Paper RM03

Equity as a Dimension of Quality: Embedding Equity into Risk-Based Quality Management

Lydia Matombo, Clinavence, Union NJ, USA

ABSTRACT

Risk-Based Quality Management (RBQM) has reshaped clinical trial oversight by reducing reliance on source data verification, embedding centralized monitoring, and reinforcing quality-by-design principles. While these frameworks have strengthened data integrity and operational efficiency, they have often failed to systematically address equity-related risks such as population representativeness, site accessibility, and health literacy. These gaps contribute to underrepresentation, introducing operational inefficiencies, and weakening the interpretability and generalizability of trial outcomes.

This paper presents a practical framework for embedding equity as a measurable, inspection-ready quality risk within RBQM oversight systems. By translating equity considerations into defined risks, key risk indicators (KRIs), quality tolerance limits (QTLs), and proportionate mitigation actions, sponsors and CROs can operationalize equity using existing RBQM tools. This approach aligns with evolving global regulatory expectations and strengthens inspection readiness, data reliability, and participant experience.

1. INTRODUCTION

RBQM is now the dominant paradigm for clinical trial oversight, emphasizing proactive risk identification, centralized monitoring, and continuous quality improvement. The revised Good Clinical Practice guideline, ICH E6(R3), reinforces this shift by establishing a proportionate, risk-based approach to trial conduct and oversight (ICH E6(R3), 2025). Quality is no longer something verified retrospectively, but something that must be built into trial design and execution.

ICH E8(R1) further reinforces this principle by framing quality as a design-stage responsibility and emphasizing the importance of identifying factors critical to quality and managing risks to those factors throughout study conduct (ICH E8(R1), 2022). Together, these guidance documents establish that trial quality is inseparable from design decisions that influence population relevance and representativeness.

Despite these signals, equity-related considerations are frequently addressed outside formal RBQM frameworks, limiting traceability, consistency, and inspection defensibility. This paper argues that equity must be explicitly managed as a dimension of quality within RBQM systems.

2. REGULATORY AND GLOBAL EXPECTATIONS FOR EQUITY

Regulatory expectations regarding population representativeness and access have shifted from encouragement to statutory obligation. Under the Food and Drug Omnibus Reform Act (FDORA, 2022), sponsors conducting certain late-stage and pivotal clinical studies are required to prepare and submit Diversity Action Plans describing enrollment goals for underrepresented populations and strategies to achieve them. FDA issued draft guidance in June 2024 outlining the expected content, scope, and timing of these plans. While formal final guidance has not yet been published, Diversity Action Plans are being operationally developed and submitted for applicable Phase 3 programs as part of routine regulatory engagement, reflecting FDA's active implementation of the statutory requirement.

In Europe, the **European Medicines Agency (EMA)** and **Heads of Medicines Agencies (HMA)** issued the *Recommendation Paper on Diversity in Clinical Trials* (2022), emphasizing that inadequate representativeness may compromise the interpretability and applicability of trial outcomes and calling for early identification and mitigation of participation barriers.

At a global level, the **African Medicines Agency (AMA)** was established through the **African Medicines Agency Treaty** (adopted 2021; entered into force 2023) to strengthen regulatory harmonization and equitable access across African Union Member States. Draft AMA regulatory and operational frameworks issued in **2024** reinforce ethical clinical research, regional relevance, and access as foundational regulatory principles, even as detailed GCP inspection guidance continues to evolve.

Ethical guidance further reinforces these expectations. The **Council for International Organizations of Medical Sciences (CIOMS)**, in collaboration with the **World Health Organization**, in its *International Ethical Guidelines for Health-related Research Involving Humans* (2021), emphasizes avoiding systematic exclusion and addressing barriers that disproportionately affect specific populations

Collectively, these signals establish that equity has entered the quality system.

3. THE GAP IN TRADITIONAL RBQM FRAMEWORKS

Traditional RBQM frameworks are highly effective at monitoring safety signals, protocol deviations, and data integrity but frequently underemphasize equity-related risks such as differential enrollment, subgroup-specific attrition, site accessibility challenges, and health literacy barriers.

These factors directly affect data completeness, trial execution efficiency, and the generalizability of results. When equity risks are managed outside centralized monitoring plans, early warning signals may be missed and corrective actions delayed until formal thresholds are breached.

ICH E6(R3) makes clear that risks affecting participant protection or data reliability must be identified and managed proactively. The gap in current practice is not intent, but operationalization.

4. EQUITY AS A MEASURABLE QUALITY RISK

Equity becomes a quality signal when it is operationalized through RBQM mechanisms. ICH E6(R3) reinforces that quality must be built in by design through identification and management of critical factors throughout the trial lifecycle (ICH E6(R3), 2025).

Applying this principle, equity-related risks can be translated into measurable KRIs and QTLs using existing RBQM tools, for example:

Table 1: Example Equity-Focused KRIs and Quality Tolerance Limits Embedded in RBQM Oversight

Risk Area	Key Risk Indicator	Quality Tolerance Limit
Diversity	Enrollment vs disease epidemiology	≥20% underrepresented populations
Access	Travel distance or missed visits	≤50 miles
Retention	Subgroup-specific dropout	≤10% difference

Embedding these measures within RBQM governance enables intentional, proactive monitoring of equity-related risks, supporting early, proportionate action and documentation in an inspection-ready manner, often before formal thresholds or escalations are triggered.

5. FROM SIGNAL TO ACTION: CENTRAL MONITORING IN PRACTICE

Central monitoring is not limited to detecting QTL breaches. ICH E6(R3) emphasizes ongoing oversight and proportionate response, requiring sponsors to adjust oversight based on emerging risks that may affect participant protection or data reliability (ICH E6(R3), 2025).

Central monitors therefore evaluate trends over time, directionality, and subgroup-specific patterns across sites. Whether using simple dashboards or more advanced analytics, the objective remains the same: to intentionally and proactively identify emerging equity risks early, while intervention is still feasible.

When trajectories indicate risk, early and proportionate actions are triggered rather than waiting for formal threshold breaches. Critically, these decisions—along with the rationale for action or non-action—are documented as part of the RBQM oversight record. Documented rationale may include assessment of trend magnitude, affected subgroups, feasibility of mitigation, and justification for proportional action or continued monitoring. This documentation creates a clear audit trail demonstrating how equity-related signals were interpreted, what actions were taken, and how those actions aligned with the assessed level of risk.

By embedding documented decision-making into central monitoring workflows, sponsors and CROs strengthen inspection readiness, demonstrating compliance with ICH E6(R3)'s expectations for continuous oversight, proportionate response, and defensible quality management.

6. PROPORTIONATE MITIGATION AND OPERATIONAL RESPONSE

Equity-related risks identified through RBQM oversight require mitigation strategies that are practical, proportionate, and operationally feasible. FDA's Diversity Action Plan guidance emphasizes that plans must specify how barriers to participation will be addressed, not merely acknowledged. In practice, this requires translating identified equity risks into concrete operational actions that can be implemented, monitored, and documented over the course of trial conduct.

Importantly, these mitigations are not separate from RBQM; they function as **operational controls** aligned with quality-by-design principles. When implemented early, they support participant protection, improve data completeness, and reduce downstream operational and regulatory risk.

Table 2 provides illustrative examples of common equity-related risks, corresponding mitigation approaches, and the associated quality and operational value. These examples are not prescriptive but demonstrate how equity risks can be addressed using existing trial execution levers.

Table 2. Examples of Equity Risks, Mitigation Strategies, and Quality Value

Equity Risk	Example Mitigation Strategies	Plain-Language Explanation	Quality & Operational Value
Underrepresentation of key populations	Define enrollment targets aligned to disease epidemiology; embedded into protocol and monitoring plans	Checks on whether enrolled participants reflect the real-world population affected by the disease	Improves regulatory credibility, reduces risk of post-marketing commitments, strengthens generalizability
Limited site accessibility in underserved regions	Select sites closer to target communities; provide travel support or decentralized options	Reduces distance and logistical burden for participants	Improves enrollment speed, reduces screen failures and dropouts
Health literacy barriers	Use plain-language consent forms; translated materials; community engagement	Helps participants understand study requirements and expectations	Improves retention, data completeness, and informed consent quality
Digital divide (limited access to ePRO/telehealth)	Offer hybrid paper/electronic options; training or loaner devices	Ensure participants can use required study tools	Reduces missing data and protocol deviations; supports inclusivity
Differential AE reporting across subgroups	Train sites on equitable AE capture; use centralized monitoring	Identifies whether safety events are being underreported in certain populations	Improves safety signal detection and confidence in safety profile
Retention gaps in vulnerable populations	Flexible scheduling; community outreach; targeted follow-up	Identifies and addresses reasons certain groups drop out more often	Protects data integrity and reduces costly over-recruitment

7. INSPECTION READINESS AND STRATEGIC VALUE

ICH E6(R3) reframes inspection readiness as a function of continuous oversight, proportionate response, and defensible decision-making rather than retrospective verification. Within this paradigm, the ability to demonstrate how risks were identified, interpreted, and addressed over time is central to regulatory confidence.

When equity-related risks are embedded within RBQM governance, sponsors and CROs can demonstrate a clear, end-to-end quality management process. Equity signals are proactively monitored through centralized oversight, interpreted in the context of trends and subgroup-specific patterns, and addressed through proportionate, operationally feasible mitigation actions. Critically, both the decisions taken and the rationale supporting those decisions are documented, creating a traceable audit trail.

These mitigation strategies support documented, risk-based decision-making and provide clear traceability between identified equity risks, actions taken, and observed outcomes. This traceability aligns directly with ICH E6(R3)'s emphasis on continuous oversight, proportionate response, and defensible quality management, and demonstrates that equity considerations are actively managed within the trial's quality system rather than addressed retrospectively.

From an inspection perspective, this approach enables sponsors and CROs to clearly articulate not only *what* actions were taken, but *why* those actions were appropriate given the level of risk at the time. Inspectors are therefore presented with evidence of intentional oversight rather than reactive remediation.

Beyond inspection readiness, this framework delivers strategic value. Sponsors benefit from stronger, more defensible submissions and reduced likelihood of late-stage surprises. CROs can demonstrate differentiated RBQM capability grounded in execution rather than process description alone. Most importantly, participants benefit from trials that are more accessible, more understandable, and more representative of the populations they are intended to serve.

8. CONCLUSION

Equity risks are quality risks. When equity considerations are treated as aspirational or peripheral, they introduce avoidable uncertainty into trial execution, data integrity, and interpretability of outcomes. When they are intentionally embedded within RBQM frameworks, they become measurable, manageable, and defensible.

This approach creates a clear win–win across the clinical research ecosystem. Sponsors benefit from stronger, more defensible submissions, improved predictability, and reduced risk of late-stage surprises or post-marketing commitments. CROs benefit from differentiated RBQM capability grounded in execution and traceability rather than process description alone. Participants benefit from trials that are more accessible, understandable, and reflective of the populations they are intended to serve, supporting both safety and trust.

Importantly, funders and public stakeholders increasingly expect this level of rigor. Whether through regulatory mandates, ethical frameworks, or funding requirements, expectations around population relevance, access, and representativeness are now explicit. Trials that fail to anticipate and manage these

dimensions risk not only regulatory scrutiny, but diminished credibility with sponsors, partners, and the communities they aim to serve.

Embedding equity into RBQM is not about adding parallel processes or incremental cost. It is about using existing oversight mechanisms more intentionally to manage risks that directly affect participant protection, data reliability, and long-term value. When equity is proactively monitored, acted upon proportionately, and documented within the quality system, organizations can demonstrate not only compliance, but stewardship of trial quality.

Ultimately, this framework aligns scientific rigor, regulatory expectations, and commercial objectives around a shared outcome: safer trials, more generalizable evidence, and defensible decision-making that stands up to inspection. When equity is measurable, it becomes manageable. When it is manageable, it becomes defensible — and when it is defensible, it strengthens outcomes for everyone involved.

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Contact Information:
Lydia Matombo
Clinavence
Union, NJ, USA
Email: lydia.matombo@clinavence.com