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# Practical Implementation of Central Statistical Monitoring

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Regulatory agencies are moving forward by encouraging alternative approaches that streamline the costs associated with clinical trials without compromising quality or scientific validity. Recent final guidance from the U.S. Food and Drug Administration (FDA) suggests that risk-based approaches should be used for clinical trials monitoring. The European Medicines Agency (EMA) in a reflection paper has taken a similar position. The industry is now considering the solutions for implementing novel monitoring strategies driven by indicators of the investigational sites' quality. A common way to achieve the evaluation of the site quality or performance is to look at predefined metrics, the so-called Key Risk Indicators (KRI). In this paper a complementary layer to KRI is introduced: an innovative Central Statistical Monitoring (CSM) approach based on advanced statistical methods and data mining tools aimed at detecting sites with abnormal data patterns. The paper demonstrates a concrete CSM implementation and illustrates how the processes can be designed. It will also discuss the requirements and the challenges of the proposed approach.

## NEW REGULATORY THINKING

Effective monitoring strategies in clinical research are vital to make certain studies are being conducted and reported correctly, while ensuring subject safety. Traditional methods that rely heavily on on-site monitoring represent a significant expense for pharmaceutical and medical device sponsors, accounting for up to 30% of the cost of a clinical trial[1]. A highly resource heavy practice, on-site monitoring techniques demand a prescribed schedule of visits every four to 10 weeks, commanding hundreds of investigator hours that sponsors and CROs can in some cases no longer afford. At the same time, the past decade has seen the cost of clinical trials sky rocket, while the rate of new drug approvals has steadily declined. If this current pace of increasing costs continues, sufficiently sized clinical trials are likely to become unfeasible. To add to the issues, when dealing with the large volumes of data that have become standard in modern studies, manual visual comparisons are inefficient at detecting erroneous patterns in data and may easily introduce error.

As a solution to these inherent challenges, regulatory agencies have shifted their thinking towards risk-based monitoring (RBM) designs that offer improved cost-efficiency for the industry, without compromising the quality of data. The FDA guidance for industry and the EMA reflection paper encourages greater reliance on centralized monitoring practices, with increased efficiency in the form of reduced SDV and less emphasis on on-site monitoring.[2,3] These documents have highlighted the fact that sponsors should be "targeting" their on-site monitoring activities and state that monitoring plans should only be developed once the unique needs and risks associated with a study have been assessed and identified. The recommendations also emphasize the importance of analyzing data on a regular basis to assess and adjust the monitoring strategy as necessary.[2,3]

One of the most common ways of targeting on-site monitoring is by remote monitoring which involves assessing the data off site and determining where issues may be prevalent. Currently these methods focus on data management metrics and trending including the use of subjective Key Risk Indicators (KRIs).

## CURRENT RBM APPROACHES

RBM strategies have historically relied on KRIs that are pre-defined by the study team and potentially reveal deviations in study conduct, while identifying poor performance in investigative sites. Predefined metrics are computed for each site and risk is controlled by closely analyzing data to identify issues. On-site monitoring frequency can then be adapted based on site performance. Although KRIs are effective to a certain degree, their implementation is far from straightforward. They need to be pre-defined, programmed, tested, and validated, and they only use part of the massive volumes of data collected in clinical trials.

In response to the widespread issues that the industry is facing, an innovative Central Statistical Monitoring (CSM) approach has been introduced that takes a more neutral view of data and offers a complementary layer to traditional KRI techniques. Based on advanced statistical methods and data mining tools aimed at detecting sites with abnormal patterns in data, this approach is helping to focus monitoring activities on centers where it is most necessary.

## CENTRAL STATISTICAL MONITORING

In contrast to traditional methods, CSM is an agnostic approach that is based on the actual clinical data. The concept behind this is that all the hundreds of patient-related variables and endpoints in a study are deemed to be indicative of quality, from lab data to CRF data, and baseline data to treatment outcomes, everything is assessed. The method compares the distribution of all variables in each investigative site with other sites, enabling abnormal data patterns to be detected. The technique uses complex and proven algorithms to drill down into individual patient data to better manage risk and determine variations between sites in order to identify statistical outliers. This enables sites that are at risk or demonstrate errant results to be identified and resources deployed as required, significantly enhancing overall quality.

By analyzing all available information, CSM is able to identify issues such as lack of variability in or implausible values that go undetected using other approaches. It can determine where issues might lie during study conduct and before significant problems occur, helping to avoid any issues arising that could put a trial at risk or jeopardize successful regulatory submissions. The approach requires minimal work for sponsors and the protocol is implemented in the same manner using the same CRF at all sites.

Throughout the duration of a study, variables are grouped by center, centers grouped by country, and countries are grouped by geographical region. The approach rests on the premise that the multivariate structure and time dependence of variables in statistical checks are highly sensitive to deviations and extremely difficult to imitate. Comparisons can be performed with either one variable at a time in a univariate fashion or with several variables, taking into account the multivariate structure of the data, or using longitudinal data when the variable is repeatedly measured over time.[4] Fabricated data will exhibit abnormal multivariate patterns that are detectable statistically. In addition, humans are known to be poor random number generators, meaning that tests on randomness can be used to detect data that have been falsified.[4]

Implementing a CSM approach can help design a more effective RBM monitoring strategy by efficiently detecting errors, sloppiness, tampering and fraud. When using CSM during a study, sponsors can take corrective action, in a timely manner, to prevent issues becoming deep-rooted and re-analyze data as part of an iterative process. The sponsor can perform focused site monitoring visits, identify CRA and site-retraining needs, or develop site tools to provide clarification on protocol and study processes. An additional benefit of CSM is that for sponsors who strategically outsource to CROs, the method can be used as an effective oversight tool to regularly check the quality of the data. The solution is therefore proving vital in informing the selection of CRO partners and investigative sites for future trials.

## IMPLEMENTATION OF CSM

CSM techniques are already being successfully used in several dozen studies to date and have demonstrated great efficiency to identify issues in clinical data. GSK Vaccines, Gilead Sciences and Cubist Pharmaceuticals have practically implemented a CluePoints' CSM solution in three relatively straight forward steps; set-up, analysis and reporting. The set-up stage of the process involved Sponsor’s data manager and CluePoints discussing the structure of the datasets and their contents before the data was uploaded. During the analysis stage, CluePoints selected statistical tests and variables, browsed and filtered results and generated outputs. The sponsor was then provided with a detailed report that explained any outliers, with data discrepancies clearly defined.

Gilead's first study utilizing a CSM approach involved 120 centers and 660 tests were conducted, generating 79,200 p-values. The tables of p-values were highly detailed and both known and unknown risks and issues were detected. The company now plans to integrate KRIs and CSM into its everyday study quality and risk management plans with the expectation of improving data quality and lowering cost. Further examples of issues that have been detected using CSM include identifying poorly calibrated equipment or technical data collection problems, missing data or data incorrectly copied from source documents, data fabricated to avoid gaps in data or modified to fall within range, as well as data falsified to make patients eligible or favor treatment. A number of case studies relating to the implementation of CSM techniques will now be reviewed.

## CASE STUDIES

### CASE STUDY 1 - IDENTIFICATION OF UNDER REPORTED ADVERSE EVENTS

CSM methods have been used in a double blind randomized phase III study in infectious disease. More than 5000 patients were involved across 150 sites in 18 countries, and a total 400 endpoints were collected. The technology was used at the beginning of the follow-up period to detect any atypical site behavior and associated patient data issues. Approximately 11,000 p-values were generated and the scoring algorithm identified one site as strikingly different from the other sites. Figure 1 shows the distribution of the scores. The center labeled INV204 had the smallest score as compared to the other centers and was clearly outside the normal distribution expected. An inspection of the individual tests that determined the statistical significance for this center revealed atypical distribution characteristics for the adverse events collected (Figure 2). The rate of adverse event was far below the

average and most reported were serious, meaning non-serious adverse events were reported less than expected. With this finding in mind, the sponsor triggered a monitoring visit of the site and the CRA ultimately confirmed a training issue. Through early discovery, the sponsor had the opportunity to take corrective actions and conduct retraining. In the subsequent runs of the CSM technology, the site was ranked down which confirmed the effectiveness of the actions.

*FIGURE 1 – Site scoring: Bubble Plot of score*

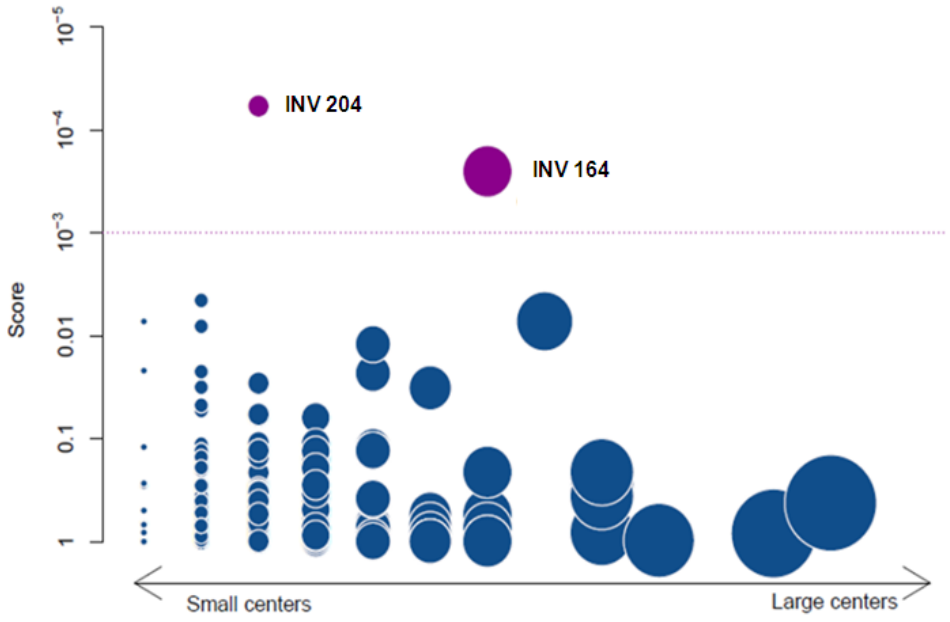
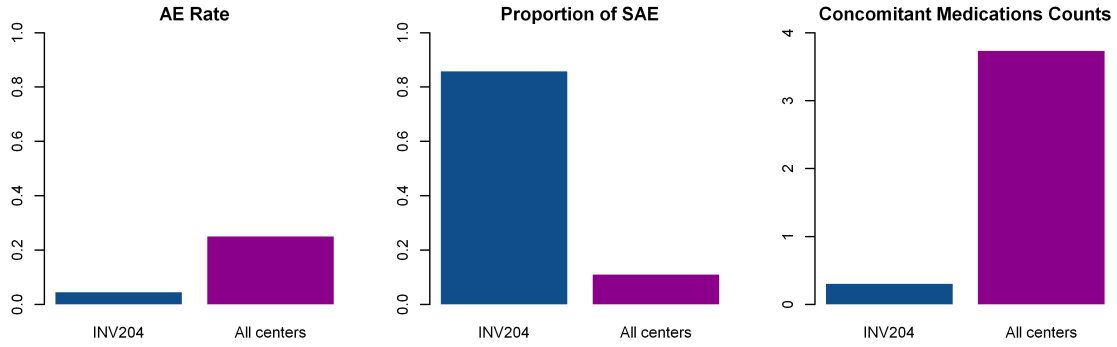



*FIGURE 2 – Distribution characteristics of adverse events*




**CASE STUDY 2 - CONFIRMATION OF FRAUD AT A CENTER WHERE PATIENT DIARIES WERE FOUND TO HAVE BEEN COMPLETED BY SITE STAFF**

In a phase III trial in vascular disease, over 4,500 patients were randomized across 160 sites and the CRF included 480 variables for 32 domains. The sponsor had a specific concern regarding a center suspected to have falsified patient questionnaires. More than 45,000 p-values were generated as part of the analysis and the scoring algorithm summarized the information from the tests into a summary indicator or "score" that pinpoints atypical centers and data subsets. In this analysis, center R38 was among the centers with the highest scores. Individual tests revealed that most of the signals were focused on patient diary data and that patients' answers in these diaries were showing distribution of values that were completely different compared to the same data from other centers. The scores are given in Table 1 for the five top sites of interest. It is interesting to note that in addition to site R38 which was known to have potential issues, other centers also exhibited atypical patterns. In an ongoing trial, it would have been beneficial to trigger on-site monitoring visits in all sites identified as outliers in the analysis.

*Table 1 – Site scoring*

| | | |
|---|---|---|
| R56 | 1 | 0.000001 |
| R38 | 2 | 0.000035 |
| R129 | 3 | 0.000550 |
| R131 | 4 | 0.000745 |
| R61 | 5 | 0.001460 |

**CASE STUDY 3 - DETECTION OF MIS-CALIBRATED EQUIPMENT**

This case study illustrates how a CSM solution can be implemented during an on-going trial to determine data discrepancies arising from unintentional device issues. A Phase III vaccine trial had enrolled over 16,000 patients across 200 centers. These centers were located across the globe in North America, Europe and Asia-Pacific. CSM analyses were scheduled to run every six months during the duration of the trial (4 years from First Patient First Visit to Last Patient Last Visit). Analyses were performed on all available clinical variables and over 60,000 p-values were generated as test results each time an analysis of the data was performed. The findings were conclusive pertaining to one of the specific test results. A number of centers from one of the countries involved appeared to have low p-values for the test on mean temperature. Figure 3 represents the distribution of p-values. The magenta bubbles correspond to the centers within the country identified as experiencing issues (Country X). Further investigation from the sponsor, in the form of an audit team being sent to these sites, revealed that all centers from Country X received mis-calibrated thermometers. Even though the magnitude of error in thermometer calibration was too small to be detected on-site by the monitors, it was revealed instantly using statistical analysis. Figure 4 clearly displays the difference in mean temperature recorded in the centers within Country X. This kind of data issue is not possible to detect either by on-site monitoring nor using subjective Key Risk Indicators (KRIs).

*FIGURE 3: Distribution of p-values for the test on mean temperature*

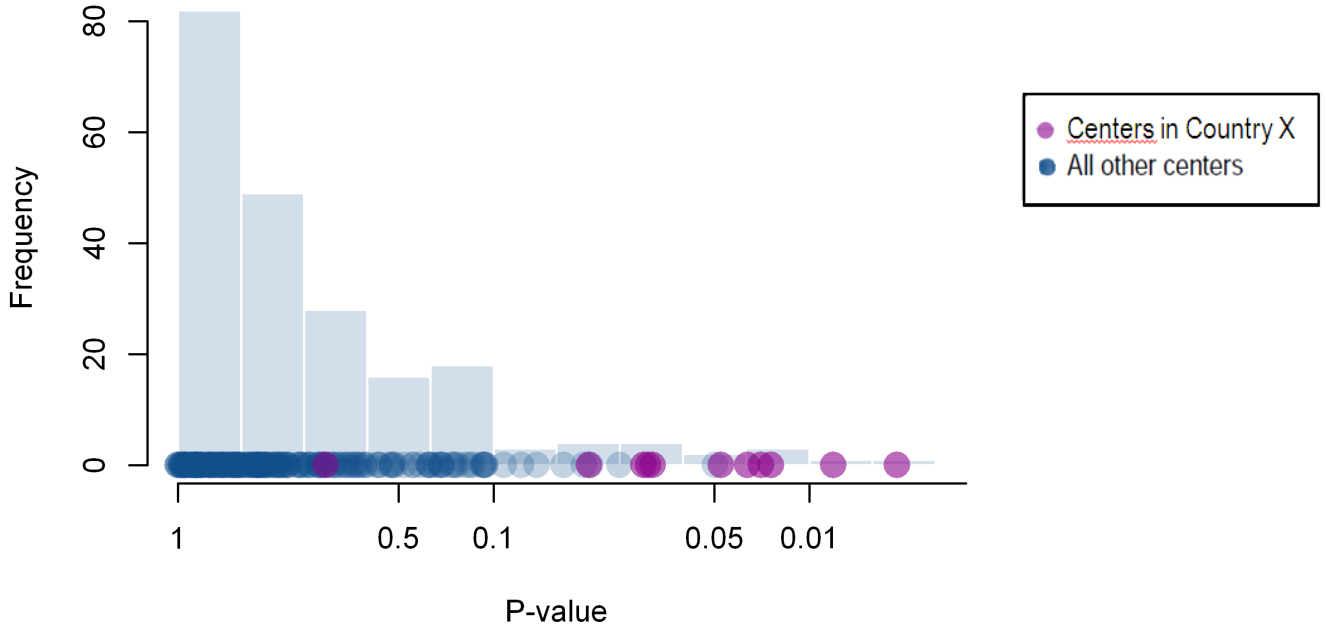
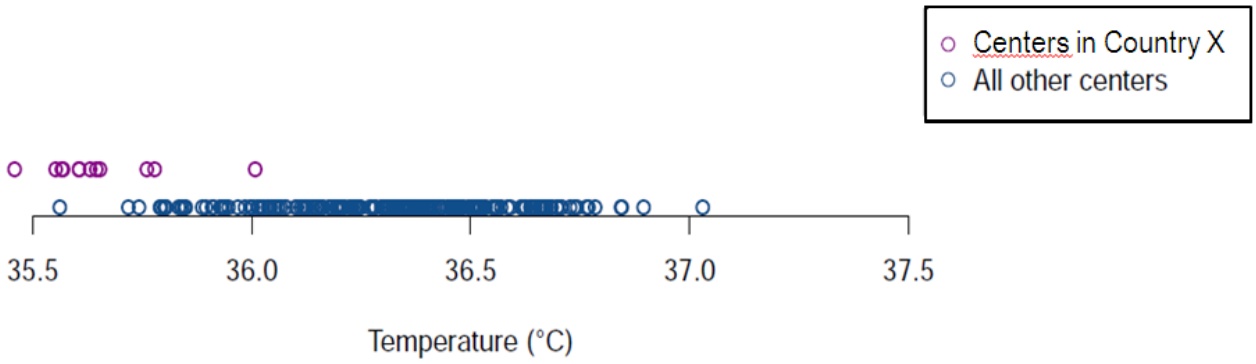



*FIGURE 4: Mean temperature by center*




## REQUIREMENTS & CHALLENGES

To successfully implement CSM, a number of important factors must be considered. For results to be significant, a certain amount of data is required for analysis, ideally at least five patients per center across at least 10 centers. This means that in the early stages of a trial or in studies that employ numerous small centers, the volume of data available may be too limited to perform statistical tests to detect abnormalities at the center level. Note that in these cases, an analysis at the country level (or any other grouping factor) might still be relevant. A further requirement of the technique is that skilled people are required to develop the engine and interpret the results meaning that data specialists are essential, while a robust programming language able to deal with a huge amount of data is also paramount.

In addition, the implementation of a CSM approach is not without its challenges and sponsors should ensure they go into the process with their eyes wide open and working with experts that can advise them on best practices. One of the most common challenges is that as CSM is reliant on computerized data, the technique may miss some types of fraud or errors that can only be detected during site visits, such as evidence provided in handwritten documents or interviews. This considered, on-site visits may be more efficient if monitors perform visits with information about unexpected data patterns identified by statistical monitoring in hand.

## CONCLUSION

In an industry notorious for its slow adoption of emerging technologies, growing consensus that risk-based approaches to monitoring are more likely to ensure subject protection and overall study quality is fuelling momentum for the use of CSM techniques. The resulting efficiencies from undertaking this approach to target 'at risk' investigative sites are now being harnessed by many sponsors and CROs alike who are experiencing tangible benefits by reducing on-site monitoring efforts through identifying those sites that are deemed to be outliers using advanced statistical techniques to analyze data. The ability of CSM to identify errant data earlier is helping sponsors to enhance their RBM strategies by providing the opportunity to eradicate any issues as they are uncovered, significantly reducing the risk of regulatory submission failure. The method's unique ability to improve data quality, drive more efficient, targeted on-site monitoring, while addressing important new regulatory guidance, is proving that there is no doubt that an objective assessment and evaluation of site quality and performance is crucial to managing risk and ultimately reducing costs.

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## RECOMMENDED READING (HEADER 1)

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