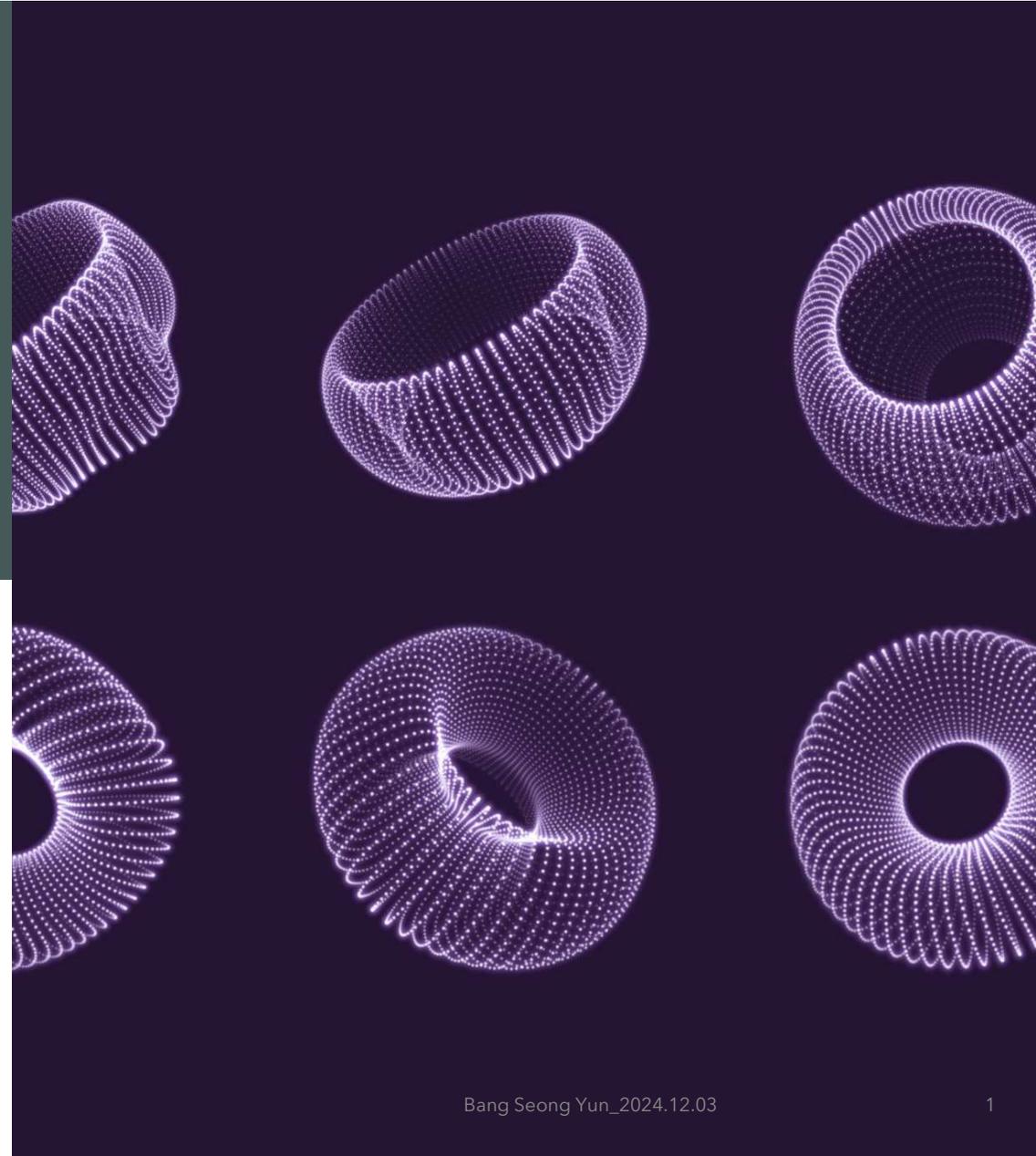


THE ADVANTAGES AND HURDLES OF RISK- BASED MONITORING FRAMEWORKS IN CLINICAL TRIALS

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Agenda

1. Risk Based Monitoring: Main Purpose, Required Activity
2. Risk Based Monitoring: Current Status
3. New Trends in Clinical Development Industry and Impact on Data Monitoring
4. The Advantages & Obstacles of RBM
5. What to do for right implementation

Relevant Questions

- Exploring how risk-based monitoring improves resource allocation by minimizing on-site monitoring visits
- How can clinical teams step back and self-analyze what risk could occur rather than rush straight in?
- Choosing the correct RBM strategy to apply to your trial to reduce the time to approval for INDs

1. Risk Based Monitoring: Main Purpose, Required Activity

“Risk Based Monitoring” in FDA guideline

Based on FDA guideline (updated April.2023, initially published Aug.2013)

FDA recommended,

“ At the protocol design stage, sponsors identify the critical data and processes necessary for **human subject protection and data integrity** for the investigation(clinical trial) and assess/determine how critical to data and processes and revise the protocol and trial plan.”

But,

“If not resolved through such revision, sponsor should determine how remaining critical risks will be identified, tracked, and managed via monitoring plan or relevant study oversight plan during the conduct of clinical trial. ”

→ This is the main purpose of sponsor’s monitoring.

Ultimate Goal

Initial risk assessment & management planning about clinical trial plan and process

Ongoing mitigation & plan update during trail

“Risk Based Monitoring” in FDA guideline

Based on FDA guideline (published Q&A for that guideline in April.2023, initially published in Aug.2013)

FDA also recommended,

“ Monitoring plans provide guidance on when and how(Duration, Frequency...) to adjust monitoring activities based on observed monitoring findings. ”

And,

“ Sponsors’ risk management processes should continue throughout the conduct of the investigation. ”

And clarified via Q&A,

“ Sponsors should document their risk assessment, including methodologies used for the risk assessment, conclusions from the risk assessment, and how the assessment was used to make

decisions on the management of the risks identified.” And also mentioned about “re-evaluation and update”

Risk based
monitoring plan

Continuous Risk Assessment
with proper methodologies

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“Risk Based Monitoring” in FDA guideline

Therefore,

The monitoring plan should include information regarding **the identified risks** and **how the monitoring methods will address those risks.**

Plan need to provide a clear explanation of the identified risks and how to be monitored, managed and mitigated or eliminated.



Does our Clinical Trial Monitoring Plan have these things ?

Risk-Based Quality Management

Risk-based quality management (RBQM) is a systematic and proactive approach to ensuring the quality and integrity of clinical trials.

- By identifying and managing risks at every stage, from protocol development to data analysis, RBQM enhances trial quality.
- The operational flow of RBQM encompasses risk identification, assessment, control, continuous monitoring, and improvement.
- This multifaceted process minimizes data errors, bias and enhances trial efficiency, leading to more accurate results.
- Safety for participants is prioritized while trial management efficiency is heightened.
- Tailored to each trial's unique requirements, RBQM involves stakeholders like sponsors, CROs, investigators, and regulatory bodies.
- Employing various tools and resources, RBQM becomes an indispensable strategy to bolster clinical trial quality across the lifecycle.

RBQM & RBM Main Components

➤ **RBQM Components (broader scope):** Encompasses all aspects of the quality management

- ✓ Risk assessment (Initial & Ongoing, Cross-functional)
- ✓ Risk mitigation
- ✓ Proactive quality management planning, communication, review, evaluation
- ✓ QTLs(Quality Tolerance Limits)
- ✓ Quality by Design (QbD)

* RBM falls under the "risk mitigation" and "review" components of RBQM.

➤ **RBM Components (monitoring focus)**

- ✓ **C**entralized monitoring
- ✓ Targeted on-site/off-site monitoring
- ✓ Reduced source data verification (SDV), Reduced source data review
- ✓ Key risk indicators (KRIs)

→ Ensuring data quality and integrity *as part of the overall quality plan.*

RBQM & RBM Methodological Differences

The core methodological difference lies in how they approach ensuring data quality and trial integrity:

- **Traditional Monitoring (pre-RBM):** Relied heavily on 100% source data verification (SDV) at all sites, regardless of risk. This was resource-intensive and not always effective in identifying systemic issues.
- **RBQM (holistic approach):** Emphasizes *proactive* risk assessment and mitigation across *all* aspects of the trial. It uses data analysis and other tools to identify and address potential issues *before* they escalate.
- **RBM (targeted monitoring within RBQM):** Within the RBQM framework, RBM utilizes a *targeted* approach to monitoring, focusing resources on the areas of highest risk. Instead of 100% SDV, RBM uses centralized monitoring, targeted on-site visits, and key risk indicators to identify and address potential issues more efficiently.

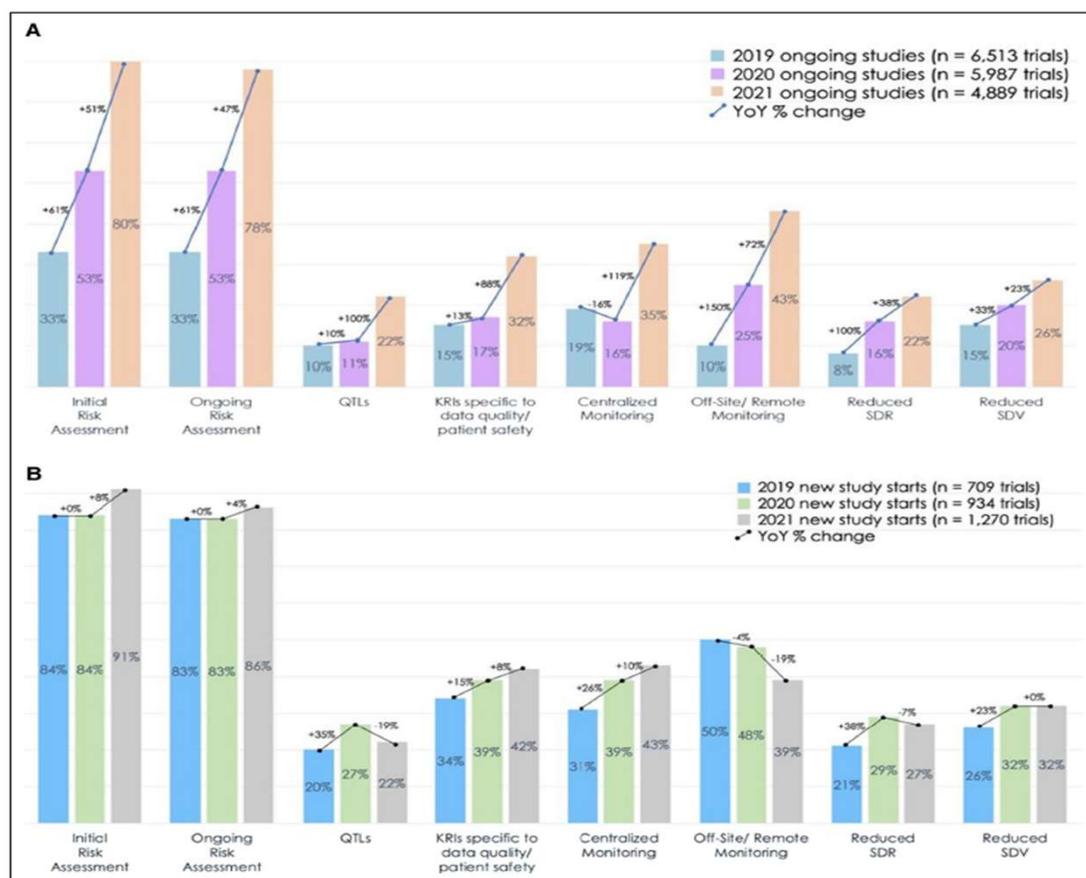
RBQM & RBM Summary of Concep. Diff

Feature	Traditional Monitoring	RBQM	RBM (within RBQM)
Focus	Data transcription accuracy	Overall trial quality	Targeted monitoring
Approach	Reactive	Proactive	Risk-driven, Adaptive
Monitoring	100% SDV	Centralized & Targeted	Risk-based selection
Resource Use	High	Optimized	Efficient

2. Risk Based Monitoring: Current Status



Status of RBM/RBQM in Clinical Trials

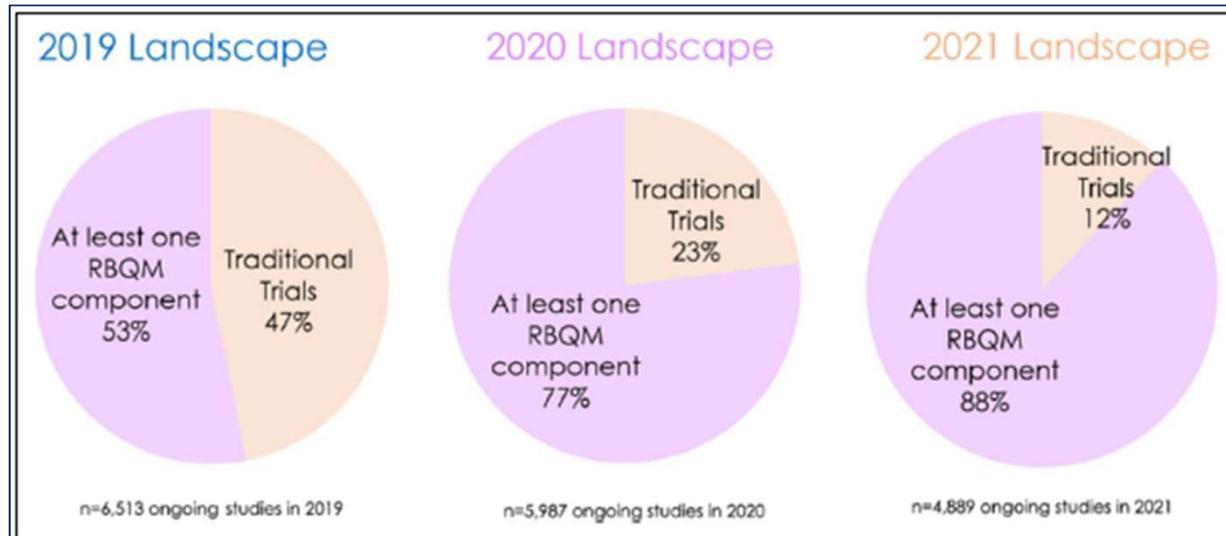


(A) Prevalence of individual RBQM components, by year, for all trials in the 2019, 2020, and 2021 data sets. Implementation of all components increased from 2019 to 2021.

(B) Prevalence of individual RBQM components, by year, for new study starts each year from 2019 to 2021. A less consistent pattern for year-over year changes in component implementation was seen for new study starts versus all trials.

Reference : [Risk-Based Monitoring in Clinical Trials: 2021 Update]
 Amy Adams, et al. *Therapeutic innovation & Regulatory Science* (2023) 57:529-537

Status of RBM/RBQM in Clinical Trials

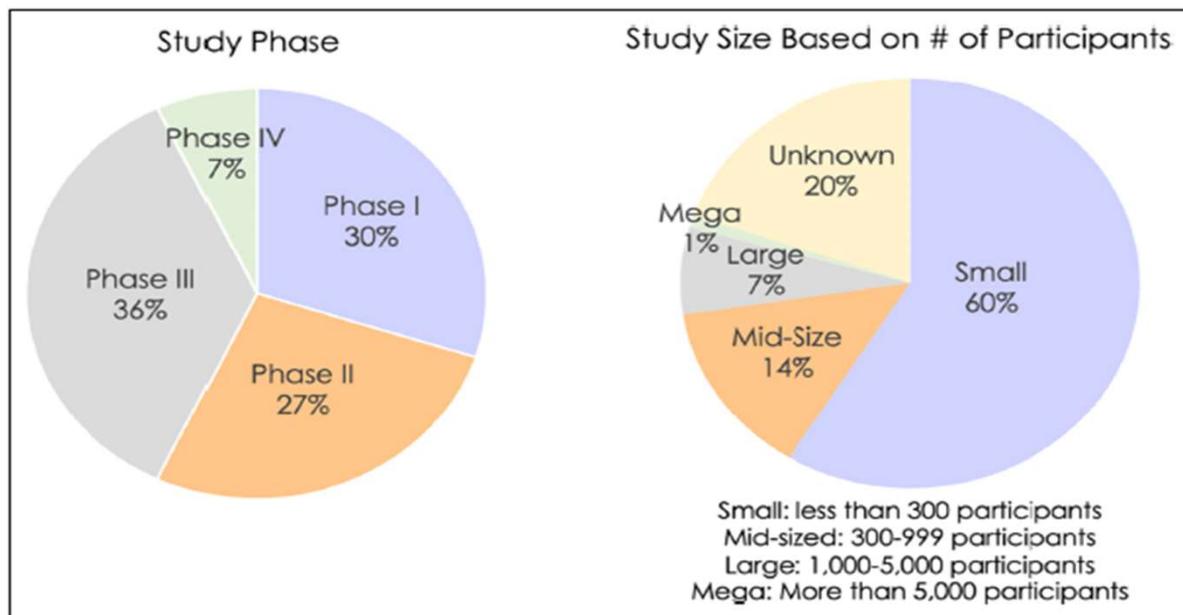


The percentage of ongoing clinical trials with at least one RBQM component grew each year, resulting in a 35 percentage-point increase from 2019 to 2021.

Reference : [Risk-Based Monitoring in Clinical Trials: 2021 Update]
Amy Adams, et al. *Therapeutic innovation & Regulatory Science* (2023) 57:529-537

Status of RBM/RBQM in Clinical Trials

< % of 2021 trials implementing at least one RBQM component >



Of the 88% or 4303 trials included in the 2021 landscape survey that implemented at least one RBQM component, 93% were Phase I–III.

The percentages of small, mid-sized, large, and mega-sized trials is roughly consistent with the breakdown by phase, as Phase III and IV trials tend to be larger, and Phase I and II trials tend to be smaller.

Reference : [Risk-Based Monitoring in Clinical Trials: 2021 Update]
Amy Adams, et al. *Therapeutic innovation & Regulatory Science* (2023) 57:529-537
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Performance of Traditional On-site Monitoring & R2BM

Based on [Yamada et al, Trials, 2024, "effectiveness of remote risk-based monitoring and potential benefits for combination with direct data capture"]

*R2BM is "Remote Risk Based Monitoring"

Conclusion from the study

- R2BM can detect 100% of the critical data and process errors without on-site monitoring, so R2BM can be used a monitoring method focusing on process control and risk identification.
- Combining R2BM with direct data capture reduces the workload of R2BM and further improves its efficiency.

Referred articles,
even remote risk
based
monitoring can
detect similar
level of errors in
critical data and
process with On-
site monitoring

Performance of Traditional On-site Monitoring & R2BM

Based on [Yamada et al, Trials, 2024, "effectiveness of remote risk-based monitoring and potential benefits for combination with direct data capture"]

The proportion of data errors in the complete dataset was 3.1% , similar to that reported in other studies, because data errors occurred in only a small percentages of the eCRF data.

Limitation of this study

- Size of the studied population

Performance of Traditional On-site Monitoring & R2BM

How to use R2BM, RBM and On-site Monitoring in actual trial environment

To increase the efficiency of resources(Time & labor) and accuracy when doing clinical data monitoring, we need to set up a monitoring plan strategically to consider how to combine each method, RBM with on site monitoring, R2BM from the beginning of trial.

3. New Trends in Clinical Development Industry and Impact on Data Monitoring



New Trends in Clinical Development

_ Emerging Technologies or Methods

Technological innovations are expected to improve the efficiency and productivity of clinical trials through the use of novel outcomes, increased patient engagement and reduced patient burden, but, in the other side, **raise regulatory and operational concerns due to the gap of each speed!**

1. Wearable Devices and Sensors

2. Artificial Intelligence and Machine Learning

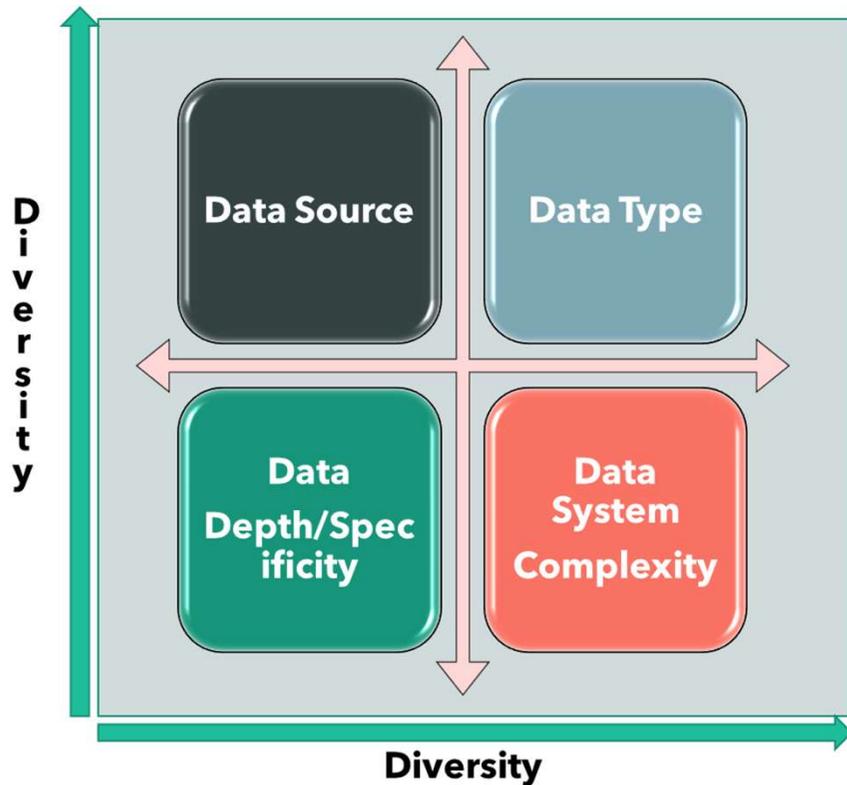
3. Virtual reality (VR) and Augmented reality (AR) & Mixed Reality(MR)

4. New Treatment and methodologies with high biological tech such like gene editing/modification etc.

5. Decentralized Clinical Trials (DCTs)

...

Key Changes in Clinical Data



Data Sources / Data Type

- EMR at site
- Remotely collected the data directly from patients
- Remotely and automatically collected data from Tools such like various type of wearable and attachable personal equipment

Data Types

- Each types of data from various sources
- Various types of biologic data, direct or modified including RWD

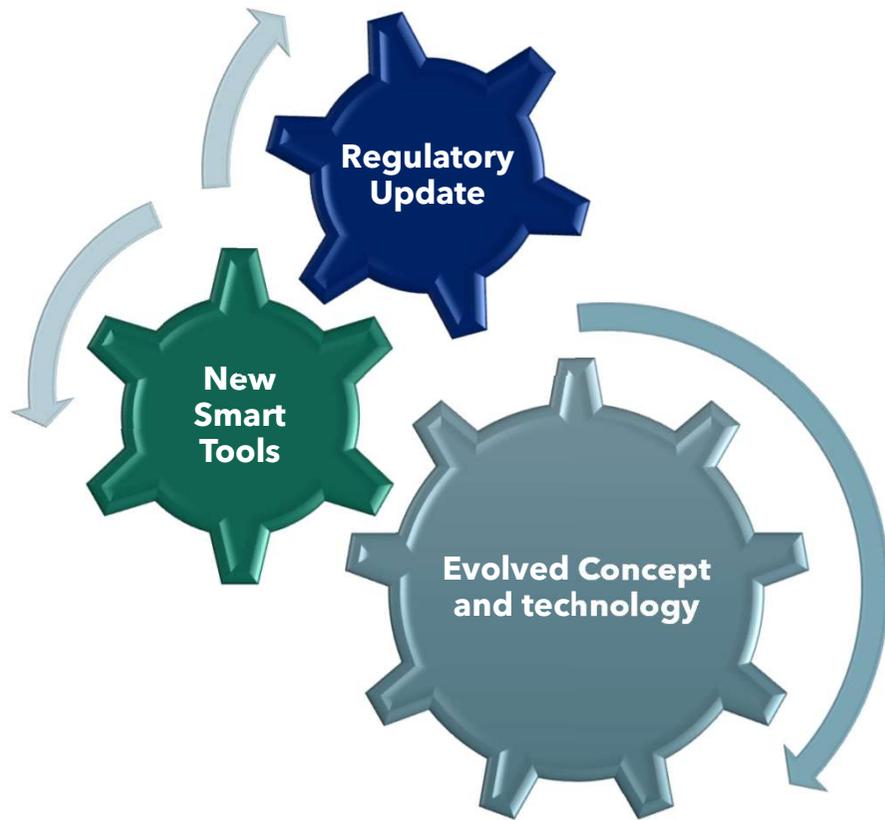
Data Depth /Specificity → Increased difficulty

- Depending on data types, more and more requires expertise to understand.

Data System Complexity

- More effort is needed to understand and validate the path through which data is collected in different types of electronic systems

Key Changes in Clinical Data Monitoring Environment



Regulatory Update

- Emphasize the efficiency and accuracy of data monitoring
- Emphasize the quality of data as well as overall quality oversight

New Smart Tools

- Tools to be able to do decentralized monitoring and data cleaning via AI/ML technologies
- Tools to collect directly from source.

Evolved concept and technology

- RBQM
- RWD
- Virtual Visit
- Direct-to-patient research(prior to real trial)

New Trends in Clinical Development

_ Regulatory Trends

Directions of Recent Regulatory Update

- Emphasizing Quality & Risk Management Oversight
- Emphasizing the efficiency of Clinical Trial / Clinical Development
- Guiding for new technology & method utilization in clinical trials
- RWD & RWE
- Decentralized Clinical Trials
- Clinical development guide for new modality

New Trends in Clinical Development

_ Regulatory Update

FDA's newly updated guideline in 2024

Newly Added Guidance Documents FDA			
Topic	Guidance	Status	Date
Clinical - Medical	Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment	Final	2/22/2024
Clinical - Pharmacology	Clinical Pharmacology Considerations for Antibody-Drug Conjugates Guidance for Industry	Final	3/01/2024
Electronic Submissions	Providing Regulatory Submissions in Electronic Format: IND Safety Reports Guidance for Industry	Final	4/01/2024
Clinical - Medical	Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics	Final	6/14/2024
Clinical/Antimicrobial	Diabetic Foot Infections: Developing Drugs for Treatment	Final	6/17/2024
Clinical - Pharmacology	Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 1 Month of Age and Older Guidance for Industry	Final	7/15/2024
Clinical - Pharmacology	Clinical Pharmacology Considerations for Human Radiolabeled Mass Balance Studies	Final	7/18/2024
Electronic Submissions	Providing Over-the-Counter Monograph Submissions in Electronic Format	Final	7/25/2024
Real World Data / Real World Evidence (RWD/RWE)	Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products	Final	7/25/2024
ICH - Multidisciplinary	M12 Drug Interaction Studies: Questions and Answers	Final	8/2/2024
Electronic Submissions	Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD	Final	9/11/2024
Clinical - Medical	Specifications Guidance for Industry	Final	9/17/2024
Clinical - Medical	Conducting Clinical Trials With Decentralized Elements	Final	9/17/2024
Clinical - Medical	Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-Regulated Medical Products	Draft	1/30/2024
Clinical - Medical	Postoperative Nausea and Vomiting: Developing Drugs for Prevention	Draft	10/17/2024
Clinical - Medical	Use of Data Monitoring Committees in Clinical Trials	Draft	2/13/2024
Clinical - Medical	Early Alzheimer's Disease: Developing Drugs for Treatment	Draft	3/12/2024
Real World Data / Real World Evidence (RWD/RWE)	Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products	Draft	3/21/2024
Safety - Issues, Errors, and Problems	REMS Logic Model: A Framework to Link Program Design With Assessment	Draft	5/07/2024
ICH - Multidisciplinary	M14 General Principles on Plan, Design, and Analysis of Pharmacoepidemiological Studies That Utilize Real-World Data for Safety Assessment of Medicines	Draft	7/05/2024
Combination Products	Purpose and Content of Use-Related Risk Analyses for Drugs, Biological Products, and Combination Products	Draft	7/08/2024
Clinical - Medical	Pediatric Inflammatory Bowel Disease: Developing Drugs for Treatment	Draft	7/19/2024
Real World Data / Real World Evidence (RWD/RWE)	Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice	Draft	9/17/2024

4. The Advantages & Obstacles of RBM



Main advantages, Expectation to RBM

1. Centralized Data Review

RBM employs central computerized reviews of clinical trial data and site metrics, allowing for targeted quality reviews and interventions rather than frequent on-site visits.

2. Proactive Quality Management

By defining safety and quality indicators in advance and reviewing data periodically, sponsors can take a proactive approach to managing quality, which emphasizes important data related to patient safety and the integrity of study results.

3. Early Problem Identification

RBM allows for the early identification of issues, enabling trial procedures to be refined and shortcomings addressed while the trial is still ongoing.

Main advantages, Expectation to RBM

4. Cost Reduction

The use of RBM can significantly lower trial expenses, making it more feasible to conduct clinical trials amidst rising costs.

5. Customized Risk Approach

RBM can tailor its risk assessments based on specific factors related to the trial, such as the disease being studied, the experience of the sponsor and site, and the characteristics of the clinical trial. This flexibility accommodates varying levels of risk tolerance.

6. Efficiency in Monitoring

The ability to assess performance based on current data facilitates a more accurate evaluation of site performance throughout the trial, rather than relying solely on periodical on-site assessments.

→ To enhance the efficiency and effectiveness of clinical trial monitoring while managing costs and ensuring patient safety.

Challenges to implement RBM

The challenges associated with implementing risk-based monitoring (RBM) in clinical trials, as highlighted in the document, include:

1. Ownership and Responsibility

A significant challenge is determining which functional area should be responsible for RBM. Effective implementation requires collaboration between diverse team members, including clinicians, monitors, statisticians, and regulatory associates. Each has a unique role in reviewing trial data and defining risk thresholds.

2. Comfort with Risk-Based Approaches

Individuals involved in clinical trials may need time to become comfortable with risk-based methodologies. Training in these unfamiliar systems is necessary, but gaining practical experience will further refine procedures and analyses.

3. Training and Familiarization

Adopting RBM requires training and familiarization with new technologies and methodologies. This can pose a barrier, particularly for teams that are accustomed to traditional monitoring approaches.

Challenges to implement RBM

4. Variable Risk Management

Acknowledging that risks can fluctuate over time introduces additional complexity. Therefore, when making decisions about interventions based on risk thresholds, it's crucial to consider this variability to prevent either overreacting or underreacting to data signals.

5. Tailoring Risk Thresholds

Setting proper risk thresholds is essential to avoid an overabundance of intervention alerts while also ensuring that true issues are efficiently addressed.

These challenges indicate the need for a collaborative approach, effective training, and ongoing refinement of risk management strategies as the implementation of RBM evolves in clinical trials.

Challenges in Korea

Key Challenges

Insufficient understanding of the Risk-Based Monitoring (RBM) concept among sponsors, CROs, and functional staff.

Inadequate emphasis on quality and risk considerations from the start.

Insufficiently trained or inexperienced monitors (CRAs, CMAs, or other staff responsible for trial data monitoring) and a lack of oversight.

Practically, Budget is usually increased to select RBM with CRO.

Limited research budgets in many biotech and small pharmaceutical companies to establish effective quality processes.

5. Things to consider for proper implementation

- ❖ Need continuous training, learning, collaboration, and refinement of processes to ensure the successful implementation of risk-based monitoring in clinical trials.
- ❖ Need to understand upcoming clinical trial environment with new technologies and drug development industry.

Recommendable actions for better implementation

1. Understanding Ownership

Effective RBM implementation requires clarifying ownership and responsibility among various functional areas. A collaborative approach involving clinicians, monitors, statisticians, and other team members is essential to harness their combined strengths.

2. Understanding the environment and internal system/process in a company(developer)

Considering the infrastructure of the company, as well as the size and type of the clinical trials to be conducted or planned, an appropriate application plan should be established.

3. Training and Familiarization

There is a need for comprehensive training on new risk-based methodologies. Comfort with these approaches will develop over time, but practical experience is key in refining the processes and methodologies used in RBM.

Recommendable actions for better implementation

4. Data Integration and Utilization

Identifying various sources of data is critical for assessing quality. Sponsors must assess the benefits and challenges of integrating these data sources into the RBM process. Special care must be taken to harness findings from monitors during on-site or remote reviews, ensuring that pertinent quality data is captured effectively.

5. Establishing Risk Thresholds

Continuous evaluation of risk thresholds is needed to prevent excessive alerts or missed issues. Understanding how periodic risks may vary over time can help tailor the response to data signals more effectively.

6. Ongoing Research and Adaptation

Further research is needed to determine the most effective models for managing the RBM process, including exploring best practices and identifying opportunities for efficiency.

7. Understand the diversity of new technologies and tools, pharmaceuticals

It is necessary to understand new trends and related technologies in clinical development, and to establish data monitoring strategies based on a more specialized and diverse understanding of data.

Eventually....

- Traditional approach to conduct data monitoring needs to be re-considered and evolved accordingly in line with the rapid changes in the current healthcare and new drug development industries.

Question ...

- Exploring how risk-based monitoring improves resource allocation by minimizing on-site monitoring visits
- How can clinical teams step back and self-analyze what risk could occur rather than rush straight in?
- Choosing the correct RBM strategy to apply to your trial to reduce the time to approval for INDs

Exploring how risk-based monitoring improves resource allocation by minimizing on-site monitoring visits

Assess/evaluate about

- Which type of remote monitoring or data capture tools will be set up in our trial?
- What kind of resources do we have for data monitoring ?

Decide / plan about

- Proper allocation each resource to each monitoring way(On-site, Remote or both) as well as to each prioritized data(Critical, Major or minor...)
- And adjust during trial depending on the critical level of data based on recognized risks.

How can clinical teams step back and self-analyze what risk could occur rather than rush straight in?

Should properly answer these and plan accordingly based on each company's infrastructure and process.

- Does the clinical team have a thorough understanding of the planned clinical trial's characteristics, particularly those related to the investigational product (IP) and the trial design ?
- What criteria are used to identify critical data?
- Do you have a robust data collection plan, as well as data processing and management plans? Additionally, do you have a comprehensive understanding of the data analysis plan?
- Do you have an appropriate internal risk assessment and assessment methodology?
- Is it possible to manage the compliance and quality of the personnel responsible for ensuring that risk-based on-site monitoring is being conducted properly?

Today's Summary

As a sponsor to plan and manage clinical trials, it is so importance for ensuring participant safety and data integrity throughout the trial lifecycle.

Recent developments, including new regulatory requirements and emerging technologies, that have increased the adoption of RBM.

RBQM is the parent(more comprehensive) framework of RBM in clinical trial, RBM should be understood based on its primary purpose, rather than as one of the site ongoing monitoring tool or method.

Although there may be differences depending on the size and type of sponsor, it is necessary to understand the responsibilities and roles in sponsor side, sponsor should set up the appropriate risk management strategy according to the situation, and set up RBM accordingly.

경청해주셔서 감사합니다.
Thank you !

