Example Where Centralised Statistical Monitoring Detected Mis-Calibrated Thermometers in a Clinical Trial

A pharmaceutical sponsor was undertaking an on-going phase III vaccine trial that had enrolled over 16,000 patients in 200 investigator sites across North America, Europe and Asia Pacific. In the early stages of the trial the sponsor wanted to gain a comprehensive evaluation of the quality of the data being generated by the study and ensure that corrective action could be taken on any problems or issues impacting the conduct of the trial. As any data issues could potentially have a negative effect on the overall success of the research program, and future regulatory submission, the sponsor required an objective review of the data collected during the trial across all geographic regions and investigator sites.

To evaluate data consistency across all participating sites, the sponsor opted to implement a centralised statistical monitoring approach that would enable all accumulated data to be examined across the trial. This would provide means to gain greater knowledge of the inner workings of its data and supplement its currently relied upon Key Risk Indicator (KRI) methods; which are operational statistics that are pre-defined by the sponsor and potentially reveal deviations in the study conduct, whilst identifying poor performance in certain investigator sites. These can include the number of protocol deviations, number of queries raised to the site, elapsed time to respond to these queries, number of patients recruited in the site and number of patients who discontinued etc. Previously the company had been relying on routine on-site monitoring and 100% source data verification (SDV), which placed considerable pressure on its overall resources and expenditure. It was anticipated that the use of statistical monitoring would allow comparisons to be made between data from all investigator sites to identify any unusual patterns or discrepancies and particularly if any sites appeared to be statistical 'outliers'.

In this particular trial the CluePoints' SMART™ statistical monitoring solution was employed to perform scheduled analyses every six months for the whole four year duration of the trial, from First Patient First Visit to Last Patient Last Visit. Although the analyses were not conducted blind to the sites, with staff being aware that an oversight of the data quality was taking place, no access was provided to the results of this assessment, so sites were not aware of their rank or the kind of problems that were detected. Therefore this posed no problems associated with bias as any information that could have led to unblinding was not provided.

Results

The Sponsor’s Data Manager and the CluePoints team worked together to understand the structure of the data sets and their content prior to analysis. Once the data was received from the sponsor, the set-up of the engine and the analysis were completed in less than 15 days. A statistical report interpreting the findings was then provided that outlined any data discrepancies across the participating sites and/or countries.

The findings in the analysis indicated that a number of sites from one of the countries involved in the trial appeared to have low p-values for its tests on mean body temperature of patients which evaluated the mean value for one site against the mean value across all sites. In the majority of trials patient body temperature is not seen as a critical endpoint, however as this was a vaccine trial, body temperature was an important measurement. This finding was particularly surprising to the sponsor because it did not expect problems to occur from inconsistencies through body temperature monitoring and so had made no allowance for this in setting the KRIs for the trial.

Figure 1 indicates the calibration issues detected in the sites in Country X, clearly showing the low p-values in this region for the test on average temperature. The magenta bubbles correspond to the sites within the country identified as experiencing a similar temperature issue, the higher the bubble, the more significant the detected issues are within a specific site. The size of the bubble reflects the sample size in that site. The solution also enables users to further drill down into the findings. By clicking on a site in the bubble plot, data endpoints, tests and datasets causing issues in that particular site can be identified.

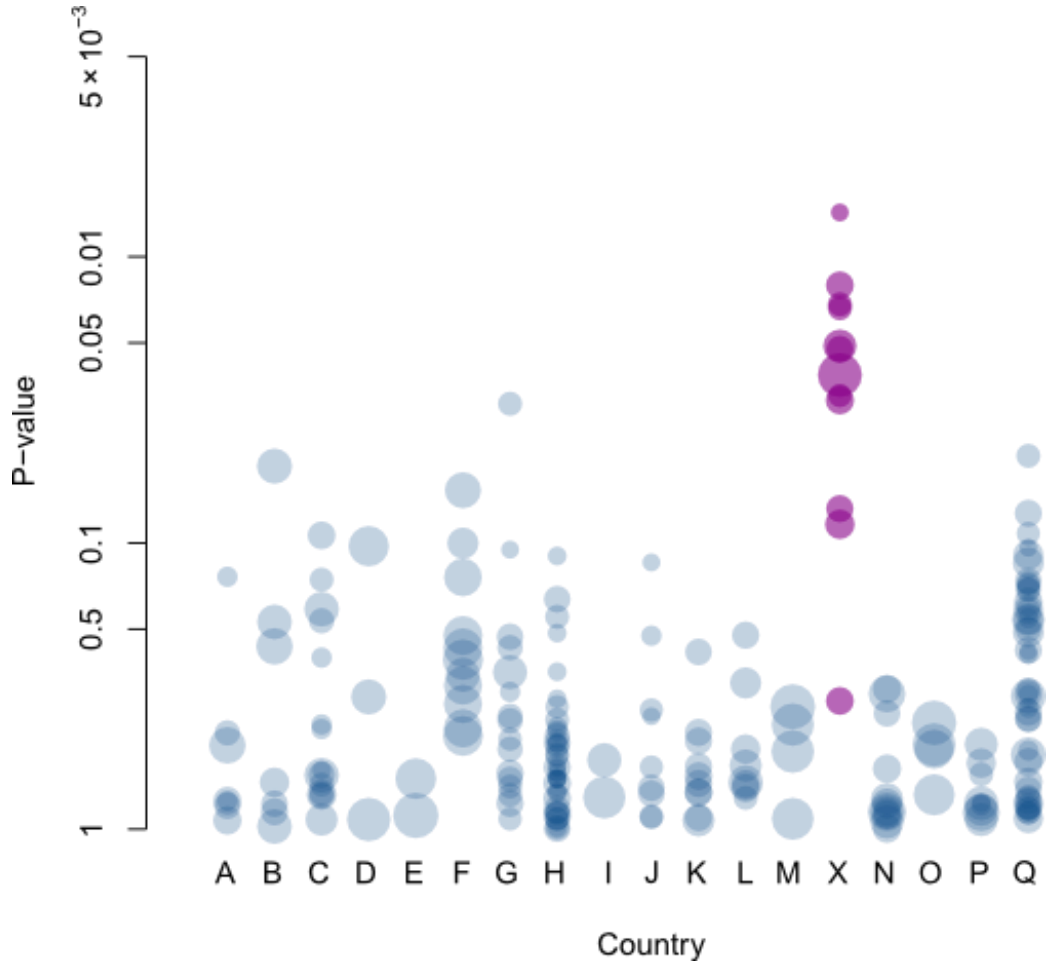
The identification of vulnerabilities at the sites in Country X enabled the sponsor to undertake targeted investigations at the affected sites which revealed that all sites in Country X had in fact received mis-calibrated thermometers. Even though the magnitude of error in thermometer calibration was too small to be detected using on-site monitoring, it was revealed instantly using statistical analysis methods. Figure 2 clearly displays the difference in mean temperature recorded in the sites within Country X.

Further to this analysis, additional analyses of the data continued to be completed every six months throughout the duration of the trial. To date, no additional problems associated with thermometer calibration have been identified.

Conclusion

In this phase III vaccine trial the central statistical monitoring solution has been able to provide a general check of data quality throughout the study and was able to identify the incidence of mis-calibrated equipment in Country X. By implementing the solution as a routine monitoring procedure from the initial stages of the trial, the sponsor was able to identify the issues early, allowing it to immediately take corrective measures by replacing all thermometers in the investigator sites in Country X. The type of data issue that was identified by the solution in this trial would have been very hard to detect either by on-site monitoring or the use of subjective Key Risk Indicators (KRIs), demonstrating the value of this type of solution in complex trials where only the use of statistical techniques can effectively improve the reliability and robustness of trial results, ensuring patient safety and the quality and integrity of the data generated.

Figure 1: Bubble Plot for the test on average temperature



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