Paper AR03

Risk Based Quality Management (RBQM) in Clinical Data Management

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ABSTRACT

Risk-Based Quality Management (RBQM) is key to ensuring patient safety and data integrity in clinical studies. This presentation, condensed from a comprehensive workshop, highlights the transformation of Clinical Data Management and the role of Centralized Monitoring in real-time data validation. We explore how to define study-specific Key Risk Indicators (KRIs) and Quality Tolerance Limits (QTLs) from protocol analysis and Critical to Quality factors. Attendees gain insights into the utilization of Centralized Monitoring technology for achieving high-quality clinical data. This session is ideal for Clinical Data Managers seeking to enhance their understanding of cross-functional data-relevant collaboration with Centralized Monitoring.

INTRODUCTION

In the rapidly evolving landscape of clinical research, the integration of a Risk-Based Quality Management approach has become imperative to enhance data integrity and participant safety. This presentation explores the fundamentals and critical benefits of implementing RBQM within Clinical Data Management (CDM). The presentation is a condensed summary of what was discussed in a RBQM workshop with Data Managers during SCDM Conference last year.

FUNDAMENTALS OF RBQM

Risk-Based Quality Management in clinical trials is a systematic approach that integrates risk assessment, control, communication, and review to ensure data integrity and compliance with regulatory standards. It is structured around the concept of Quality by Design and the differentiation between System Level and Study Level implementations.

QUALITY BY DESIGN

RBQM is deeply rooted in the principles of Quality by Design (QbD), which emphasizes proactive planning to ensure high standards of quality are maintained from the start of a clinical trial. This approach involves identifying potential risks in advance and designing processes to mitigate them, thereby ensuring the integrity and reliability of trial data.

CRITICAL TO QUALITY FACTORS

Critical to Quality Factors (CtQs) are essential elements that directly impact study quality, participant safety, and data reliability. The formulation of CtQs involves detailed analysis of study objectives and endpoints, ensuring that key study processes are designed to achieve high quality standards.

CRITICAL PROCESSES AND DATA

Critical Processes and Data (CP&Ds) are fundamental components that ensure the successful delivery of Critical to Quality factors. Understanding CP&Ds is essential for maintaining the quality and integrity of clinical trial data.

Critical Processes are specific procedures and workflows necessary to achieve and ensure the CtQs in a clinical trial. They are identified based on their impact on study quality and participant safety. These processes are essential for the faithful execution of the trial protocol and for obtaining reliable and interpretative results. Critical Data refers to the key pieces of information required to validate the successful execution of CtQs. This data is pivotal in demonstrating the outcomes of study processes and ensuring compliance with regulatory requirements.

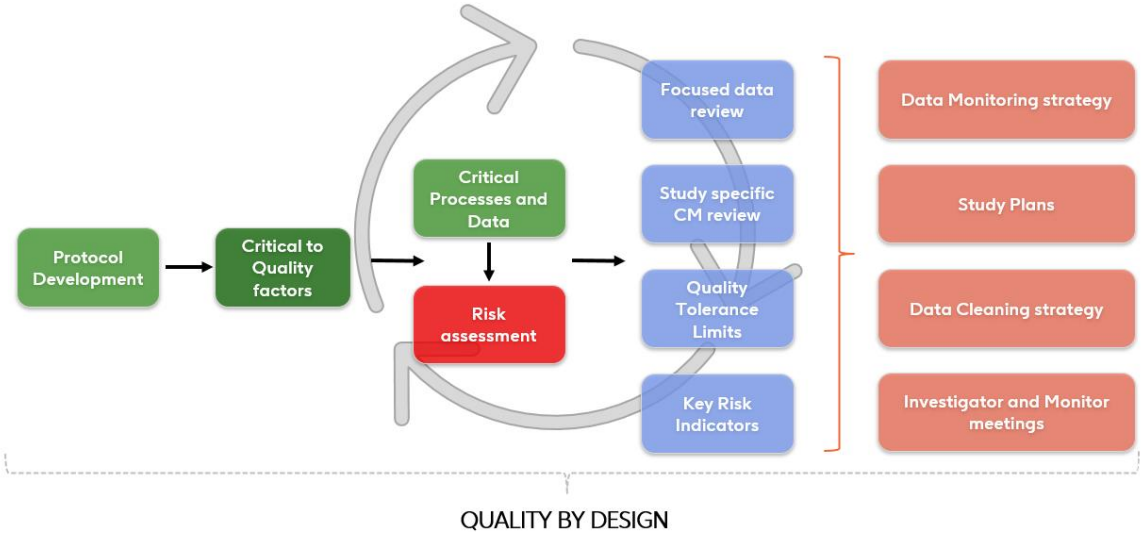
RISK ASSESSMENT

In clinical trials, risk assessment related to Critical to Quality factors is an essential component of Risk-Based Quality Management. First, we need to identify potential risks related to Critical to Quality factors. Each CtQ factor must be examined to determine potential risks that could impact the study outcomes. This involves understanding the trial objectives and endpoints thoroughly. Next step is to assess impact, likelihood and detectability of the risk. Evaluate the impact of each identified risk on the trial's safety and quality, alongside the likelihood of occurrence. This often involves qualitative and quantitative assessments and requires a thorough understanding of past trials, current practices, and regulatory guidelines. Based on the analysis, prioritize the risks that require more intensive monitoring or additional mitigation strategies. Focus on risks that have high impact and/or likelihood.

MITIGATION STRATEGIES

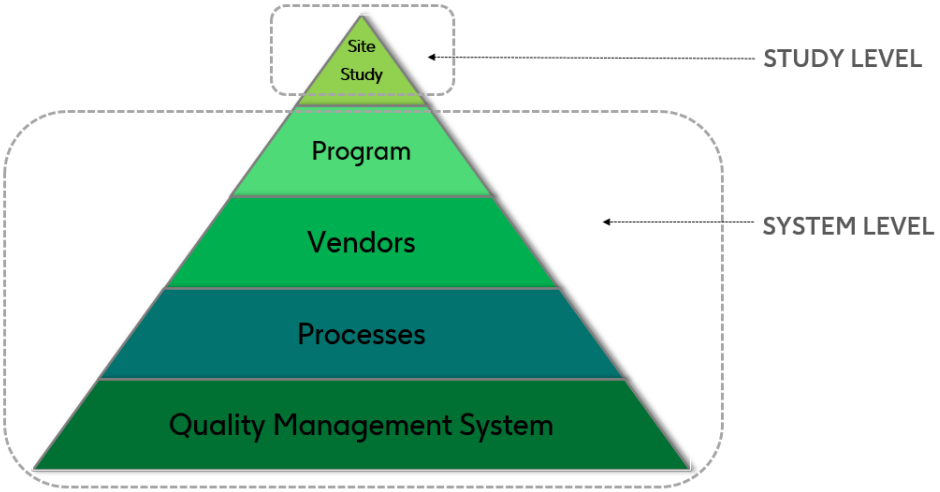
Create plans and procedures to manage and mitigate these risks. Strategies can include focused data review, study specific Centralized Monitoring reviews, Quality Tolerance Limits (QTL), Key Risk Indicators (KRI). Continuously assess the effectiveness of risk management strategies and adapt them based on real-time data and evolving trial conditions. This ensures that the CtQs remain achievable as the study progresses.
Regularly review statistical outputs to identify potential anomalies or trends indicative of emerging risks.

Risk assessment in relation to CtQs is designed to proactively identify and manage study-specific risks that could compromise participant safety or data reliability, thus supporting a more targeted and efficient approach to quality management in clinical trials.



RBQM AT A SYSTEM LEVEL

It's important to note that RBQM is not just at a project level, but at a system level. The system-level RBQM involves embedding risk-based strategies throughout the entire organizational framework rather than confining them to individual projects. This requires developing comprehensive policies and procedures that align with both industry best practices and regulatory standards, such as guidance from the FDA and EMA. RBQM at a system level is also an entire program factor, vendors that support the program and study, processes and overall, a Quality System Management.



WHY DO WE IMPLEMENT RBQM?

REGULATORY FACTOR

With the finalization of ICH GCP E6 R3 on January 6, 2025, clinical research is evolving, placing a stronger emphasis on Quality by Design, risk-proportionate oversight, and trial efficiency. RBQM is now at the core of clinical trials, shifting the focus from traditional oversight to a proactive, quality-driven approach. Also, FDA recommends that "Sponsors should identify risks, including to protocol-driven processes, that could affect human subject protection and data integrity. The risk assessment should include an evaluation of the potential causes, likelihood of detection, and severity of the consequences of risks to critical data or human subject protections. There are various risk assessment methodologies and tools that can be applied to clinical trials.". In addition to that, EMA released the "Reflection paper on risk-based quality management in clinical trials", in which they say: "It is necessary to establish a risk-based

quality management system for which the ultimate principles are reliability of the trial results and the wellbeing and safety of trial subjects. This system is based on identification of trial priorities and mitigation of the significant and serious risks and establishing tolerance limits within which different processes can operate."

DATA VOLUME FACTOR

Clinical data science is a rapidly growing interdisciplinary field that combines the knowledge of healthcare and data science to enhance patient care and improve healthcare outcomes. With the advancement of technology, the healthcare industry has been generating an enormous amount of data. Today, approximately 35% of the world's data volume is being generated by the healthcare industry. By 2025, the annual compound growth rate of data for healthcare will reach 36%. That's 6% faster than manufacturing, 10% faster than financial services, and 11% faster than media & entertainment.

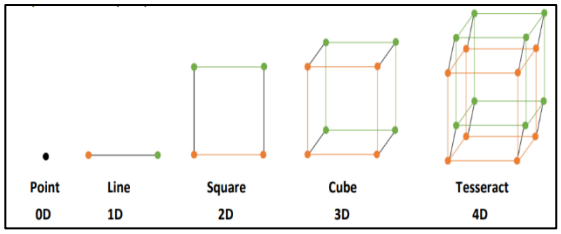
The Tufts Center for the Study of Drug Development research, which was based on 220 recently completed protocols, suggests that phase 3 clinical trials generate an average of 3.6 million data points, roughly three times the volume of data collected by late-stage studies a decade ago.

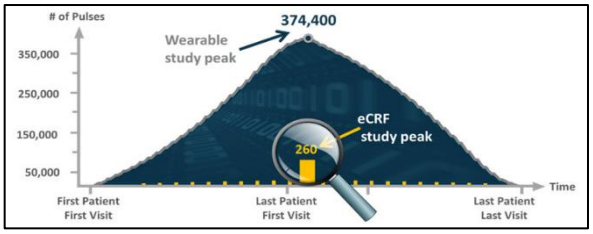
A potential 10 million opportunities for error are estimated per trial.

Even with a "good" error rate of 1 in 1,000, this would yield 10,000 errors. However, actual error rates are often much higher.

In addition to the volume and diversity of study data, the quality is also of concern. In a study conducted by Harvard Business Review, 97% of critical data used in business decisions contains errors or is incomplete.[3] Another study found that most executives are not confident enough in the accuracy of their data and analytics to take data-driven actions.

Based on these numbers we can see that the healthcare industry must find a way to accurately and efficiently manage this influx of critical study data.





CRITICAL TO QUALITY FACTORS AND CRITICAL PROCESSES AND DATA

WHAT ARE CRITICAL TO QUALITY FACTORS

Set of factors that are critical to study quality because they have an impact on:

- Protection of study participants
- Reliability and interpretability of the study results
- The decisions made based on the study results
-

CtQ is a broad term stating everything needed to achieve the study success in the matter.

Examples:

- Informed Consent

Standard CTQ name that might be made study specific, if needed:

"Critical to quality is to ensure that Informed Consent is obtained and documented appropriately for all subjects in line with required regulations"

- Investigational Product
- Primary & Confirmatory secondary endpoints
- Critical subject safety measures
- Intercurrent Events
- Key Study Population aspects
- Measures to prevent study bias
- Study or program specifics required for the study submission, answering the governance expectations

WHAT ARE CRITICAL PROCESSES AND DATA

Critical Processes – processes that are listed separately and are required to deliver CTQs

Critical Data – information that is needed to proof delivery of CTQs

EXAMPLES OF CRITICAL TO QUALITY FACTORS AND CRITICAL PROCESSES AND DATA:

Example 1:

Objectives	Endpoints
Primary	
To **demonstrate the non-inferiority** of the investigational study intervention in terms of relative efficacy as compared to the active comparator against **laboratory-confirmed ILI** caused by influenza subtypes/lineages contained in the investigational study product (ILI – Influenza like illness)	First occurrence of laboratory-confirmed cases of ILI at least 14 days after dosing, caused by influenza A subtypes H1N1 or H3N2 or influenza B-VIC according to the case definition

Critical to Quality factor related to the Primary Endpoint:

Ensure the effective Influenza like illness events collection starting 14 days after dosing via ILI symptoms reporting and confirmed via laboratory tests.

Critical Processes:

- ILI symptoms collection via eDiary/phone call
- ILI onset date collection
- Swabs collection
- Investigational study intervention
- Subject Retention, etc.

Critical Data:

- ILI symptoms
- ILI onset date
- Swab test results
- Date of IP administration
- Date of the study discontinuation, etc.

Example 2:

Objectives	Endpoints
Primary	
To evaluate the efficacy of Investigational Product 200 mg subcutaneous (SC) given every 6 months versus placebo in participants with uncontrolled HES receiving standard of care (SoC)	•Frequency of HES flares during the 52-week study intervention period

Critical to Quality factor related to the Primary Endpoint:

To enroll and retain in the trial Subjects with historically confirmed uncontrolled HES, receiving standard of care.

Critical Processes:

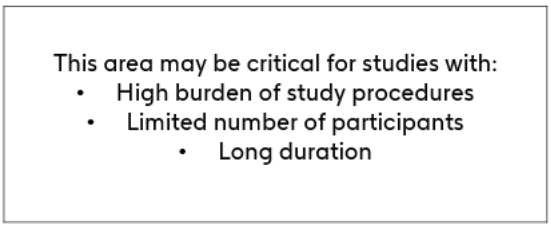
- Disease characteristic collection
- Collection of eosinophils
- Subject retention, etc.

Critical Data:

- HES flare data
- HES therapy data
- Eosinophil results
- Medical History data, etc.

Example 3:

Participant retention



Critical to Quality Factor related to participant retention:

Critical to quality is to ensure that participant retention in the study prior to the analysis of primary or confirmatory objectives is high.

Critical Processes:

- Subject retention
- Study conclusion, etc.

Critical Data:

- Date of withdrawal
- Reason for withdrawal
- Conclusion form, etc.

CENTRALIZED MONITORING

ROLE OF CENTRALIZED MONITORING

In the FDA's "Guidance for Industry - Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" we can read: "Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians) at a location other than the sites at which clinical investigation is being conducted. Centralized monitoring processes can provide many of the capabilities of on-site monitoring as well as additional capabilities."

Components of Centralized Monitoring can be Key Risk Indicators (KRI), Quality Tolerance Limits (QTL), Central Statistical Monitoring as well as targeted Centralized Monitoring reviews.

KEY RISK INDICATORS

Key Risk Indicator metrics are quantifiable measures derived from available data that correlate with identified risk factors during the risk assessment phase. While KRIs offer numerical insights, they might lack contextual depth. Therefore, qualitative insights gathered from interactions with on-site monitors and study coordinators are crucial and should be integrated with KRIs to accurately analyze risks and determine appropriate mitigation strategies. The goal of central monitoring extends beyond merely measuring and mitigating risks; it also aims to provide a comprehensive understanding of the processes being evaluated, enabling the adoption of the most effective control strategies.

<table>
<tr><th colspan="3">KRI thresholds examples</th></tr>
<tr>
<td>Relative score

The Relative Score reflects how atypical a center (entity) is compared to all centers (whole study) (observed vs expected).</td>
<td> 
</td>
<td>Absolute value

The Absolute Value is a specific test calculation result used in particular KRI.

<u>Observed value</u> – test result computed for each site.

<u>Expected value</u> - test result computed for the study.</td>
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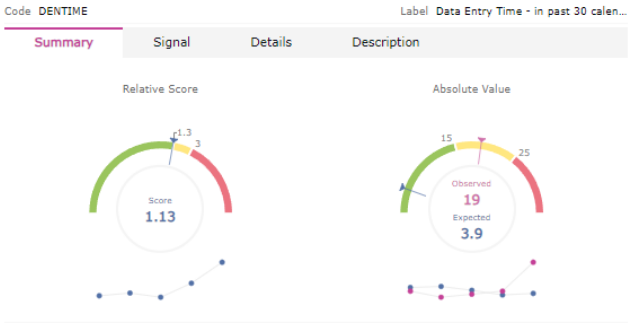
<td>Relative threshold

Detect risk (KRI color) based
on how atypical a center is compared to all centers (observed vs. expected). The highest the score, the most atypical the site is.</td>
<td> 
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<td>Absolute threshold

Detect risk (KRI color) based on the center's observed value compared to predefined threshold e.g., data entry timelines.</td>
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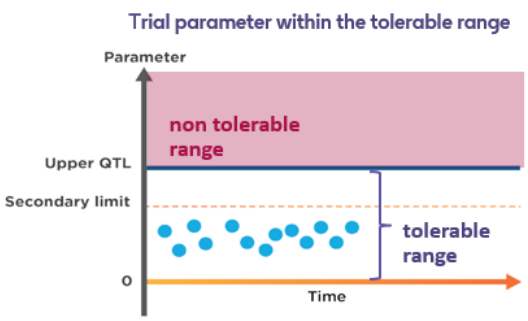
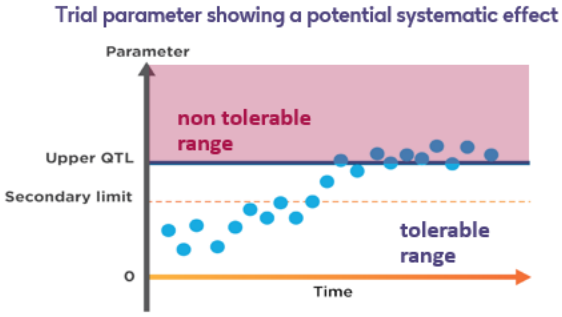
QUALITY TOLERANCE LIMITS

A QTL is a level, point, or value associated with a parameter that, when a deviation is detected, should trigger an evaluation to determine if there is a possible systemic issue. ICH GCP E6 R3 says: "Where relevant, the sponsor should set pre-specified acceptable ranges (e.g., quality tolerance limits at the trial level) to support the control of risks to critical to quality factors. These pre-specified ranges reflect limits that when exceeded have the potential to impact participant safety or the reliability of trial results. Where deviation beyond these ranges is detected, an evaluation should be performed to determine if there is a possible systemic issue and if action is needed."

When defining QTLs, consider what is most critical to the study	• Primary/secondary endpoints • Sometimes supportive endpoints • Highest risk related to data integrity/subject safety • Link QTL with risks and CP&Ds
Study teams determine at what timepoint and frequency the QTLs will be assessed in the study	• Set start of QTL review when expected amount of data is collected • If data is insufficient for QTL review the report should contain appropriate clarification • Expected recruitment rate and visit schedule should be considered in planning frequency of QTL review • Each study has a specific QTL





CENTRAL STATISTICAL MONITORING

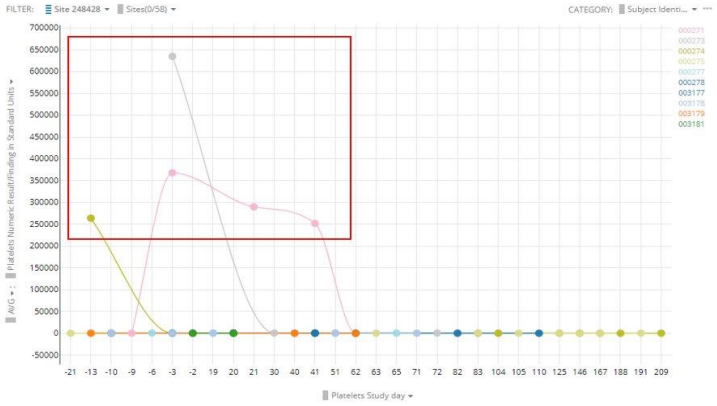
Central Statistical Monitoring is a holistic statistical review of the clinical trial data performed to identify unusual patterns, outliers, trends or atypical data distributions, and detect anomalies that may impact trial data quality. Anomaly detection is based on a series of statistical tests comparing data distributions from each site to all other sites. Other use cases: outlier detection, time series analysis, between- and within-subject variability, duplicate patients' detection.

EXAMPLES:

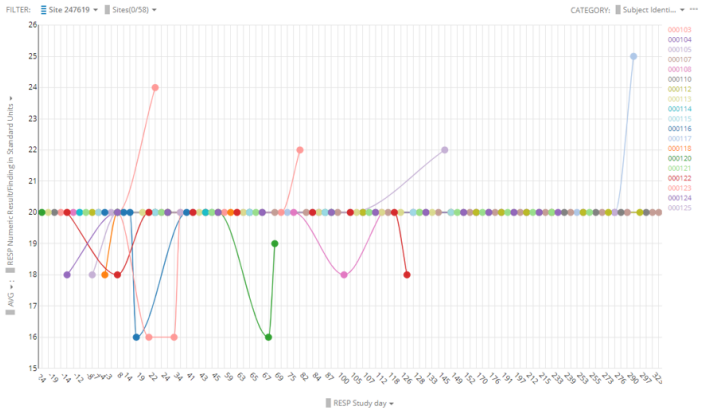
EXAMPLE 1: UNUSUALLY HIGH VALUES

1) **Platelets, PLAT (LB.PLAT.LBSTRESN)**

Unusually high values (above 100'000) in 5 measurements:



EXAMPLE 2: LOW VARIABILITY OF DATA

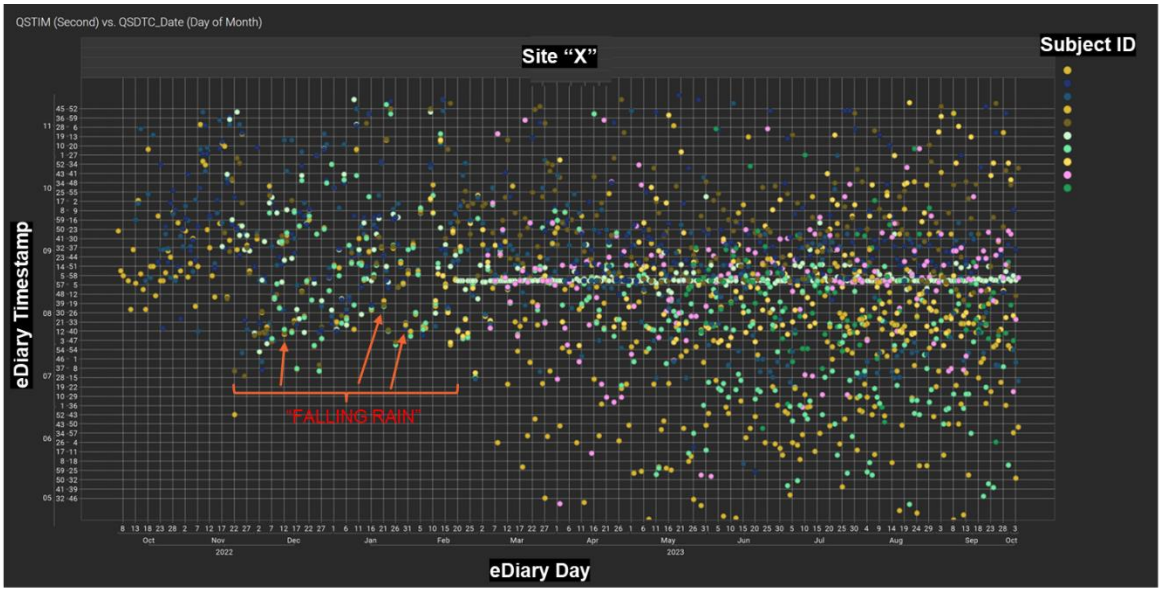


TARGETED CENTRALIZED MONITORING REVIEWS

Targeted Central Monitoring Review is study specific fit for purpose data analysis that is a mitigation to a risk related

to a critical process or data. Different systems and visualizations can be used to provide a study team with valuable information on study condition in specific – critical to quality – areas.

Example: eDiary timestamps



1. Site "X" caught Central Monitoring attention due to Falling Rain eDiary Timestamp pattern observed between certain time interval (eDiary Timestamps being very close to one another).
2. Observation triggered investigation resulting in Site for Cause Audit.

IMPORTANCE OF RBQM AND HIGH-QUALITY DATA VISUALIZATIONS

IMPORTANCE OF RBQM

- Enhanced Focus on Critical Data: RBQM prioritizes monitoring resources towards areas with the highest risk, allowing organizations to focus on the most critical aspects of clinical trials and research. This ensures that significant issues affecting trial outcomes are identified and managed promptly.
- Improved Data Quality: By focusing on risk-based priorities, RBQM ensures that the data collected is pertinent, accurate, and consistent, leading to higher reliability and credibility in research findings.
- Regulatory Compliance: Regulatory bodies like the FDA and EMA encourage adopting RBQM to enhance compliance with good clinical practice (GCP) guidelines. This increases the likelihood of trial approvals and minimizes regulatory risks.
- Adaptive Trial Design: RBQM fosters a more flexible trial design, allowing real-time modifications based on evolving risks, which can optimize the trial's success rate and ensure better decision-making processes.

IMPORTANCE OF HIGH-QUALITY DATA VISUALIZATIONS

- Facilitating Data Interpretation: High-quality data visualization converts complex datasets into visual formats, making it easier for stakeholders to understand and derive insights quickly. This is particularly useful in communicating results to non-expert audiences.
- Spotting Trends and Patterns: Effective visualizations can reveal trends, patterns, and outliers that might not be immediately apparent in raw data formats, thereby aiding in better strategic decision-making.
- Enhancing Engagement: Visualizations can engage users more effectively than static data reports, leading to increased user interaction and understanding, which is crucial for stakeholder engagement.
- Real-Time Monitoring: In dynamic fields like clinical trials, real-time visual dashboards can help monitor ongoing progress and issues, allowing timely interventions and proactive management.
- Supporting Data Storytelling: Data visualization is a powerful tool for storytelling, enabling researchers to convey narratives around data findings in a way that is both compelling and easily digestible.

Both RBQM and high-quality data visualization are integral to effective data management, especially in fields requiring high precision and reliability such as clinical research. They contribute significantly to operational efficiency, cost reduction, improved compliance, and better stakeholder communication.

CONCLUSION

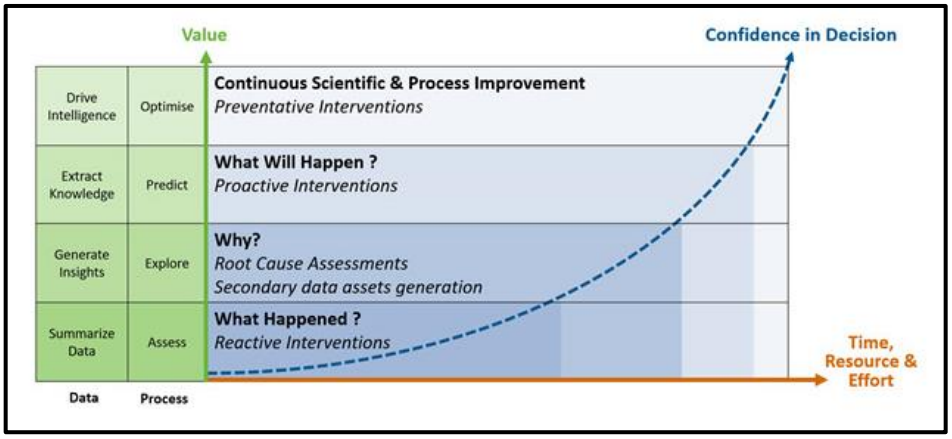
RBQM significantly helps to build up confidence within Clinical Data Managers in decisions by:

1. **Optimized Resource Allocation:** Clinical data managers can leverage RBQM to allocate resources more

efficiently by focusing on high-risk areas, thereby enhancing overall productivity without compromising data integrity.

2. **Enhanced Data Quality and Integrity:** By prioritizing critical data, RBQM ensures the accuracy and consistency of the data collected, which is vital for reliable analyses and the success of clinical trials.
3. **Improved Compliance and Regulatory Alignment:** Implementing RBQM aligns with regulatory guidelines from bodies like the FDA and EMA, reducing the risk of non-compliance and facilitating smoother regulatory reviews and approvals.
4. **Facilitation of Adaptive Trial Management:** RBQM supports adaptive and flexible trial designs, allowing data managers to respond swiftly to emerging risks and make necessary adjustments in real-time to safeguard trial outcomes.
5. **Better Decision-Making:** With RBQM, clinical data managers are equipped with clearer insights and risk assessments, which facilitate informed decision-making and strategic planning.
6. **Strengthened Focus on Patient Safety:** By ensuring that high-risk areas within trials are closely monitored, RBQM contributes to enhanced patient safety, a top priority in clinical research management.
7.

In summary, RBQM provides clinical data managers with the tools and methodologies to manage trials more effectively, ensuring high data quality, regulatory compliance, and operational efficiency, all of which are fundamental to successful clinical trials.



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