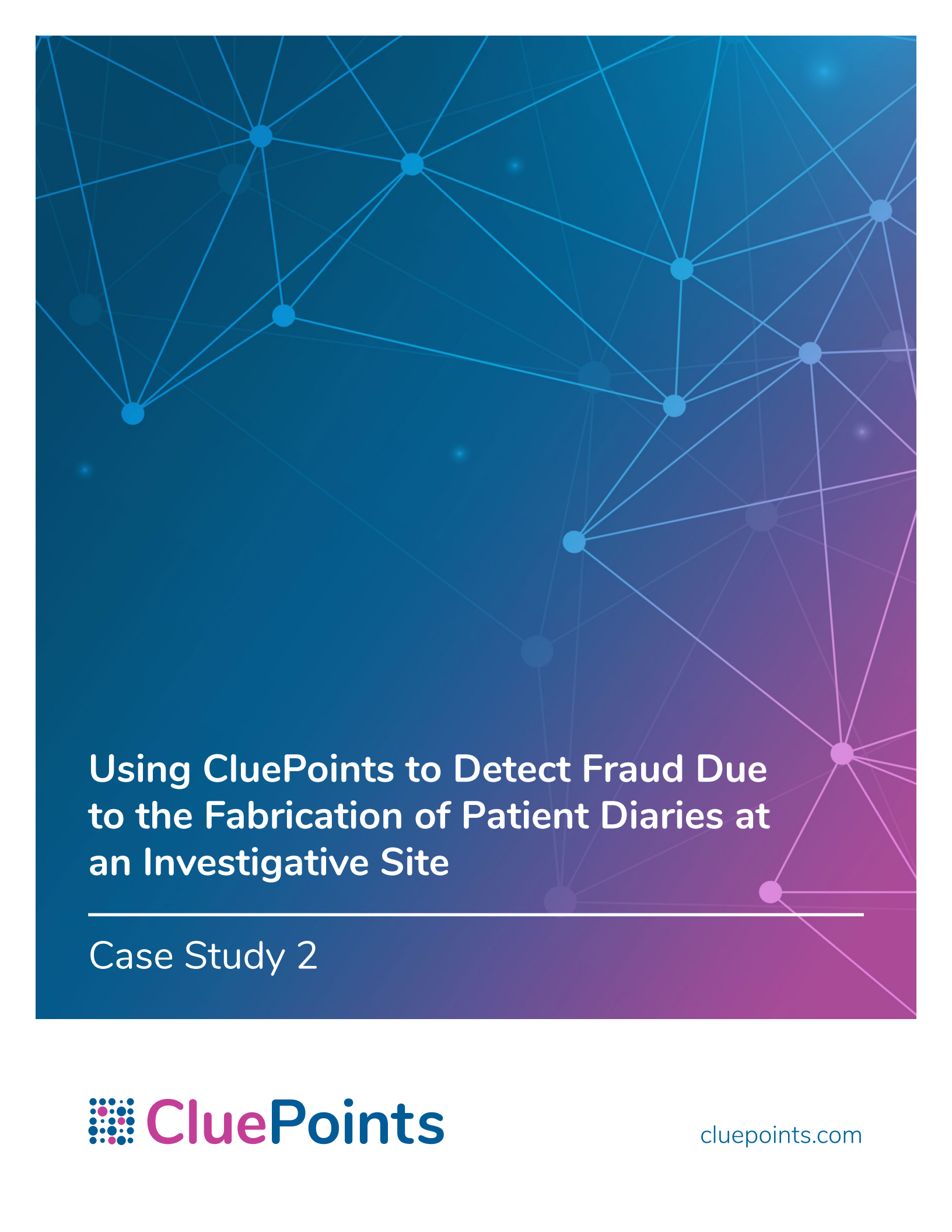




Using CluePoints to Detect Fraud Due to the Fabrication of Patient Diaries at an Investigative Site

Case Study 2

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Using CluePoints to Detect Fraud Due to the Fabrication of Patient Diaries at an Investigative Site

The use of patient diaries is frequently used in clinical research to capture detailed insights directly from participants without oversight by study administrators. Though highly beneficial, the very nature of this tool leaves it open to the potential for entries to be falsified. A leading pharmaceutical company had been losing confidence in the data being generated through patient diaries at an investigative site involved in a phase III trial in patients with vascular disease. To verify its concerns, the sponsor used CluePoints' Central Statistical Monitoring solution to provide an assessment of the quality, accuracy and integrity of study data.

Challenge

The pharmaceutical company was involved in a phase III study of vascular disease involving more than 4,500 randomized patients, across 160 investigative sites. The trial design incorporated the use of diaries to collate patient reported outcomes (PROs) and assess the overall experience of their condition. The same electronic case report form (eCRF) was used across the study and included 480 variables across 32 domains. During the course of the trial, the sponsor had a specific concern regarding the integrity of the data being produced by one particular investigative center involved in managing the delivery of the trial. As any inaccuracies in the information gathered could seriously jeopardize regulatory submissions, the sponsor acquired an objective evaluation of the data collected across the entire trial to help pinpoint any inconsistency in the information that was being generated by the various sites.

The CluePoints Solution

To further investigate fraudulent activity in this clinical trial, the sponsor used CluePoints to evaluate data consistency across sites within the clinical trial. 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.

Results

About 160,000 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 extensive analysis. The scoring algorithm summarized the information from the tests into a summary indicator or Data Inconsistency Score (DIS) that pinpoints atypical centers and data subsets. In this analysis, center 191 (rank 2) was among the centers with the lowest scores. Individual tests were then conducted, which revealed that most of the signals focused on the data collected through the patient diary questionnaires. The responses that patients had provided in these diaries indicated distributions of values that were completely different compared to the same data provided by the other centers participating in the study. Based on the scores, centers are assigned a rank, shown in Figure 1 for the five top sites of interest (i.e., sites with the lowest score).

It is interesting to note that in addition to site 191, which was known to have potential issues, other centers also exhibited atypical patterns. If the trial were ongoing trial at the time of this analysis, the sponsor would have found it highly beneficial to trigger on-site monitoring visits for all sites identified as outliers in the CluePoints analysis. Figure 1 depicts an image of the top level findings via the CluePoints' web application. The pink circles represent the outlying centers, the higher the bubble, the more significant the detected issues are within a given center. As the chances to identify outliers increase with the number of centers in the study, the plot also offers users an adjustable FDR (False Discovery Rate %) that takes multiplicity into account. Indeed, the FDR details the probability to detect a center as an outlier when it is not one. The smaller the FDR, the more confident a center is truly an outlier¹. In addition, by clicking on a center in the bubble plot, the user can drill down into the findings to identify the data endpoints, tests and datasets causing the issue in that particular center.

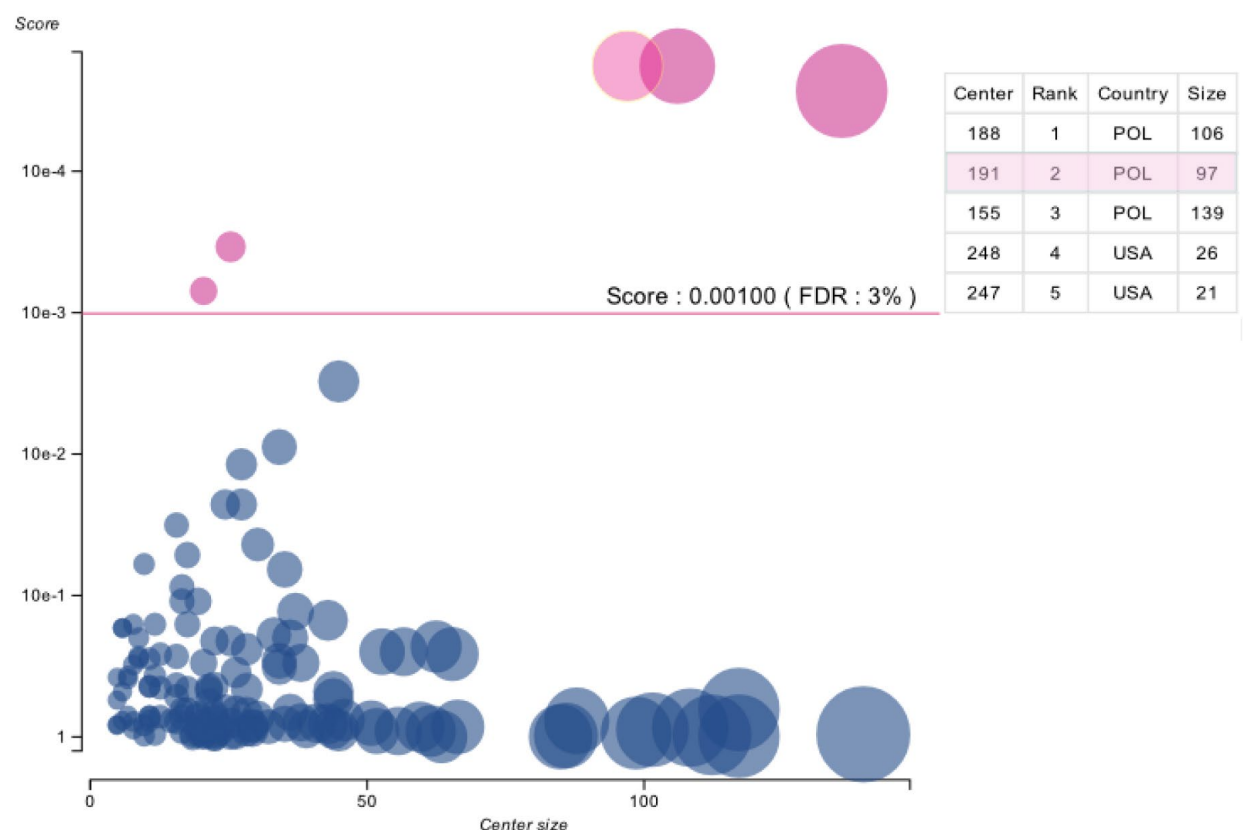


Figure 1:
Visualization of outlying centers

¹ Venet D, Doffagne E, Burzykowski T, Beckers F, Tellier Y, Genevois-Marlin E, Becker U, Bee V, Wilson V, Legrand C, Buyse M. A statistical approach to central monitoring of data quality in clinical trials. *Clinical Trials* 2012; 9: 705-713 Buyse M. Fraud detection. In: *Encyclopaedic Companion to Medical Statistics* (Everitt B, Palmer C, eds.), Arnold Publishers Ltd, London, 2010.

Desmet L, Venet D, Doffagne E, Timmermans C, Burzykowski T, Legrand C, Buyse M. Signal detection and power in central statistical monitoring of multicenter trials. Submitted, 2013.

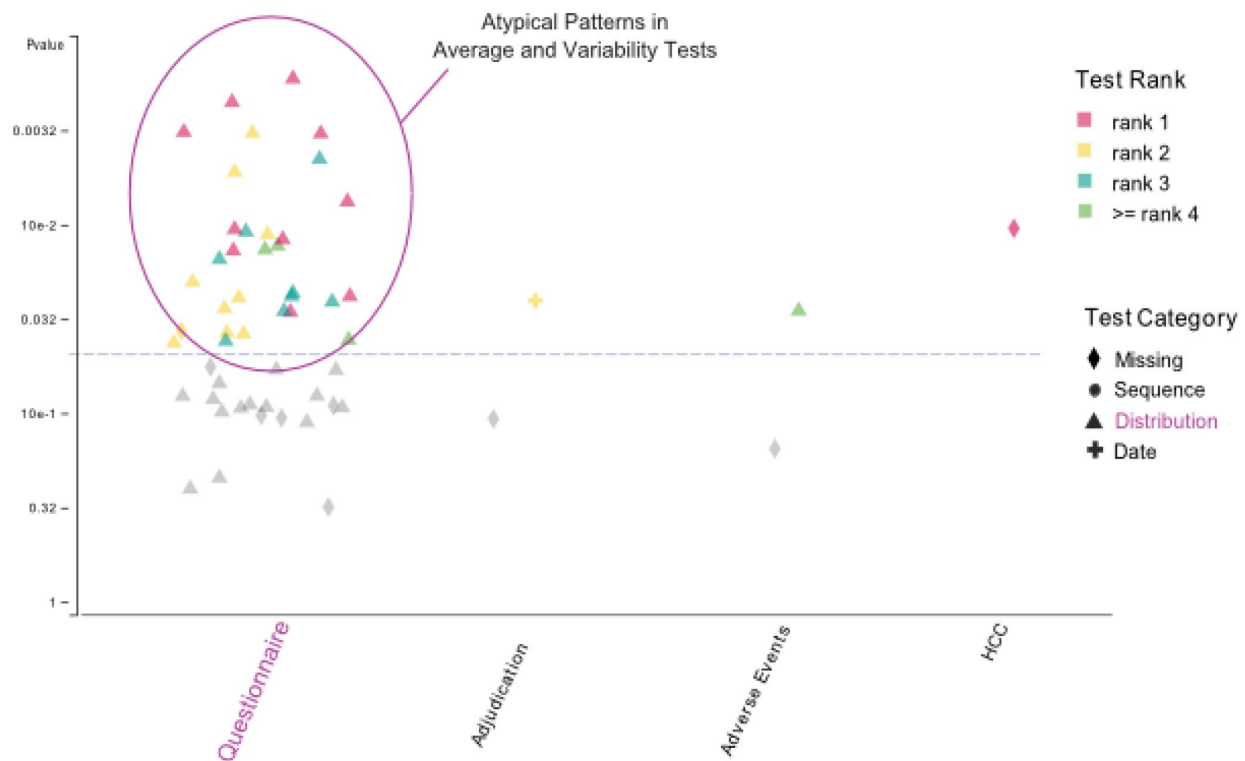


Figure 2:
Domains with significant findings for center 191

Depending on the different symbols, Figure 2 shows the category of data issues for the significant domains (that is to say the domains in which some tests generated p-values inferior or equal to 0.05; above the dashed, blue horizontal line).

The symbol's color indicates the rank (resulting from the scores) assigned to center 191 for particular tests within specific domains, comparing the results with those of other centers. This confirms the data suspicions around center 191 due to a problem with the patient diaries in the questionnaire domain.

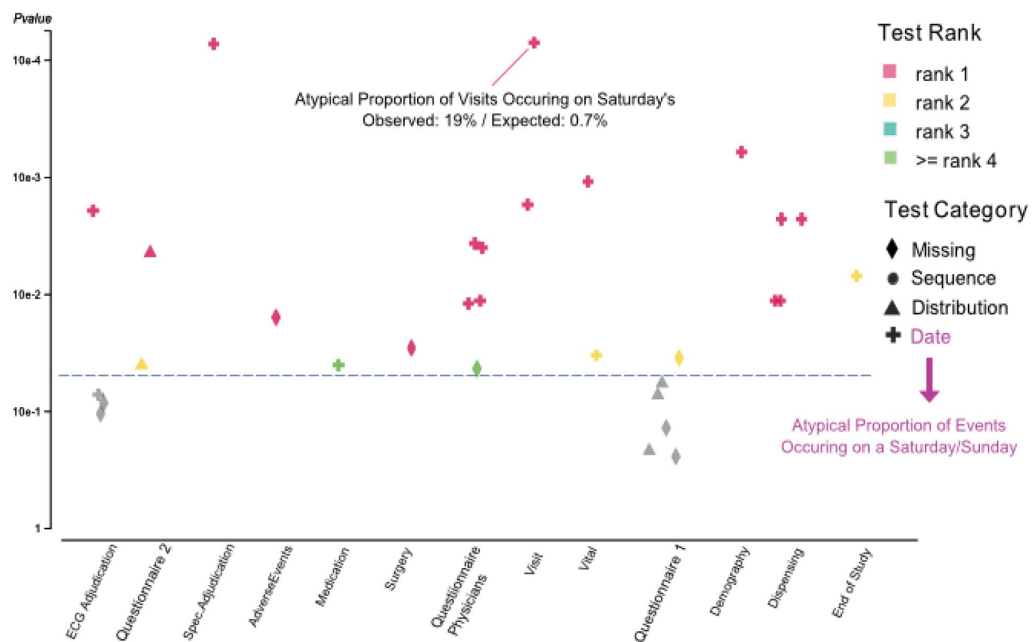


Figure 3:
Domains with significant findings for center 188

Center 188 was ranked 1 which was a particularly surprising result as the sponsor did not suspect this center to be outlying. Figure 3 indicates that several domains presented significant date related issues, with the proportion of Saturdays and/or Sundays being unusually high for the records within these domains.

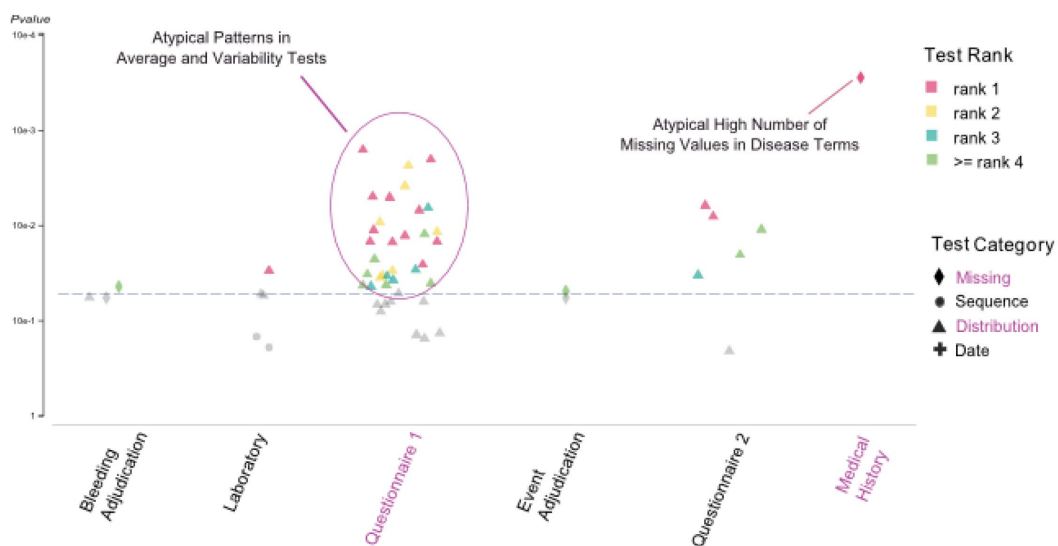


Figure 4:
Domains with significant findings for center 155

CluePoints also spotted unexpected data issues for center 155 (rank 3) related to distribution tests in the questionnaire domain (Figure 4). Hence the quality of this center's data was also compromised from issues associated with patient diaries. The distribution tests can reveal atypical mean, higher proportion of outliers and/or low variability among the values.

Conclusion

CluePoints was able to confirm a known fraud, as well as to suggest other data issues in this completed trial, as a result of its unique ability to deliver relentless interrogation of data, while requiring minimal work from the study team. Had CluePoints been used while the study was on-going, the sponsor would have been able to pinpoint the suspected issues much sooner and able to quickly target all the centers 'at risk'. However, running CluePoints after study completion can also be useful to reject certain sites from future trials. The value of using CluePoints' solution lies in its powerful and timely ability to identify anomalous data and site errors, providing the sponsor with improvements in clinical data quality, optimization of on-site monitoring, and a significant reduction in overall regulatory submission risk.

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

