



Applying Central Statistical Monitoring to find anomalies and address quality issues in clinical trial data

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What is RBQM & Centralized Monitoring?

Risk Based Quality Management (RBQM)

RBQM of clinical trials is targeted strategic approach that supports study teams in focusing on the most important aspects and allocating resources in areas which bring the most significant value.

The aim of RBQM is to focus monitoring & oversight activities on **critical data and processes** most likely to affect **participant safety** and **data quality**, so that mitigation plans to address errors can be set up quickly and effectively before they compromise outcome of the trial.

The FDA definition of **centralized monitoring** states that it: *“Consists of 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 the clinical investigation is being conducted.”**

* Guidance for Industry; Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring (FDA, 2013); <https://www.fda.gov/media/116754/download>

Risk Based Quality Management (RBQM)

Monitoring activities

Examples of sponsor activities to ensure data quality during the course of the trial:

- Site monitoring
- Data Management review
- Medical review
- Safety monitoring
- Statistical review
- Central Monitoring

Risk Based Quality Management (RBQM)

Monitoring activities

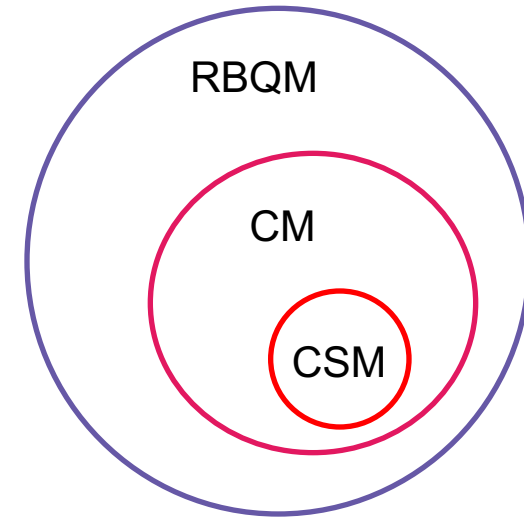
Examples of sponsor activities to ensure data quality during the course of the trial:

- Site monitoring
- Data Management review
- Medical review
- Safety monitoring
- Statistical review
- **Central Monitoring**

Central Monitoring Team

Reviews during the course of the trial

- Quality Tolerance Limit (QTL) monitoring
- Site reviews - Key risk indicators (KRIs)
- Targeted central monitoring: activity-based review of clinical data that is a mitigation to an asset-specific or study-specific risk related to critical process and data.
- **Central Statistical Monitoring (CSM)**



Central Statistical Monitoring (CSM)

Central statistical review

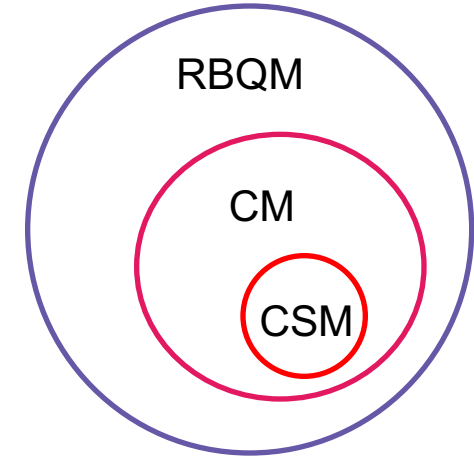
- Unsupervised statistical monitoring based on assumption that data from all centers should be comparable and statistically consistent.
- Central statistical review is a holistic statistical review of the clinical trial data performed to identify unusual patterns, outliers, trends or atypical data distributions, and detect anomalies that may impact trial data quality.
- Aims to identify potential risks.
- Cost-effective complement to other data management and monitoring techniques.*

* Trotta L, Kabeya Y, Buyse M, et al. Detection of atypical data in multicenter clinical trials using unsupervised statistical monitoring. Clinical Trials. 2019; 16(5):512-522
doi:10.1177/1740774519862564

Central Statistical Monitoring (CSM)

Central statistical review

- Successive introduction of CSM to applicable studies:
 - at least 5 sites with 10 or more subjects OR
 - at least 10 sites with 5 or more subjects
- Variables from all clinical data domains are considered (case report forms, patient-reported outcomes, laboratory results)
- Review is based on anomaly score calculated for each site that meet score calculation criteria



Central Statistical Monitoring (CSM)

Finding anomalies

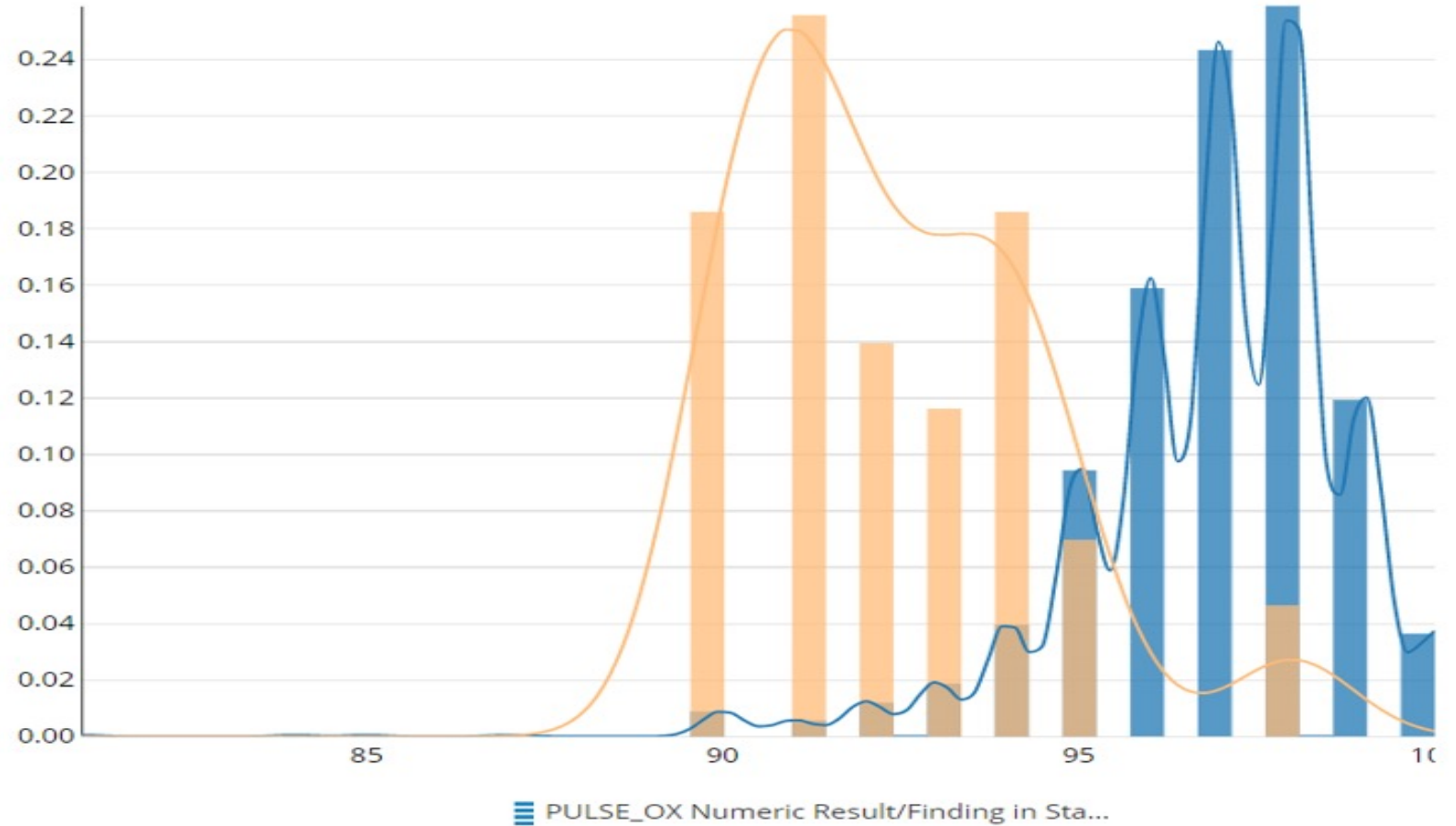
- A series of statistical tests comparing distributions of variables from each site to all other sites
- Tests are relevant to the type of variable (continuous, factor, date)
- At least 10 records of a variable for a site required for testing
- Variable score: a highest value of negative logarithms of p-values from all tests
- Site anomaly score: highest variable score for a site adjusted for site size

$$\left. \begin{array}{l} v_1 \left\{ \begin{array}{l} \xrightarrow{\text{Test}_{11}} p_{11} \text{ (p-value)} \\ \vdots \\ \xrightarrow{\text{Test}_{1k}} p_{1k} \text{ (p-value)} \end{array} \right\} \text{score}_{v_1} = \max_{1 \leq x \leq k} (-\log p_{1x}) \\ \vdots \\ v_n \left\{ \begin{array}{l} \xrightarrow{\text{Test}_{n1}} p_{n1} \text{ (p-value)} \\ \vdots \\ \xrightarrow{\text{Test}_{nm}} p_{nm} \text{ (p-value)} \end{array} \right\} \text{score}_{v_n} = \max_{1 \leq x \leq m} (-\log p_{nx}) \end{array} \right\} \text{anomaly score} = \max_{1 \leq x \leq n} (\text{score}_{v_x}) \times \text{modulation factor}$$

Site with different mean value

Site A (amber) has different distribution profile of oxygen saturation values compared to all other sites in the trial (blue).

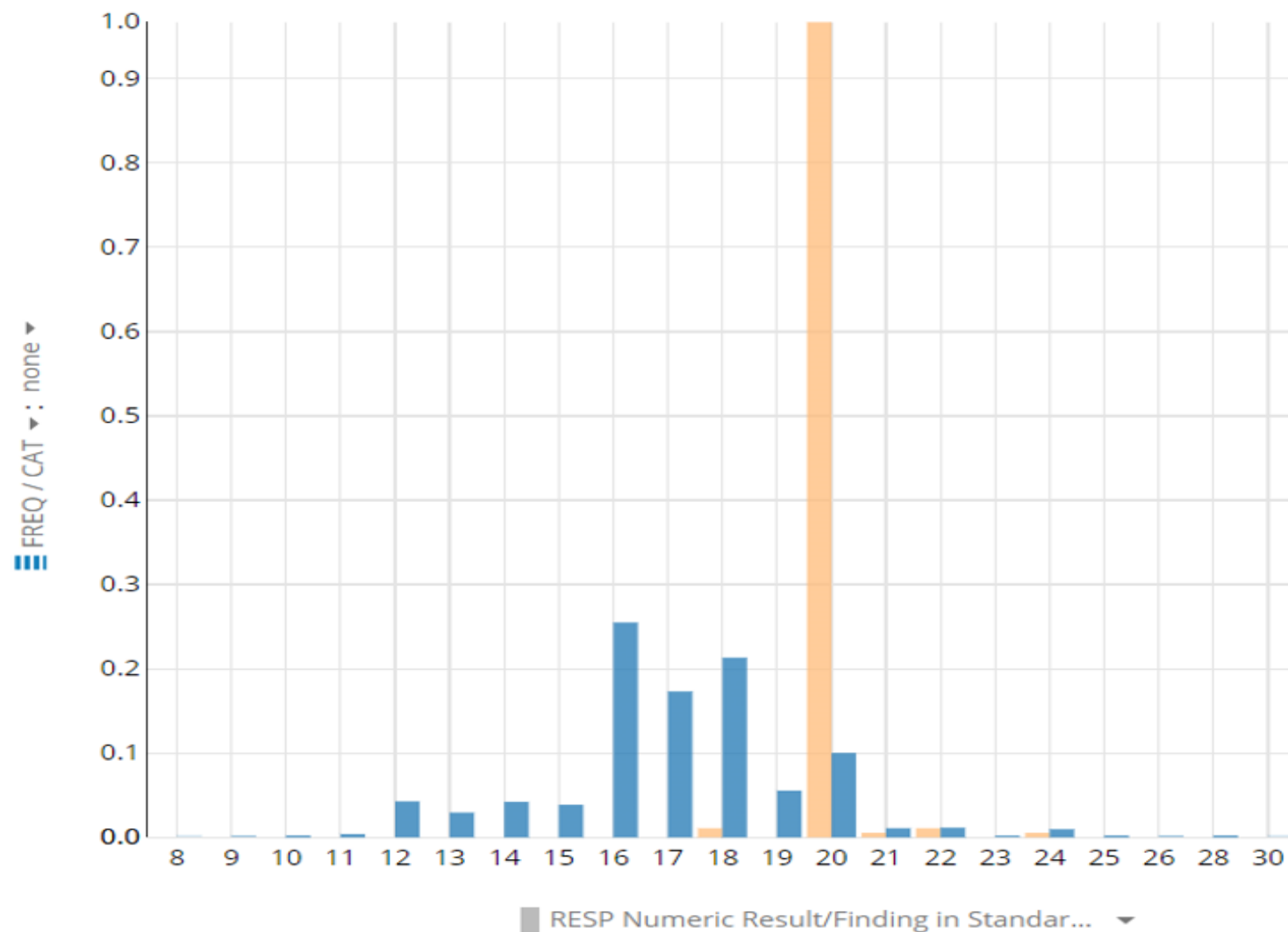
Potential reasons: different subject population, incorrect device calibration



Site with low variability

Site B (amber): low variability of respiratory rate measurement.

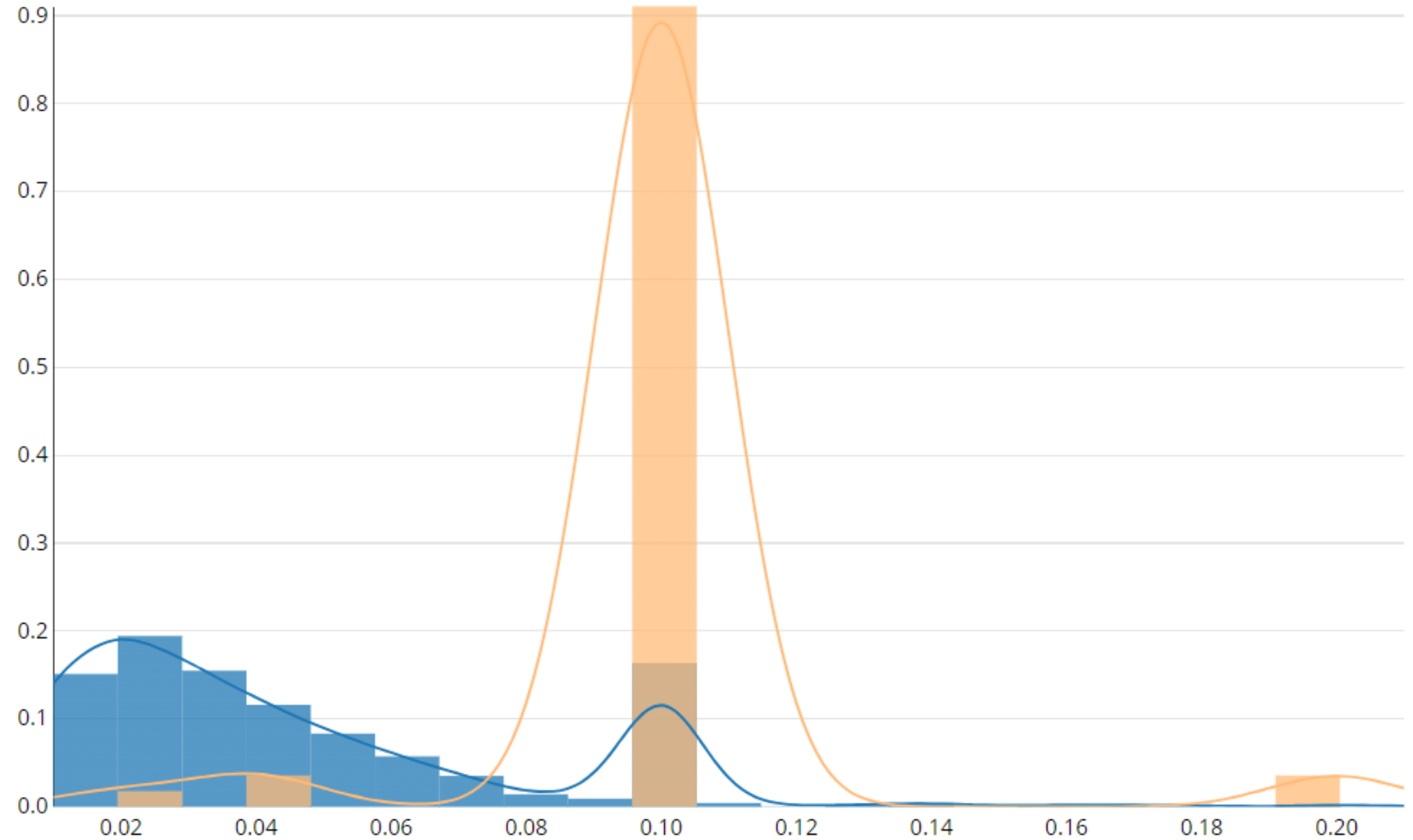
Potential reasons: result fabrication, low precision of measurement



Site with digit preference

Site C (amber): only specific set of values are recorded

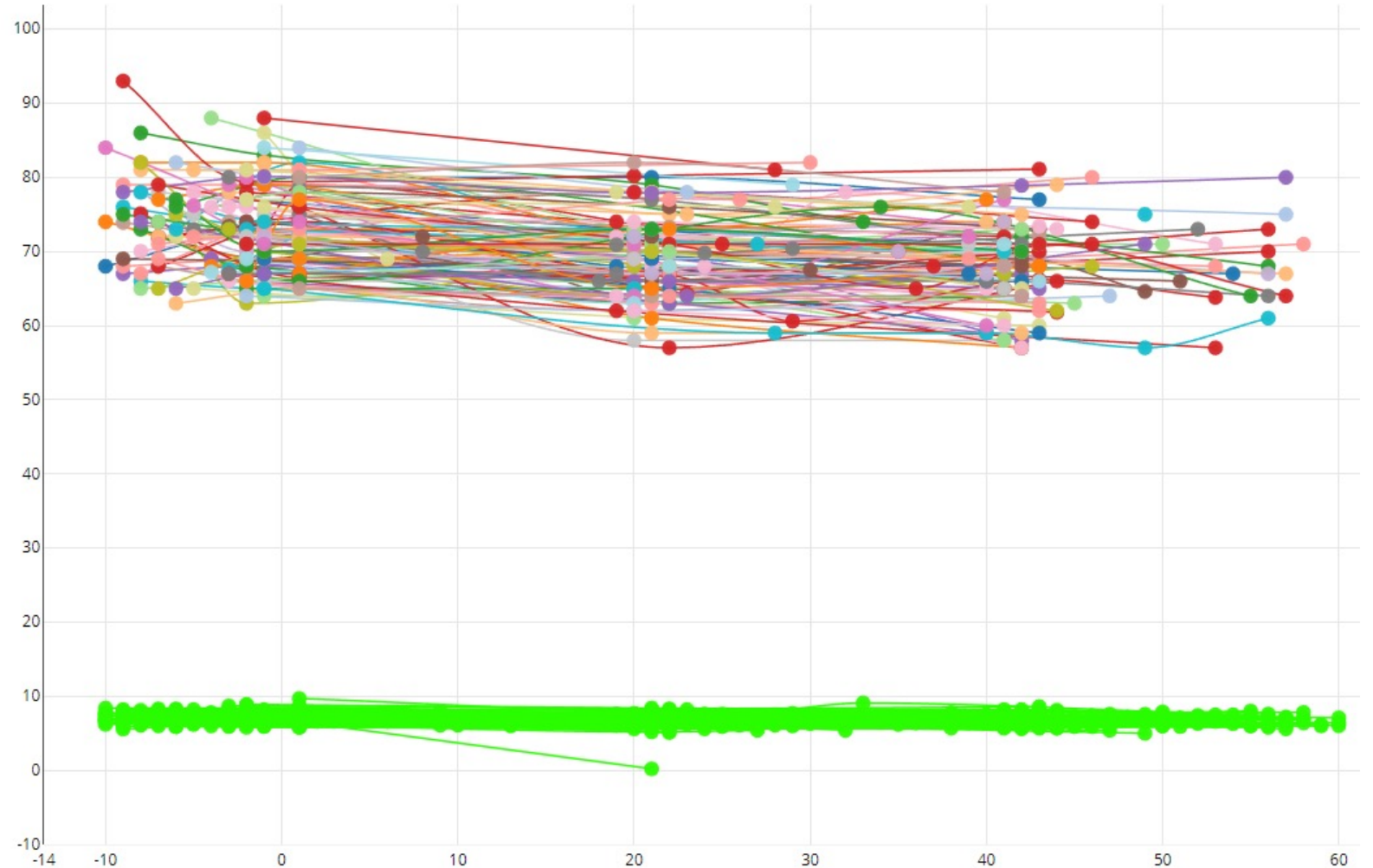
Potential reason: different measurement precision level



Unit reporting issue

Site D (green): consistent outlying values, order of magnitude difference from the rest of results.

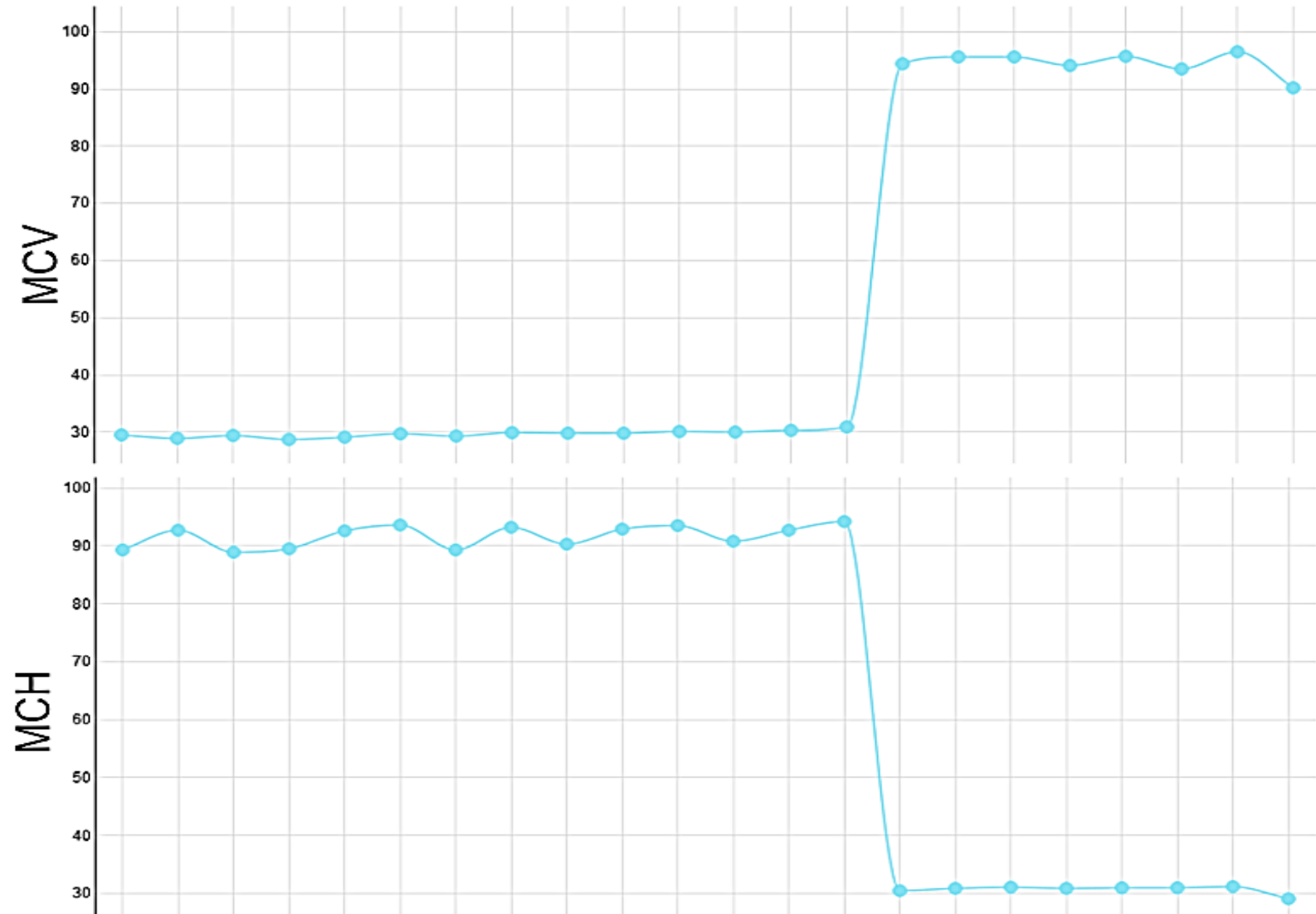
Potential reason: missing or incorrect unit information



Switched values of two variables

Sudden shift in subject's
MCH and MCV values

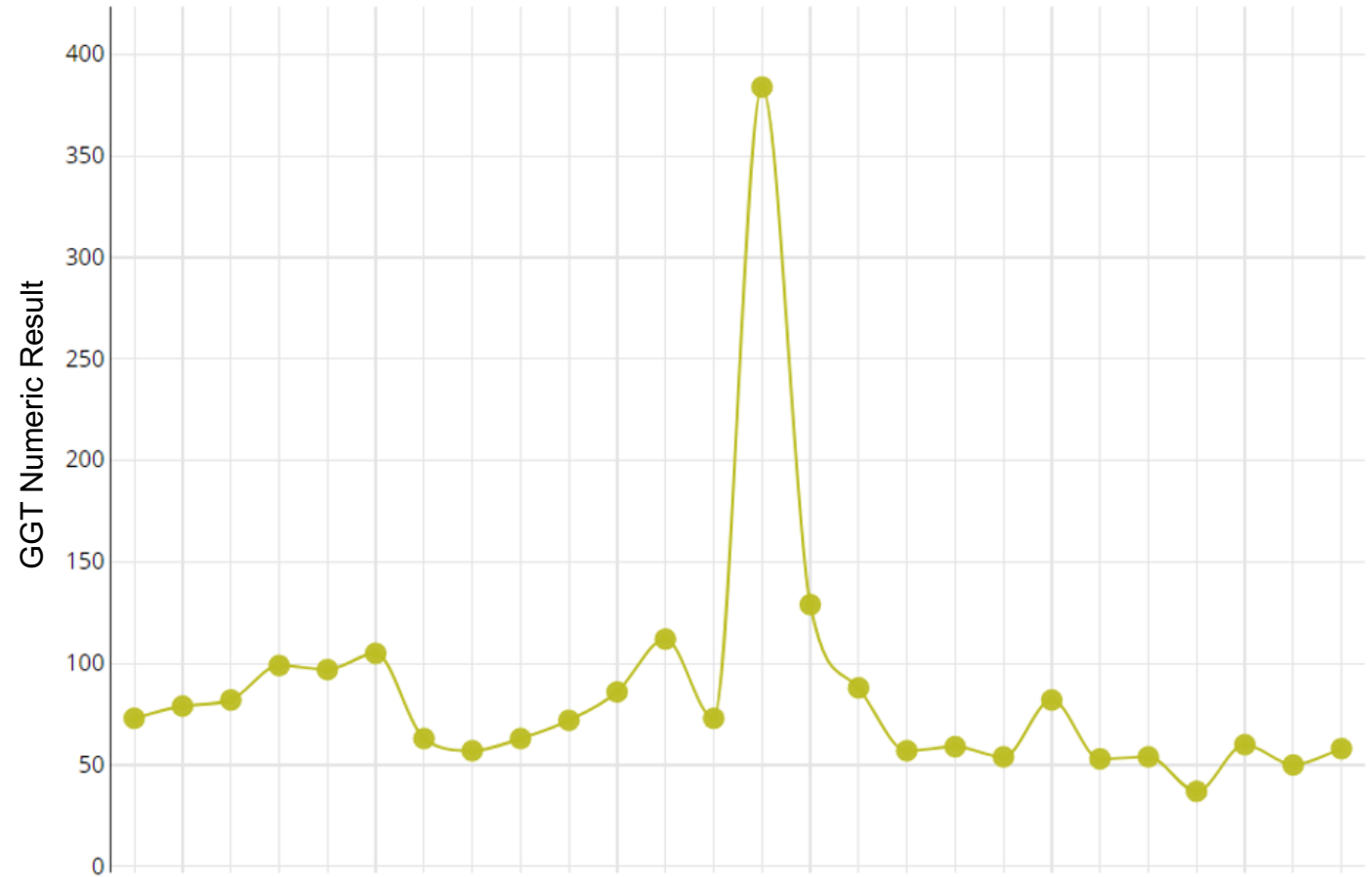
Data entry issue – values
switched



Individual outliers

Example: increase in GGT blood concentration

Large deviation in enzyme concentration could be interesting due to a potential safety issue.



Central Statistical Monitoring (CSM) Implementation

- Central Statistical Monitor reviews the scores & provides description of the pattern or signal observed in data.
- Periodic report with observations & signal highlight recommendations
- Meetings & discussions with study team and other relevant stakeholders

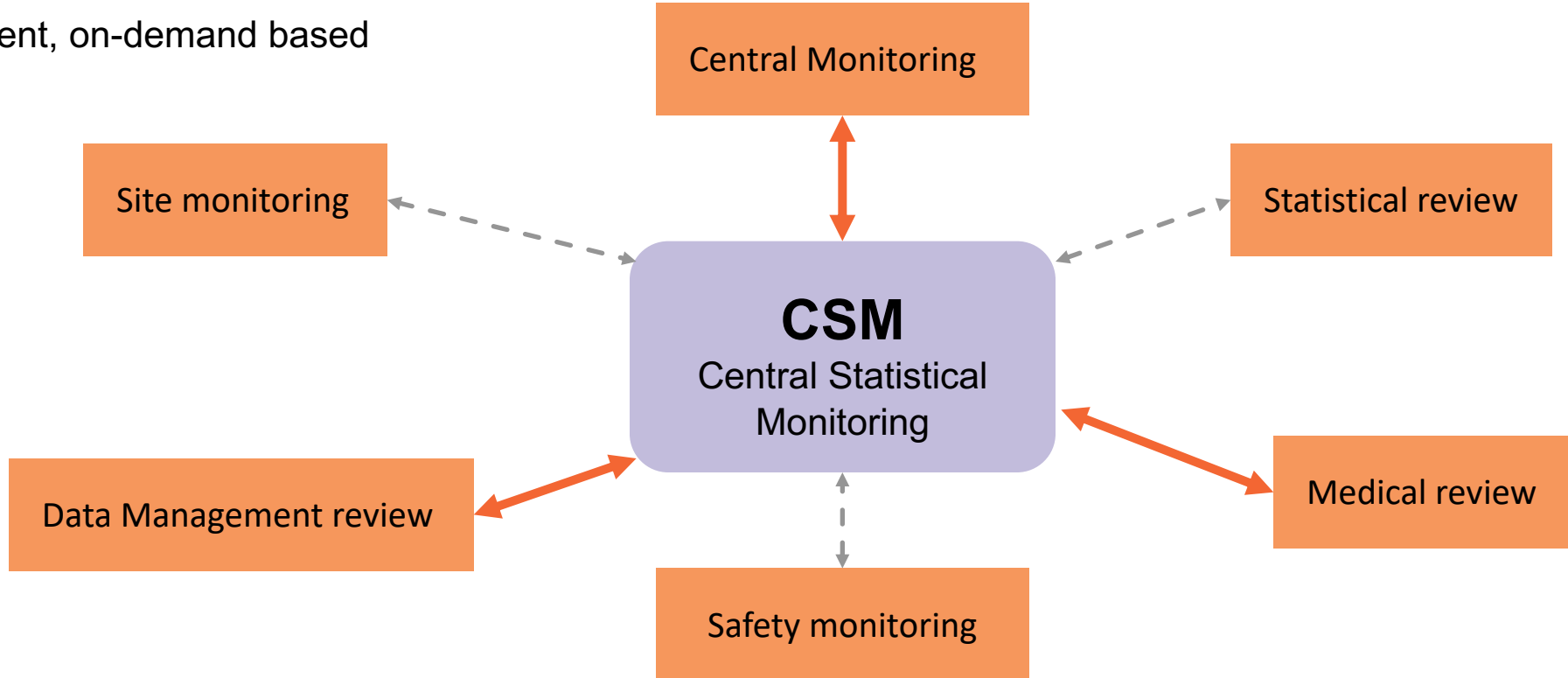


Central Statistical Monitoring (CSM)

Interactions with monitoring roles & activities

— regular, as part of central stat review

- - - less frequent, on-demand based



Central Statistical Monitoring (CSM)

Challenges

- Processing larger datasets (e.g. vaccine trials)
- Building awareness of the meaning of observations and associated risks
- Complex trial design: adaptive design – early arm closure, diverse sub-studies, early arm closure
- Concentration of population cohorts – characteristics of population specific for a location

Central Statistical Monitoring (CSM)

Plans for development

- Application earlier in the trial (with fewer data)
- More focus on patient profiles
- Duplicate patients detection
- Closing the gap between CM & CSM activities

References

- Guidance for Industry; Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring (FDA, 2013); <https://www.fda.gov/media/116754/download>
- Trotta L, Kabeya Y, Buyse M, et al. Detection of atypical data in multicenter clinical trials using unsupervised statistical monitoring. Clinical Trials. 2019;16(5):512-522. doi:10.1177/1740774519862564
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- Monge ZA, Chen M, Lobanov VS, et al. A Hybrid Statistical-Machine Learning Approach to Anomaly Detection in Clinical Trial Data; 2020 APAC Symposium

Acknowledgements

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Thank you!