How CluePoints Detects Miscalibrated Equipment in a Clinical Trial

Case Study 3

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How CluePoints Detects Miscalibrated Equipment in a Clinical Trial

The accuracy and precision of measurement equipment, such as those used to monitor patients' vital signs during a clinical trial, can have a significant impact on both patient safety and the validity of study data. When conducting studies across multiple investigative sites and geographies it can be extremely challenging for sponsors to identify and take corrective action on issues related to mis-calibrated equipment, with significant risk that problems may not be identified. A pharmaceutical sponsor wanted to gain a comprehensive evaluation of the quality of the data being generated in an on-going phase III vaccine trial. To do this, the sponsor implemented CluePoints' Central Statistical Monitoring solution to provide an objective review of the data collected throughout the course of the trial across multiple geographies and investigative centers. The results of the analyses yielded surprising findings related to the calibration of instrumentation used at the investigative sites.

Challenge

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 investigative centers.

To evaluate data consistency across all participating sites, the sponsor opted to implement a centralized statistical monitoring approach that would enable all accumulated data to be examined across the trial. This would provide means to supplement its current Key Risk Indicator (KRI) methods and garner greater knowledge of the inner workings of its data.

Previously the company has been relying on routine on-site monitoring and 100% 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 investigative sites to identify any unusual patterns or discrepancies and particularly if any sites appeared to be statistical 'outliers'.

The CluePoints Solution

To provide on-going analysis of data in this clinical trial, the sponsor used CluePoints to evaluate data consistency across all participating sites. Aligned with guidance from the FDA and EMA, CluePoints' system employs unique statistical algorithms to support traditional on-site monitoring and drive a risk-based monitoring strategy. The system is driven by a powerful engine known as SMART™, a software solution that examines if the data collected are consistent across all investigative sites, and if they are not, identifies those centers that differ substantially from the others. In this trial, the CluePoints solution will be used 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.

Results

Analyses were performed on all available clinical variables. Over 60,000 P-values were generated as test results using the SMART engine. The findings in the analysis were conclusive pertaining to one of the specific test results. A number of centers from one of the countries involved in the trial appeared to have low P-values for its tests on mean temperature which evaluated the mean value for one center against the mean value for all other centers. This finding was particularly surprising to the sponsor as it did not expect problems to occur from inconsistencies through 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 centers in Country X, clearly showing the low P-values in this region for the test on average temperature. The magenta bubbles correspond to the centers within the country identified as experiencing issues (Country X).

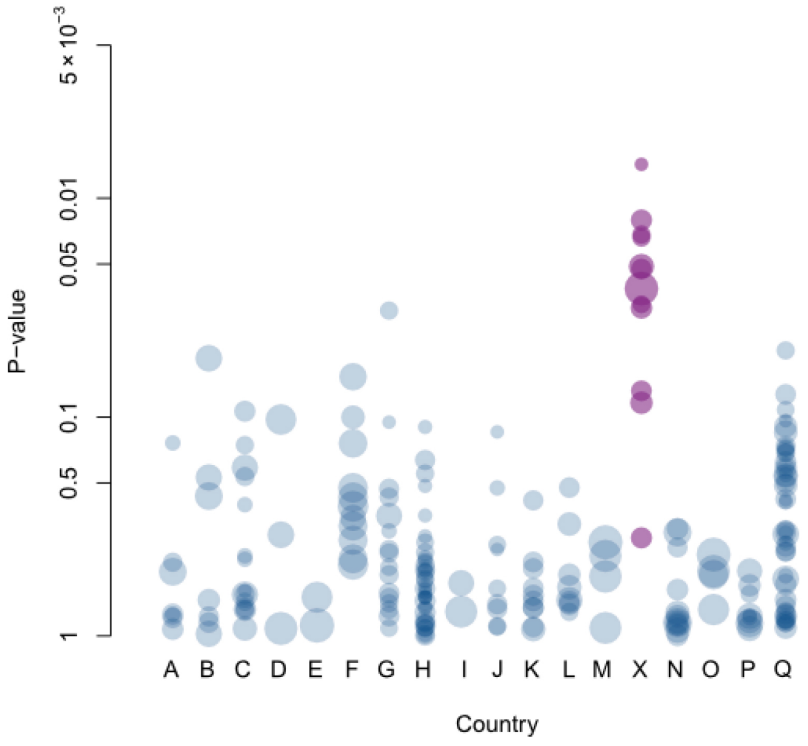


Figure 1:
Bubble Plot for the test on average temperature

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 centers 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 centers within Country X.

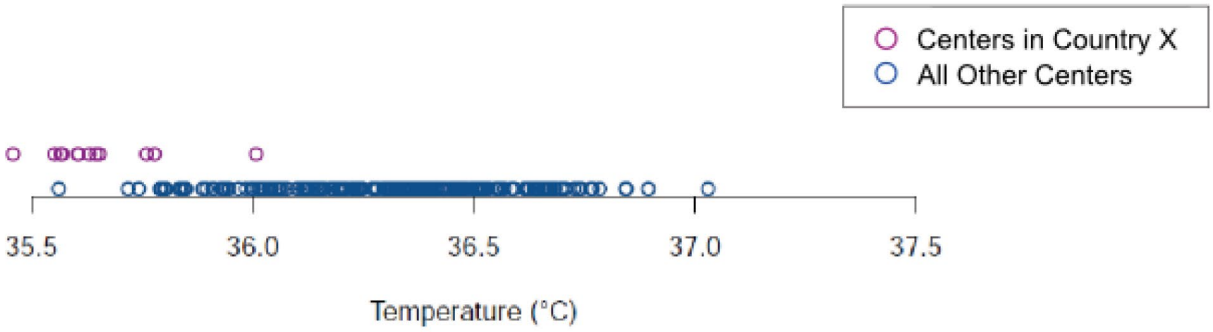


Figure 2:
Mean temperature by center

Further to this analysis, additional analyses of the data are continuing 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 CluePoints 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 investigative centers in Country X. The statistical monitoring solution provided the sponsor with the ability to detect anomalies in data across all its investigational centers in multiple countries worldwide, thereby guiding and validating where the sponsor needed to focus its monitoring efforts on sites that were indicated to be at risk. This can significantly reduce regulatory submission risk by providing the best quality data set based on objective interpretation of information. 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.

Trial Information

Indication: cardiovascular disease
Centers: 160
Patients: 4,500+
Variables: 480
Domains: 35
Countries: 10
P-values: 160 Centers x 1000 Tests (on 480 variables)
= 160,000 p-values


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