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From Information to Insights: Harnessing Centralized Monitoring in RBQM to proactively identify and mitigate risks in Clinical Trials

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ABSTRACT

In the dynamic landscape of clinical trials, effective Risk Based Quality Management (RBQM) has emerged as a pivotal strategy to enhance data quality and patient safety, as the volume and complexity of clinical trial data continues to grow. Centralized Monitoring (CM) is a key enabler of RBQM guided by Critical to Quality Factors (CtQFs), powered by Key Risk Indicators (KRIs) and governed by Quality Tolerance Limits (QTLs), form a robust and proactive system for outlier detection.

RBQM addresses the cornerstone of clinical trials like trial data reliability, subject safety and adequate data for successful end point. We will elaborate on these principles through case studies around: Vitals (Within/Across patient variability), Assessments (Time/Date Analysis), IP (Compliance/Missed and Overdose) and Evaluable Data (QTL). Central Monitoring (CM) enhances clinical trial oversight by utilizing sophisticated tools, such as statistical detection, cross-site and cross-subject comparisons and Key Risk Indicator (KRI) trends, to identify critical outliers in data reliability, safety, efficacy and subject retention. Through real-time monitoring, CM swiftly detects anomalies and potential risks, allowing for immediate interventions that maintain trial integrity and safeguard participant safety. These proactive measures facilitate rapid responses to unexpected issues, fostering trust among stakeholders and improving overall trial outcomes. By ensuring transparency, optimizing data quality and adhering to regulatory standards, CM supports adaptive trial designs and enhances participant engagement, ultimately contributing to the successful completion and credibility of clinical research endeavors.

INTRODUCTION

Clinical trials have regulatory guidance (notably ICH E6 R2 and the latest E6 R3) has shifted the field toward quality-by-design and risk-based strategies. Around the turn of the century, drug sponsors faced growing pressures: high-profile drug safety problems, a slowdown in new drug innovation around patent expiries and steadily increasing trial complexity. These trends lengthened development timelines, raised costs and squeezed profits, forcing the industry to rethink how trials are run.

Data shows the scale of the change. Tufts CSDD reported that between 2005 and 2015 trials became much more complex; procedures per patient rose by 68%, data volume increased by 88% and the number of countries per study doubled. This added complexity increased operational risks for recruitment, retention, data collection and the overall credibility of trial results needed for regulatory approval. Regulatory reviews highlighted the consequences of poor quality control. An analysis of FDA marketing submissions from 2000 to 2012 found that problems with trial quality caused about one-third (32%) of first-cycle review failures - roughly 16% of all submissions. These findings showed that traditional, exhaustive on-site monitoring was no longer adequate. Together, these trends made a strong case for Risk-Based Quality Management (RBQM) and centralized monitoring as more scalable, data-driven ways to protect participants, preserve data integrity and improve the efficiency of clinical development.

Adoption of RBQM has accelerated: a 2023 Tufts CSDD survey found that sponsors and CRO organizations had implemented RBQM elements in 57% of active clinical trials.

This review focuses on Risk-Based Quality Management (RBQM) and centralized monitoring as scalable, data-driven solutions for safeguarding participant safety and data integrity in contemporary clinical trials. We summarize the conceptual framework, regulatory context, statistical methods for centralized surveillance and practical implementation

considerations, with the goal of helping sponsors and investigators adopt effective, proportionate quality management approaches.

Data Quality Challenges: Why RBQM Is Needed

Good data are essential for any clinical trial. Poor data can harm patients, slow or block regulatory approval and cause problems during FDA pre-approval inspections (PAIs), which check that submitted data are accurate and complete. Problems with data happen for many reasons. When patients fill in diaries themselves, entries can be false. Large, multi-site trials make checking data harder. Relying only on Source Data Verification (SDV); manually checking case report forms against medical records become slow, costly and often impractical as data volumes grow.

Evidence that monitoring only at sites misses problems TransCelerate tested whether centralized monitoring can find fabricated or noncompliant data better than site visits alone. They used a COPD trial dataset (178 sites, 1,554 subjects) and had experts inject fabricated data into 7 sites (43 subjects). Multiple statistical checks were run on vitals, spirometry, visit dates and adverse events and a cross-functional team developed an algorithm to flag suspicious sites.

Key results (summary):

- The algorithm flagged suspicious sites across simulated studies and detected most of the fabricated sites (detection rates varied by simulation).
- Sensitivity and specificity were generally above 70% (one simulation was lower).
- The study showed that statistical monitoring, combined with expert review, can reliably supplement site monitoring.

Defining RBQM: Technology-Driven Trial Oversight

Risk-Based Quality Management (RBQM) expands the ideas of Risk-Based Monitoring (RBM) across the whole clinical trial. RBQM helps protect participants and improves the chance of trial success. It is supported by major regulators (FDA, EMA, ICH). By identifying and prioritizing the most important data and processes, technology-enabled RBQM provides a focused safety net for both patient safety and study reliability.

Implementing RBQM: a simple step-by-step approach using Quality by Design

RBQM follows Quality by Design (QbD) principles and applies them from planning through closeout. The approach is about finding, controlling and communicating risks so the trial runs reliably. ICH E6(R2) outlines the key elements an RBQM system should cover:

QbD is used during protocol design to build quality in. Once the protocol is final, RBM applies those QbD findings operationally: redo the risk assessment to address any remaining operational risks, put mitigation plans in place and monitor them during the study. This leads to more targeted, data-driven site oversight and ongoing risk management throughout the trial.

Where Centralized Monitoring fits in RBQM

RBQM is the quality system that plans, prioritizes, monitors and adapts controls to reduce “errors that matter” to patient safety and trial reliability. Regulators explicitly allow and encourage centralized monitoring; a remote, data-driven evaluation of accumulating study data alongside or in place of some on-site activities.

- ICH E6(R2): The sponsor may choose centralized monitoring (remote, timely evaluation of accumulating data) as part of a systematic, prioritized, risk-based approach to monitoring, documented in the monitoring plan.
- EMA Reflection Paper: Endorses risk-based quality management and highlights the use of statistical central monitoring to detect issues and target on-site follow-up.

Centralized Monitoring: A core enabler of RBQM

Centralized Monitoring (CM) is a data-driven, remote approach to evaluating clinical trial quality across sites and subjects. Rather than relying solely on routine, broad on-site Source Data Verification (SDV), CM aggregates and analyses trial data centrally to identify trends, outliers and emerging risks so that corrective actions can be targeted, timely and proportionate.
CM leverages statistics, metadata and integrated data streams to provide early, scalable and targeted oversight of trial quality. When implemented with robust data integration, validated analytics, multidisciplinary review and clear governance, CM reduces risk, saves resources and strengthens the integrity of clinical trial results.

- **Start with CtQ factors → driving monitoring strategies**
  Critical-to-Quality (CtQ) factors are the study-specific elements that, if poorly executed or measured, would meaningfully threaten participant safety or the credibility of primary outcomes. CtQs are identified during protocol design and risk assessment; they anchor what you monitor centrally and how intensely.
  In practice,
  CtQs → Critical Processes & Data → selection of KRIs (site-level oversight) and QTLs (study-level guardrails), with CSM running in parallel to discover unanticipated risks.

- **KRIs: site-level early-warning metrics**
  Key Risk Indicators (KRIs) are predefined metrics that track known risks linked to CtQs, typically benchmarked across sites (and sometimes regions/subjects). Examples include AE/SAE reporting rates, missed key assessments, protocol deviation rates, visit-to-entry cycle time, query burden and query turnaround time.
  Industry leaders emphasize that KRIs are essential but not sufficient; they must be paired with unsupervised statistical checks (targeted monitoring/study specific KRIs) to catch unknown risk patterns.
  Why it matters: KRIs align day-to-day oversight with CtQs and make cross-site comparisons objective, helping detect training gaps, process failures or under-reporting before they affect outcomes.

- **QTLs: study-level guardrails**
  Quality Tolerance Limits (QTLs) are study-wide thresholds for metrics critical to overall validity/safety (e.g., percentage of primary endpoint assessments outside visit windows; rate of key protocol deviations; SAE reporting timeliness). Breaches indicate a systemic issue requiring root-cause analysis, documented justification and corrective action.
  Central Monitoring platforms offer QTL modules to monitor, flag, document and justify deviations. EMA's RBQM paper specifically calls for defining metrics for oversight and managing tolerance limits for quality.
  Why it matters: QTLs keep leadership focused on trial-level drift (not just site outliers), supporting sponsor accountability and regulatory inspection readiness.

- **Data Quality Assessments (DQAs): the unsupervised approach**

  A Data Quality Assessment (DQA) is a structured analysis that uses statistical tests across all clinical and operational data to identify unusual patterns that may signal risks to data integrity or trial conduct. DQAs generate large matrices of p-values which are summarized into **Data Inconsistency Scores (DIS)** to highlight anomalous sites.
  DQA is a core mechanism of RBQM because it:

- Provides objective, quantitative checks against CtQ failures
- Identifies unknown risks beyond KRIs and QTLs
- Supports targeted monitoring and efficient use of resources
- Enhances audit readiness with evidence-based decision-making

➔ **Statistical Measures of Data Quality and Consistency**

What CM Monitors

- Rates of missing data, Protocol deviation frequencies, Visit-window adherence, Query volumes and resolution times, Variability in continuous endpoints (lab values, vitals, scale scores).

Why It Matters

Central Monitoirng Platform (CMP) uses robust, independent statistical tests to surface systematic irregularities, such as: Unexpected variability, Implausibly low variability, Abnormal distributions across sites or subjects

Such statistical “signals” often indicate: Training or process gaps, Poor data entry practices, Measurement errors and **Potential fraud or data fabrication**

By spotting these early, CM can direct targeted follow-up rather than relying on broad SDV or onsite visits.

➔ **Cross-Site and Cross-Subject Comparisons**

What CM Monitors

- Site performance vs study benchmarks, Site-to-site comparisons (e.g., enrollment, AE reporting, data timeliness), Subject-level patterns across and within sites (identical values, repeated sequences, unusual clustering)

Why It Matters

CMP excels at site-level outlier detection, identifying when: A site behaves differently from its peers, Subjects within a site show unexpected homogeneity or extreme values, Operational performance drifts away from norms.

These comparative analytics help pinpoint sites needing intervention, potentially due to: Lack of compliance, Operational inefficiencies, Misunderstanding of protocol, **Suspiciously uniform data (a classic fraud indicator).**

➔ **Trend Detection and Temporal Analytics**

What CM Monitors

- SAE reporting lags, Dropout rates, Visit cycle times, Time-series patterns in operational KPIs

Why It Matters

CMP incorporates temporal analytics to detect: Gradual drifts (e.g., worsening data quality after staff turnover), Sudden shifts (e.g., step changes in AE reporting), Emerging process or safety issues. Trends are **early warning signals**, allowing teams to act before problems escalate or impact trial integrity.

➔ **Outlier and Anomaly Detection (Univariate & Multivariate)**

What CM Monitors

- Extreme individual values (z-scores, robust estimators), Multivariable outliers, Site-level anomalies across composite endpoints.

Why It Matters

CMP uses multivariate statistical engines to detect anomalies that traditional monitoring misses, including: Falsified or duplicated data, Measurement bias (e.g., device calibration issues), Sites with unusual combinations of metrics (e.g., low AE rate + perfect compliance + identical vital signs). The multivariate approach is particularly powerful because risk rarely manifests in a single variable, but in patterns.

➔ **Metadata and Operational Signals (EDC/ePRO/Labs)**

What CM Monitors

Timing of data entry (batching, late entries, odd-hour spikes), Query history and edit patterns, Device upload and lab result timestamps.

Why It Matters

CMP emphasizes the importance of metadata, which often reveals the underlying behavior of sites: Bulk data entry before monitoring visits, Identical timestamps across subjects, Delays between assessments and entry, Mismatch between IRT dispensation and eCRF records. These signals often highlight process lapses long before content data appears problematic.

CENTRAL MONITORING STRATEGIES - INSIGHTS FROM CLINICAL TRIAL CASE STUDIES:

RBQM addresses the cornerstone of clinical trials like trial data reliability, subject safety and adequate data for successful endpoint. We will elaborate on these principles through case studies around:

- **Vitals (Within/Across patient variability):**

  Aim: Identifying significant variations in vital signs that could indicate safety concerns or data irregularities.

  CM Approach:

  - CM highlights variability across patients for vitals like heart rate, blood pressure, and temperature.
  - Algorithms process large volumes of data to identify patterns of variability.
  - Determine if variations fall within expected ranges or signify potential safety concerns.

- **Case Study 1 - Vital Signs - Respiratory Rate (Higher Rate of Propagation)**

Internal Patient Identifier	Visit Name	Respiratory Rate
118000	Day 1 (Visit 5)	18
118000	Day 1 (Visit 5)	18
118000	Week 4 (Visit 6)	18
118000	Week 4 (Visit 6)	18
118000	Week 8 (Visit 7)	18
118000	Week 8 (Visit 7)	18
118000	Week 16 (Visit 9)	18
118000	Week 16 (Visit 9)	18
118000	Week 20 (Visit 10)	18
118000	Week 20 (Visit 10)	18
118002	Day 1 (Visit 5)	18
118002	Day 1 (Visit 5)	18
118002	Week 4 (Visit 6)	18
118002	Week 4 (Visit 6)	18
118002	Week 8 (Visit 7)	18
118002	Week 8 (Visit 7)	18
118003	Day 1 (Visit 5)	18
118003	Day 1 (Visit 5)	18
118003	Week 4 (Visit 6)	18
118003	Week 4 (Visit 6)	18
118003	Week 8 (Visit 7)	18
118003	Week 8 (Visit 7)	18

Image Source: CluePoints

Central Monitoring observation:

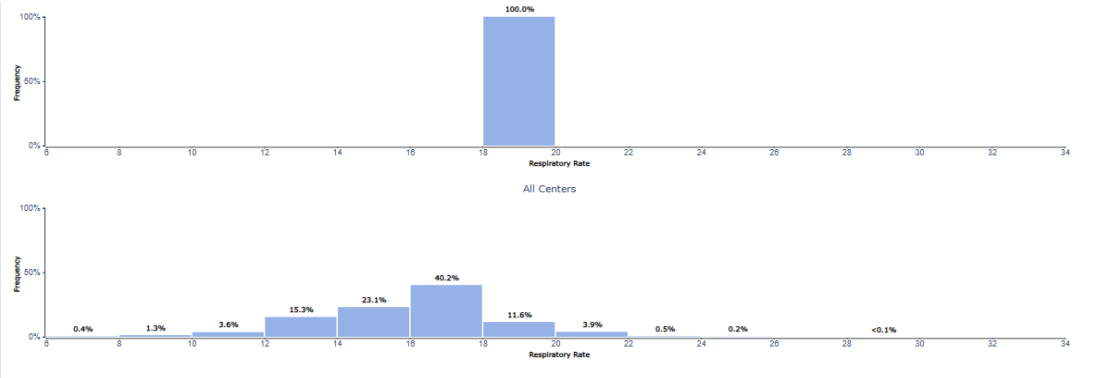
- ✓ 03 subjects – multiple visits per subject.
- ✓ RR recorded as 18 breaths/min at every visit.
- ✓ No within-patient or across patient variability observed.

Why this triggered review?

- ✓ RR is a physiological parameter and expected to vary.

Identical values across visits suggest systemic propagation.

A.



Next month outcome after CM

B.

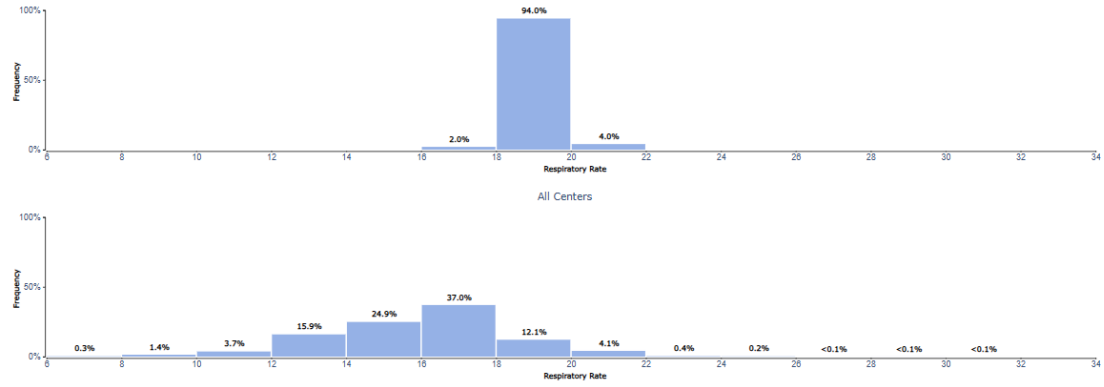


Image Sources (A and B): CluePoints

- **Case Study 2 – Pulse RATE (Respiratory Infection Trial)**

Subject #	Pulse Rate
Subject 1	72
Subject 2	48
Subject 3	104
Subject 4	96
Subject 5	88
Subject 6	102
Subject 7	68
Subject 8	112

Key Observations: All the recorded values are divisible by 4.

No odd number respiratory rates observed.

Possible Explanations Identified	Outcome after CM intervention
• Measurement Practice Variability: Pulse Rate measured for 15 seconds and multiplied by 4. Instead of direct 1 minute observation as per protocol. • Process Standardization Bias Use of rounding or shortcut measurement techniques. Site level habit rather than subject-driven variability. • Training or SOP gap Inadequate understanding of protocol-defined measurement method.	• Targeted Site Action: Site contacted for clarification and retraining. Measurement procedure reviewed and reinforced. • Data Quality Impact: Improved variability in subsequent data. • RBQM Value Demonstrated: Early detection without on-site visit Focused intervention instead of blanket SDV.

- **Assessments (Time/Date Analysis):**

Aim: Maintaining consistency and reliability of assessments according to protocol-defined timeframes.

CM Approach:

- CM focuses on ensuring assessments are carried out in alignment with protocol-defined timeframes.
- Identifies risks introduced by delays, missed assessments, or deviations that affect data quality.

- **Case Study 1 - Time & Date Analysis**

  ePRO assessments completed during onsite visit:

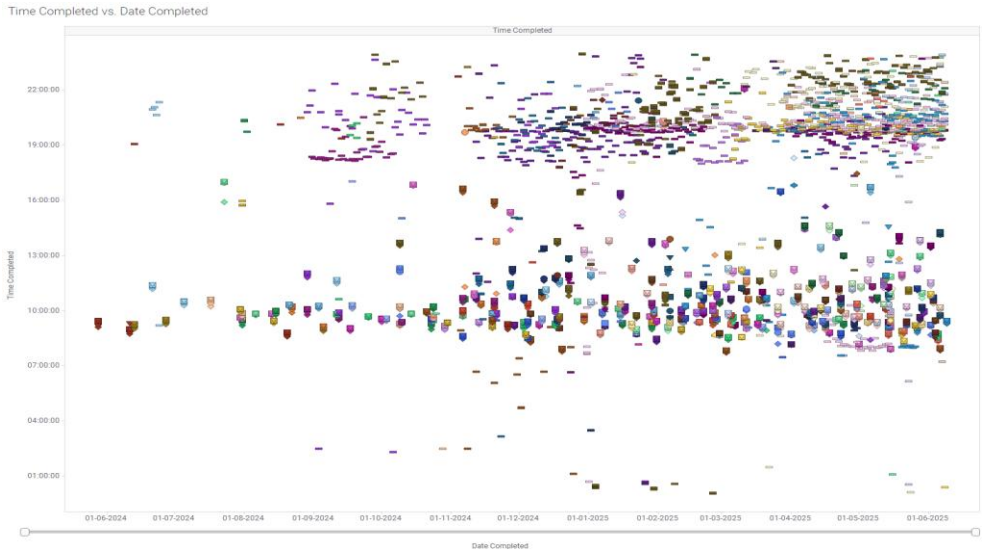


Image Source: Spofire

Scenario 1: ePRO Assessments to be completed during onsite visits

Image Source: Spotfire

Data Signal Observed:

- ➢ Data analysed-
- ePRO completion date and time stamps
- Visit type: Onsite clinic visit
- Expected completion window: During clinic hours
- ➢ Observed pattern-
- Visit date: 11-March-2025
- ePROs completed around 22:09 (10:09 PM)
- Entry outside normal operating hours.

Scenario 2: ePRO Assessments to be completed during onsite visits

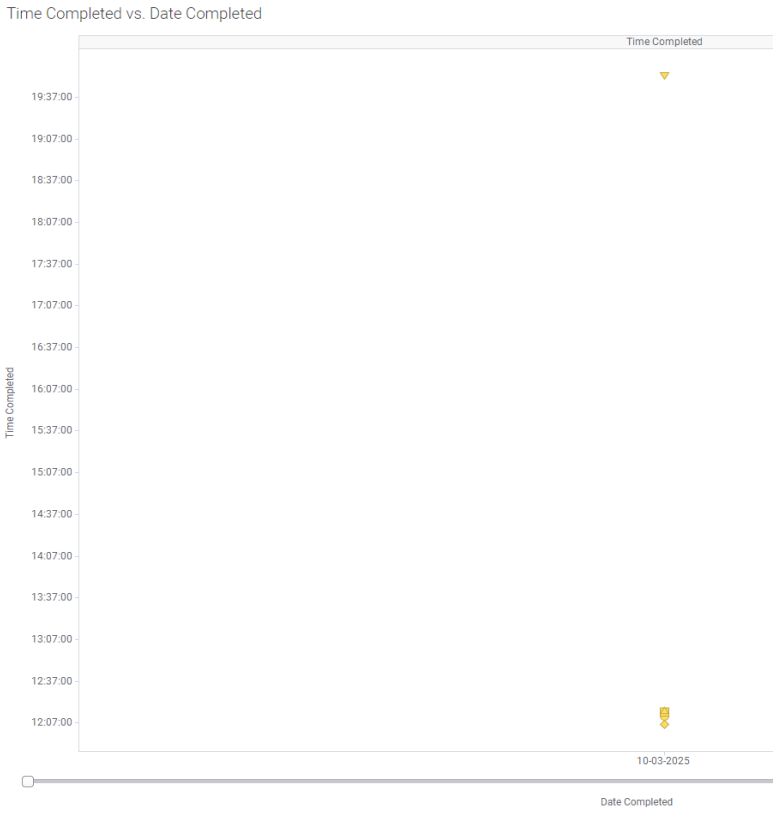


Image source: Spotfire

Finding: From the above scattered plot we can see that for a particular subject at Visit Dated 10Mar25, Some ePROs completed around 12:00 PM & Remaining ePROs completed around 19:52PM (Around 8 hours gap in assessments)

Is it usual for a subject to be at site for 8 hours?

- **Case study 2: Daily Dosing Diary:**

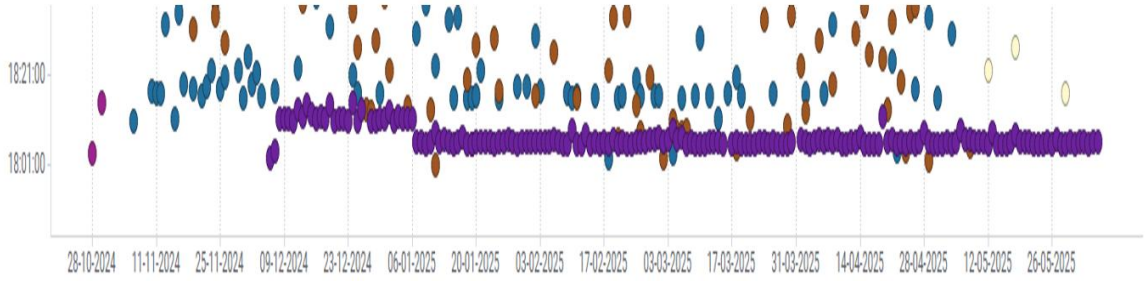


Image Source: Spotfire

Findings: In the above scattered plot, we can see that there is one subject who is completing the dosing diary everyday almost at the same time (06:05 PM to 06:11 PM).

- **IP (Compliance/Missed and Overdose):**

  Aim: Ensuring correct investigational product administration, compliance (Missed/Overdose) and patient safety.

  CM Approach:
  - CM triggers alerts when compliance falls below acceptable thresholds.
  - Triggers alerts when potential overdoses may have occurred.
  - Assesses factors that could lead to missed doses (e.g., medication complexity, patient forgetfulness, lack of understanding).
  - Assesses factors that could lead to overdoses (e.g., dosage errors, miscommunication).

  Benefits:
  - Reduces the risk of trial disruption due to non-compliance.
  - Enhances data quality related to IP administration.

- **Case study:** A with genetic disorder study using IP in the form of Ointment (to be applied topically)
  Challenges:
  Confusion over correct amount of ointment application (ointment/gel based IP).
  Potential for IP sharing with non-participating family members (genetic disorder context).

  Mitigation:
- Training: Site & Subjects trained on IP usage guidelines.
- Dosing Cards: Provided to patients for uniform IP application.
- IP Weighing: Tubes weighed before dispensing and upon return. Visualizations identify non-compliance trends.
- ePRO Dosing Diaries: Subjects record doses daily, allowing central identification of missed doses.

  Benefit: Ensures consistent IP exposure and accurate efficacy assessment

- **Evaluable Data (QTL):**

  Aim: Identifying inconsistencies or irregularities that threaten data integrity and evaluability.

  CM Approach:

  - CM enhances data integrity by flagging inconsistencies or irregularities across sites.
  - Includes identifying typographical errors, missing data, or implausible data points needing immediate attention.
  - Ensures evaluable data is maintained through real-time analysis.
  - Allows for early detection of deviations or anomalies that breach QTLs.

  Impact: Highlights data points that fall outside of acceptable boundaries, ensuring high-quality data for analysis.

CONCLUSION:

Central Monitoring (CM) enhances clinical trial oversight by utilizing sophisticated tools, such as statistical detection, cross-site and cross-subject comparisons and Key Risk Indicator (KRI) trends, to identify critical outliers in data reliability, safety, efficacy and subject retention. Through real-time monitoring, CM swiftly detects anomalies and potential risks, allowing for immediate interventions that maintain trial integrity and safeguard participant safety. These proactive measures facilitate rapid responses to unexpected issues, fostering trust among stakeholders and improving overall trial outcomes. By ensuring transparency, optimizing data quality and adhering to regulatory standards, CM supports adaptive trial designs and enhances participant engagement, ultimately contributing to the successful completion and credibility of clinical research endeavors.

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CluePoints / Tufts CSDD Analysis – RBQM Adoption and Clinical Trial Quality

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