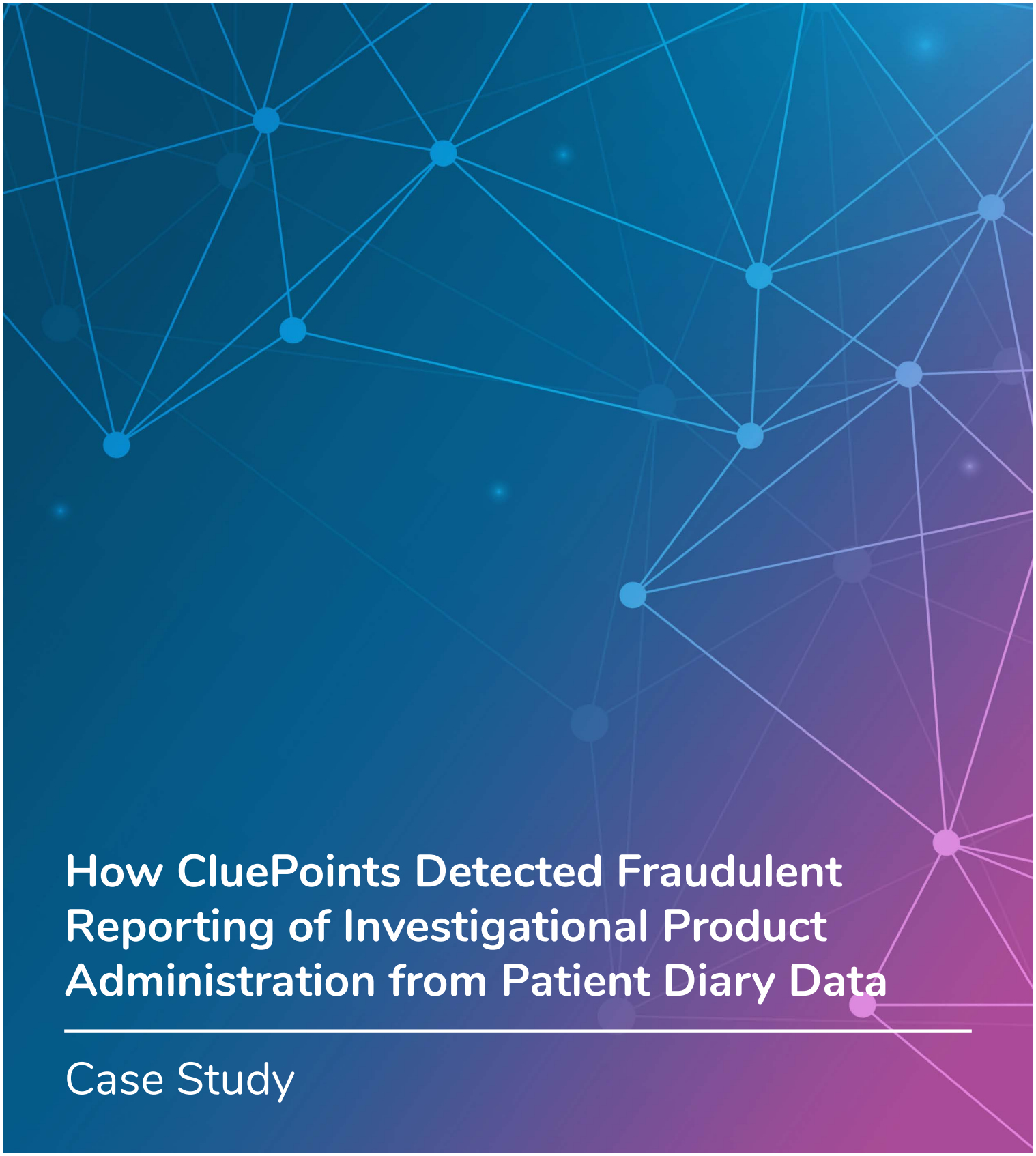


How CluePoints Detected Fraudulent Reporting of Investigational Product Administration from Patient Diary Data

Case Study

CluePoints

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How CluePoints Detected Fraudulent Reporting of Investigational Product Administration from Patient Diary Data

Patient diaries are increasingly used in clinical trials to capture information such as outcomes or treatment intake directly from the patients. A pharmaceutical company was conducting a large phase III cardiovascular trial where information about Investigational Product administration by patients was collected at the sites before randomisation and through patient diaries after randomisation. The Sponsor was looking for a fast and efficient solution to detect potential issues at the study sites and in patient data. CluePoints was chosen to perform an overall data quality assessment of their data throughout the course of the trial.

Challenge

A pharmaceutical company was conducting a randomized, double-blind, placebo-controlled, parallel-group phase III cardiovascular study involving ~30,000 randomized patients across ~1,300 sites. The study was designed so that every patient goes through two periods (Figure 1)

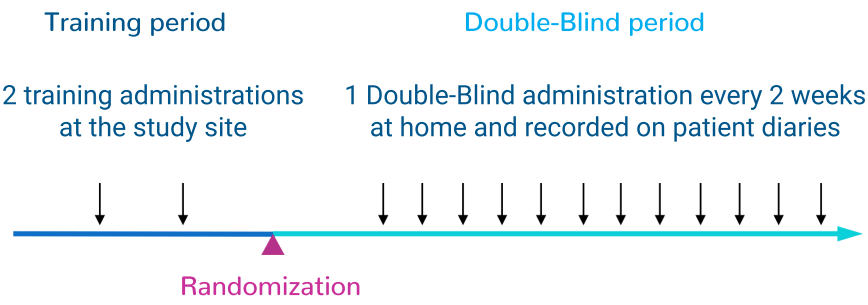


Figure 1: Study design

Prior to randomization, the patients were trained to self-administer the Investigational Product (IP) by twice injecting themselves with a placebo under the Investigator's surveillance (product administration training). After randomization, IP was to be self-administered by the patients every two weeks and the administration had to be reported via the patient diary (Double-Blind administration). The Investigator was then responsible for completing a treatment log based on the patient's diary responses. Data from the treatment logs were eventually entered in the eCRF by the Investigator or the Study Coordinator. Since the same Protocol and eCRF were used across all study sites, a Central Statistical Monitoring approach was an ideal data interrogation tool.

The CluePoints Solution

Aligned with FDA, EMA and ICH E6 guidance documents, CluePoints' Central Monitoring Platform employs a set of unique statistical algorithms to support a Risk-Based Monitoring strategy. The algorithms are clustered within the SMART™ Engine, a powerful software product that evaluates how the data from every centre or patient differs from the data across all centres / patients and identifies those centres that differ substantially. In this trial, an overall assessment of the quality of the whole clinical database was scheduled to be evaluated by CluePoints every quarter throughout the course of the trial.

Results

A total of 989,272 individual test scores were produced after analysing all clinical and operational variables using the SMART™ Engine. Since the Sponsor was interested in knowing whether some centres display atypical patterns of IP administration, CluePoints also derived for each centre the time intervals between the patients' successive Double-Blind injections of IP. This variable was included in the analysis and the SMART™ Engine was used to compare the variability of those intervals in every centre with the overall variability across all centres.

Every centre's individual test scores were aggregated in a summary indicator called the Data Inconsistency Score (DIS) (Figure 2). The higher the DIS for a particular centre, the more statistically different the site is.

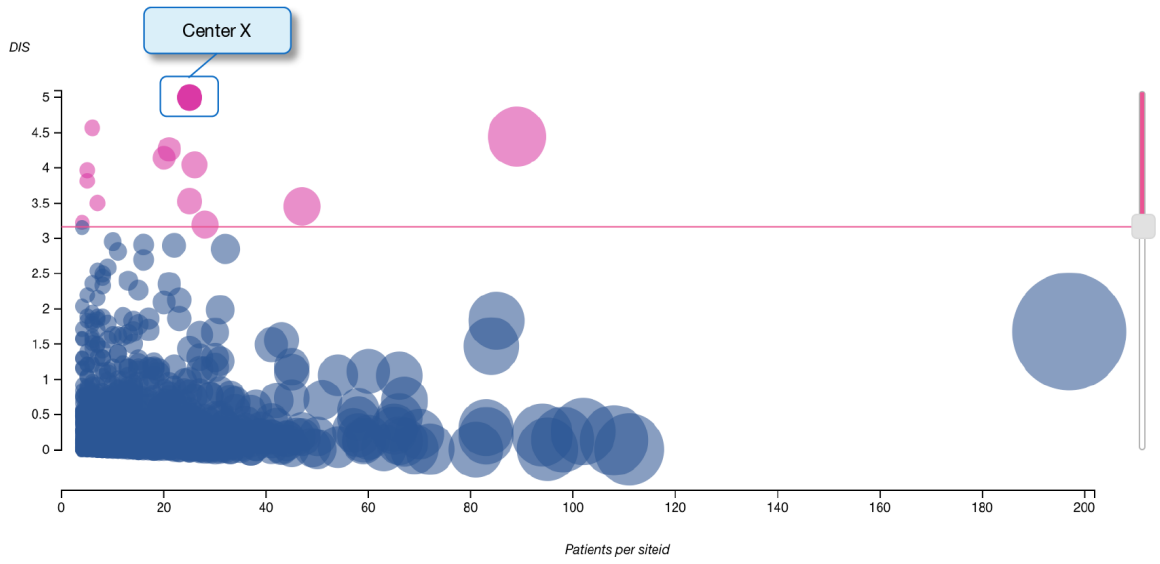


Figure 2:
Bubble Plot showing the centres' DISs (Y-axis) and sizes (Xaxis). All outlying centres are highlighted in magenta.

Centre X was the most outlying centre with the highest DIS. Among Centre X's significant test scores, one revealed that the time intervals between patients' successive Double-Blind injections of IP were ~11.6 times less variable than expected (0.00184 observed vs. 0.0213 expected; Figure 3). Indeed, even though the Protocol states that the IP must be selfadministered every fourteen days during the Double-Blind period, a natural variation in the interval from one injection to the next is expected. Centre X is ranked 12 for this test, meaning it has got the 12th most outlying result of all centres.

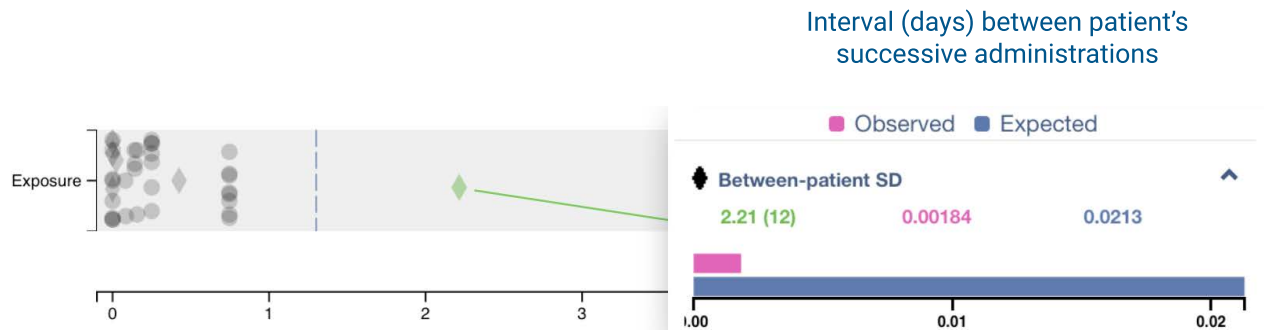


Figure 3:
Centre X's results for the variability of time intervals between patients' successive Double-Blind IP injections. Centre X's observed variability (in magenta) is lower than the expected variability (in blue).

Figure 4 presents the injection profiles of Center X's patients who received at least one Double-Blind IP injection.

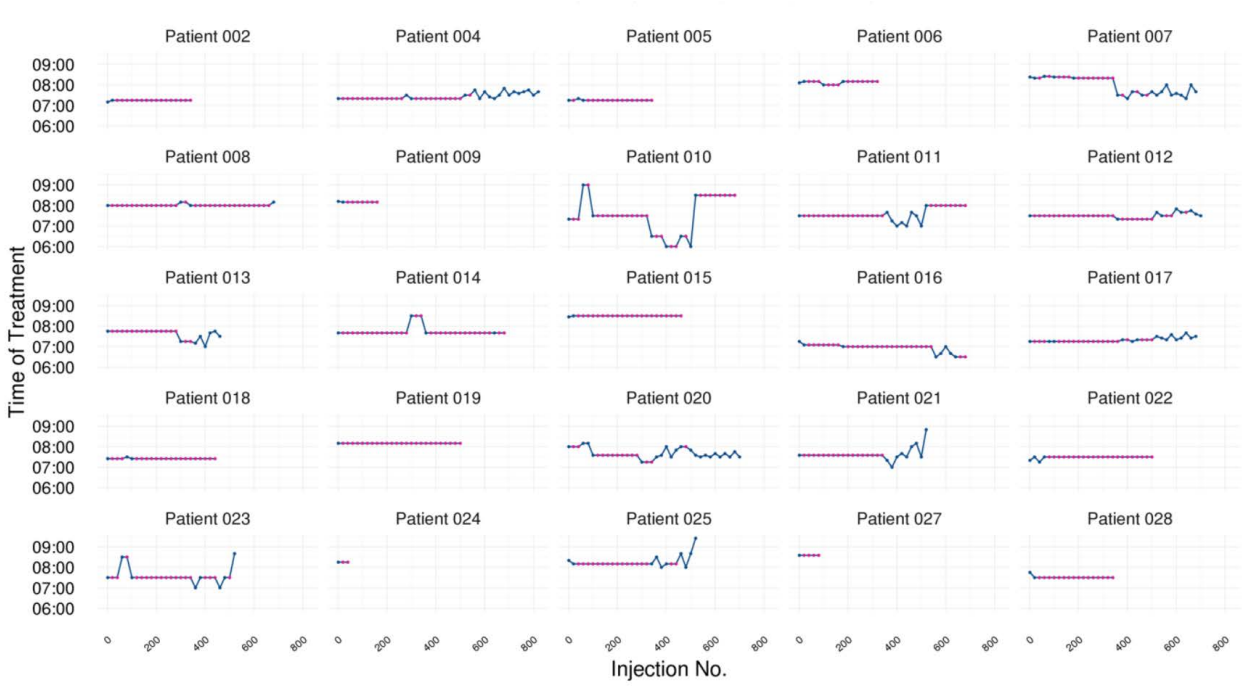


Figure 4:
Times (Y-axis) of successive Double-Blind IP injections (Xaxis) recorded in Centre X, per patient. Injections that take place exactly 14 days to the minute after the patient's previous administration are highlighted in magenta.

From Figure 4 it is clear that Centre X displays an excessive number of injections performed exactly 14 days – to the hour and minute – after the patient's previous injection. Such a high regularity in the data is highly unlikely, which suggests that those data might have been altered or that the patients were not properly trained about the importance of accuracy in IP administration reporting. This conspicuous finding triggered an action on behalf of the Sponsor to check that the instructions about IP administration were properly followed at Centre X.

Interestingly, the SMART™ Engine detected the same kind of finding – a significantly low variability in the time intervals between the patients' successive Double-Blind IP injections – in 30 other centres, which represents 2.5% of all the centres that reported at least one Double-Blind IP injection.

The Sponsor was delighted that an independent analysis supported their initial suspicion and Centre X was subsequently terminated due to study misconduct; upon further investigation by the local monitors several patients appeared to have received training injections at the site at exactly the same times as each other, which confirmed the falsification of training IP injection data.

Consequently, the Sponsor wished to assess whether the training of IP injections was properly undertaken and followed the Protocol at the other study sites too (Figure 1). CluePoints, therefore, conducted an additional analysis of the eCRF data related specifically to IP administration training. The gaps between every pair of successive placebo intakes (regardless of which patient they were administered to) were examined in turn in every centre. This allowed CluePoints to classify an intake as either:

a) performed within a fairly long period that allows the Investigator to effectively supervise the patients' training; or

b) executed too close in time to another placebo intake recorded in the centre, with the extreme case of some intakes being recorded as performed at exactly the same time by the same Investigator.

The SMART™ Engine was used to compare every centre's proportion of IP training injections where the proximity was too close with the overall study proportion.

44 centres (3.3% of the centres where training was dispensed at least once) presented a significantly high proportion of training IP injections that were too close in time across patients. Strikingly, Centre X had the most outlying score for this test. Upon investigation of the patient-level data from the eCRF by CluePoints, it was shown that 23 out of the 53 training injections performed in Centre X took place within too short a period following the preceding injection (Figure 5).

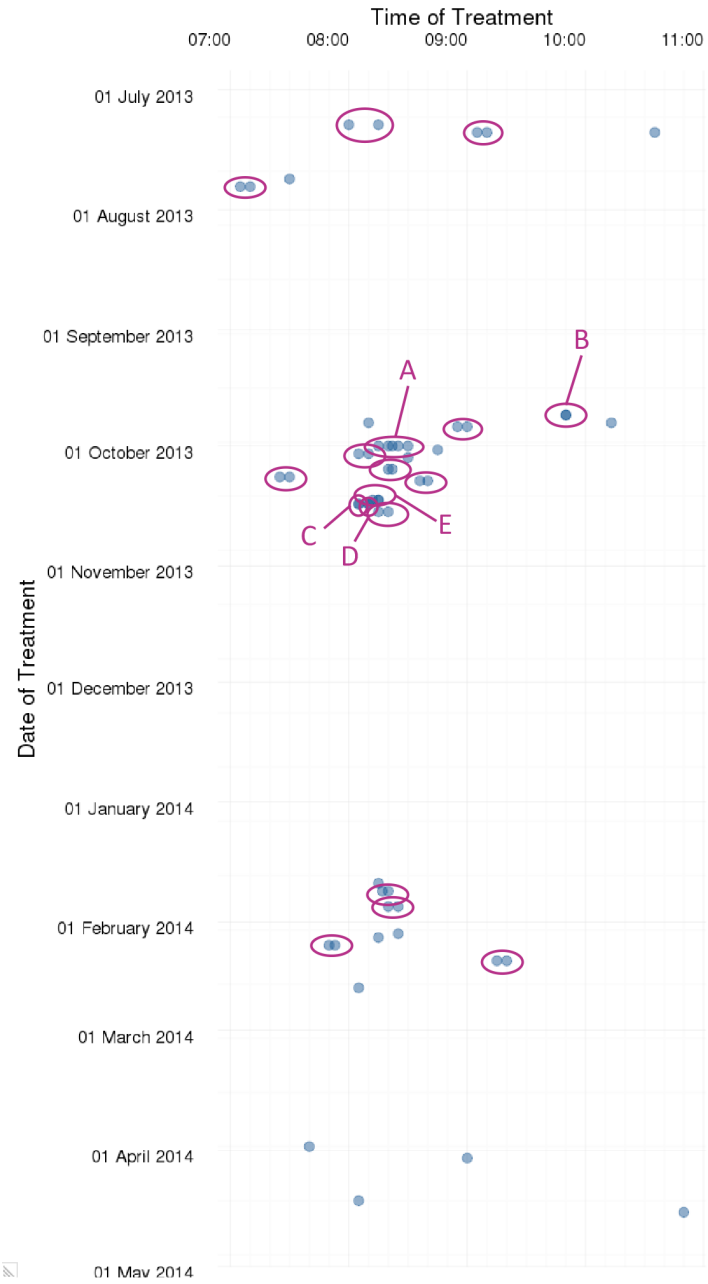


Figure5:
Training injections by date (X-axis) and time (Yaxis) in Centre X. Injections that take place too soon after the preceding one recorded in the centre are circled in magenta.

For instance, five of this Centre X's patients (Patients 012, 013, 014, 015 and 016) were each administered an injection during a 15-minute time frame (Figure 5, circle A). Even more unlikely, four pairs of patients received injections at exactly the same hour and minute: 006 and 007; 014 and 016; 012 and 015; 017 and 019 (Figure 5, circles B-E).

Conclusion

Reporting of IP administration is a crucial aspect of a trial conduct, and patient diaries used for assessing treatment compliance are at greater risk of falsification. Even though audit details were not provided, the eCRF data was exploited by CluePoints to confirm fraud in the IP administration data of a centre that was subsequently closed by the Sponsor. This allowed the sponsor to use an independent and unsupervised body of evidence to submit to regulators as the reason for excluding that site's data. CluePoints also brought to light atypical patterns in the IP administration data of other centres that would certainly benefit from additional monitoring by the Sponsor. In addition, CluePoints suggested data issues in other domains critical for patient safety and study conduct in several centres and throughout the course of the trial. The value of the CluePoints solution lies in its powerful and timely ability to identify inconsistent data and sites, allowing the Sponsor to improve data quality and optimize on-site monitoring.

Trial Information

Indication: Cardiovascular Disease
Centers: 1,300
Patients: 30,000+
Variables: 11,000
Domains: 30
Countries: 60
Individual Test Scores: ~990,000


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