Working with CluePoints to Detect Anomalies in Electronic Patient-Reported Outcomes

Case Study 5

CluePoints

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The use of electronic devices in clinical trials has grown exponentially, with a range of solutions now available to the industry that provide clever ways to optimize the collection of patient-driven eData. Offering many benefits to clinical research due to their innate ability to enhance data quality and efficiency for the collection of electronic patient reported outcomes (ePRO), while also improving data analysis and trial management, devices such as electronic patient diaries have become common practice within today's clinical trials. However, despite the clear advantages, these devices are still subject to the potential for misuse and fraudulent activity that can negatively impact the quality of the data they collate. A pharmaceutical sponsor wanted to gain an understanding of the quality of the data in a phase III trial in chronic disease. To determine the accuracy and integrity of the resulting data during study conduct, the sponsor selected CluePoints' Central Statistical Monitoring solution that helped detect fraudulent activity related to the use of electronic devices used to complete patient diaries.

Challenge

During the course of a randomized double-blind Phase III trial into chronic disease, the pharmaceutical sponsor wanted to conduct a thorough analysis of the data being generated. The placebo-controlled trial, which took place across 10 countries, involved more than 500 patients and 74 different investigative centers. The case report form (CRF) used for the 12 week study collected information on approximately 500 variables across 50 domains, on which a total of 694 tests were performed. The primary objective of the trial was to evaluate the efficacy of the drug versus placebo, with secondary objectives of evaluating the safety, tolerability, effect on quality of life and effect on symptoms of the drug versus a placebo over 12 weeks of treatment.

Safety was assessed by adverse event recordings, clinical laboratory tests, physical examination, ECG recordings, vital sign measurements, concomitant therapy recordings, and regular safety reviews. In addition, ePRO data was collated through the use of electronic patient diaries. In this trial, the sponsor was looking for an objective and independent evaluation of the data being produced that would help identify any erroneous results that could impact the overall quality of the study and, ultimately, the future regulatory submission.

The CluePoints Solution

To provide comprehensive analyses of data in the trial, the sponsor implemented CluePoints to evaluate consistency across all 74 centers involved. 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 centers, and if they are not, identifies those centers that differ substantially from the others.

Results

Approximately 33,000 p-values (a single p-value being the probability of an observed result arising by chance) were generated by the SMART engine for this trial. The CluePoints scoring algorithm summarizes the information from all tests performed and assigns a summary indicator or Data Inconsistency Score (DIS) to all investigative centers. The distribution of these scores is shown in Figure 1. It is clear that amongst the anomalous centers located at the top of the graph, Center 18 has the lowest score and is therefore ranked first.

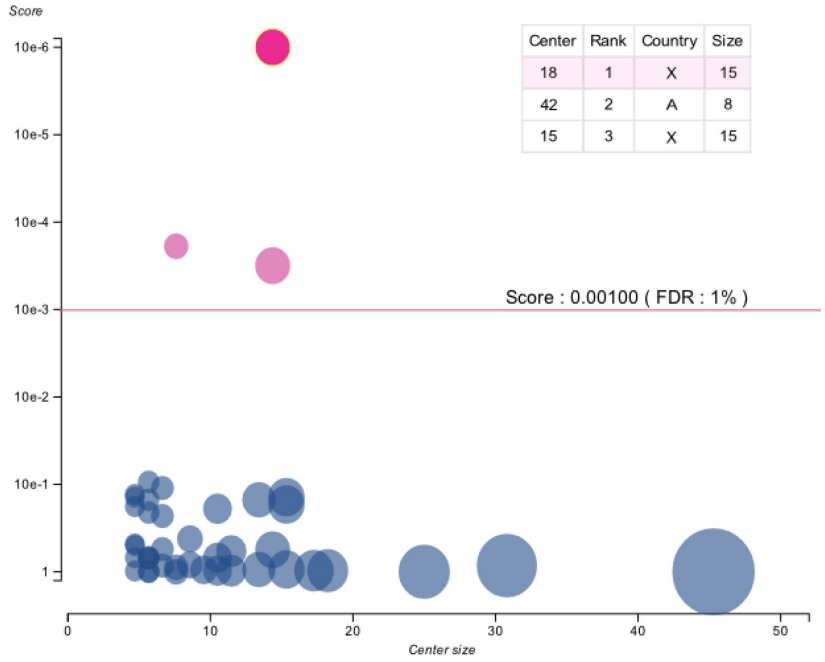


Figure 1:
Bubble Plot showing the distribution of Data Inconsistency Scores

Through examining the data issues detected at Center 18, concern was raised about the presence of abnormal patterns in the entry times recorded across three electronic daily diaries. More specifically, the times observed for the patients in Center 18 seemed to be strongly concentrated around 6pm. This marked a striking difference when compared to the varying times recorded in all other study centers. Figure 2, Figure 3 and Figure 4 show the hours of the patients' data entry times for the three diaries.

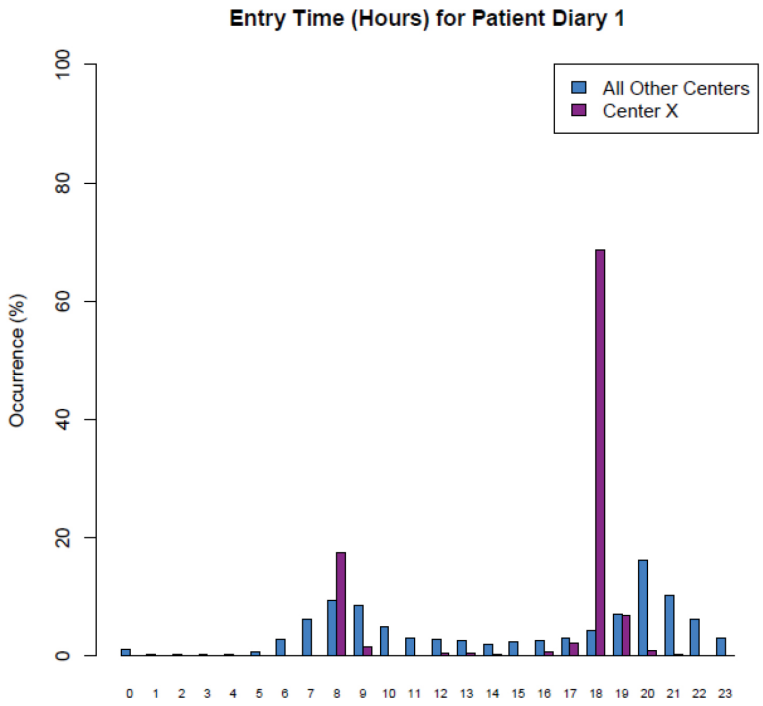


Figure 2:
Entry time for patient diary 1

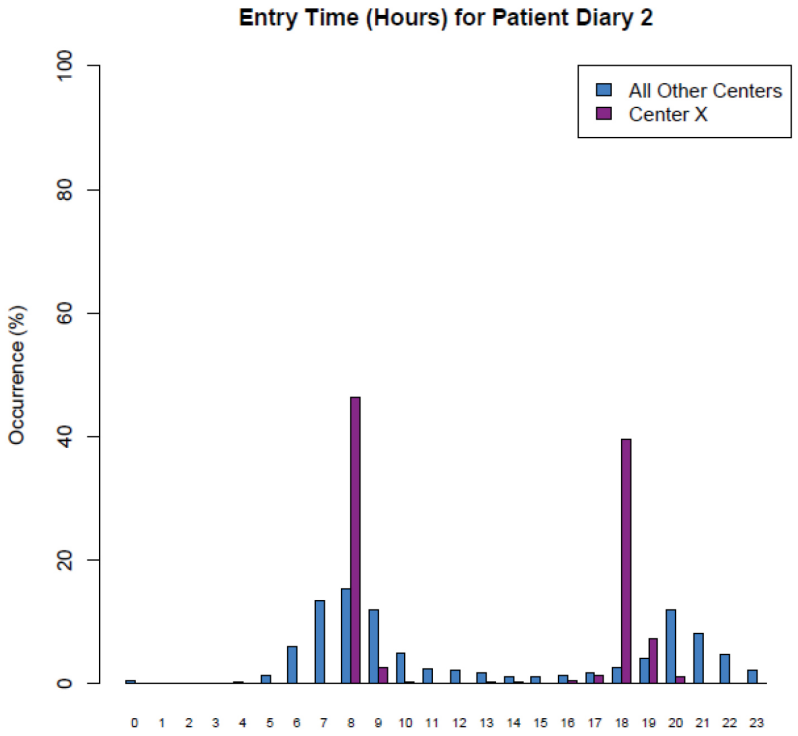


Figure 3:
Entry time for patient diary 2

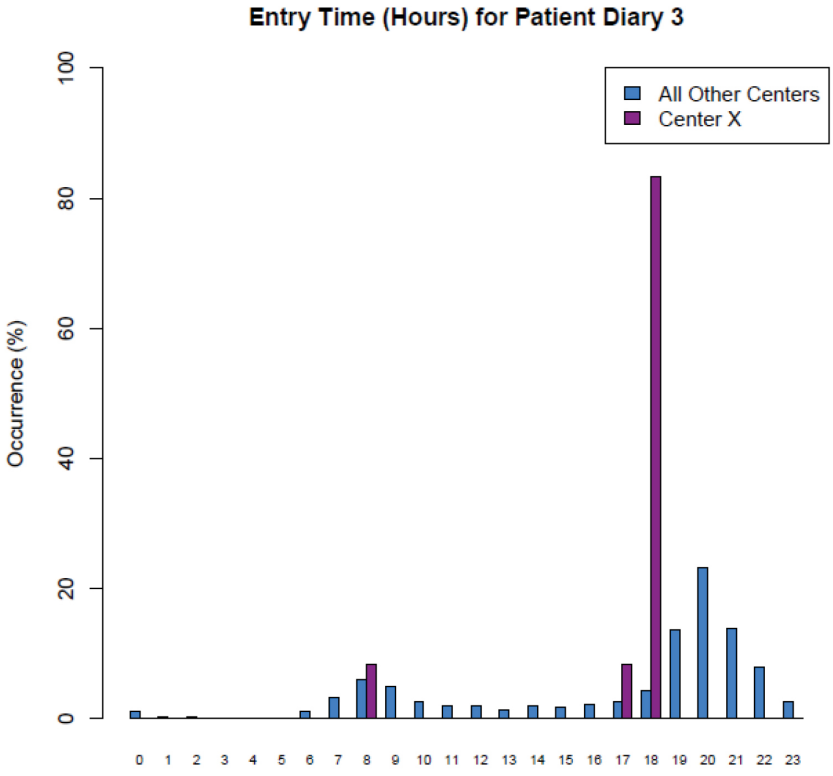


Figure 4:
Entry time for patient diary 3

The bars in magenta correspond to the entry time hours of the patients in Center 18. The blue bars correspond to the hours observed in all other centers. It is clear that across all other study centers, aside from some small peaks in the morning and in the evening, the observed entry times are diverse and spread out. In contrast, the time at which the data was entered by the patients of Center 18 is clearly concentrated around 6pm, and to a lesser extent, around 8am. Following discussion with the sponsor, this concentration of entry times could however be explained by the devices' alarm clock being equally pre-programmed across all patients in this center.

To investigate the electronic patient-reported outcomes more extensively, CluePoints performed additional tests specifically designed to assess the correlation between entry times recorded on the same day. These tests not only confirmed Center 18 as being anomalous regarding the entry times, but also detected an additional center with ePRO issues.

The CluePoints solution revealed a center (Center 83) for which the data entry of different patients took place on approximately all the same days, and, more specifically, on successive time points with only seconds or minutes in between.

For every day on which data entry was observed, the different data entry time points across the four patients in Center 83 are shown in Figure 5.

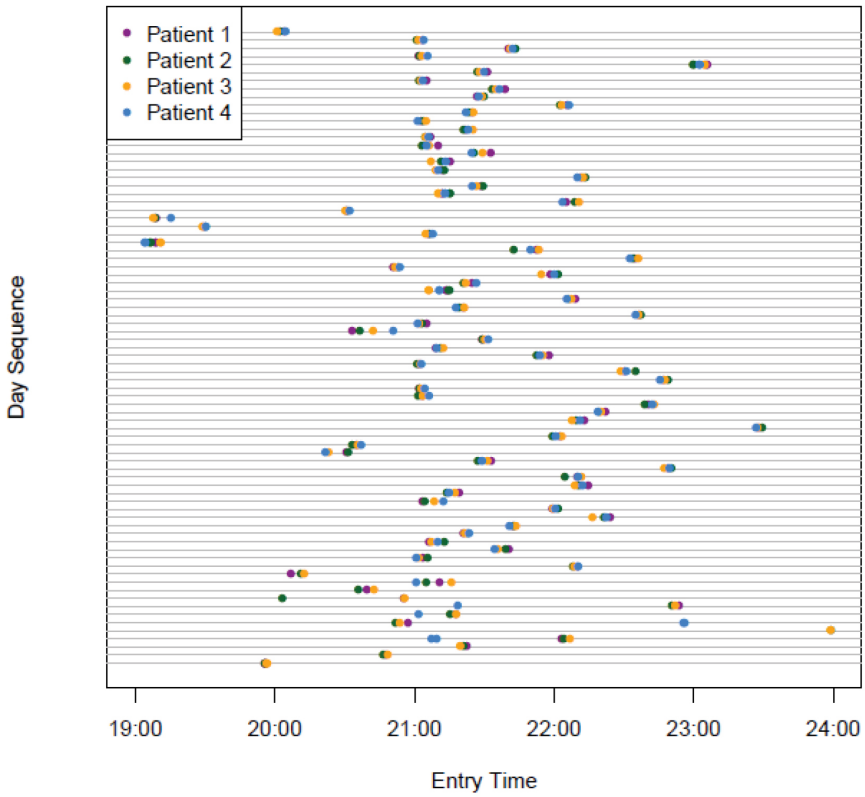


Figure 5:
Data entry time points across the four patients in Center 83

It is clear that the data entry occurred on the same days across all patients and is concentrated between 8pm and 11pm. Most significantly, for all days the times of data entry for the four patients are consecutive with only a short period in between. For comparison purposes, Figure 6 shows the graph for a center with a normal tendency of patient diary data entry.

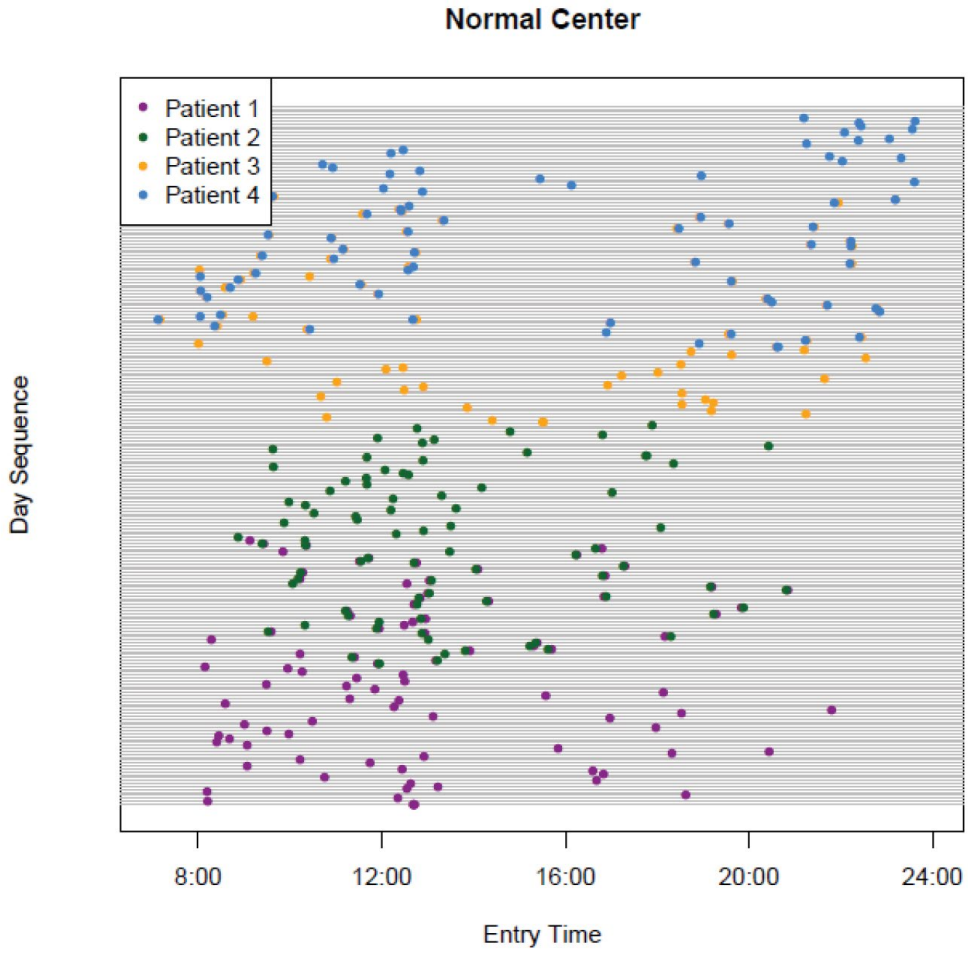


Figure 6:
Graph showing a center with a normal tendency of diary data entry

Conclusion

Deeper research at the center which CluePoints identified to be at risk suggested that the diaries were not completed by the true patients, but one after another by the site investigator himself. Based on the findings of the CluePoints solution, the pharmaceutical sponsor decided to exclude the fraudulent investigative center from the remainder of the study to ensure the validity and the quality of the clinical trial data was preserved. In this trial, the SMART engine's use of complex statistical algorithms allowed the sponsor to drill down into individual patient data to better manage risk and determine the variations between centers in order to identify the outlier. This ability to identify centers that are at risk or demonstrate errant results enables resources to be deployed as needed, or, as in this instance, certain investigative centers to be completely excluded from future trials. As a result, sponsors are not only able to improve results throughout a trial, but can reduce regulatory submission risk by providing the best quality data set possible.

Trial Information

Indication: Chronic Disease
Centers: 74
Patients: 500+
Variables: 500
Domains: 50
Countries: 10
P-Values: Approximately 33,000 p-values


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