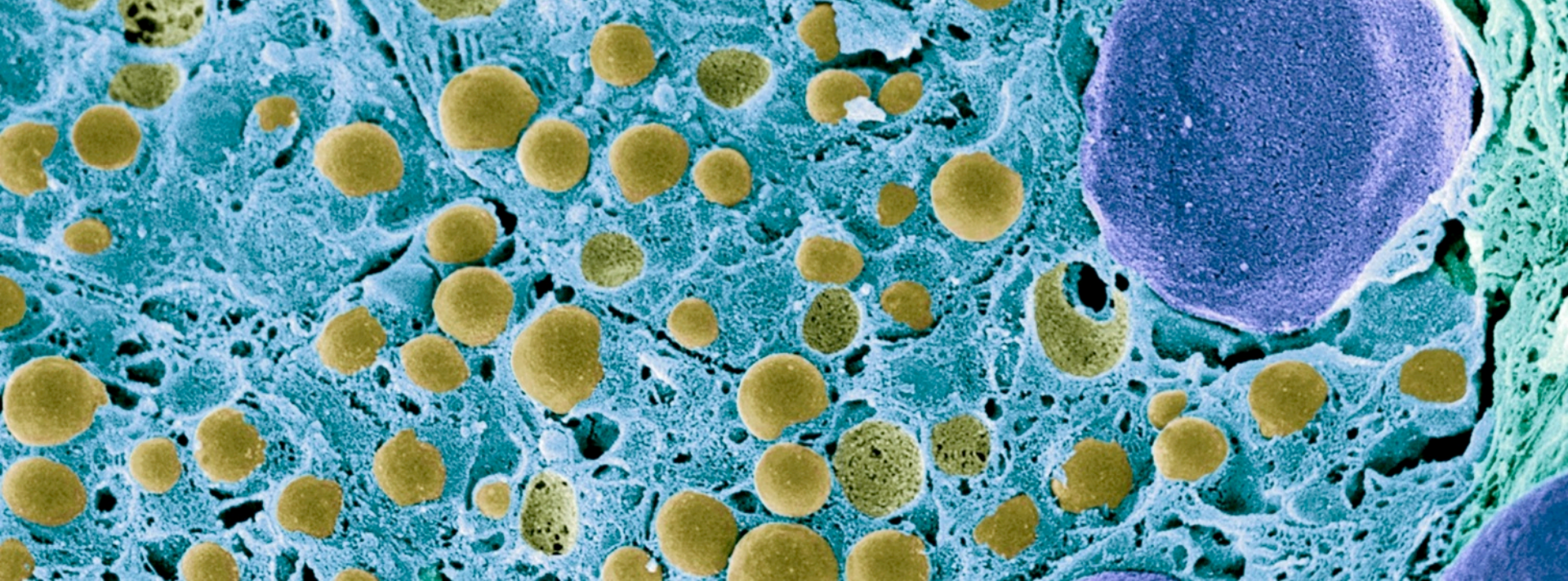




Central Statistical Surveillance (CSS) In Clinical Trials

November 2018

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Pictured above: Pancreas tissue

Disclaimer

- Presentations are intended for informational purposes only and do not replace independent professional judgment. Statements of fact and opinions expressed are those of the participants individually and, unless expressly stated to the contrary, are not the opinion or position of the Janssen Pharmaceuticals or its affiliates.

Agenda

- Introduction and Background
- Literature
- Methods
- Requirements
- Central Statistical Surveillance at J&J
- Conclusions

Introduction and Background

- How do ensure reliable clinical data to optimise safety and efficacy of new treatments?



Introduction and Background

- How do ensure reliable clinical data to optimise safety and efficacy of new treatments?
 - On-site monitoring



Introduction and Background

- How do ensure reliable clinical data to optimise safety and efficacy of new treatments?
 - On-site monitoring
 - Centralised monitoring
 - Identify when on-site visits are required
 - Using metrics to support Decision making
 - Risk based approach



Introduction and Background

- How do ensure reliable clinical data to optimise safety and efficacy of new treatments?
 - On-site monitoring
 - Centralised monitoring
 - Central Statistical Surveillance (CSS)
 - Statistical tools to identify errors, trends, patterns, outliers, ...
 - Detecting data issues that remain undetected by standard methods
 - » unintentional data errors
(i.e. calibration errors, sloppiness in data entry, ...)
 - » fabricated or falsified data



Literature

- Venet et al. (2012)
 - “Central monitoring through advanced statistical and bio-informatic methods can detect abnormal patterns in the data. It can also help improve the effectiveness of on-site monitoring by prioritizing site visits and by guiding site visits with central statistical data checks. ”
 - Structured nature of clinical data
 - Case study

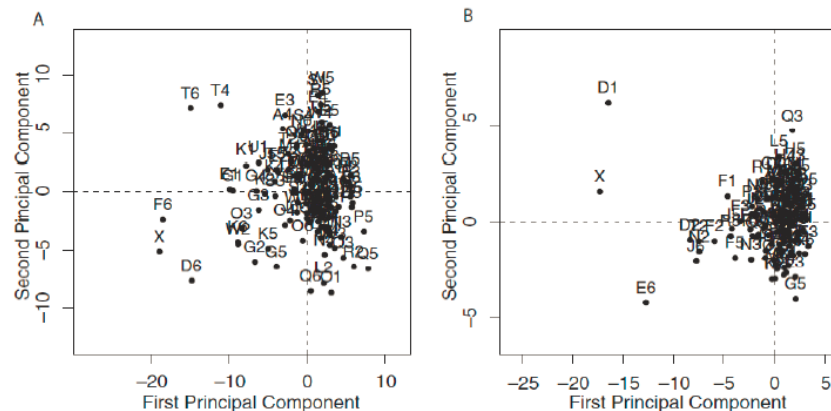


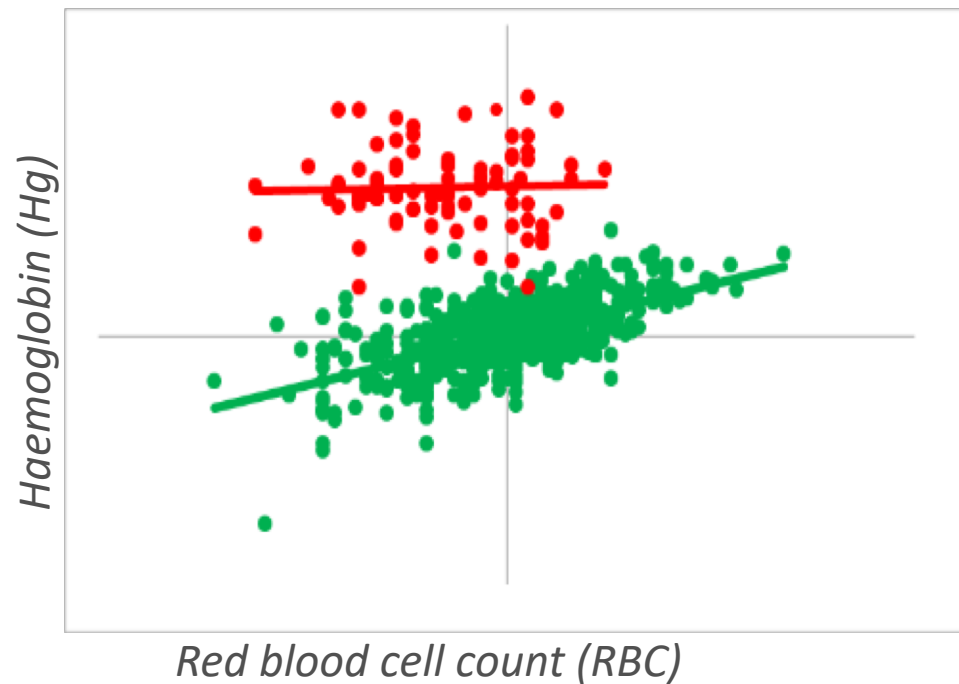
Figure 2. Principal component analysis of p -values. Centers are identified by a letter (denoting the country) and a number, except for center X where fraud had been identified. Centers far from the origin behave differently from the bulk of centers around the origin and are therefore more likely to be problematic. Panel A: analysis based on all data. Panel B: analysis based on patient-questionnaire data. PCA: Principal component analysis.

Literature

- Kirkwood et al. (2013)
 - Overview of methods:
 - dates
 - outliers
 - digit preference
 - variable means
 - inliers
 - correlation checks
 - variance checks
 - ...
- Knepper et al.(2016)
 - Overview of techniques currently applied in biopharmaceutical industry

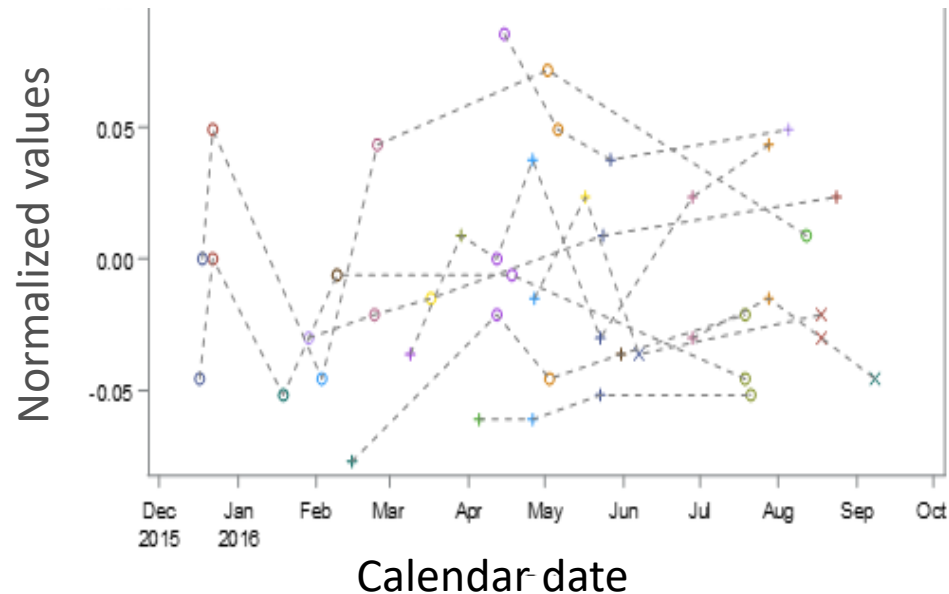
Methods

- Structured nature of clinical data:
 - Different measures taken from the same subject at the same time should be related to each other (to varying degrees)



Methods

- Structured nature of clinical data:
 - Protocol ensures all subjects are comparable
 - Subjects from one site should 'behave' the same as subjects from other sites
 - Within a subject, values should not vary too much from visit to visit



Methods

- CSS looks at:
 - Relationships between parameters (RBC vs Hg)
 - Subject profiles
 - All available data
 - Lab values
 - Questionnaire results
 - Vital signs
 - ...
- Comparing each site against all other sites
- Summarizing resulting p-values through PCA

Requirements

- User friendly and easy to interpret
- Ability to quickly identify data quality issues on live data
 - Allows study teams to focus monitoring resources
- Applicable across our full development study portfolio

Requirements

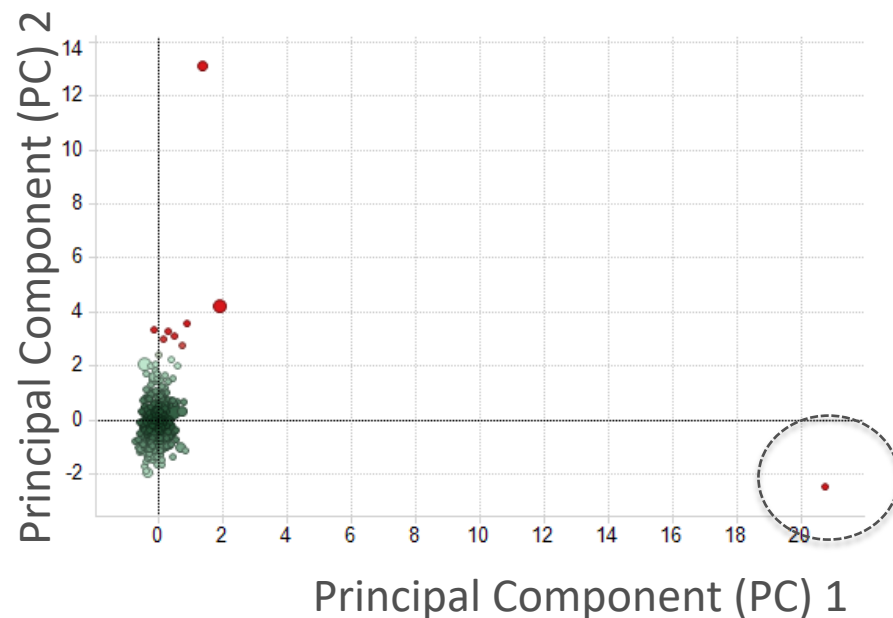
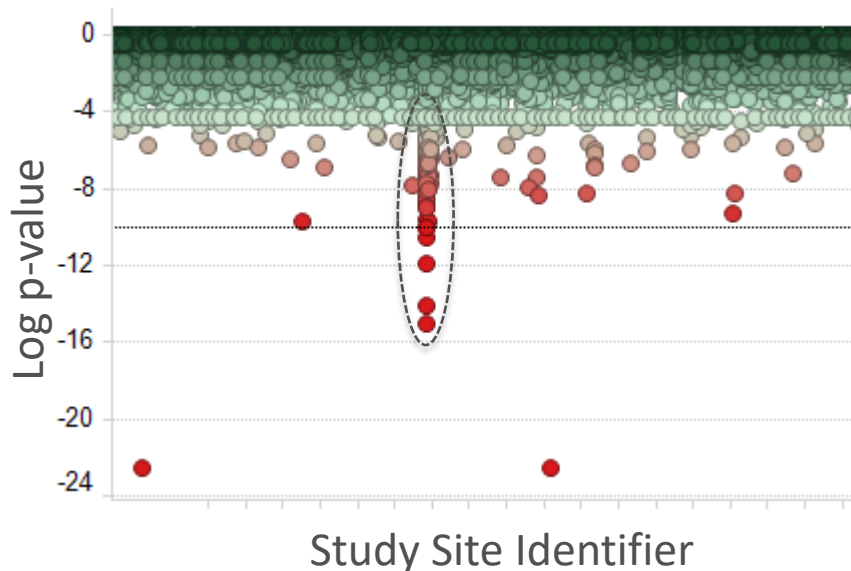
- A stable platform to run the analytics
 - SAS®
 - Proof of Concept
 - Job of Jobs on LSAF (Lauwers & Noirfalise, 2017)
 - AWS running R (production environment)
 - Linux 40 vCPUs instance (m4.10xlarge)
 - R with package 'parallel'
 - Already faster than LSAF (+avoiding worries from LSAF admins)
 - Scales nicely, nearly doubles performance on 72 vCPUs c5.18xlarge (testing/backup)
 - VPCx, virtual private cloud computing, so within JnJ firewall
 - Security and data integrity
 - Direct and safe integration with in house data visualisation

Requirements

- A comprehensive visualisation tool
 - TIBCO Spotfire®
- A dedicated team to
 - Run the analytics regularly on all full development studies
 - Interpret and evaluate the results and present this to the clinical teams

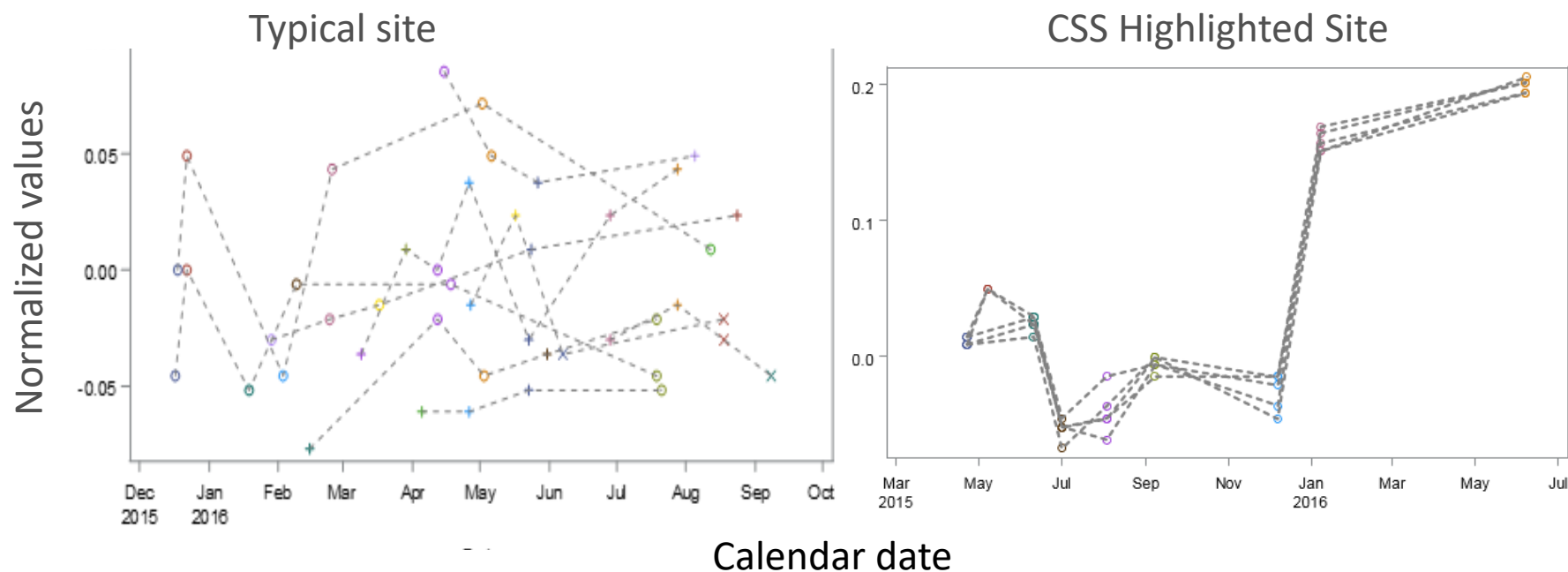
Central Statistical Surveillance at J&J

- Case study (1) – CSS confirmed site with known data quality issues



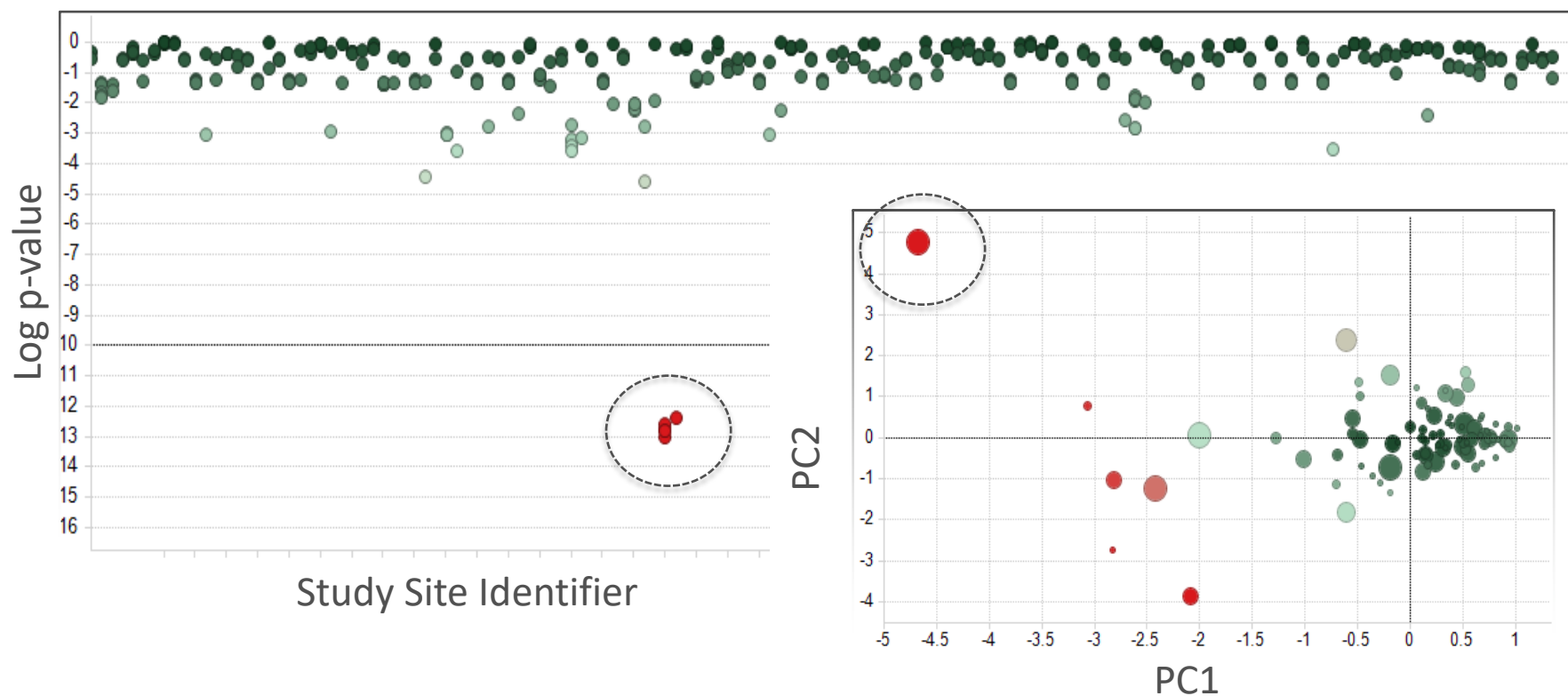
Central Statistical Surveillance at J&J

- Case study (1) – CSS confirmed site with known data quality issues



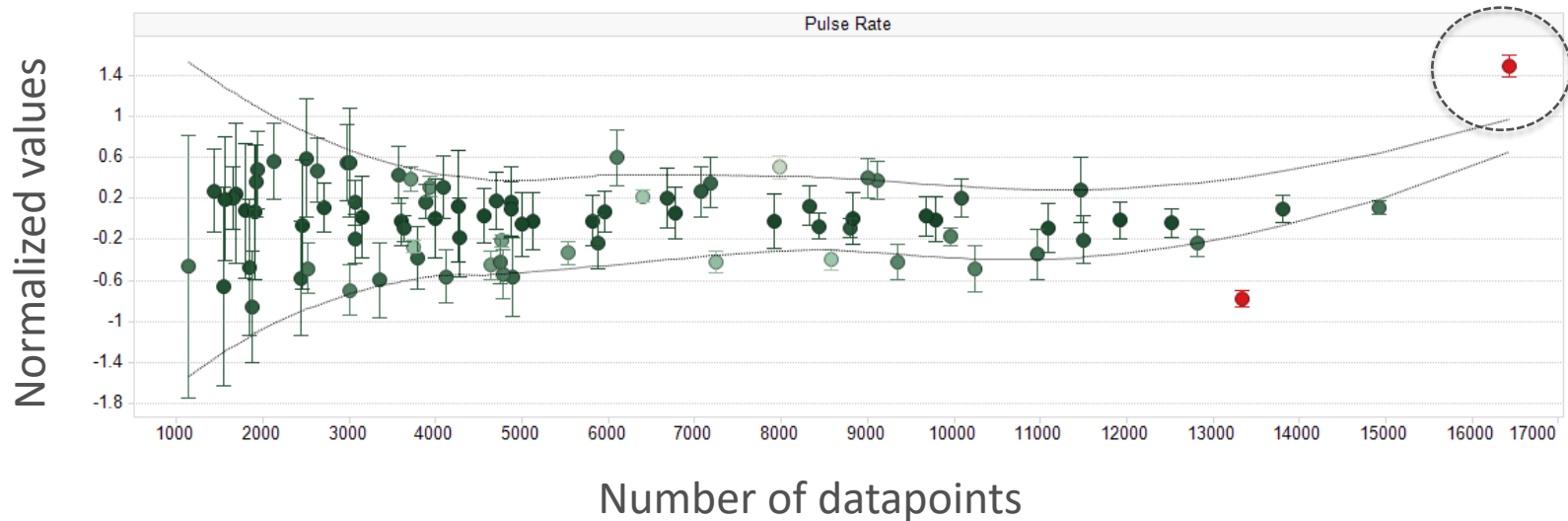
Central Statistical Surveillance at J&J

- Case study (2) – CSS confirmed site with known data quality issues



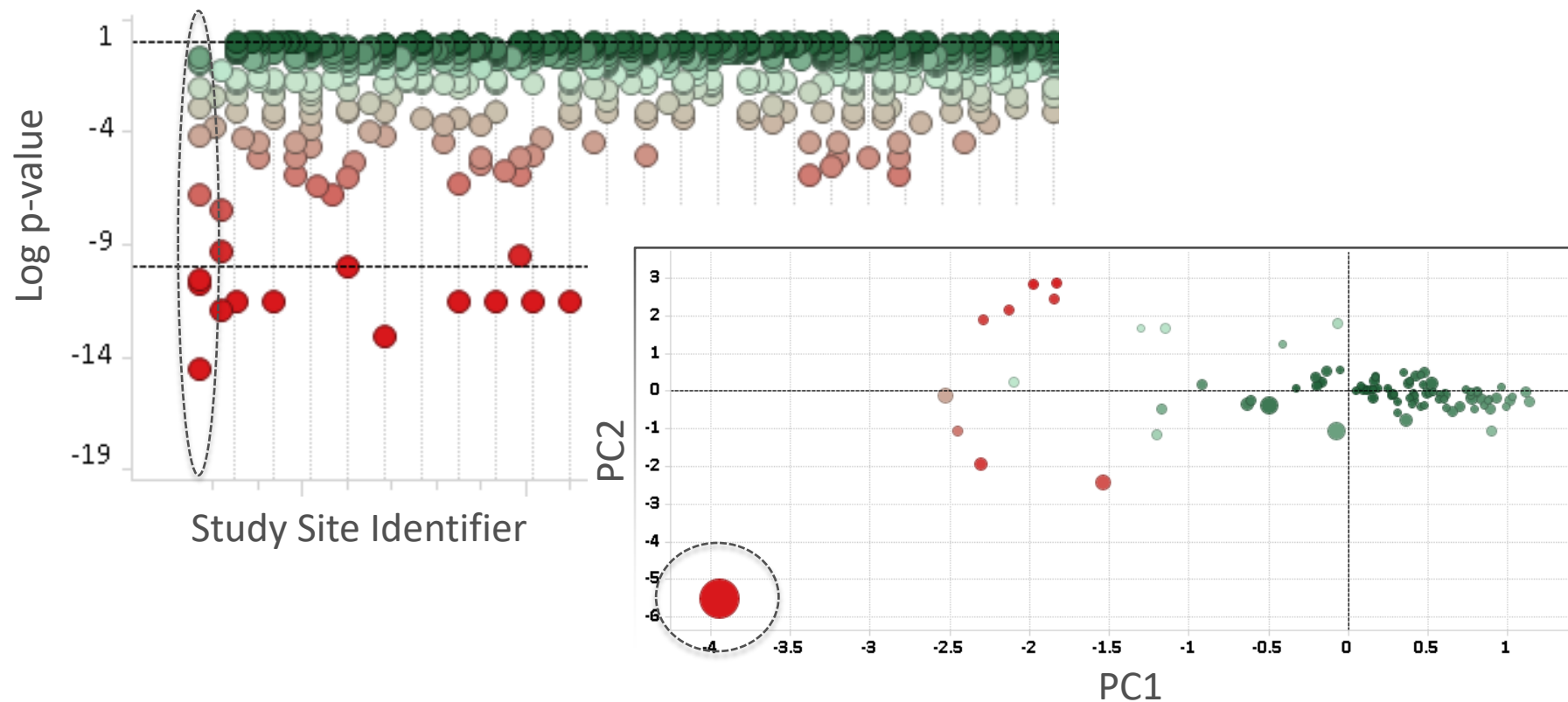
Central Statistical Surveillance at J&J

- Case study (2) – CSS confirmed site with known data quality issues



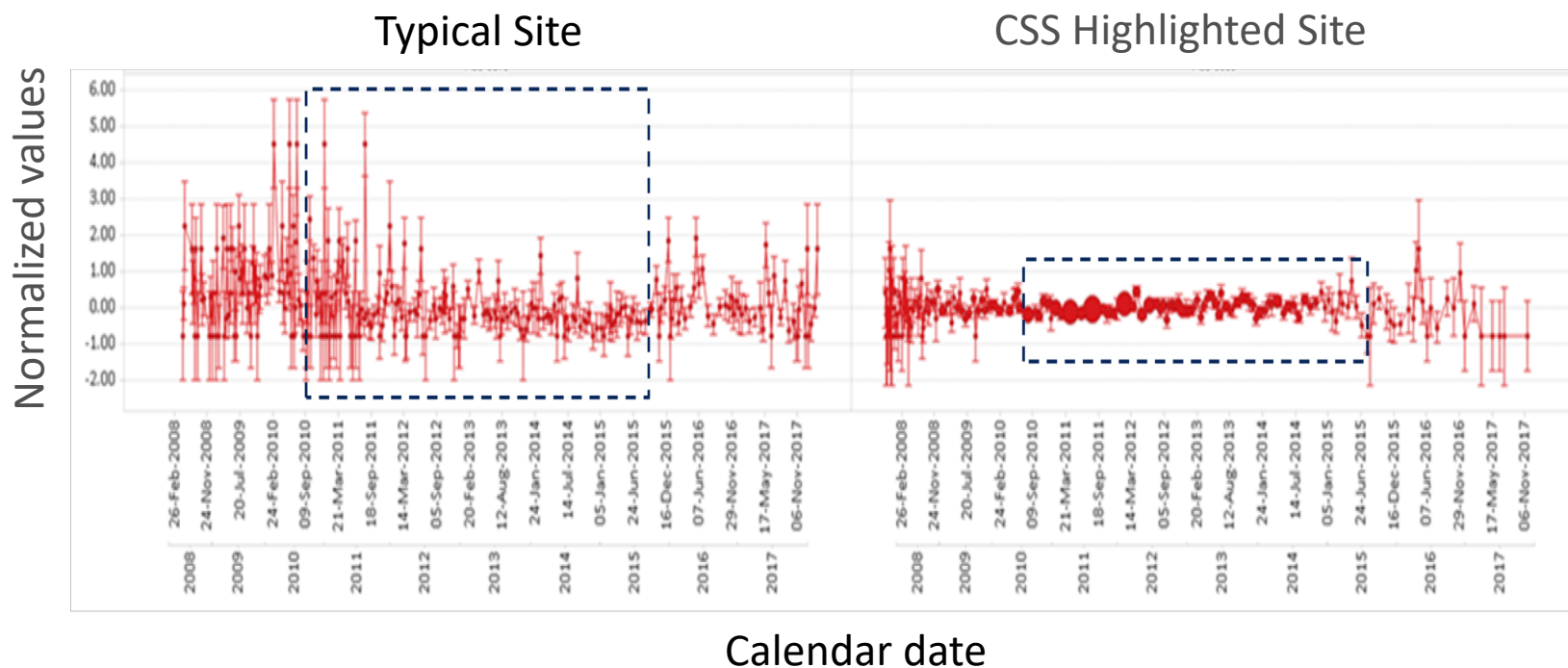
Central Statistical Surveillance at J&J

- Case study (3) – CSS on an active study



Central Statistical Surveillance at J&J

- Case study (3) – CSS on an active study



Conclusions

- Central Statistical Surveillance presented here is an efficient and effective technique to identify sites with possible systematic data errors. It has been shown to confirm sites with known data quality issues
- Allows for data anomalies to be detected during the trial, so that:
 - Root cause analysis can be completed
 - Mitigation actions can be taken as needed
- Two key advantages:
 - Another layer of protection for subject safety and data quality
 - Early detection of critical data issues that could jeopardize overall study data
- By shifting the traditional monitoring paradigm of 100 percent source data verification to a focused quality review, the site-facing team can shift priorities to a strategic scope in site monitoring and management

Thank you

**Kris Lauwers
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Giordano lo Regio**

5-Nov-2018

References

- Kirkwood et al, 2013. Application of methods for central statistical monitoring in clinical trials. Clinical Trials 10: 783–806.
- Knepper et al. 2016. Detecting Data Quality Issues in Clinical Trials: Current Practices and Recommendations. Therapeutic Innovation & Regulatory Science 50(1): 15-21
- Lauwers, K. & Noirfalise, R. 2017. Job of Jobs. Proceedings of the Pharmaceutical Users Software Exchange Conference, Paper CT14.
www.lexjansen.com/phuse/2017/ct/CT14.pdf
- Venet D, Doffagne E, Burzykowski T et al, 2012. A statistical approach to central monitoring of data quality in clinical trials. Clinical Trials 9: 705–713

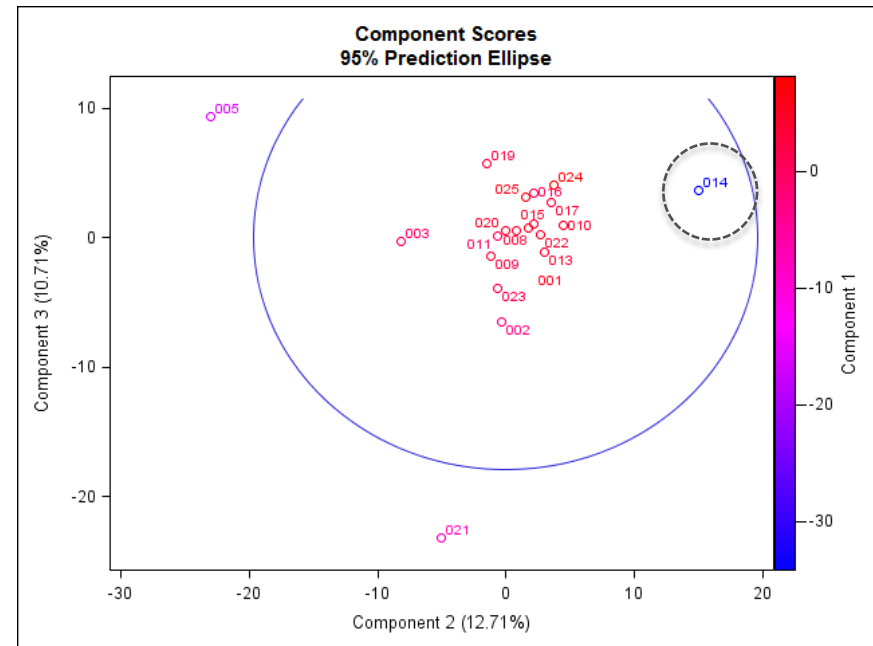
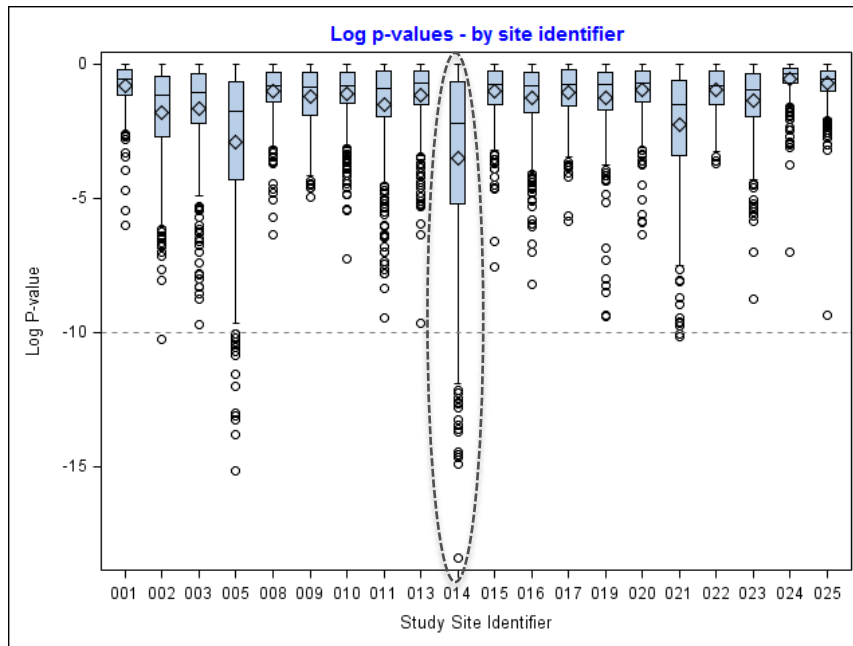
Backup slides

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5-Nov-2018

Proof of concept

- Analysis of means



Proof of concept

- Mean values
 - Selection of 20 parameters
 - Mean values at site 14 are either higher or lower than expected

