CASE STUDY

Catching the Unseen: How a Top 50 Sponsor Uncovered Data Manipulation with Centralized Statistical Monitoring (CSM)

When a Phase II Cardiovascular & Metabolic study showed suspicious creatinine clearance values at one center, an audit confirmed data manipulation. The Sponsor then used CluePoints' Centralized Monitoring Platform (CMP) to transform study oversight.

The Role of Centralized Monitoring in Modern RBQM

Centralized monitoring is a key component of Risk-Based Quality Management (RBQM). It enables proactive detection of critical-to-quality (CtQ) risks during clinical trials, identifying both pre-identified and unanticipated issues.

Centralized monitoring consists of three main elements: Centralized Statistical Monitoring (CSM), Key Risk Indicators (KRIs), and Quality Tolerance Limits (QTLs). CSM assesses hundreds of variables and converts the P-values for each site into a Data Inconsistency Score (DIS), which is recalculated as study data accumulates.

A site is flagged as 'at-risk' or atypical when its DIS reaches a significant threshold (DIS ≥ 1.3, corresponding to a P-value > 0.05).

An analysis of 1,111 sites across 159 clinical trials showed an 83% improvement in sites using CSM, compared to a 56% improvement in sites without it.[1]

Regulators also support RBQM and centralized approaches. ICH E6 (R3) highlights centralized monitoring's role in identifying sites or processes for targeted monitoring.[2]

This case study demonstrates the value of CSM as a component of central monitoring implementation. It presents an anonymized example from a top 50 pharmaceutical company, where CSM identified a center manipulating rescreening samples to enroll ineligible patients.

Study Context & Challenge

A top 50 Sponsor conducted a Phase II Cardiovascular & Metabolic study involving over twenty centers and 100+ patients.

During the final listing reviews for the Clinical Study Report (CSR), the biostatistics team flagged an unusual pattern in creatinine clearance values (eGFR)—a primary endpoint. This raised concerns that aligned with the monitoring team's observations of inconsistent lab data favoring participant eligibility.

In response, the Sponsor conducted an audit, which revealed that site staff had manipulated creatinine clearance samples. Consequently, the center's data was deemed unreliable and excluded from endpoint analyses.

The study applied centralized monitoring techniques, including critical data identification, risk assessment, KRIs, and QTLs. However, the existing RBQM platform lacked Data Quality Assessment (DQA) capabilities and a standardized approach to CSM. When evaluating alternative platforms, the Sponsor identified CluePoints as a standout option.

Yet, CSM concepts were not well understood within the broader organization. To demonstrate their value and practical application, the Sponsor chose this study to pilot CluePoints' CMP. With its complete dataset and confirmed site-specific data issues, the study offered an ideal opportunity to assess whether CluePoints' CMP could accurately detect the problematic data.

Introducing CluePoints' Centralized Monitoring Platform (CMP)

CluePoints' CMP uses AI-powered CSM to uncover insights that traditional data quality control methods often miss. It directs researchers' focus to the most relevant data points, ensuring efficient and targeted analysis.

The primary tool used in this case was the DQA module. The DQA applies a suite of advanced statistical tests to detect atypical patterns in clinical data that may indicate issues with study conduct or data reliability. Unlike KRIs and QTLs, which rely on prior risk assessments, the DQA operates in an unsupervised manner across most or all study data.

Results from the DQA analysis are visualized in the DQA Dashboard, featuring:

- **Bubble Plot:** Highlights the most atypical entities (centers, regions, or patients).
- **Extreme Score Plot:** Emphasizes atypical variables across all entities.

Each site, patient, or region receives an overall DIS, which is a weighted average of statistical test results. This score allows the study team to quickly pinpoint and prioritize high-risk sites for further review.

Users can drill down from both plots to investigate specific data anomalies. If an issue is identified, it can be flagged as a signal and assigned to the study team for further investigation.

Our Data Quality Challenge Methodology

The challenge for CluePoints was divided into two phases.

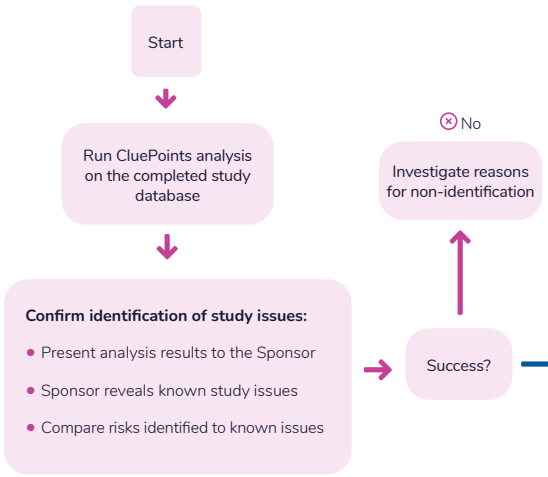
Phase 1: Analyze Completed Study

Phase 1 involved analyzing the completed study to determine whether CluePoints could accurately identify the problematic center(s) that the Sponsor team had uncovered late in the execution phase. To ensure objectivity, the CluePoints team was blinded to the nature and extent of the issues until after the initial analysis and results were shared.

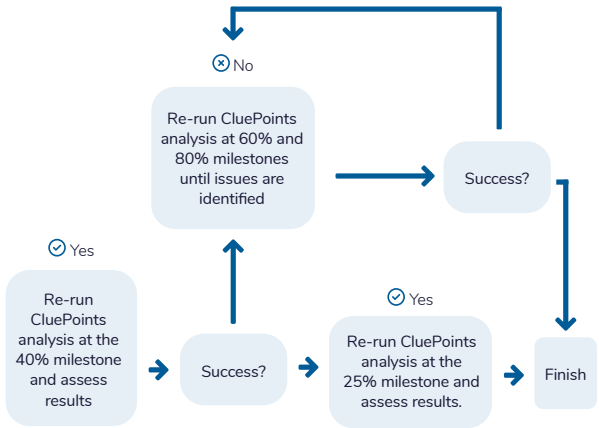
Phase 2: Assess Earliest Detection of Issues

If Phase 1 was successful, Phase 2 aimed to evaluate how early the issues could have been detected using the DQA module. CluePoints re-ran the analysis at the 40% milestone and then again at 25%, reviewing the results at each stage. This iterative approach continued, moving to earlier milestones until the issues were identified.

Phase 1:



Phase 2:



Phase 1 Breakdown: Analysis of Completed Study

When CluePoints analyzed 100% of the study data, the DQA identified the problem center as the second most atypical, with a DIS of 1.24.

The CMP detected high variability and low mean Albumin Creatinine Ratio (ACR) values, frequent dramatic changes in ACR rates, and an unusually high number of unscheduled visits, primarily for urine sample collection during the randomization period.

These findings aligned with the Sponsor audit team's conclusion that site staff had combined multiple void samples to artificially qualify subjects who had previously failed screening due to ineligible eGFR levels.

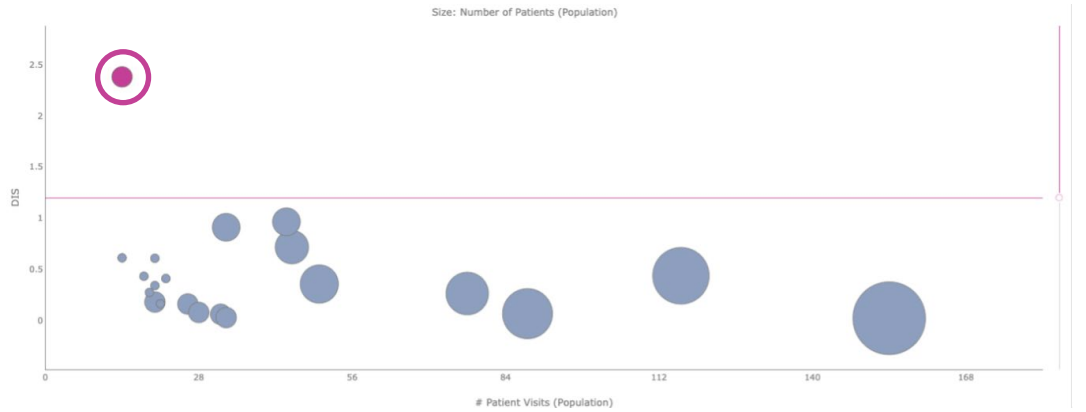
Additionally, the DQA uncovered issues not previously identified by the Sponsor team, including high within-patient variability in electrocardiogram (ECG) values and atypical mean and variability across multiple other lab results.

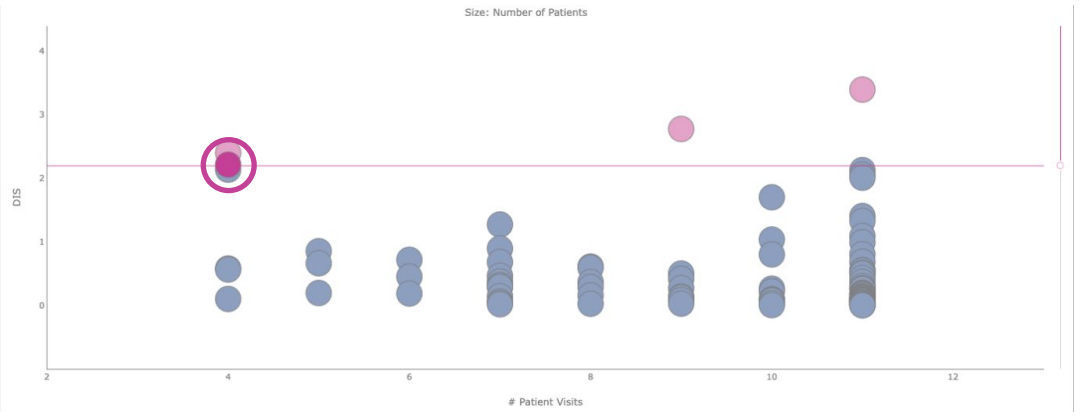
Phase 2 Breakdown: Assess Earliest Detection of Issues

In Phase 2, CluePoints re-ran the DQA analyses on snapshots representing earlier timepoints from the center with previously identified issues. The center remained highly atypical across these earlier stages.

At 40% progress, the center had a DIS of 2.38, well above the outlier threshold of 1.3, ranking it the most atypical of all centers. At 25% progress, the center was excluded from center-level analysis because only one patient had been enrolled. However, in the patient-level analysis, that single patient was flagged as outlying with a DIS of 2.21, making them the fourth most atypical.

At each timepoint, the risks identified by CluePoints consistently aligned with the audit findings and the issues the Sponsor identified later in the study.





The Impact of Early Detection

CluePoints' DQA identified the problem center at least eight months earlier than the Sponsor team, detecting issues only four months after the center's first-subject-first-visit (FSFV). The patient-level analysis flagged the subject as atypical when the center randomized its first subject.

In contrast, the Sponsor only became aware of the issues near the end of the study through clinical team reviews and ad hoc statistical analyses conducted in preparation for the final database lock. The delayed identification led to several risks and impacts:

1. Patient safety risks due to the potential misreporting of safety information
2. Study timeline delays from the postponed database lock
3. Regulatory risks with possible delays or denials of marketing approval

After identifying the problem data, excluding it from the analysis posed the additional risk of insufficient power to prove key endpoints. If the issue had remained undetected until a regulatory inspection, it could have damaged the study's perceived data quality.

While the Sponsor applied some RBQM approaches, this challenge underscores the value of CSM as a proactive risk detection tool. Unlike supervised controls such as KRIs and QTLs, CSM provides independent insights into unanticipated emerging risks. It also offers direct cost savings by reducing study timelines and increasing the likelihood of successful outcomes.

Move from Delayed Discovery to Early Intervention with CluePoints

This case study highlights the powerful role of CSM in enhancing risk detection and quality oversight, enabling earlier identification of problem centers and more proactive decision-making. With CluePoints' CMP, you can strengthen your study's integrity, mitigate risks, and accelerate your path to successful outcomes.

- **Early Detection:** CluePoints identified the problem center eight months earlier than the Sponsor, detecting issues four months after the FSFV.
- **Accurate Risk Identification:** The DQA flagged the center as the second most atypical, with a DIS of 1.24.
- **Patient-Level Insights:** At 25% progress, CluePoints identified a single patient as highly atypical with a DIS of 2.21, ranking fourth in severity.
- **Risk Mitigation:** Early detection reduced the risk of patient safety issues, timeline delays, and regulatory setbacks.
- **Enhanced Oversight:** The Sponsor recognized the value of proactive monitoring, applying CSM for improved study outcomes and data integrity.

References 1. https://link.springer.com/article/10.1007/s43441-024-00613-w
2. https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf

About CluePoints

CluePoints is the premier provider of RBQM and data quality oversight software. We're leveraging the potential of artificial intelligence using advanced statistics and machine learning to determine the quality, accuracy, and integrity of clinical trial data both during and after the study.

Aligned with guidance from the FDA, EMA, ICH, and MHRA, CluePoints supports central and on-site monitoring, medical review, and quality risk management to drive a holistic risk-based strategy in all trials. Coupled with thought leadership and consulting expertise to aid pre-study risk assessment, identification of risk controls, and solution implementation, you now have everything you need to adhere to global regulatory guidance. The result is positive clinical development outcomes, increased operational efficiency, lower costs, and reduced regulatory submission risk as part of the industry paradigm shift to RBQM.

Contact Us Today to Learn How We Customize Smart Solutions for Better Clinical Trials

cluepoints.com/contact