The Identification of Severe Propagation in Vital Sign Measurements Using the CluePoints Solution

Case Study 6

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In clinical trials, questions about propagation, or alternatively stated, the replication or duplication of vital sign measurements, may be raised when sequences of values are observed. Issues of propagation have been reported in trials that involve measurements being repeatedly collected across numerous patient visits to an investigative centers. The occurrence of sequences in this instance may reveal investigator errors or sloppiness, and could indicate that the values of interest have not actually been measured on a particular visit, meaning that values from a previous visit have been re-entered or even invented instead. A pharmaceutical sponsor wanted to gain a comprehensive analysis of the data collected in a phase III ophthalmology trial, specifically related to a subset of four datasets including adverse events, concomitant medication, vital signs and demography. The sponsor chose to implement the CluePoints' Central Statistical Monitoring solution after trial completion to assess the quality, accuracy and consistency of the study data.

Challenge

After completion of a phase III ophthalmology trial of more than 800 patients randomized across 62 centers and involving the collection of 120 variables across four domains, the sponsor wanted to conduct a comprehensive analysis of the quality, accuracy and consistency of the study data generated. The sponsor was looking to obtain a thorough overview of potential data issues across all centers involved in the trial. To do this, the sponsor chose to implement a centralized statistical monitoring approach. It was anticipated that the use of this technique would provide an objective review of a sample of the data collated across the trial, while providing an indication of any unusual data patterns.

The CluePoints Solution

To provide a comprehensive review of data in this clinical trial, the sponsor used CluePoints to evaluate data consistency across all participating centers. Aligned with guidance from the FDA and EMA, CluePoints' system employs unique statistical algorithms to 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 centers, and if they are not, identifies those centers that differ substantially from the others. In this trial, the CluePoints solution was used post study completion to analyze a sample of the data collected throughout the duration of the trial. A subset of four datasets were analyzed to illustrate the ability of CluePoints to run on a smaller set of variables, including adverse events, concomitant medication, vital signs and demography. These four domains were chosen because they are representative of variables present in all clinical trials across all therapeutic areas.

Results

Analyses were performed on the clinical variables, with 5,100 P-values generated as test results using the SMART engine. The CluePoints scoring algorithm summarizes the information from the tests into a summary indicator or Data Inconsistency Score (DIS) that pinpoints atypical centers and data subsets. The distribution of these scores is shown in Figure 1, from which it is clear that in this analysis one center stands out as strikingly different from all the other centers involved in the trial.

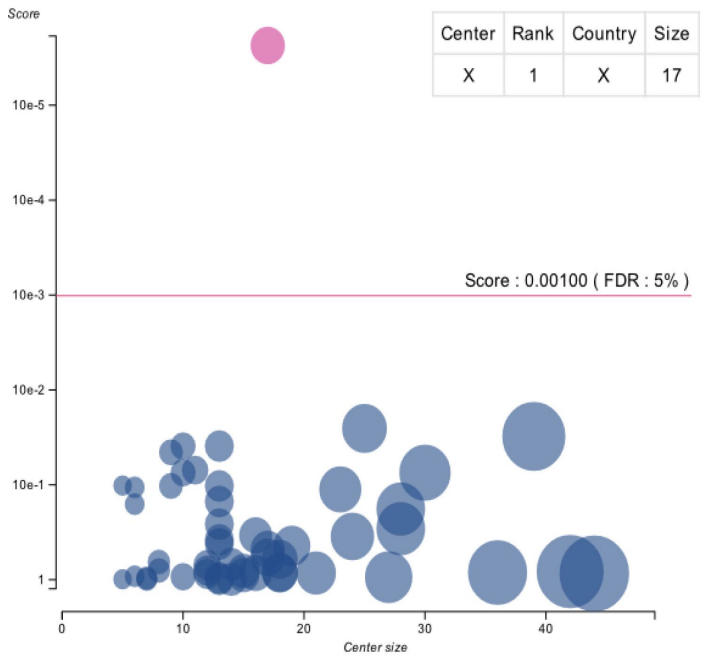


Figure 1:
Bubble plot showing the distribution of Data Inconsistency Scores

Center X has the lowest score and is therefore ranked first. Detailed examination of the individual tests that were conducted revealed severe propagation in the collection of a number of vital sign measurements. For Center X, propagation issues were detected for three variables in the vital sign domain (Figure 2) including respiration rate per minute, systolic blood pressure and diastolic blood pressure. As indicated in Figure 2, the propagation rate observed amongst the respiration measurements of the patients in Center X is more than 95%. In contrast, a rate of only 32.8% is expected, based on data from all other centers.

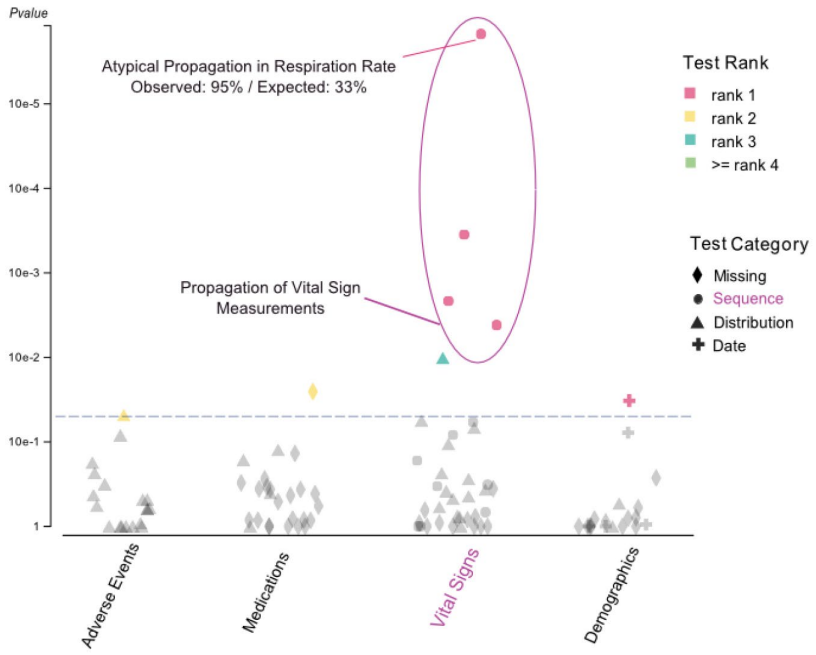


Figure 2:
Propagation issues detected for three variables in the vital sign domain

The propagation in Center X regarding the patients' respiration rates is illustrated in Figure 3. The patients' respiration rates observed across different visits are given for five centers, denoted A, B, C, D and X. Centers A, B, C and D were randomly selected amongst all study centers in addition to Center X. Within a given center, every line in the graph represents one patient. The colors in the sequences correspond to different respiration rate values.

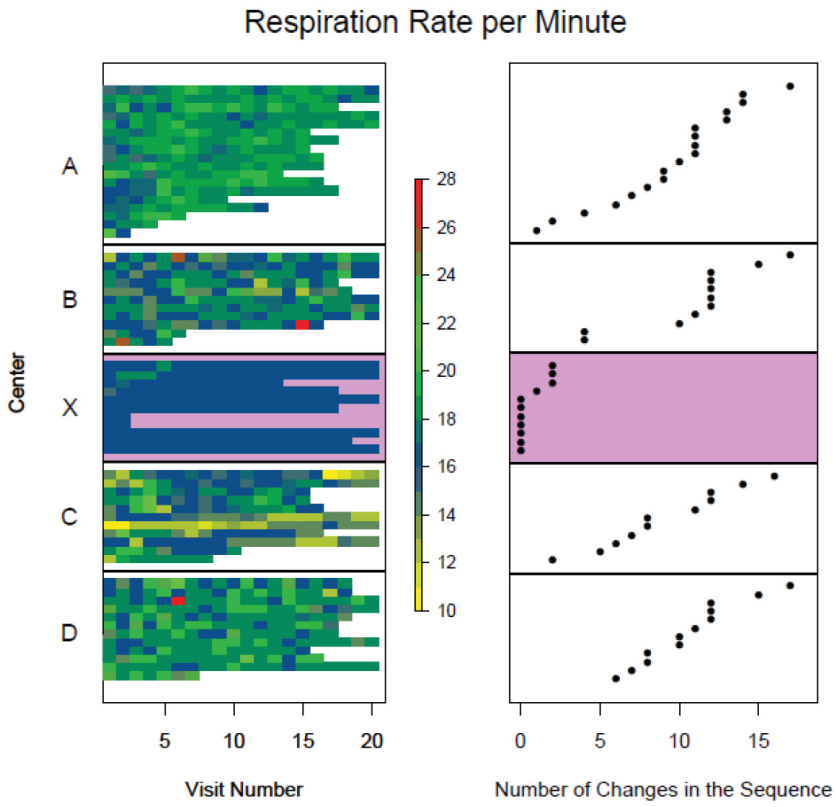


Figure 3:
Patients' respiration rates observed across different visits

The graph shows that for seven of the 11 patients in Center X with at least two measurements, exactly the same respiration rate is observed across all visits. In addition, for the remaining four patients, strong propagation is detected. Moreover, not only within the sequences of the patients, but across all patients in Center X, exactly the same respiration rates (more specifically, 16 breaths per minute) are observed.

In addition to the respiration rate sequences, the number of changes (jumps) in each corresponding sequence is given. It is clear that large proportions of the measurements observed for the patients in Center X are propagated, as the maximum number of jumps equals two. For the other four centers in the graph, normal patterns of respiration rates and consequently higher numbers of jumps are observed.

Conclusion

In this clinical trial, CluePoints was able to pinpoint an anomalous center due to substantial evidence of inconsistency being discovered in its vital sign data when compared to the data collected at other centers during the study. Had the solution been implemented while the trial was still on-going, the issues could have been detected much sooner, providing the sponsor with the opportunity to improve on-site monitoring, take corrective actions, or perform re-training at the centers identified to be 'at risk'. The use of the CluePoints solution in this trial demonstrates its distinct ability to unveil data patterns that reflect unanticipated differences in important aspects of trial conduct, ensuring that data are statistically consistent across all centers involved in a trial.

Trial Information

Indication: Ophthalmology
Centers: 62
Patients: 800+
Variables: 120
Domains: 4
Countries: 8
P-Values: 5,100


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