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RbQM: An Intersection of Cross-Functional Collaboration of Clinical, Analytics, Statistics and Technology Domains for Better Clinical Trial Governance

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ABSTRACT

The evolution of traditional monitoring clinical trials to RBM (Risk Based Monitoring) to RbQM (Risk based Quality Management) is a paradigm shift. Traditional monitoring typically comprises of on-site monitoring visits, at a frequency of every 4-8 weeks, with 100% source data verification (SDV). Traditional monitoring is highly resource intensive, high cost, and has found to have minimal impact on quality of the clinical investigation.

RBM calls for risk-based monitoring and appropriate use of centralized monitoring. RbQM calls for an interdisciplinary approach drawing upon diverse domains such as Medical, Clinical, Data Management & Statistics. It also calls for deployment of diverse skills such as Protocol comprehension, Monitoring (central & sites), Data Analytics, Data Visualization, Data Storytelling, basics of Statistics & Algorithmic Thinking (programming). All of this culminates into Integrated Data Review (IDR) of the trial data.

This paradigm shift is a mammoth change management exercise, both at individual (study member) and collective level (project team). Uniform and pan-industry level adoption of RbQM is therefore, a function of effective Change management. This paper walks through the methodology of effective change management for implementing RBQM.

INTRODUCTION

Evolution: Change is the only constant

There are fundamental laws of our universe. Evolution is one such fundamental law, because change is the only constant. Think about it! Elaborating this point with an example, in the book **'The Evolution of Physics'**, written by Albert Einstein & Leopold Infeld, they trace the development of ideas in physics from the rise of mechanical view, The decline of the mechanical view, Field relatively & Quanta. As clinical researchers, we can see in our own domain of evolution from Paper CRFs to Electronic Data Capture, to Wearables in clinical trials.

Clinical monitoring activities and clinical data review has been constantly evolving over the decades. The traditional monitoring of 100% SDV, SDR evolved into RBM (Risk Based Monitoring) and then into RbQM (Risk Based Quality Management). The earlier approach of monitoring 100% clinical data shifted to proactive risk management, focus on CD&P (critical data & critical process), setting up QTL (Quality Threshold Limits), deploying technology for Data visualization & analytics, and harnessing power of Statistics, CSM (Central Statistical Monitoring) on the large datasets to identify patterns, predict and detect anomalies.

How It All Started?

Duke Clinical Research Institute, TIMI Study Group, an academic research organization, initiated the conversation for a newer approach, rather than the traditional monitoring. The trials conducted by TIMI indicated, the amount of monitoring didn't seem to have a profound effect on study quality.

A survey, **what is the Cost of GCP-related activities?** was conducted within the Swedish Association of the Pharmaceutical Industry members, in the year 2005. 97% (n=250) of the Ph-III trials performed in Sweden were surveyed. Approximately 50% of the trial budget was attributed to GCP-related activities. 50% of the GCP-related cost was related to Source Data Verification (SDV). A vast majority (71%) of respondents did not support the notion that these GCP-related activities increase the scientific reliability of clinical trials.[1]

A metadata study, Evaluating SDV as a QC measure in Clinical Trials, conducted by Sheetz et al in 2014, supports the hypothesis that generalized SDV has limited value as a quality control measure and reinforce the value of other risk-based monitoring activities. In total, 1168 phase I-1V studies across 53 sponsors showed a median of only 1.1% of the total e-CRF data was corrected by SDV. Only 3.7% of e-CRF data was corrected by any data-cleaning method. Therefore, a large chunk of 96.3% data entered by sites is not corrected by any method. Even though the percentage of AEs or SAEs that are recorded within 1 or 7 days following on-site monitoring, median values are 7.5% and 11.8%. SAE that are recorded within 1 or 7 days following on-site monitoring, median values are 1.7% and 3.6% respectively. Among 1376 major or critical audit findings reported over 29 months period, approximately only 11% of findings are related to SDV. Only 0.65% of critical audit findings were related to SDV.

In August-2013, USFDA released a guidance to industry, **Oversight of clinical investigations – A risk-based approach to monitoring**. The FDA 2013 guidance main points were: 1. 100% SDV is not mandated, 2. Abandon 100% SDV, 3. Appropriate use of centralized monitoring and technological advances, 4. Process: define critical data and processes, conduct risk assessment & prepare risk-addressing monitoring plan employing the right mix of central and onsite. Remote evaluation (location other than the clinical site), centralized monitoring complement on-site monitoring.

In November-2013, European Medicines Agency published a Reflection paper on **Risk based quality management in clinical trials**. Quality in this context is commonly defined as fitness for purpose. Clinical research is about generating information to support decision making while protecting the safety and rights of participating subjects. The quality of information generated should therefore be sufficient to support good decision making. EMA encourages more systematic, prioritized, and risk-based approaches to quality management system-wide, and recommends use of a quality by design approach across all aspects of trial design, including a trial monitoring plan.

Risk-Based Quality Management Systems

In March-2018, E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) came into existence. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (R2) Good Clinical Practice guidance and in ICH E8 (R1) General Considerations for Clinical Studies,

points towards integrating Risk-based monitoring approaches into an efficient clinical trial quality management system (QMS). The Clinical Trials Transformation Initiative's Quality by Design project recommends quality be built into the scientific and operational design and conduct of clinical trials from the outset and revisited throughout the conduct of the clinical trial. The emphasis is on identifying the 'critical to quality factors (CtQ)' at the planning stage and monitoring them during the execution stage.

In ICH E6 GCP Section 5.0, the key highlights were:

5.0.4 Risk Control: (…) **Predefined quality tolerance limits** should be established, taking into consideration the medical & statistical characteristics of the variables as well as the statistical design of the trial, to **identify systematic issues** that can impact subject safety or reliability of trial results. Detection of **deviations** from the predefined **quality tolerance limits** should **trigger** an evaluation to determine if action is needed.

5.0.7: Risk reporting: The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken **in the clinical study report** (ICH E3, section 9.6 Data Quality Assurance).

Risk-based monitoring approach shifted the sponsor focus from non-risk-based approaches involving on-site monitoring with 100% SDV, to important and likely risks to overall investigation quality, risks to human subject protections, data integrity and quality management system (systematic quality management). The four most important aspects of trial quality are:

Area	Failure	Most frequent reasons
Population	The population recruited is not the intended population of a trial	Insufficient disease severity – no need for additional treatments
Intervention	The population is not exposed to the intervention as planned/intended	Low compliance, premature discontinuation of treatments
Data collection/endpoint	The data showing if the intervention is effective is incomplete or inaccurate	Missing assessments, lot to follow-up, variability of assessments
Bias	Something influences the study arms differently	Management of adverse events changes patient readout.

Industry response:

Industry responded positively, with multiple sponsors and CROs implementing risk-based monitoring approaches. In 2013, TransCelerate BioPharma came out with position paper on Risk-based monitoring methodology. **Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials.** This paper drew upon 1168 studies and concluded 100% SDV doesn't change a lot. 96.3% of data entered by sites is not corrected by any method (SDV corrections, Auto-Queries, Other Corrections).

TransCelerate conducted several RBM studies over the years, and these have appeared in industry publication, DIA's Therapeutic Innovation & Regulatory Science (TIRS).

1. Defining a Central Monitoring Capability: Sharing the experience of TransCelerate BioPharma, Part 1 (2014)
2. Technology considerations to enable risk-based monitoring methodology, Part 1 (2014)
3. Evaluating Source Data Verification as a quality control measure in clinical trials (2014)
4. December 2015: TransCelerate Risk-based monitoring technology considerations, Part 2 (2015)
5. Defining a central monitoring capability: sharing the experience of TransCelerate BioPharma's approach Part 2 (2015)
6. Detecting data quality issues in clinical trials: current practices and recommendations (2015)
7. Statistical monitoring in clinical trials: best practices for detecting data anomalies suggestive of fabrication of misconduct (2016)

TransCelerate BioPharma developed and piloted a methodology for implementing risk-based monitoring that was adopted in some form by several of its member companies.

RBM 1.0 came into existence. This methodology uses quality risk management, starting with building QbD into trials and including use of risk indicators and risk thresholds to trigger an action such as increased data scrutiny and site follow up. The key components in RBM 1.0 are 1. RACT (risk assessments), 2. Define SDV/SDR levels based on critical data and overall risks, 3. KRIs driven central & site monitoring.

With time, RBM 1.0, evolved into RbQM. The evolution of this model was: 1. Data Visualization, 2. QTL (Quality Tolerance Limits), 3. CSM (Central Statistical Monitoring). CSM uses statistical methods on high volume datasets to discover anomalies: especially sensitive to data fabrication and can discover unforeseen errors.

Association of Clinical Research Organization (ACRO) in 2019, conducted their first survey to quantify the adoption of RBM/RBQM. ACRO paper laid out the definition of RBM & RBQM by breaking it down into 8 components.

RBM:

1. Initial cross-functional risk assessment
2. Ongoing cross-functional risk assessment
3. Quality Tolerance Limits (QTLs).

RbQM:

4. Key risk indicators (KRI)
5. Centralized monitoring
6. Off-site/remote-site monitoring
7. Reduced source data verification (SDV)
8. Reduced source data review (SDR)

In RbQM, the clinical research team, is expected to bring in wide array of knowledge, skills, with an inter-disciplinary mindset and deployment of technology to proactively plan for quality, mitigate risks and focus on what matters the most in a trial, rather than every datapoints.[3]

Change Management Is a Big Challenge:

The evolution of traditional monitoring into RBM and into RbQM, is a paradigm shift and not just an incremental change.

TransCelerate explicitly calls out integrating change management for successful implementation of RbQM. *Change management is the practice of aligning values, culture, people and behaviours to new modes of operation (…) successfully integrating change management into RBM adoption will be critical. This includes educating and involving new and potential adopters about the nuances of RBM, debunking myths surrounding RBM, and creating awareness campaigns and comprehensive training tailored to key stakeholders., shared understanding of scope of tasks, roles and responsibilities across the entire stakeholder ecosystem.*

Risk-Based Quality Management (RBQM) requires a blend of **technical understanding** (risk methodologies, data analysis, modeling), **analytical skills** (critical thinking, problem-solving, data interpretation), **strategic mindset** (linking risk to business goals, understanding risk appetite), and strong **soft skills** (communication, stakeholder management, adaptability) to proactively identify, assess, and mitigate risks for better quality and compliance, especially with guidelines like ICH GCP.

RbQM Core Knowledge:

- Risk Management Frameworks: Understanding principles from ISO 31000, ICH GCP E6/E8, and implementing tools like Risk Assessment and Categorization Tools (RACT), Key Risk Indicators (KRIs), and Quality Tolerance Limits (QTLs).

- **Data & Technology:** Proficiency in data analysis, statistical modelling, data visualization, and relevant software (e.g., Python/R for advanced roles) to gain insights from large datasets.

- **Regulatory Compliance:** Deep knowledge of relevant industry regulations (e.g., clinical trials) and quality standards (ISO 9001, ICH).

- **Business Acumen:** Understanding business objectives, risk appetite, strategic goals, and how risks impact overall performance.

RbQM Essential Skills:

- **Analytical & Critical Thinking:** Ability to interpret complex data, identify patterns, challenge assumptions, and make sound judgments.

- **Problem-Solving:** Developing practical solutions and implementing corrective/preventive actions.

- **Strategic Planning:** Aligning risk management with organizational strategy

and objectives.

- **Communication:** Effectively conveying risk information, findings, and recommendations to diverse stakeholders.

- **Adaptability & Agility:** Responding effectively to changing risk landscapes and making timely decisions.

- **Data-Driven Decision Making:** Using data to drive decisions rather than relying solely on traditional, intensive monitoring.

- **Stakeholder Management:** Building relationships and fostering collaboration across departments.

RbQM Practical Application:

- **Risk Identification & Assessment:** Systematically identifying potential risks and opportunities.

- **Risk Mitigation:** Developing strategies to reduce, transfer, avoid, or accept risks (the 5 Rs: Readiness, Response, Reduction, Recovery, Review).

- **Centralized Monitoring:** Using real-time data to detect anomalies and performance issues remotely.

- **Continuous Improvement:** Fostering a culture of proactive risk management for ongoing quality enhancement.

Therefore, transitioning from traditional monitoring to RbQM is a paradigm shift. In this transformative journey, we must recognize the challenges (roadblocks) lying in front of us. Far from a definite list, let me list out the most probable challenges:

[4]**Challenges in Change Management:**

- Breaking silos and cross-functionally reviewing and critique Study Protocol during the planning phase, for identifying the critical process & critical data (CP&D), and identifying the scientific risks.
- Breaking silos and embracing interdisciplinary approach within the organization: Clinical, Data Management, Statisticians, Medical Monitors, Central Monitors, Medical Data Reviewers, Pharmacovigilance, Technology partner etc., collaborating to plan and execute RBQM strategy.
- Breaking silos in data review and embracing Integrated Data Review (IDR).
- Organizational changes for aligning to RbQM workflow, by role redundancy, new roles and merging of multiple roles for negating overlaps.
- Change in mindset for site personnels, CRA for moving away from conventional SDV and embracing technology, data-driven decision making.
- Change in mindset and Upskilling for data visualization, data analytics and data storytelling
- Investment in digital infrastructure for multiple data ingestion, data visualization, onboarding Tech partner, make or buy decisions, process transformations: changes in SOPs, WI and conducting road shows for communication

Therefore, within an organization and at pan-industry level successful adoption of

RbQM is a function of Effective Change Management, by individuals (study members) and the collective (project team).

Effective Change Management:

Industry surveys and research consistently point us towards high failure rates of change management in organizations. Estimates suggest this failure rates can be as high as 70%. Such high failure rates can be a matter of grave concern for us, as we are on our own journey from traditional monitoring to RbQM.

As famously said by Socrates, “The secret of change is to focus all of your energy not on fighting the old but on building the new.”

For overcoming the above listed challenges, we can focus on building the new, by Interdisciplinary coordination, L&D and upskilling, marriage of technology driven central monitoring with on-site visits by CRA, top down approach balanced with taking all key stakeholders together, risk management framework and governance plan, identify the right tech vendor (not too many), piloting RbQM on the right studies and deriving the proof of concept (PoC) and proof of value (PoV) for large scale adoption etc.

However, such change management efforts will be chaotic, unstructured and not focused, until the effort is channeled through a systematic framework.

“If you want to go fast go alone; if you want to go far go together.” – African proverb.

In the context of an organization, the change management journey is not about an individual but about the collective, as expressed in the African proverb above. So, an evidence-based Change Management[5] i.e. the science-informed practice of managing planned organizational changes is an imperative for successful transition from traditional monitoring to RbQM.

Last but not the least, making change perceived as a routine is an effective approach. Research by Gartner shows establishing change as a routine is three times more effective than the inspirational approach[6]. Routinising the change means helping project teams see change as normal, regulating discomfort, and building intuitive responses to new situations. In other words, embedding the iterative and exponential tweaking of traditional monitoring to RbQM into the process, workflow with minimal disruption is a key component for effective change management.

Keeping all of this in mind, I propose the **ADKAR** Change Management approach for transitioning from traditional monitoring to RbQM. ADKAR offers a structured, people-centered approach that helps address these challenges by guiding each individual through the stages of awareness, desire, knowledge, ability, and reinforcement. By focusing on individual transformation and collective, Clinical Research Team can achieve smoother transitions from traditional monitoring into RBQM.

Deployment of ADKAR Change Management Methodology for Successful Outcome:

The ADKAR Change Management Model is a structured framework, it can be helpful for Clinical Research Team to navigate successful transformations, from traditional monitoring to RBQM approach by focusing on five key phases: Awareness, Desire, Knowledge, Ability, and Reinforcement. This model simplifies the often-complex process of change by breaking it into clear, achievable steps for both individuals and for the Project Team. By addressing these stages in sequence, Project Team can increase adoption, reduce resistance to change, and ensure sustained long-term success of transitioning from traditional monitoring to RbQM.

ADKAR model: a systematic path for transforming from traditional monitoring to RBQM approach

ADKAR element	Definition	What you hear	Triggers for building
A Awareness	Of the need for change	I understand why?	**Why? Why now?** *Regulatory Requirement, to reduce Cost & Timeline, Improve Quality.* What if we don't? *Failure cost for trials will be significantly upwards.*
D Desire	To participate & support the change	I have decided to	**WIFM? (What's In It for Me)** *Alignment with Organization's Strategy, New SOPs, Regulators, Industry trend.*
Knowledge	On how to change?	I know how to	**Need to know?** *Gain diverse knowledge (Clinical, Medical, Statistics, Therapeutic Area, Central Monitoring, Data Management, Trial Design, Risk Management, Project Management etc.)* *Gain diverse skills (Critical Thinking, Protocol Interpretation, Clinical Monitoring, Programming, Data Literacy, Data Analysis)*
A Ability	To implement required skills & behaviours	I am able to	**Size of the K-A Gaps, Barries in Capacity** *L&D, Upgrading Knowledge, Upskilling* *Practice (hands-on experience)* *Growth Mindset, Right Behaviours (Collaboration)*
R Reinforcement	To sustain the change	I will continue to	Sustain, Mechanisms, Measurements: M*entoring, Guidance, Coaching, Constructive feedback, rewards & recognition.*

CONCLUSION

Risk-Based Quality Management (RBQM) is an inter-disciplinary field which requires a blend of **technical understanding** (risk methodologies, data analysis, modeling), **analytical skills** (critical thinking, problem-solving, data interpretation), **strategic mindset** (linking risk to business goals, understanding risk appetite), and **strong soft skills** (communication, stakeholder management, adaptability) to proactively identify, assess, and mitigate risks for better quality and compliance, especially with guidelines like ICH GCP.

Due to it's inter-disciplinary nature, transition from traditional monitoring to RbQM (Risk based Quality Management) is a paradigm shift and not just an incremental change. Hence, the successful evolution of Traditional Monitoring to RbQM (Risk based Quality Management) is a function of Effective Change Management.

Call For Action:

Effective Change Management!

ADKAR Change Management model can facilitate the successful transformation from traditional monitoring to RbQM, by raising Awareness, enhancing Desire, growing Knowledge, developing Ability and by Reinforcing cross-functional collaboration and positive attitudes, growth mindset and behaviors (teamwork).

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RECOMMENDED READING

1. ICH Guidelines ICH Official web site : ICH
2. TransCelerate Risk Based Monitoring TransCelerate - Risk Based Monitoring - Clinical Trials

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