

#PP01. Central Statistical Monitoring

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Background

As required by regulators, sponsors should ensure that trials are adequately monitored. Both the FDA and EMA have embraced a Risk-Based Monitoring approach. ICH GCP E6 (R2) recommends employing a combination of on-site and centralised monitoring, which includes the use of statistical analyses to identify trends in the data (e.g. consistency within and between sites).

Covance has recently developed a new data analytics tool to perform Central Statistical Monitoring that is part of the Xcellerate® suite, Xcellerate® Statistical Review.

Data from a Phase III, multicentre, randomised, double-blind study was analysed using Xcellerate® Statistical Review. At the time of the analysis, several hundred patients had been randomised from close to 100 sites and completed an average of 3 post-randomisation visits.

Methodology

Xcellerate® Statistical Review uses a statistical approach to centralised monitoring to identify sites that are different from other sites. This is based on the combination of p-values from a large number of statistical tests performed on the clinical data, comparing the distribution of variables for each site compared to all other sites.

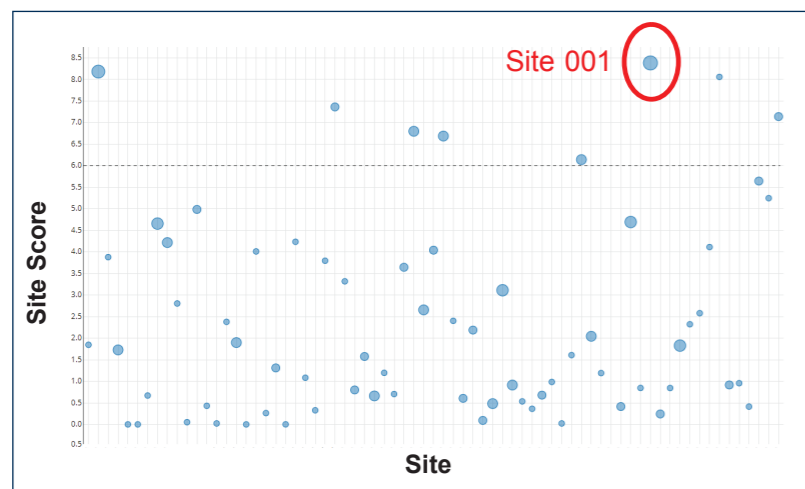
A site score is calculated for each site by taking the negative log (base 10) of the smallest p-value for a site following adjustment for multiplicity using Benjamini-Hochberg methodology.

The higher the site score the more different that site is from the other sites.

Central Statistical Monitoring was performed by reviewing automated visualisations based on a real-time snapshot of data.

Step 1 – Identify Sites with a High Site Scores

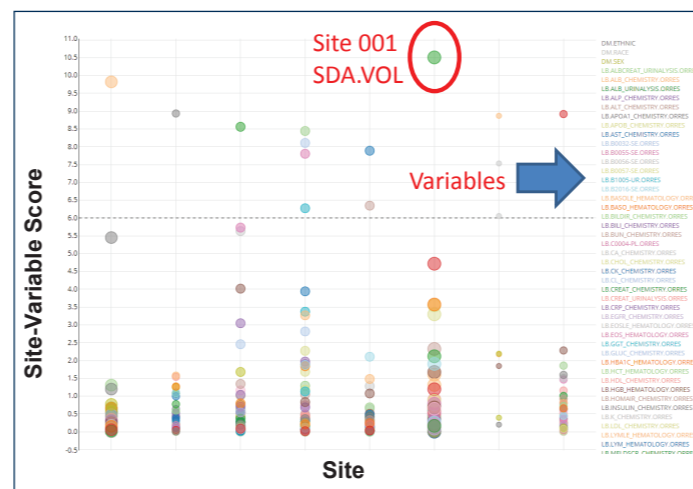
The first step identified sites with a site score above the pre-defined threshold. Each bubble in the site-score plot represents a site. The size of the bubble represents the number of patients.



As shown above, 8 sites were identified with a site score above the pre-defined threshold of 6, which indicates a false positive rate of 1 in a million. Site 001 was the highest scoring site with a site score of 8.4.

Step 2 – Identify Influential Variables

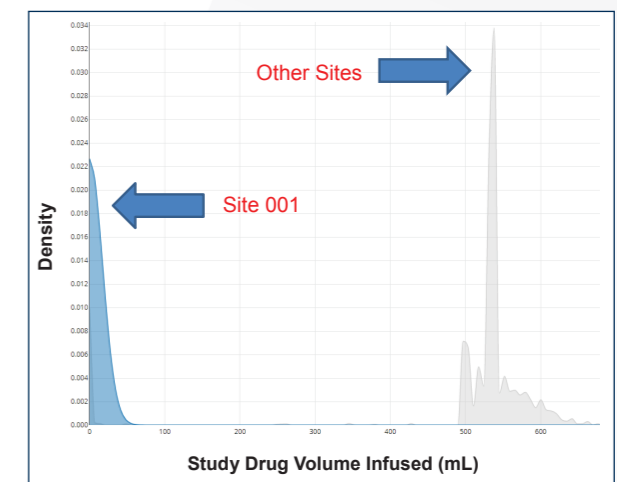
In the second step, variables that contribute most to the high site score were identified. Each bubble in the site-variable score plot represents each variable contributing to the site score.



The volume of study drug infused was the most influential variable contributing to the high site score for Site 001.

Step 3 – Explore the Site Level Data

The third step compared the distribution of the data for the most influential variables at the high scoring site compared with all the other sites.



This visualisation shows a different distribution for study drug volume infused at Site 001 (shown in blue) compared with all the other sites (shown in grey). On further inspection of the subject level data it was found that 0mL was infused for 9 patients at this site, instead of 500mL as stated in the protocol. This was a serious finding related to treatment compliance.

Other Findings

Below are examples of issues found that were flagged by the statistician and escalated to the study team for further review:

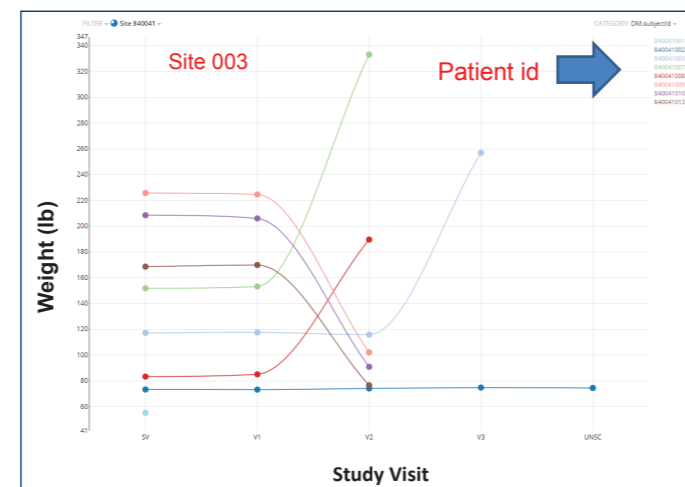
Further Site Training Required



As shown in this histogram, all patients at Site 002 reported "No" to the question about Diet and Lifestyle advice.

This finding was notified to the Project Leader early in the study. An additional monitoring visit was initiated rapidly where it was found that the site had misunderstood the importance of diet and lifestyle. Additional site training was provided and further monitoring visits were scheduled based on a targeted Risk-Based Monitoring approach.

Misreporting of Units



The subject-level data plot on the left shows values for weight recorded at each visit for patients at Site 003. Each line represents a patient.

Upon further inspection it was found that weight had been collected in inconsistent units across multiple visits for several patients. For example, weight had been recorded in both lb and kg instead of lb only. A data query was raised and the data was later corrected accordingly.

Conclusions

- Central Statistical Monitoring can help detect signals early and guide a Risk-Based Monitoring approach.
- The initial findings from this case study have shown that Xcellerate® Statistical Review can allow statisticians to easily explore the data and identify potential data issues, thereby improving data quality.
- Covance is currently assessing the effectiveness of Xcellerate® Statistical Review in a couple of pilot studies prior to large scale roll out across the business.

Acknowledgements

The author would like to express thanks to her colleagues at Covance including Adam Baumgart, Stephen Jones, Aaron MacKey, Neha Sharma and Mike Walega.