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REPLACING SOURCE DATA VERIFICATION AND REVIEW WITH RISK BASED MONITORING IN CLINICAL TRIALS

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Summary

Risk-Based Monitoring (RBM) in clinical trials is an adaptive approach that directs resources toward areas of highest risk to trial quality and patient safety. This contrasts with traditional monitoring methods that rely on extensive on-site visits and complete Source Data Verification (SDV) and Review (SDR). Traditional monitoring is extremely costly, accounting for up to 30% of total trial expenses[1]. Empirical evidence shows that RBM can use less than half of the resources demanded by traditional monitoring[2], without affecting the quality of the trial. Despite the potential benefits of RBM, industry adoption has been slow. Many sponsors and Contract Research Organizations (CROs) hesitate to abandon traditional practices due to regulatory concerns and the need for new technologies. The Food and Drug Administration (FDA) has been encouraging RBM use since 2013[3], but widespread adoption remains limited.

To accelerate RBM implementation, the FDA should:

1. Introduce regulatory incentives, including expedited review processes
2. Expand RBM training for reviewers and industry stakeholders
3. Launch a joint NIH-FDA pilot program implementing 100% RBM approaches in selected NIH-funded studies
4. Increase federal funding for automated trial monitoring technology

If the pilot program succeeds, the National Institutes of Health (NIH) should consider requiring all future funded trials to adopt a complete Risk-Based Quality Management (RBQM) approach. These measures address key adoption barriers: perceived regulatory risk, implementation costs, and organizational resistance to change.

These incentives address key barriers to RBM adoption: perceived regulatory risk, implementation costs, and organizational resistance to change. By offering tangible benefits, this proposal aims to accelerate the shift towards more efficient, data-driven monitoring practices in clinical trials, continuing to ensure trial quality and patient safety while potentially reducing costs.

Challenge and Opportunity

Reliance on SDV, which involves comparing every data point in trial records with original sources, drives up the cost of clinical trial monitoring with little value (identifying data errors that matter) in return. While thorough, it's incredibly resource-intensive. On-site visits, extensive SDV, and overall compliance burden with Good Clinical Practice have been estimated to account for between 30%[4] and 50%[5] of total trial costs in various studies. A 2014 HHS report[6] on trial costs estimated that study monitoring might account for between 15-30% of trial costs, and also recommends increasing RBM uptake as an intervention. Empirical evidence supports the shift towards more efficient monitoring methods, as studies have shown[7] that SDV often identifies random errors that have little impact on trial results and clinical conclusions.

RBM emerged as a new paradigm within the broader RBQM framework, aiming to make monitoring more targeted and strategic. RBM encompasses five components:

- Key risk indicators (KRIs)
- Centralized monitoring
- Off-site monitoring
- Reduced SDV
- Reduced SDR

RBQM adds three additional risk assessment and quality control elements. RBM/RBQM represents a more efficient alternative[8] to the classical clinical trial framework. One study comparing RBM to extensive on-site monitoring found that the latter approach used more than twice[9] the resources compared with the former with no important benefits.

Despite proven benefits and the FDA issuing guidance[10] promoting its use beginning 2013, industry adoption of RBM/RBQM has been surprisingly slow. By 2019, 53% of trials[11] included at least one RBQM component. However, the percentage of trials implementing the more significant elements of RBM, like centralized monitoring and reduced SDV/SDR was much lower, standing at 10% and 15% respectively. The COVID-19

1 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3520949/
2 https://pubmed.ncbi.nlm.nih.gov/28786330/
3 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/risk-based-approach-monitoring-clinical-investigations-questions-and-answers
4 https://pubmed.ncbi.nlm.nih.gov/15864237/
5 https://www.academia.edu/9531694/Quality_assurance_within_the_scope_of_Good_Clinical_Practice_GCP_what_is_the_cost_of_GCP_related_activities_A_survey_within_the_Swedish_Association_of_the_Pharmaceutical_Industry_LIF_s_members
6 https://aspe.hhs.gov/sites/default/files/migrated_legacy_files//44516/rpt_erg.pdf
7 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3520949/
8 https://www.acrohealth.org/wp-content/uploads/2023/11/FINAL-RBQM-PAPER-1-10-23.pdf
9 https://pubmed.ncbi.nlm.nih.gov/28786330/
10 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oversight-clinical-investigations-risk-based-approach-monitoring
11 https://www.acrohealth.org/wp-content/uploads/2023/11/FINAL-RBQM-PAPER-1-10-23.pdf

pandemic, however, demonstrated the industry's capacity for rapid change. Contract Research Organizations (CROs) swiftly pivoted to remote monitoring practices when on-site visits became impossible. While remote monitoring is not the same as central monitoring (a component of RBM), this adaptability suggests that broader RBM adoption is feasible given the right incentives.

Still, the shift is far from complete: only 43% of studies starting in 2021[12] implemented centralized monitoring, and 27%[13] did both centralized monitoring and reduced SDV/SDR. To accelerate this shift, a combination of legislative and executive actions could be considered. These might include regulatory fast-tracks for RBM-utilizing trials, and mandated RBM pilot programs for federally funded studies. Such initiatives could drive innovation, reduce trial costs, and ultimately accelerate the drug development process, benefiting both patients and the healthcare system at large.

Plan of Action

The slow adoption of Risk-Based Monitoring (RBM) in clinical trials stems from several factors[14]. Sponsors and Contract Research Organizations (CROs) are hesitant to reduce Source Data Review (SDR) and Source Data Verification (SDV), fearing missed adverse events or regulatory issues. Other barriers include unfamiliarity with RBM practices, perceived complexity, logistical challenges, technology requirements, and misconceptions about regulatory acceptance. To address these commonly cited barriers, we propose the following actions:

1. **Recommendation One:** The FDA should implement a tiered incentive system for clinical trial applications that incorporate comprehensive risk-based monitoring (RBM) practices. For trials implementing all five core RBM components (key risk indicators, centralized monitoring, off-site/remote-site monitoring, reduced source data verification, and reduced source document review,) the FDA could offer a fast-track review process, committing to reviewing Investigational New Drug (IND) applications within 20 calendar days instead of the standard 30 days*. For trials implementing at least three RBM components, the FDA could offer a 25 day review commitment. This tiered approach addresses the current piecemeal implementation revealed in studies. By offering tangible benefits, the FDA would encourage more comprehensive RBM adoption while still rewarding incremental progress.
2. **Recommendation Two:** To address knowledge gaps and misconceptions about RBM, the FDA should launch a comprehensive education and training initiative in collaboration with the Association of Clinical Research Organizations (ACRO) and other industry stakeholders. This initiative should specifically target the barriers identified in the ACRO survey[15], such as concerns about regulatory acceptance of data and sponsor reluctance on certain types of trials. The program should include:
    a. Detailed guidance documents on RBM best practices, with emphasis on how RBM fits into the larger risk-based quality management (RBQM) framework.
    b. A series of workshops and webinars addressing common misconceptions, such as the incorrect assumption that RBM methodology data are less likely to satisfy regulators.
    c. An online resource center featuring case studies from the COVID-19 pandemic, which demonstrated the effectiveness of remote monitoring in maintaining data quality and patient safety.
    d. Specialized training for FDA reviewers to ensure consistent evaluation of RBM plans across different therapeutic areas and trial phases.
3. **Recommendation Three:** The FDA should establish a pilot program in collaboration with NIH to demonstrate the effectiveness of RBM in government-sponsored clinical trials. This program should:
    a. Select a diverse set of NIH-funded trials across different therapeutic areas, mandating the use of comprehensive RBM approaches.
    b. Implement the full spectrum of RBQM components, including initial and ongoing cross-functional risk assessments, quality tolerance limits, and all five RBM components.
    c. Collect and analyze data on the efficiency and effectiveness of RBM compared to traditional monitoring approaches, focusing on metrics such as the number of critical protocol deviations detected, time to detection,overall trial quality, and the reporting of adverse effects and serious adverse effects.
    d. Publish regular updates and a final comprehensive report on the outcomes of these trials, providing real-world evidence to support broader industry adoption.

* To clarify, FDA currently requires that trial sponsors wait at least 30 days between submitting an Investigational New Drug (IND) application and beginning a trial, so that reviewers can check protocol for safety concerns.

12 https://www.acrohealth.org/wp-content/uploads/2023/11/FINAL-RBQM-PAPER-1-10-23.pdf
13 https://www.acrohealth.org/wp-content/uploads/2023/11/FINAL-RBQM-PAPER-1-10-23.pdf
14 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8082746/
15 https://www.acrohealth.org/wp-content/uploads/2023/11/FINAL-RBQM-PAPER-1-10-23.pdf

e. Use the insights gained from this pilot to refine FDA guidance on RBM implementation and to develop standardized metrics for assessing the quality and effectiveness of RBM approaches in future trials.

f. Conditional on the success of this pilot, NIH should strongly consider adopting rules that require all NIH-funded trials to use a 100% RBQM approach.

4. **Recommendation Four:** Beyond implementation of existing RBQM practices, FDA and NIH have a role to play in pushing the basic science of it forward. Specifically, funding research on automation and incorporation of cutting-edge technologies like Artificial Intelligence for:

    a. monitoring trial data for duplication or deletion or improper entry;

    b. adverse event monitoring;

    c. selection of trial sites;

    d. improving trial adherence.

    These would be natural fits for the NIH's National Center for Advancing Translational Sciences (NCATS) institute, as well as FDA's longstanding interest in regulatory science.

Conclusion

Transitioning to risk-based monitoring will improve the cost-effectiveness of clinical trials. By implementing a tiered regulatory incentive system, enhancing education and training, pilot programs, and funding research on new RBM methods, the FDA and NIH can accelerate the adoption of RBM across industry and academia. These measures not only address current barriers to implementation but also pave the way for a more adaptive, data-driven approach to clinical trial monitoring.

About the Author

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