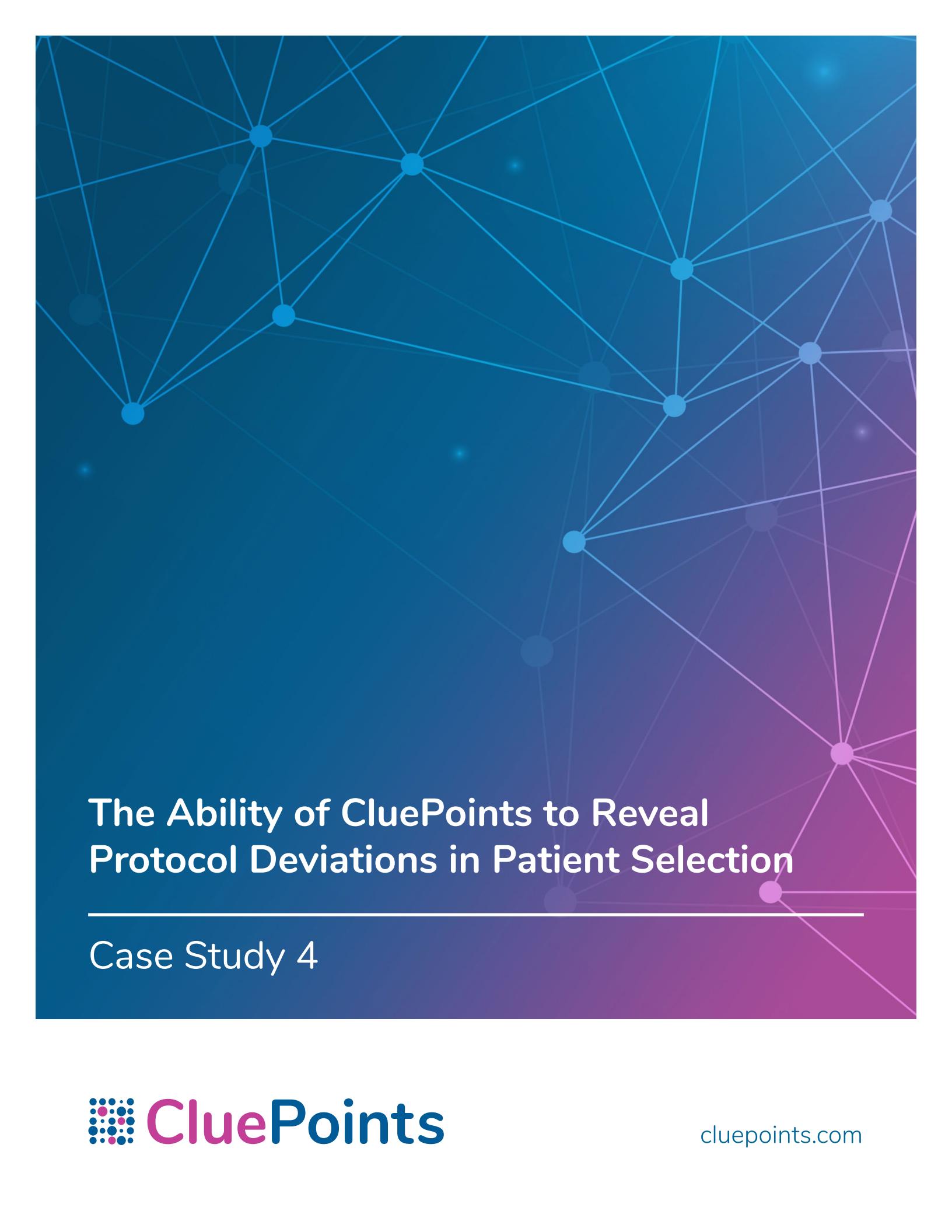




The Ability of CluePoints to Reveal Protocol Deviations in Patient Selection

Case Study 4

Index

Challenge

The CluePoints Solution

Results

Conclusion

Trial Information

The Ability of CluePoints to Reveal Protocol Deviations in Patient Selection

Every clinical trial protocol requires a set of criteria to be developed that describes the types of patients who are eligible to take part in the research, with the aim of creating a desired population from which study data can be collected. Patients are included in a trial only when they have satisfied a set of inclusion and exclusion standards based on the research objectives of a particular study and covering factors such as age, disease stage, gender and treatment history. These eligibility standards are put in place to ensure that new approaches are tested on similar groups of people, so that it is clear to which groups a clinical trial's results apply. If the specified selection criteria are not strictly adhered to, the resulting data will be unreliable and less generalizable due to the variation in the characteristics of the selected patients. During a phase III trial in cardiovascular disease, a pharmaceutical sponsor requested a data analysis using the CluePoints Central Statistical Monitoring solution. The use of the solution resulted in the identification of an investigative center with highly abnormal data patterns concerning patient selection and treatment discontinuation.

Challenge

In the middle of a phase III trial in cardiovascular disease, the pharmaceutical sponsor requested a comprehensive analysis of the research data that had been generated to date. The trial involved over 19,000 patients across 1,139 investigative centers in 25 countries, with the objective of demonstrating the efficacy of a drug in reducing cardiovascular mortality or non-fatal myocardial infarction. Information on more than 1,000 variables across 43 domains was collected during the course of the study using a single case report form (CRF), on which a total of 997 tests were performed. The sponsor wanted to gain a complete understanding of the quality of the data being collected, so any issues or concerns could be addressed while the trial was on-going. It was anticipated that this would not only serve to verify the integrity of the data, but would also help minimize the risk associated with the future regulatory submission.

The CluePoints Solution

To deliver an in-depth interrogation of the research data, the sponsor selected to implement the CluePoints solution that would provide a detailed indication of the quality of the data collected. 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 others.

Results

For this particular trial 997 tests were carried out on 836 scored centers and 833,492 potential p-values (a single p-value being the probability of an observed result arising by chance) were generated by the SMART engine. The CluePoints scoring algorithm summarizes the information from all tests performed and assigns a summary indicator or Data Inconsistency Score (DIS) to all centers. The distribution of these scores and sizes of the centers are represented in Figure 1.

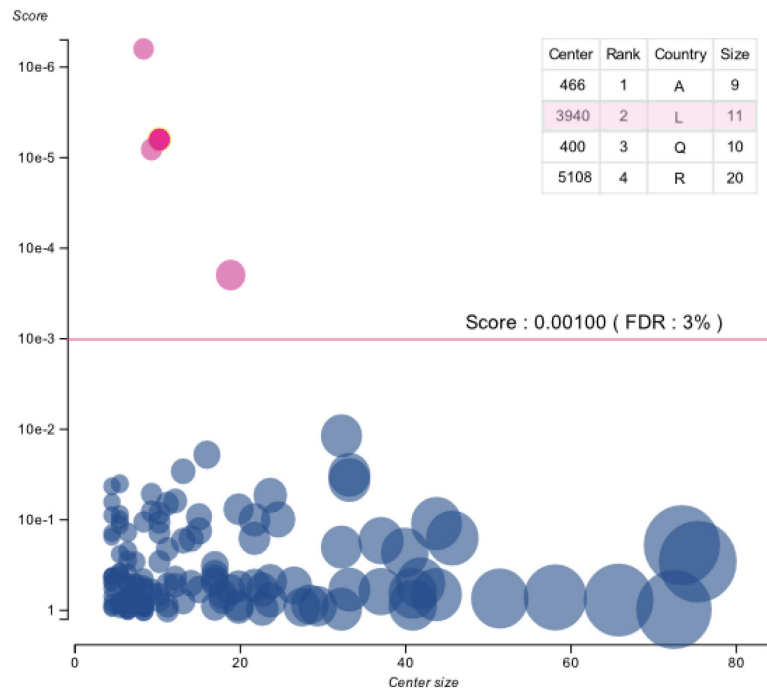


Figure 1:
Distribution of Data Inconsistency Scores (DIS) and center sizes

Amongst the study sites with the lowest DIS, Center 3940 was ranked second and, therefore, was identified as an ‘at risk’ center. Further investigation into the details of the findings revealed severe protocol deviations in patient selection and an abnormally high incidence of treatment discontinuation amongst the patients in this center. An overview of the results for Center 3940 is provided in the Center Profile Plot in Figure 2.

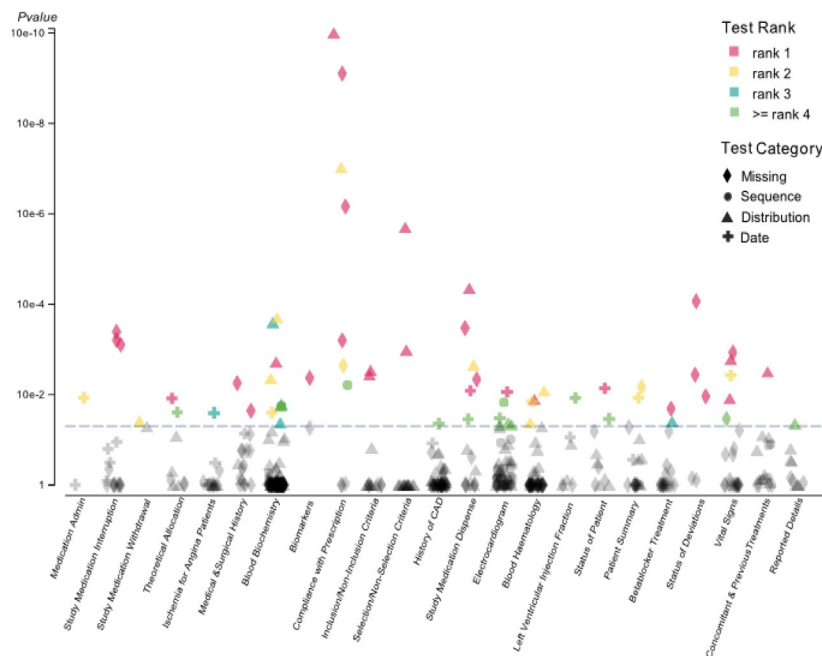


Figure 2:
Center Profile Plot for Center 3940

The Center Profile Plot visualizes all the individual tests performed for one specific center, with tests grouped by the different domains present. The category and rank for every test is indicated. The rank of a center for a specific test is assigned by ranking the p-values observed for that test across all sites in the study. A center's test results for a specific domain are only included in its Center Profile plot if at least one significant test in the domain is present.

The group of findings indicated in Figure 3 relates to the domains including information on inclusion and exclusion criteria.

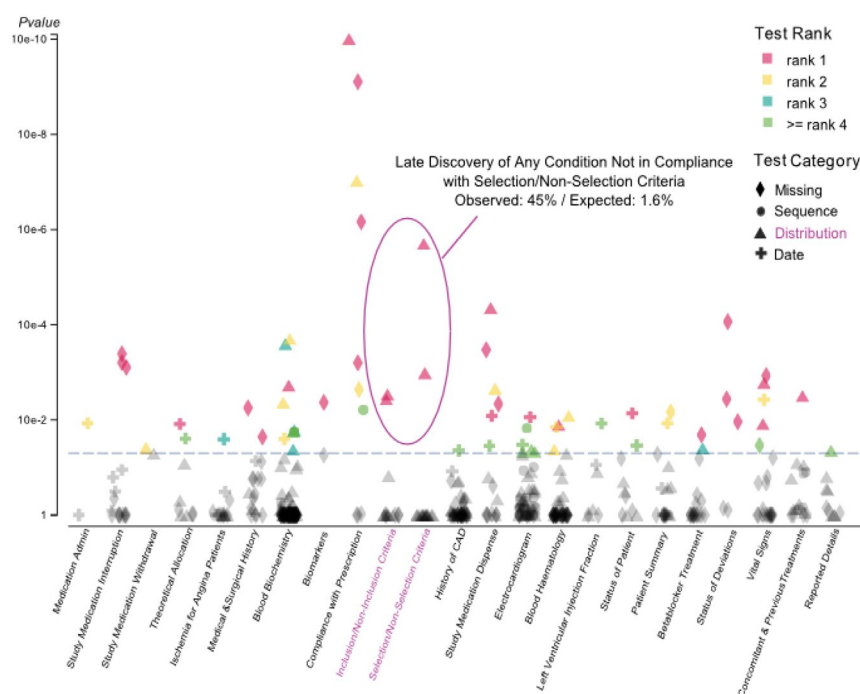


Figure 3:
Domain findings are highlighted relating to inclusion and exclusion criteria

It was revealed that after randomization, 45% of the patients in Center 3940 were not in compliance with the trial's protocol instructions on the selection and/or non-selection of patients. As indicated in Figure 3, the expected occurrence across patients of such protocol deviations is only 1.6%. In Center 3940 only 36% of the randomized patients showed evidence of coronary artery disease (CAD) although this was a necessary criterion for the patients to be included in the trial. Also, the protocol stated that patients with an implanted cardiac device could not be selected. However, for two of the 11 patients (18%) in Center 3940, the presence of such a device was reported.

Due to the incorrect selection of patients, the findings indicated that the presence of treatment interruption and treatment discontinuation was highly prevalent in Center 3940. This was concluded from the tests highlighted in Figure 4, which reported abnormally high numbers of observations in the domain on medication discontinuation. Through the analysis it was found that the occurrence of comments reporting a reason of treatment discontinuation was 10 times greater across the patients in Center 3940 than expected.

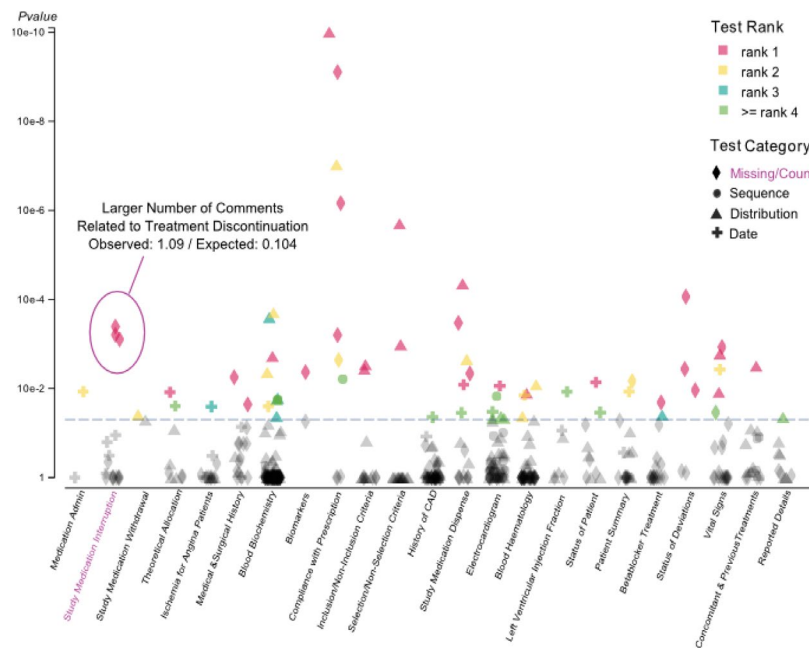


Figure 4:
Tests on Center 3940 indicated a larger number of comments related to treatment discontinuation

Multiple anomalies were also detected at the center regarding prescription compliance and study medication dispense (see tests indicated in Figure 5).

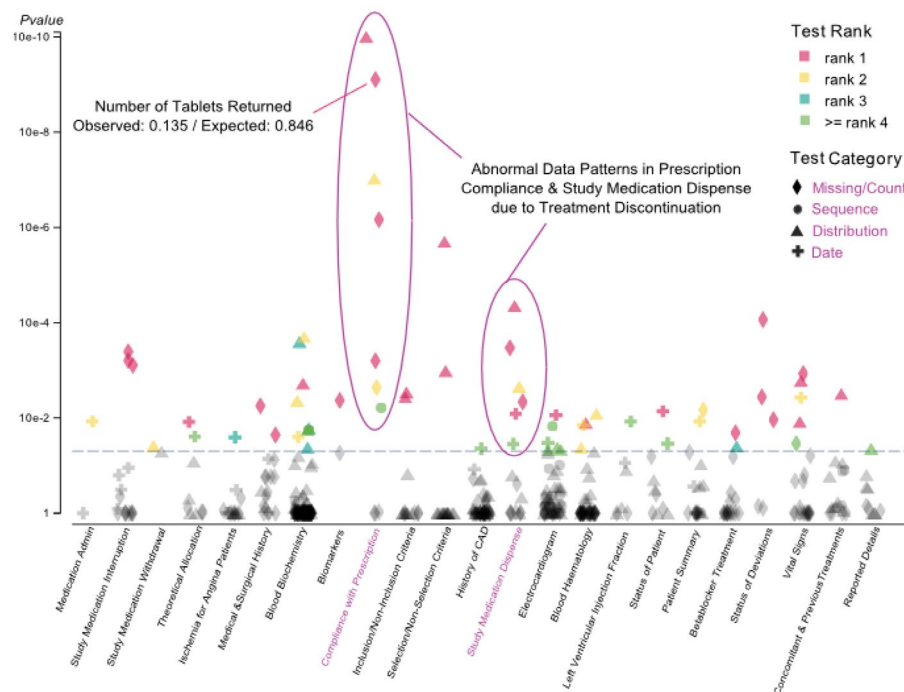


Figure 5:
Detected anomalies regarding prescription compliance and study medication dispense

During the course of the trial it was noted that very little information was collected on medication return. Therefore, it could be concluded that all inconsistencies observed in these domains resulted from the abnormal tendency of treatment discontinuation across the patients in Center 3940.

Conclusion

Based on the results from the analysis, the pharmaceutical sponsor scheduled a target review of the abnormal data patterns detected. The intervention of the solution in this on-going clinical trial was highly valuable as the additional monitoring and auditing at Center 3940 ensured full protocol compliance in the remainder of the research and, consequently, resulted in the generation of valid clinical trial data. Using intelligent statistical techniques in this trial demonstrates CluePoints' strengths in providing detailed interrogation of large and complex data sets. As a result, the solution provides sponsors with an objective assessment of the quality of their clinical research data, allowing them to make accurate and timely decisions about the future conduct of the study and, ultimately, produce an error-free regulatory submission.

Trial Information

Indication: Cardiovascular Disease

Centers: 1,139

Patients: 19,000

Variables: 1,000

Domains: 43

Countries: 25

P-Values: 833,492

