Evaluation of Data Errors and Monitoring Activities in a Trial in Japan Using a Risk-Based Approach Including Central Monitoring and Site Risk Assessment

(Paper Review by Narshion Ngao)

Disclaimer

- Most messages and definitions have been extracted from the paper directly.

Risk Based Monitoring

- **Risk-Based Monitoring (RBM)** is a clinical trial monitoring approach that focuses on identifying, assessing, and mitigating risks to ensure data integrity and participant safety while optimizing resource allocation.
- Instead of relying on 100% source data verification (SDV) at all trial sites, RBM uses risk assessment strategies to prioritize monitoring efforts where they are most needed.

Key Components of RBM - overview

1. **Risk Assessment & Planning –** Identifying potential risks that could impact trial quality, such as protocol deviations, site performance issues, or data inconsistencies.
2. **Centralized Monitoring –** Using statistical and analytical techniques to detect anomalies, trends, or outliers across study sites remotely.
3. **Targeted On-Site Monitoring –** Conducting site visits based on risk signals rather than a fixed schedule, allowing for efficient allocation of monitoring resources.
4. **Technology & Data Analytics –** Leveraging electronic data capture (EDC), machine learning, and dashboards to track risks in real time.
5. **Regulatory Compliance –** Aligning with guidelines such as ICH E6 (R2), which emphasizes a risk-based approach to monitoring.

ICH E6(R2), FDA, EMA, PMDA – All have included it in their regulations for clinical trials

However, SLOW uptake by Trials

1. Fear of making large investments in advanced RBM technology
2. Claims that RBM is suited by large complex trials
3. Fear of erroneous data to be in both critical and non critical data when on-site monitoring is reduced

- Partial SDV (targeted) has been compared to 100% SDV in studies. No major differences noted.

Objectives of this study

1. Whether a simple RBM without advanced technology will produce satisfactory results in terms of managing data and safety risks.
2. Whether an RBM provides benefits in a low-risk trial with minimal complexity.
3. Whether an RBM can ensure quality regarding all errors in eCRF and source data, minimize protocol deviations, and optimize the monitoring resource utilization.

Trial Information

- Open label multicentre trial to evaluate safety, tolerability and efficacy of a drug (tofogliflozin) in type 2 diabetes patients.
- 67 participant enrolled
- 11 sites
- End point – change in HbA1c.

Risk Assessment and Categorization

- Identified a Risk Assessment & Categorization Tool (RACT)
- Formulated a Risk Mitigation plan for identified risks
- RBM constituted Clinical Research Associates (CRA), Central Monitors, Data Managers, & statisticians
- Developed a Monitor-driven Risk Assessment Categorization Tool (MRACT)
- Monitoring Plan
  - Came up with: -
    1. Partial switching sites – to do RBM activities
    2. 100% SDV and SDR sites – for baseline monitoring activities
  - Table 1 gives a summary of all monitoring activities.
  - After the last patient last visit, SDV and SDR was done on all data points that had not been done.

Results

- Errors per subject corrected:-
  - 100% SDV sites – 24.3
  - Partial switched – 21.8
- When SDV/SDR was performed after completion on partial switched sites – No corrections needed for high-risk data
- Partial switched sites:
  - had lower on-site monitoring errors
  - On-site monitoring was only for low-risk category data
  - Off-site monitoring – had higher errors corrected than 100% SDV sites
  - Corrections by central monitoring was for medium-risk data only
  - On-site monitoring time was > 1 hour less (9.67hrs compared to 11.99hrs)
  - Reduced SDV and SDR by 30%

Discussion – take aways

- ICH E6 (R2) – shifts emphasis to reliability of results.
  - Its important to ascertain what process is more effective & efficient.
- The correction rate for on-site monitoring was 2.5%, that for transcription error was 0.7%, and that for lack of data entry was 0.1%. We thus ascertained that the contributions were made purely by SDV, and the correction rate was likely lower than that in the previous study.
- This suggests that SDV should have a greater focus on critical data.

Conclusion

- RBM can be successfully implemented with site risk assessment & central monitoring with no investment in technology.
- RBM seems more reliable and less strenuous than 100% SDV & SDR approaches.
- Off-site monitoring can be more effective with targeted critical data and critical processes.

Types of Monitoring - Summary

Aspect	Risk-Based Monitoring (RBM)	On-Site Monitoring	Off-Site Monitoring	Central Monitoring	Remote Monitoring
Definition	Proactive, data-driven monitoring focusing on trial risks and critical data.	Physical site visits to verify compliance and protocol adherence.	Monitoring without site visits but with site interactions (calls, emails).	Statistical and data-driven monitoring from a central location.	Monitoring using electronic systems, reducing site visits.
Primary Focus	Risk assessment, targeted monitoring, real-time data review.	Source Data Verification (SDV), patient safety, protocol adherence.	Site engagement, document review, compliance checks.	Data consistency, site performance analysis, protocol deviations.	Real-time monitoring using EDC and cloud platforms.
Monitoring Location	Combination of on-site, off-site, and central monitoring.	At clinical trial sites.	Off-site via digital or phone communication.	Central location (e.g., sponsor's office).	Remote via cloud-based tools.
Data Verification	Focused SDV on critical data; automated risk-based checks.	100% or partial SDV via source document review.	Partial SDV through electronic records review.	Statistical methods detect anomalies.	Electronic data verification via EDC.
Use of Technology	Advanced analytics, risk detection algorithms, dashboards.	Minimal; relies on manual checks and visits.	Uses email, calls, and limited trial data access.	Uses AI, analytics, and machine learning for detection.	Uses cloud platforms, remote data access, and video calls.
Resource Efficiency	High – reduces unnecessary site visits and SDV.	Low – requires significant resources and travel.	Moderate – reduces travel but requires interaction.	High – scalable and cost-effective.	High – minimizes travel while maintaining oversight.
Site Burden	Lower than traditional monitoring, adjusted based on risk.	High – requires frequent site visits and document access.	Medium – requires coordination with monitors.	Low – automated and centralized.	Low – minimal site disruption.
Regulatory Support	Supported by ICH E6 (R2), FDA, EMA, PMDA.	Standard practice but shifting toward RBM.	Supported as part of hybrid monitoring.	Strongly encouraged by ICH, FDA, EMA, PMDA.	Increasingly supported as part of risk-based strategies.
Cost	Lower – targeted monitoring reduces expenses.	High – frequent visits and manual checks increase costs.	Moderate – reduces travel expenses.	Lower – automated and centralized.	Lower – minimizes travel and manual workload.
Flexibility & Adaptability	Highly flexible – adjusts based on risk.	Low – fixed visit schedules.	Medium – adaptable but manual.	High – real-time data-driven decisions.	High – adjustable based on trial needs.