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Central Statistical Surveillance in Clinical Trials

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ABSTRACT

In addition to subject safety and ethical treatment of study subjects, data quality in clinical trials is a crucial factor. Data quality issues can arise due to intentional and non-intentional noncompliance with protocol procedures, which can compromise the validity of study results. Detecting quality issues is a primary focus of risk-based monitoring. However, data inconsistencies/patterns may be difficult to uncover via standard monitoring methodology. Janssen has developed an automated Central Statistical Surveillance (CSS) analysis system that allows detection of these unusual data patterns, which may indicate potential data quality issues at investigative sites participating in multicenter clinical trials. The potential benefits of CSS in enhancing clinical trial quality are multifaceted. Monitoring frequency can take a more focused approach in targeting those sites where poor data quality is suspected. Moreover, CSS provides trial teams with a prioritization strategy to move site monitoring and management to a more strategic scope, resulting in a shift in an eventual shift in the traditional monitoring paradigm.

INTRODUCTION

A successful clinical trial is defined by results that can withstand the rigor of scientific and regulatory evaluation for safety and efficacy. Hence, quality assurance practices and quality control procedures are a top priority of every clinical trial, as outlined by Good Clinical Practice guidelines [(1)]. These practices typically focus on 1) identifying critical data in support of major endpoints and trial objectives and 2) providing analytics in support of central and local review of critical source data. However, there is growing evidence that additional statistical surveillance is needed to detect data anomalies and unusual data patterns [(2)]. Therefore, at Janssen, we developed an automated detection system (CSS) providing in-depth insights on clinical data quality issues.

ADVANCED ANALYTICS

The objective of the CSS analysis is to identify intentional or unintentional noncompliance and significant data quality issues thereby effectively adding another layer of protection for subject safety and data quality. The methodology is based upon defining naturally occurring relationships in clinical data and identifying differences at site level.

These naturally occurring relationships are investigated at three levels: between clinical parameters, between subjects and within subjects.

- Between clinical parameters:

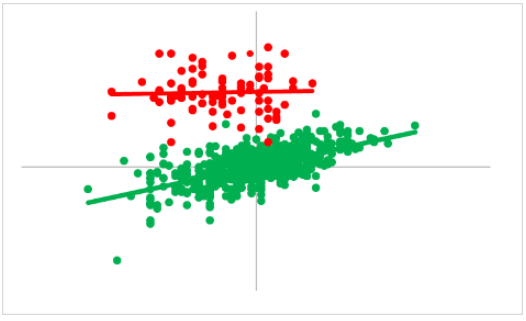

Figure 1: Red blood cell count (RBC) x Hemoglobin (Hg) values within a study.

Consider this (fictive) example: There is a very clear relationship between RBC and Hg (green dots). However, looking at the red dots from one specific site it becomes clear that this relationship does not hold. This site has a data quality issue.

- Subject profiles over time: the RBC value at one subject's visit is related to the value of previous visit(s). Sites with consistently different subject profiles should be investigated.

- Between subjects: RBC values across subjects are not naturally related. We have a data quality issue if RBC values of subjects within a site are very (dis)similar as compared to other sites.

We also investigate clinical data as they become available at a clinical site, during each subject's visit. This allows us to identify sites with for instance temporal malfunction of lab equipment, change in site staff.

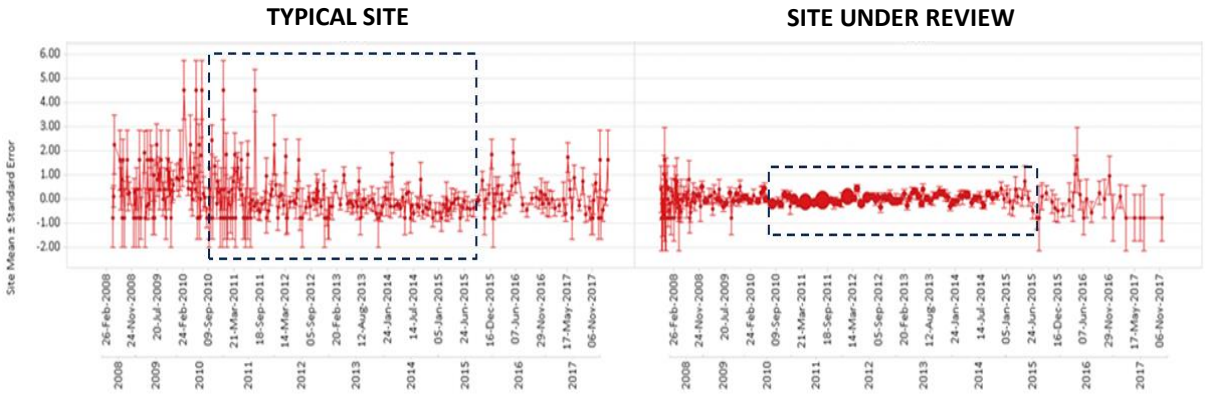

Figure 2: Log normalized values of a clinical parameter (e.g. RBC) by actual data collection date. Data variability from 2010 until 2015 was considerable lower than expected.

Sites that differ consistently in any of these relationships are easily identified through a comprehensive TIBCO Spotfire® visualization tool allowing in depth investigation of the actual data patterns. Operationally, we have organized a dedicated core team at Janssen that analyzes the CSS output, writes reports to highlight key items of interest and then presents it to the clinical study team. This team has an in-depth knowledge of site/protocol nuances and is able to identify the next steps for investigation and mitigation at the clinical site.

CONCLUSIONS

The CSS analysis allows for early detection of critical data quality issues that could potentially jeopardize the validity of studies with possible downstream implications to regulatory approvals. It can also identify sites with confirmed data quality issues; therefore, enabling more efficient and focused site monitoring. Applying CSS strategy as a standard approach will most likely drive a shift in the traditional site monitoring paradigm in the future by reducing the need for source data verification and a one-size-fits-all structured monitoring visit frequency.

REFERENCES

1) International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. [Last accessed on 2016 Dec 15]. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf .
2) Venet D, Doffagne E, Burzykowski T et al (2012) A statistical approach to central monitoring of data quality in clinical trials. Clin Trials 9:705–713