

## Central Statistical Monitoring

Tammy McIver, Covance, Maidenhead, UK

### ABSTRACT

As required by regulators, sponsors should ensure that trials are adequately monitored. 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. range and consistency within and between sites).

This paper describes a statistical approach to centralised monitoring that can be used 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. The results help to identify non-random anomalies.

Data from a case study, analysed via Xcellerate<sup>®</sup> Statistical Review, a new tool developed by Covance to perform central statistical monitoring, will be used to illustrate the applicability of this methodology in the identification of potential issues in the data.

### INTRODUCTION

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

Data from a Phase III, multicentre, randomised, double-blind study was analysed using Xcellerate<sup>®</sup> Statistical Review. At the time of the analysis, 429 patients had been randomised from 86 sites and completed an average of 3 post-randomisation visits.

### METHODOLOGY

Xcellerate<sup>®</sup> 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.

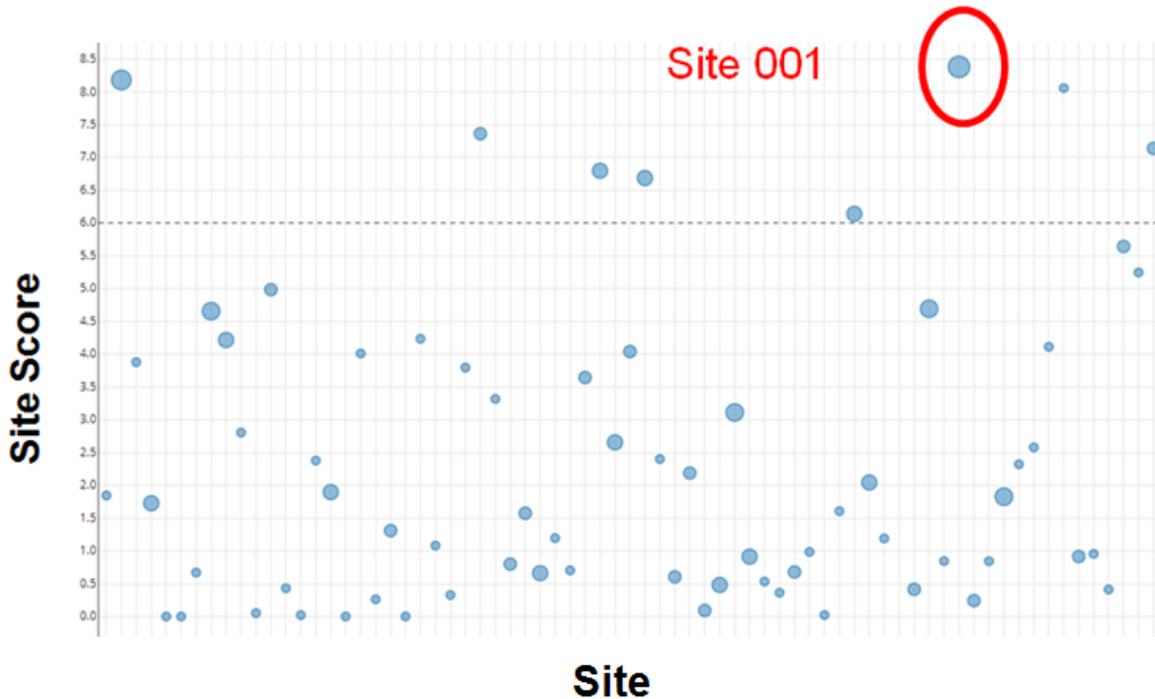
The higher the site score the more different that site is from the other sites.

The following steps outline the process used for Central Statistical Monitoring using Xcellerate<sup>®</sup> Statistical Review:

#### ***Step 1 – Identify Sites with a High Site Scores***

The first step was to identify sites with a site score above the pre-defined threshold. Figure 1 shows an example of a Site-Score plot. The site-score is shown on the vertical axis. The higher the site score the more different that site is from the other sites. The site number is shown on the horizontal axis (note: actual site numbers are not displayed to maintain client confidentiality). Each bubble in the site-score plot represents a site. The size of the bubble represents the number of patients, so the larger the bubble the greater the number of patients at that site.

Figure 1 – Site Score Plot



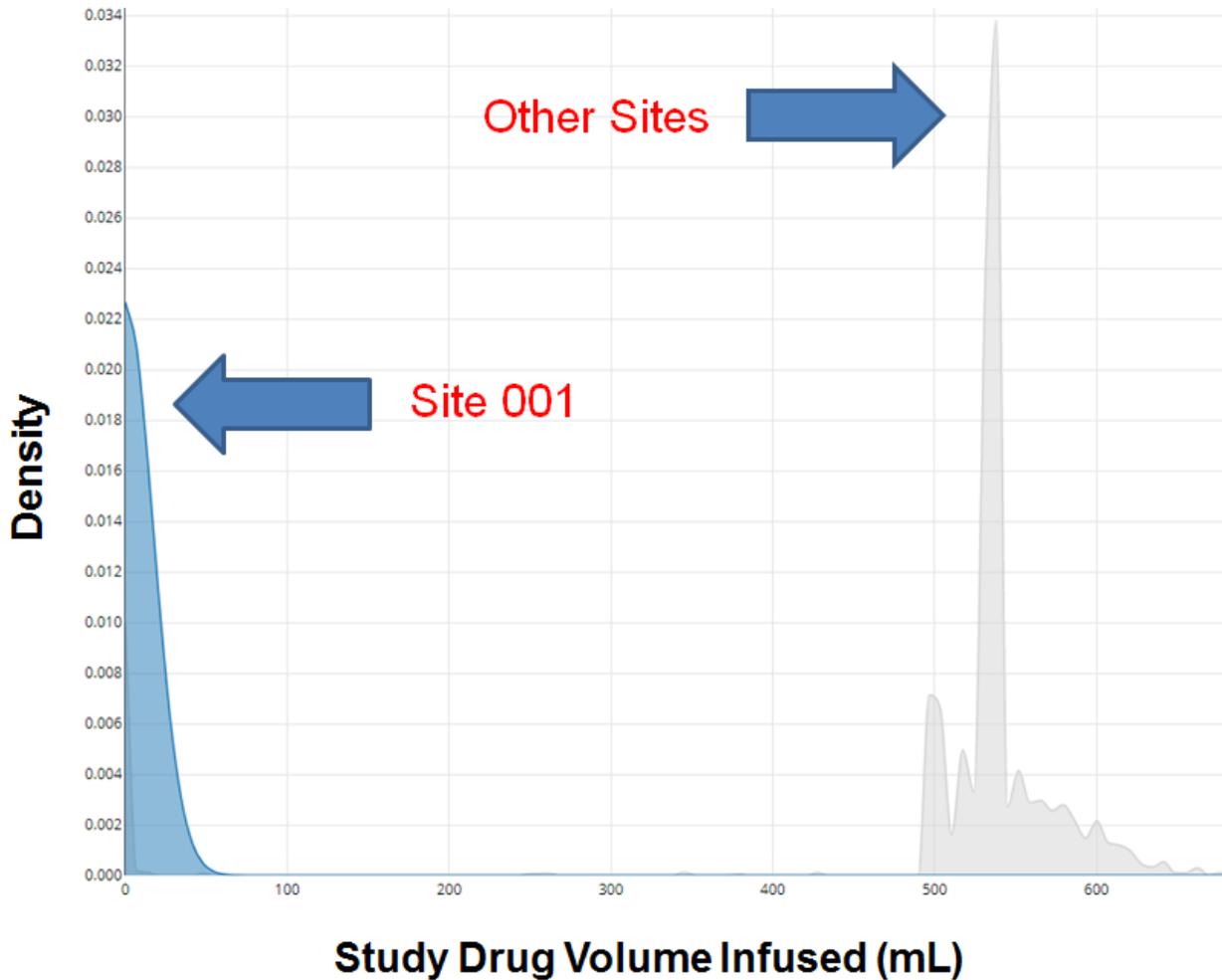
As shown above, 8 sites were identified with a site score above the pre-defined threshold of 6, which indicates a false positive rate of 1 in a million. Site 001 was the highest scoring site with a site score of 8.4.

**Step 2 – Identify Influential Variables**

The second step was to identify the variables that contribute most to the high site score. Figure 2 shows an example of a Site-Variable Score Plot. The higher the site-variable score the more influential that variable is to the site score. The site-variable score is shown on the vertical axis. The site is shown on the horizontal axis. Each bubble in the site-variable score plot represents each variable contributing to the site score. The variables are shown on the right of the display.



Figure 3 – Site Level Data Plot for Study Drug Volume Infused



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.

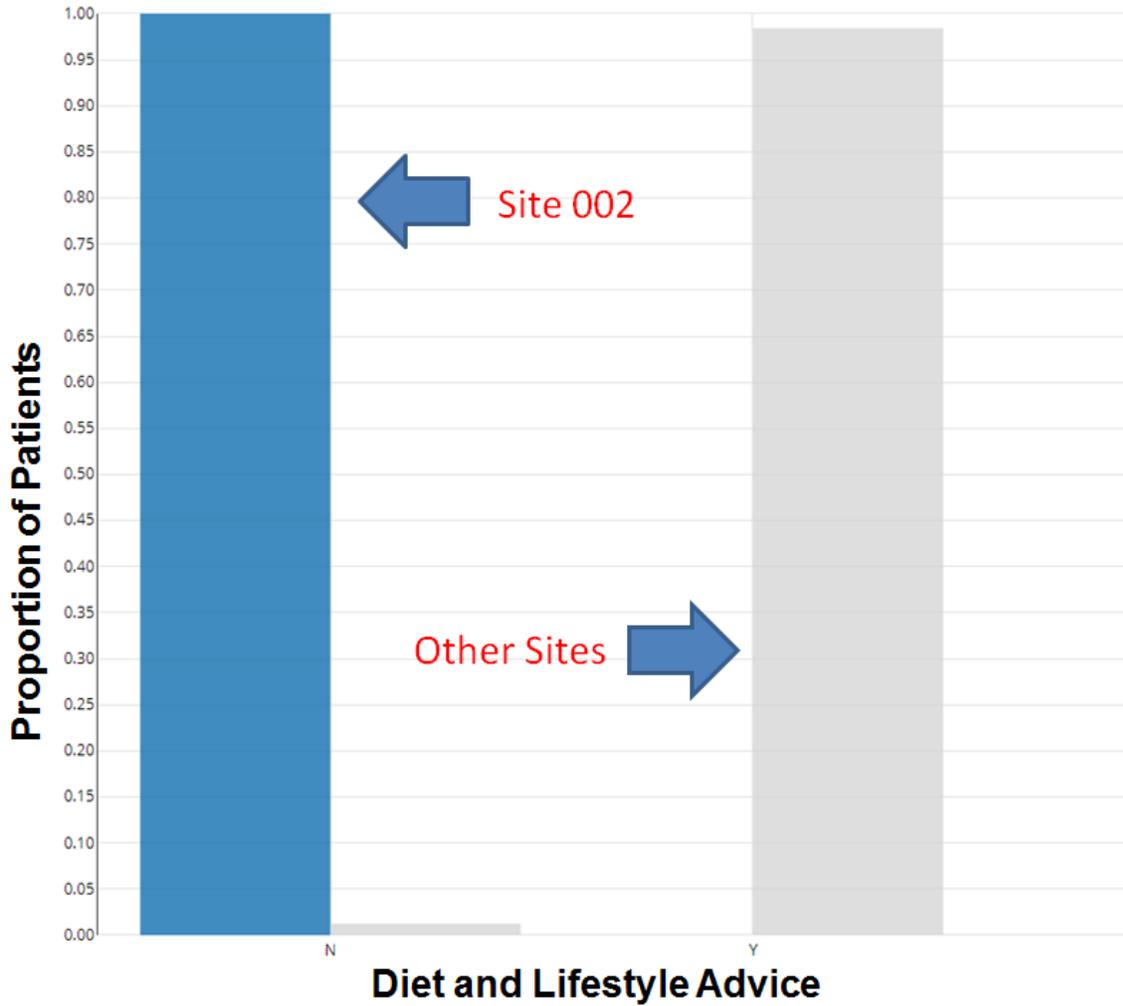
**Other Findings**

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

**Further site training required**

Diet and Lifestyle was very important for the study analysed in this paper. As show in Figure 4, all patients at Site 002 reported “No” to the question about Diet and Lifestyle advice.

Figure 4 – Site Level Data Plot for Diet and Lifestyle Advice

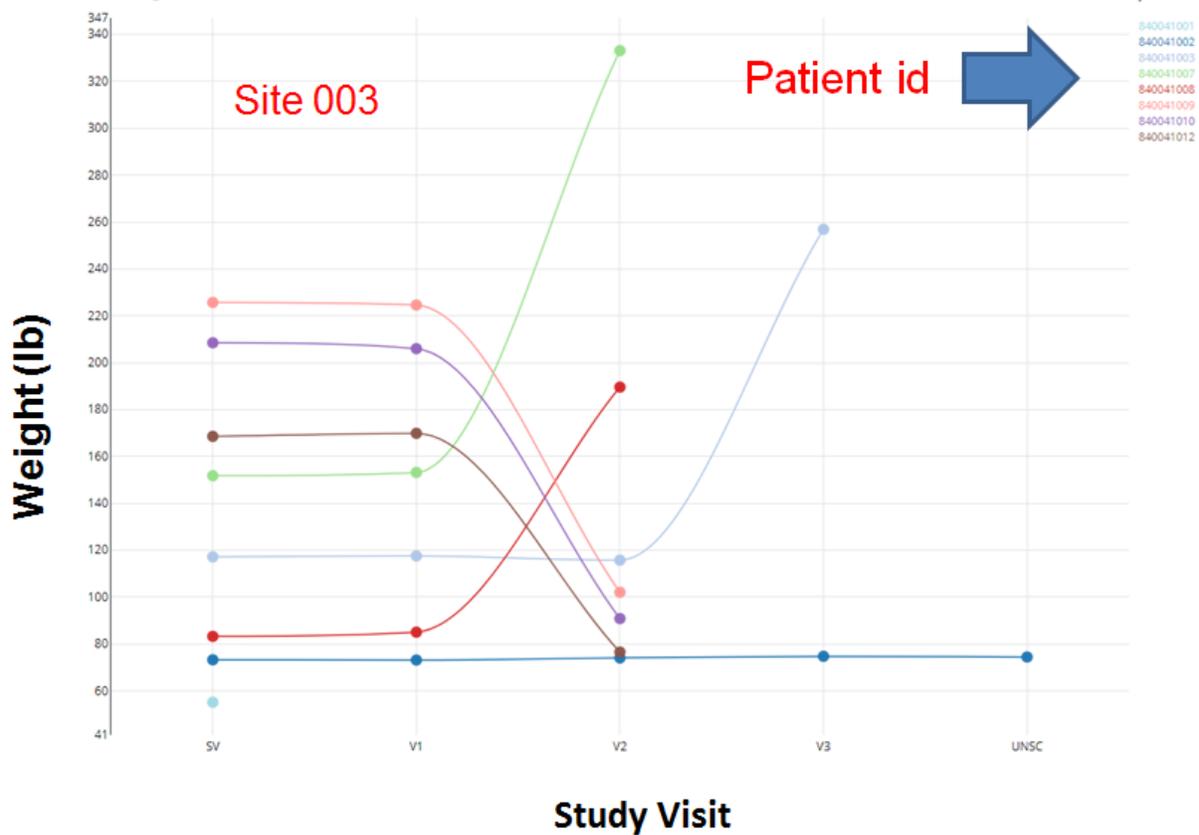


This finding was notified to the Project Leader early in the study. An additional monitoring visit was initiated rapidly where it was found that the site had misunderstood the importance of diet and lifestyle advice. Additional site training was provided and further monitoring visits were scheduled based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

**Misreporting to units**

Figure 5 is show an example of a Patient Level Data Plot. This shows values for weight recorded at each visit for patients at Site 003. Each line represents a patient. As shown there is a large variability in the data across patients between visits, some patients have a steep decrease in weight and some patients have a steep increase in weight.

Figure 5 – Subject Level Data Plot



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.

**CONCLUSION**

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. This will improve data quality.

Covance is currently assessing the effectiveness of Xcellerate® Statistical Review in a couple of pilot studies prior to large scale role out across the business.

**REFERENCES**

Benjamini Y and Hochberg Y (1995) Controlling the false positive rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society, Series B. 57(1) 289-300.

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### **CONTACT INFORMATION**

Your comments and questions are valued and encouraged. Contact the author at:

Tammy McIver

Covance

Osprey House, Maidenhead Office Park, Westacott Way

Maidenhead / SL6 3QH

Work Phone: 01628 548 000

Fax: 01628 548 234

Email: [tammy.mciver@covance.com](mailto:tammy.mciver@covance.com)

Web: [www.covance.com](http://www.covance.com)

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