Paper AR01

ICH E6 R2: How Statistics Drive Improvement in Data Quality

Erik Doffagne, CluePoints, Ottignies-Louvain-la-Neuve, Belgium

ABSTRACT

The ICH E6 R2 guidance stresses the importance of centralized monitoring, especially by leveraging statistical analyses in order to assess data quality as traditional methods might not be sufficient to distinguish reliable data from unreliable data.

The aim of this presentation is to review the state-of-the-art methodology for detecting various data integrity issues such as data manipulation, inconsistent data, data outliers, etc. The paper will also discuss how statistical methodology fits into an overall quality risk management strategy.

INTRODUCTION

ICH E6 R2 [1] recommends that sponsors adopt a risk based approach to define the nature and extent of the monitoring efforts. Section 5.18.3 of the guidance stresses the importance of centralized monitoring :

"*Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.*"

The concept of centralized monitoring is centered around three pillars:

- Data Surveillance
- Key Risk Indicators (KRIs)
- Quality Tolerance Limits (QTLs)

DATA SURVEILLANCE

The goal of Data Surveillance is to detect quality issue and potential study misconduct by identifying atypical patterns and anomalies in the data. Statistical methods have been shown to be effective in assessing data quality [2, 3]. The key tenet is that the sites participating in a given study have a common database structure inherited from the CRF design. This makes it possible to compare sites and identify those whose data are inconsistent with others. Methods relying on the use of large number of statistical tests are particularly effective in identifying unexpected or unusual patterns in trial data. Various forms of study misconduct can be detected with this approach, from intentional data fabrication or alteration, to site sloppiness and training issues

Figure 1 provides an illustration of quality issue that can be detected by statistical methods. In this illustration it is evident that there is a carry-over of values between visits for systolic blood pressure. This kind of pattern can be detected using statistical methods examining within patient variability. The key for detecting quality issues is to use statistical methods that are designed to look at specific patterns that might have clinical or operational relevance.

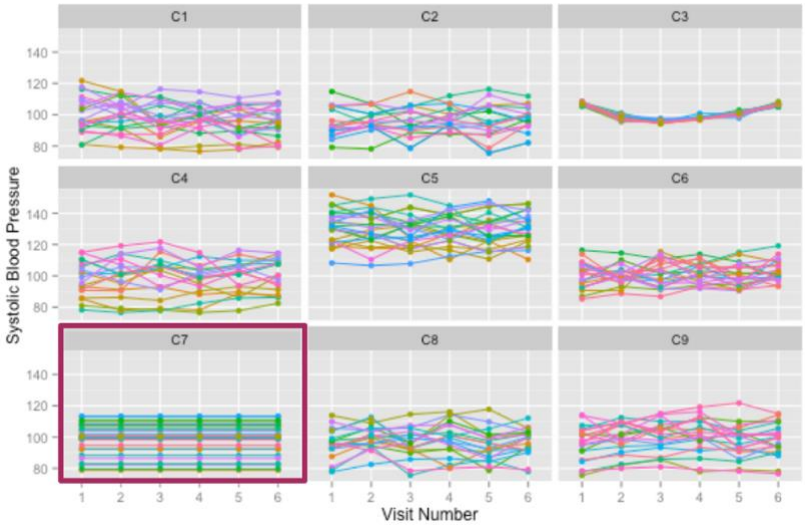

FIGURE 1 – Example of carry over visit after visit for site C7

KEY RISK INDICATORS

Key Risk Indicators (KRI) are based on predefined metrics, which are chosen to assess different dimensions of the site performance such as quality, timeliness and efficiency [4]. Those risk indicators target areas of particular interest such as CRF Completion, Adverse Events and Protocol compliance among other operational and clinical metrics. In addition to generic indicators which can be used regardless of the therapeutic area, a number of study-specific risk indicators are added.

Usually, it is not necessary to have more than 10 to 25 indicators. It is good practice not to define too many indicators as it quickly becomes operationally challenging and time consuming to review the dashboard. The study risk assessment conducted at the outset of the study allows stakeholders to define which indicator will be required in order to mitigate potential study specific risks.

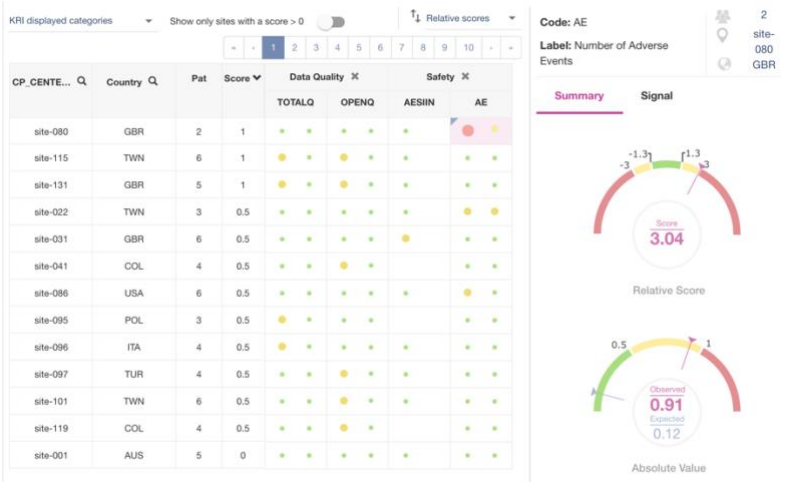

FIGURE 2- KRI example

QUALITY TOLERANCE LIMITS

ICH E6 (R2) describes in Section 5.0.4:

"Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed."

Quality Tolerance Limits can be seen as being a "KRI" at the study level. The main goal is to detect systemic issues within the trial [5]. It is recommended to select a limited number of parameters in the region of 5 to 6 key metrics to ensure focus on what matters most. The parameters used for each study are usually based on medical knowledge and historical data and these aspects are used to guide the selection. In addition, the study risk assessment also serves as a key driver to identify the areas at risk that would require additional scrutiny.

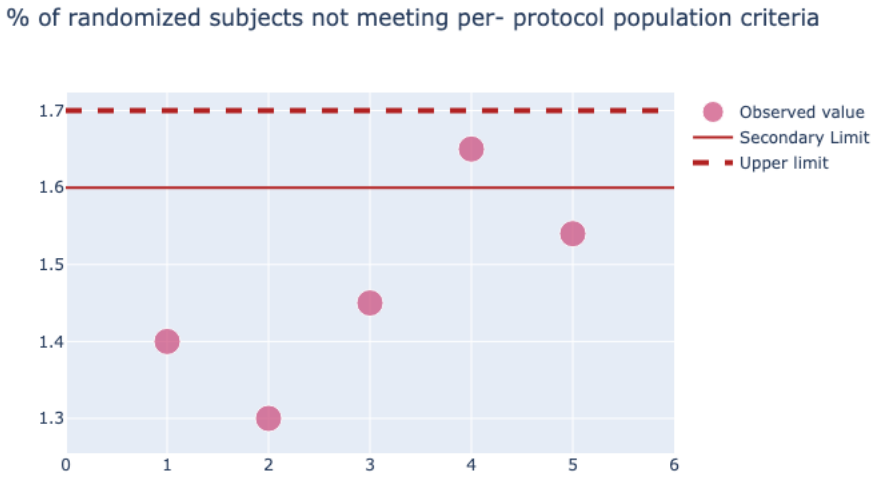

FIGURE 3 – QTL example

CONCLUSION

ICH E6 R2 offers sponsors and CROs alike the opportunity to focus efforts on what matters most by relying on centralized and unsupervised statistical assessments of data quality. Data Surveillance, Key Risk Indicators and Quality Tolerance Limits are key enablers for a successful Risk-Based Monitoring implementation. Besides having the right tools and well-designed processes, the change management process required for successful adoption should not be underestimated.

The use of these kind of techniques to interrogate data with statistical methods is not limited to pharmaceutical companies and CROs. There is an interested as well from the regulator side with the FDA actively looking at analyzing data in order to target sites at risk for inspection [6]. This regulatory risk-based approach to selecting sites for inspection is yet another key driver for adoption amongst global sponsors and will undoubtedly increase the chances of submission success.

REFERENCES

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CONTACT INFORMATION

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

Erik Doffagne
CluePoints
Avenue Albert Einstein 2a
1348 Ottignies-Louvain-la-Neuve
+ 32 10 77 89 10
Email: erik.doffagne@cluepoints.com
Web: www.cluepoints.com