The Value of the CluePoints Solution in Identifying Under-Reported Adverse Events in a Clinical Trial

Case Study 1

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The Value of the CluePoints Solution in Identifying Under-Reported Adverse Events in a Clinical Trial

Adverse events which occur during the course of clinical trial participants' involvement in a research project must be appropriately identified, recorded and reported to ensure continuing patient safety and the quality, accuracy and integrity of trial data. Failure to correctly identify non-serious and serious adverse events, and deal with them adequately, while also following the required reporting procedures, can have significant implications on clinical research and regulatory submissions.
A pharmaceutical sponsor had specific concerns about some investigative sites involved in a phase III study in infectious disease. To validate the sponsor's concerns, the company implemented CluePoints' Central Statistical Monitoring solution to provide an overview of data issues across all sites involved in the trial.

Challenge

The sponsor was conducting a double blind phase III randomized study of infectious disease. More than 5,000 patients were randomized across 150 sites in 18 different countries, with the case report form (CRF) collecting a total of 400 variables. The sponsor knew that some sites had little clinical research experience, and hence required a comprehensive assessment of the reporting of clinical data across all investigative sites to objectively determine any inconsistencies. This would enable the sponsor to pinpoint any information generated by a site that stood out as inconsistent from the data produced by the various other sites.

The CluePoints Solution

To provide an overall assessment of the data reported by all sites 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 was used to perform an analysis at the beginning of the follow-up period to detect any atypical site behaviour and associated patient data issues.

Results

Approximately 11,000 p-values (a single p-value being the probability of an observed result arising by chance) were generated by the SMART engine as part of the data analysis. The CluePoints' scoring algorithm summarized the data from the test into a summary indicator or Data Inconsistency Score (DIS) that identifies atypical sites and data subsets. The algorithm pinpointed one investigative site as strikingly different from all other sites involved in the trial. The distribution of the scores for the study sites are shown in Figure 1. The center labeled INV204 had the smallest score, and therefore had the most inconsistent data compared with all other sites.

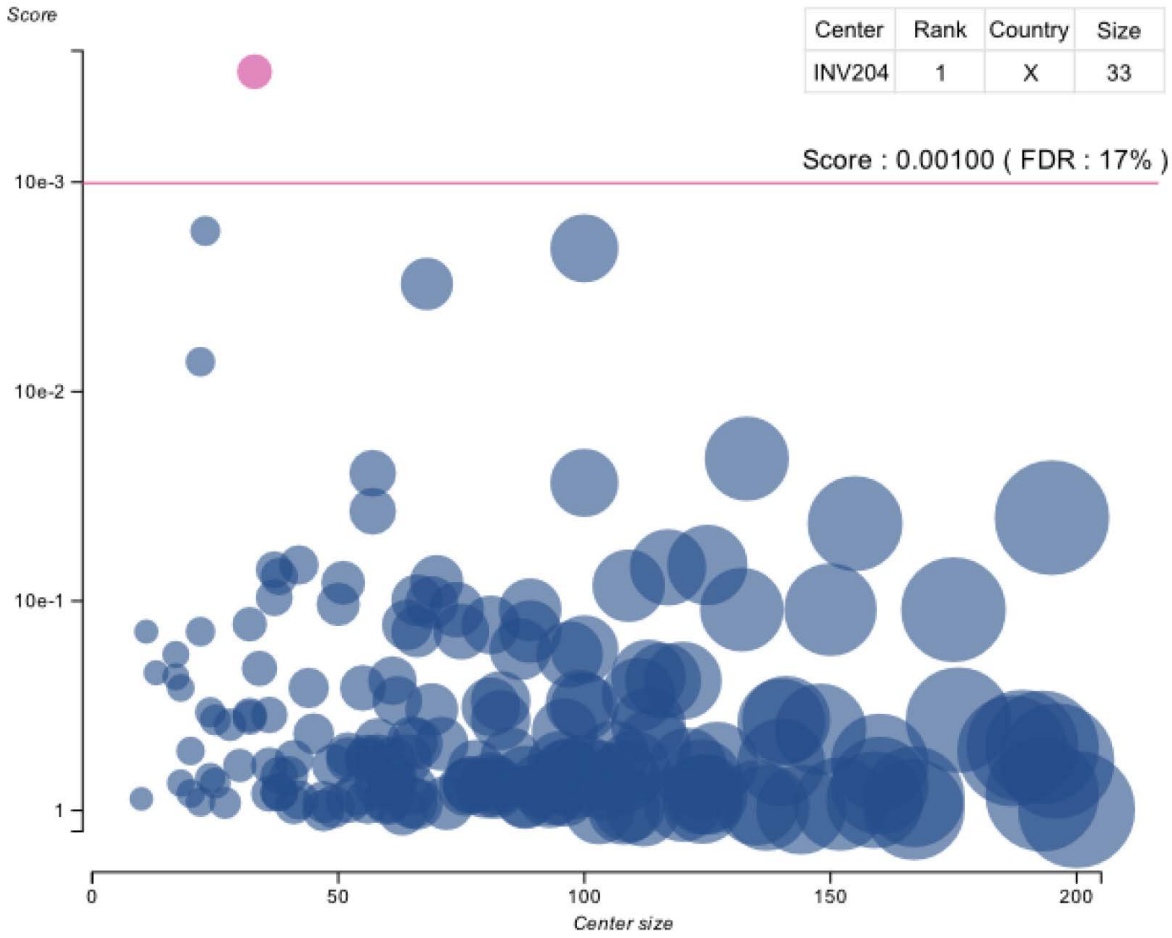


Figure 1:
Site scoring - Bubble plot of score

An inspection of the individual tests that determined the statistical significance for site INV204 revealed atypical distribution characteristics for several variables, including the adverse events collected, as show in Figure 2. The information generated by the study site indicated that on the one hand, the rate of adverse events was far below average, while on the other hand, most of the adverse events identified were serious. This indicated that non-serious adverse events were reported less than expected.

In response to the results of the analysis, the sponsor triggered an on-site monitoring visit where the clinical research associate (CRA) confirmed a training issue for the site.

Another view on the findings showing the data issues in the AE domain related to the missing and the distribution tests (representative of the AE proportion).

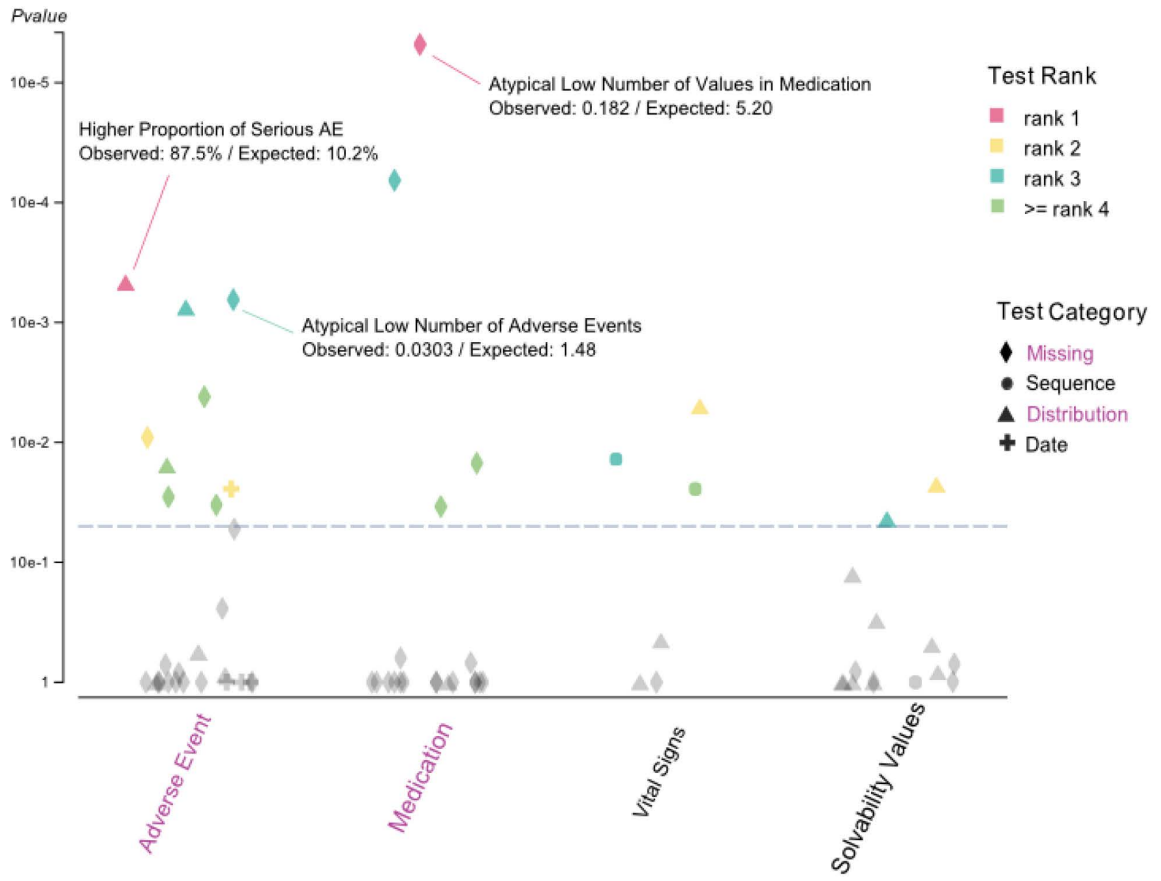


Figure 2:
Categories of data issues by significant domain for center INV204

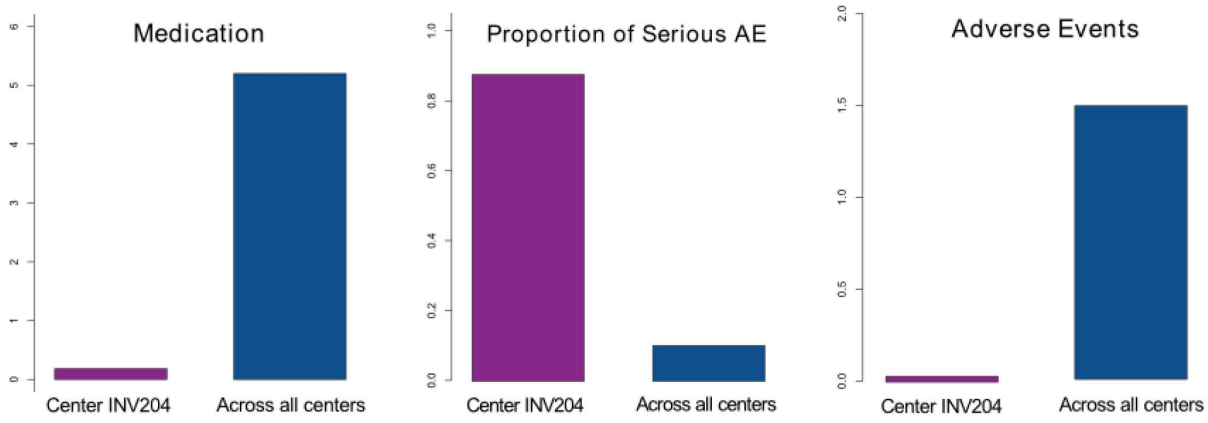


Figure 3:
Distribution characteristics of adverse events

Conclusion

The CluePoints solution was able to confirm the sponsor's suspicion about certain investigative sites with little experience in clinical research. The system's timely ability to identify anomalous data, in particular the under-reporting of adverse events at site INV204s helped the sponsor enhance the overall efficiency of its monitoring process, delivering improvements in clinical data quality and optimization of on-site monitoring, while significantly reducing regulatory submission risk. As a result of the early discovery of the issue, the sponsor had the opportunity to take corrective action and perform re-training at the affected site. In the subsequent runs of the CluePoints solution, the site was ranked down which confirmed the effectiveness of the actions taken. The use of the CluePoints solution in this trial demonstrates the system's unique capability to offer a simple and pragmatic approach to assessing the quality and integrity of clinical trial data.

Trial Information

Indication: Infectious Disease
Centers: 150
Patients: 10,000+
Variables: 400
Domains: 45
Countries: 18
P-Values: 150 Centers x 74 Tests (on 400 variables) = 11,000 p-values


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