issues/risks
- Central and off-site monitoring are the foundation
- Tailor methodology to available technology
- Timely data entry and query resolution are critical
- Communication plans should be tailored for efficiency
- RBM expectations could be formalized in SOPs

PSI RBM Adoption Process

- Cross-functional RBM Taskforce/Identification of internal RBM champions
- RBM process and roles
- Procedural coverage (Guidelines, Plans, QSDs)
- RBM platform vendor selection/qualification process
- Development of internal tools
- RBM Awareness Training program (company/country/department level)
- Dedicated resource allocation / tailored training program

PSI RBM Methodology: Step 1

Risk Assessment → Critical data/processes → Risk mitigation → RBM Plan → Ongoing Evaluation

Cross-functional team:

- Central Monitoring Manager
- PM
- Therapeutic Area Lead
- Medical Affairs (MMs, Safety & PVG, Lab Support)
- Data Management
- Statistics
- Sponsor's experts

Additional team members:

- Vendor Management (Several and/or unfamiliar vendors)
- Regulatory Affairs (New regions/countries)
- Clinical Supplies (Complex study supplies logistics)

DOCUMENTATION OF RISK ASSESSMENT PROCESSES

- Team alignment on "what matters"
- Focused Risk Assessment

CONSISTENT APPROACH TO ASSESSMENT

- Each category has a series of questions
- Provides examples of high, medium, and low risks
- Assess for impact, probability and detectability

OUTPUT

- Determines the Overall Risk Level for monitoring activities
- Provides direction for focused monitoring and mitigation

mRACT

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1. SAFETY | 3. COMPLEXITY | 5. SUBJECT POPULATION | 7. ENDPOINTS | 9. STUDY MEDICATION | 11. BLINDING | 13. GEOGRAPHY
2. STUDY PHASE | 4. TECHNOLOGY | 6. DATA COLLECTION | 8. EXPERIENCE | 10. IP LOGISTICS | 12. OPERATIONAL COMPLEXITY | 14. OTHER RISKS

1. SAFETY

Category weight 1.0

#	Objective/Questions for discussion	Considerations	Select most suitable option/answer from drop-down list	Question weight	Risk Score	
1.1	Per the Medical Monitoring and Safety team with Medical Monitor (MM) confirm what is the safety risk to the subject?	*Identified risks from the Medical Monitoring and Safety team which have predetermined rules for determining safety risk with confirmation from the Medical Monitor*		1.0		
1.2	Is the compound a marketed product?	*If this is not a marketed product, the safety profile may change. If new events are identified, it could impact the overall risk/benefit profile. There are listings and surveillance to identify safety events.*				
1.3	Is the risk greater than or less than the Standard of Care(SOC)?			1.0		
1.4	Is this compound/class known to have any serious side effects/toxicity?	*Consider any protocol-specific reporting requirements for (S)AEs and endpoints*		1.0		

PSI RBM Methodology: Step 2

Critical Data

- Support primary and key secondary objectives
- Critical to subject safety
- Support decision-making about efficacy of the IP

Critical Processes

- Supporting data quality/integrity
- Supporting subject safety
- Support ethics and GCP compliance

PSI RBM Methodology: Step 2

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CRITICAL DATA DEFINITION

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Critical data refers to data that will be used to make decisions about the investigational product's safety and efficacy profile, including:

- *Data that support primary and key secondary objectives*
- *Data critical to subject safety, such as SAEs and/or events leading to discontinuation of treatment*

#	Critical Data Description	Risk Description Suggested format: If [event] occurs due to [cause], then [negative impact] may result	Rationale	Source	Comments
1	Clinical Signs/Symptoms of CABP panel containing 4 assessments at all time points [especially Screening, TOC and ECR (collected within the ECR window - 96 +/-24 hours)]	If Clinical Signs/Symptoms of CABP panel containing 4 assessments at all time points not collected at Screening due to any reason, we have no baseline data for comparison. If not collected at ECR, we have no data for the primary endpoint, if not collected at TOC, we have no data for the secondary endpoint.	Primary Endpoint	CRF	
5	Respiratory Specimens and Blood Culture Collection/Results	If no Respiratory Specimens and Blood Culture specimens are collected at Screening due to any reason we have no baseline specimen. If no specimen collected prior to rescue therapy for any reason we can't assess the micro response. If no follow-up cultures collected for blood, we can't assess the progress.	Secondary Endpoint	CRF	And Central Lab
6	Stratification factors: PORT Class (Randomization page), Prior antimicrobial treatment, COPD/Asthma history	If any mistake with the stratification, this can cloud influence on the statistical results and the treatment assignment.	Eligibility	IWRS	And CRF

PSI RBM Methodology: Step 2

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CRITICAL PROCESSES DEFINITION

Remove comments

Critical processes are used to derive the critical data, including:

- *Processes that underpin critical data, subject safety and ethical treatment, such as seeking appropriate medical consultation or scheduling extra visits/procedures in the event of significant clinical or laboratory findings*
- *Processes that underpin the integrity of these data, such as blinding or referring specified events for adjudication, controlling inter-rater variability*

GENERATED AUTOMATICALLY (based on m-RACT question Edit Critical Process ☐ Hide rows with no associated risk

The below critical processes are generated automatically based on questions defined as High or Medium Risk in the RACT questionnaire.
In order to define the list of processes (and corresponding risks) that will be considered as critical for this Study, follow these steps:
1. Define if a risk can be associated to each of the critical processes listed below, by selecting "YES" or "NO" in the "Associated Risk" column
2. Enter the "Risk Description" in the corresponding column
3. You can edit the "Critical Process Description" if necessary (by clicking on the "Edit Critical Process Descriptions" button)

#	Critical Process Description	Related RACT question	Option/answer selected	Risk Score	Risk Description Suggested format: If [event] occurs due to [cause], then [negative impact] may result	Associated Risk?	Comments
1	Safety management & medical monitoring	1.2: Is the compound a marketed product?	The compound is not a marketed product, or the compound is a marketed product but is being studied in an unapproved indication	🔴	As the compound was approved for other indication (ABSSSI) there is not enough safety and effecacy data for pneumonia.	YES	The compound was approved for ABSSSI
	DM: Data collection; Safety management & medical monitoring	6.2: What is the time lapse between data entry and availability for central review?	EDC + limited number of external data sources	🟡			5 laboratory data sources - Covance (safety and micro), labs, PPD for PK

PSI RBM Methodology: Step 3

Risk Response Planning

- Mitigating action
- Functional plans impact

Define Key Risk Indicators (KRIs)

- Review Critical Data & Processes
- Use the Risk Indicator Library

Define KRIs thresholds & actions

- When to act/what to do

PSI RBM Methodology: Step 4

RISK ASSESSMENT > CRITICAL DATA/PROCESSES > RISK MITIGATION > RBM PLAN > ONGOING EVALUATION

CENTRAL MONITORING

- Aggregated study data analysis (trends/outliers)
- Study level KRI(s)

OFF-SITE MONITORING

- Remote assessment of site issues/data/performance
- Site level KRI(s)
- Remote contacts with sites, re-training

ON-SITE MONITORING

- Assessment of site quality
- GCP compliance assessment
- Review data not accessible remotely

PSI RBM Methodology: Step 5

Risk Assessment > Critical data/processes > Risk mitigation > RBM Plan > Ongoing Evaluation

Cross-functional team meetings

- Central Monitoring Manager
- Project Manager
- Therapeutic Area Lead
- Medical Affairs
- Data Management & Statistics
- Sponsor's experts

Central Monitoring Manager – ongoing signal review

PSI RBM Tool Box

PSI Project Risk Management Tool

- m-RACT (Modified Risk Assessment Categorization Tool)
  - Critical processes & data
  - KRIs library

PSI Smart Monitoring Planning

- Adaptive monitoring planning based on the volume of data and pre-defined KRIs

Project Risk Management Plan

Monitoring Plan Template

RBM Platform (RBM Vendor Solutions)

- Risk assessment
- Data integration (EDC, external data, CTMS)
- KRI/Data Visualizations
- RBM workflows/Issue management
- Statistical data monitoring (outliers & data trends identification, data variability monitoring, fraud detection)

EDC with TSDV capabilities

- Pre-defined & ongoing adjustment of SDV levels

RBM Budgeting Implications

Abbreviated Risk Assessment Tool

- General level of risk
- RBM strategy for the study

Targeted Monitoring

- Initial monitoring level
- Additional pool of visits

External RBM Platform

TSDV component of the EDC platform

Conclusion: Three Main Points

1. Risk Management is a new *modus operandi* applicable for all studies
2. Doing RBM requires cross-functional effort
3. RBM is independent of SDV level

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Thank you

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