

ICH E6 R2: How Statistics Drive Improvement in Data Quality

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Erik Doffagne – *Product Manager*

Centralized Monitoring

The concept of centralized monitoring is centered around three pillars:

1. Data Surveillance
2. Key Risk Indicators (KRIs)
3. Quality Tolerance Limits (QTLs)

Data Surveillance

- Goal: 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
- Various forms of study misconduct can be detected with this approach, from intentional data fabrication or alteration, to site sloppiness and training issues

Detecting Data Quality Issues in Clinical Trials: Current Practices and Recommendations

David Knepper, MS, MBA¹, Christian Fenske, MPH²,
Patrick Nadolny, MS³, Alun Bedding, PhD⁴, Elena Gribkova, MSc⁵,
John Polzer, DVM, MS, MS⁶, Jennifer Neumann, CCDM⁷,
Brett Wilson, BSP⁸, Joanne Benedict, MS⁹, and Andy Lawton, CSTAT¹⁰

A statistical approach to central monitoring of data quality in clinical trials

David Venet^{a,b}, Erik Doffagne^a, Tomasz Burzykowski^{a,c}, François Beckers^d,
Yves Tellier^d, Eric Genevois-Marlin^e, Ursula Becker^f, Valerie Bee^g,
Catherine Legrand^h and Marc Buyse^{c,i}

Sponsored Special Section by TransCelerate BioPharma: Original Research

Statistical Monitoring in Clinical Trials: Best Practices for Detecting Data Anomalies Suggestive of Fabrication or Misconduct

David Knepper, MS, MBA¹, Anne S. Lindblad, PhD²,
Gaurav Sharma, PhD², Gary R. Gensler, MS², Zorayr Manukyan, PhD³,
Abigail G. Matthews, PhD², and Yodit Seifu, PhD⁴

Data fraud in clinical trials

Research Article

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(www.interscience.wiley.com) DOI: 10.1002/sim.0000

Linear mixed-effects models for central statistical monitoring of multicenter clinical trials

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C. Legrand^a and M. P.

Statistics
in Medicine

CLINICAL
INVESTIGATION

Detecting Data Quality Issues in Clinical Trials: Current Practices and Recommendations

Therapeutic Innovation
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Statistical methods can help to detect
areas at risk and improve data quality

STATISTICS IN MEDICINE
Statist. Med. 18, 3435-3451 (1999)

THE ROLE OF BIOSTATISTICS
IN DETECTION AND TREATMENT

Int J Clin Oncol
DOI 10.1007/s10147-015-0877-5

REVIEW ARTICLE

Data-driven risk identification in phase
central statistical monitoring

Catherine Timmermans¹ · David Venet² · Tomasz Burzykowski³

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Linear mixed-effects models for central
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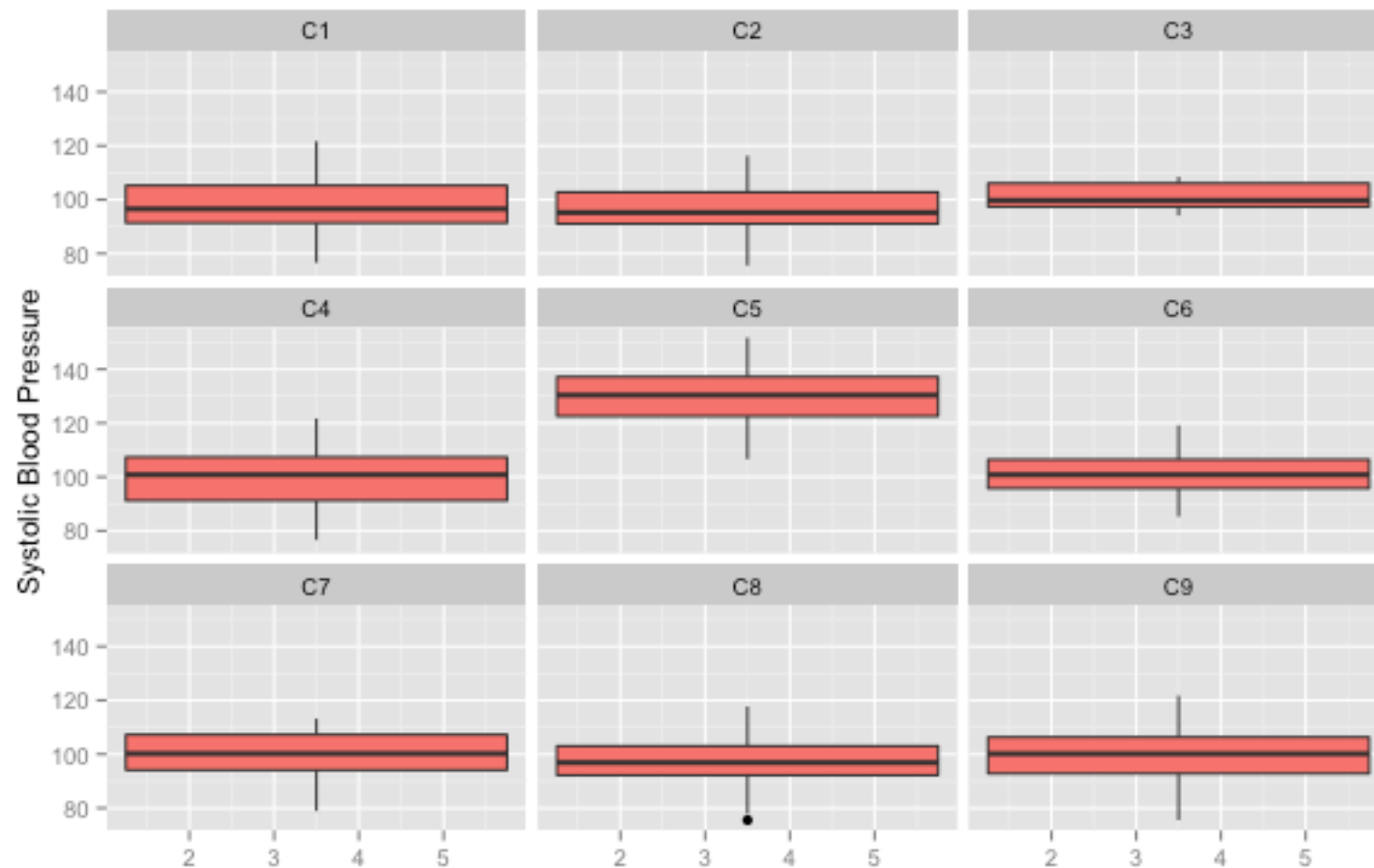
Statistics
in Medicine

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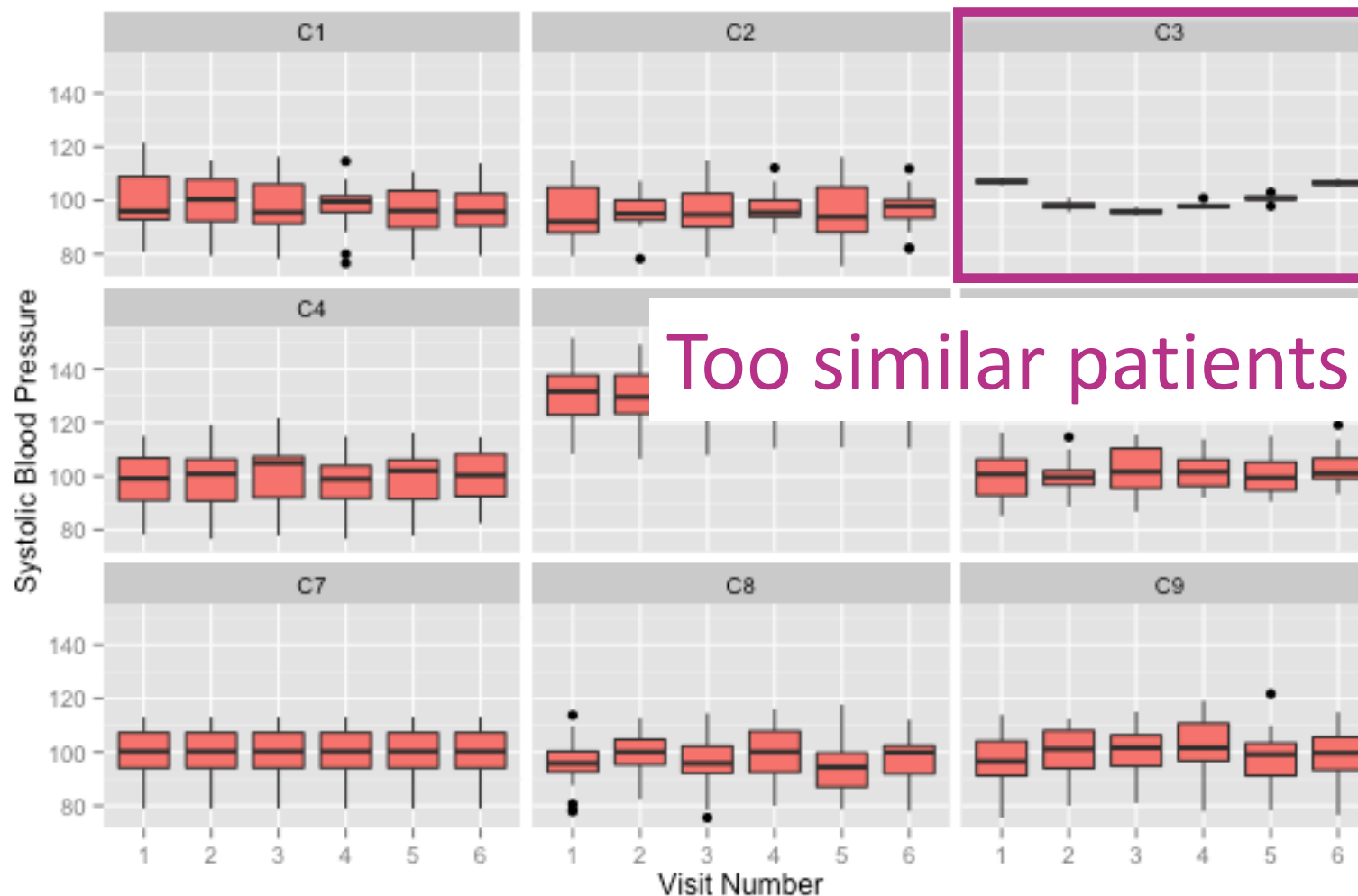
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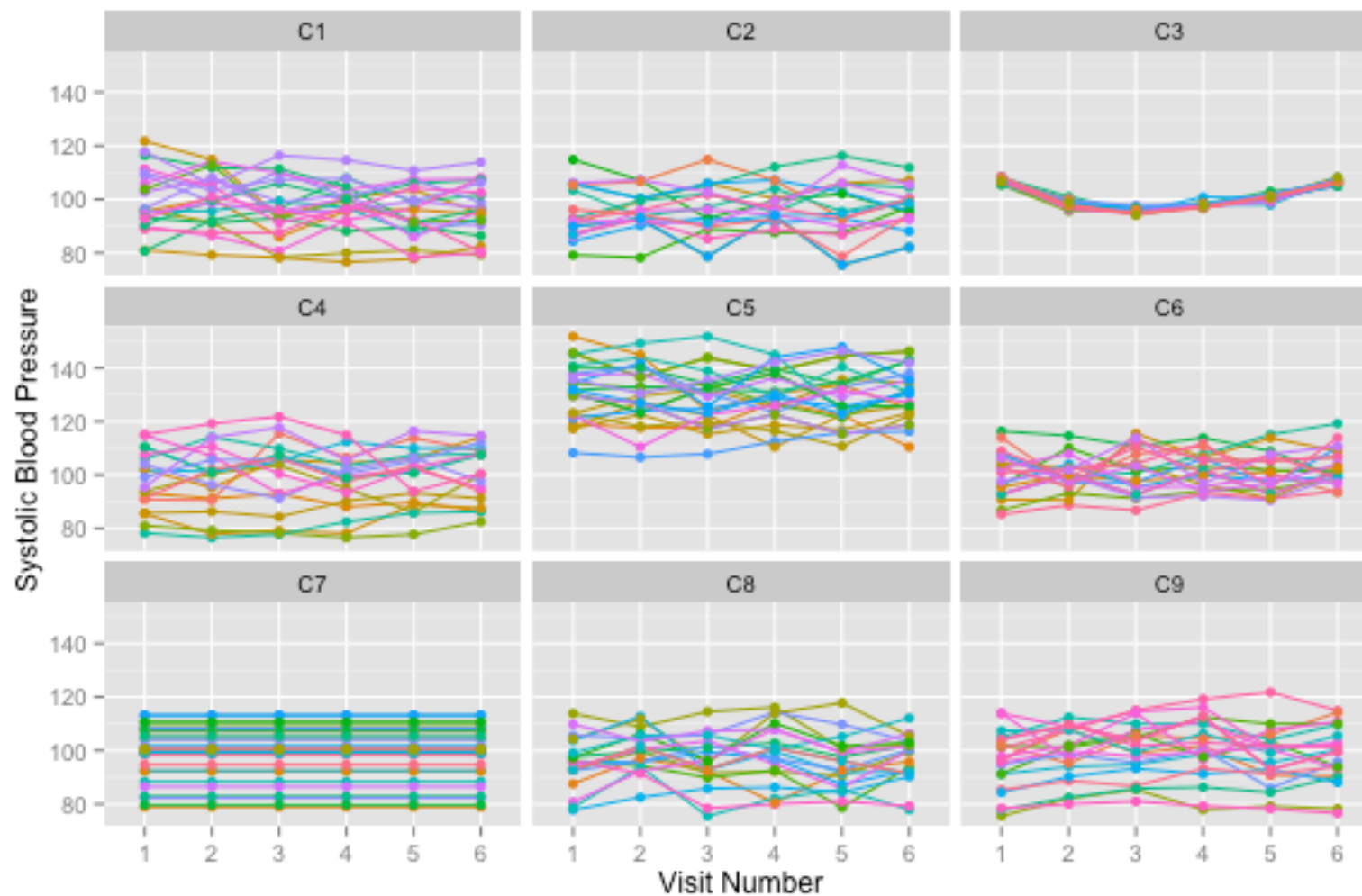
What patterns can be detected?



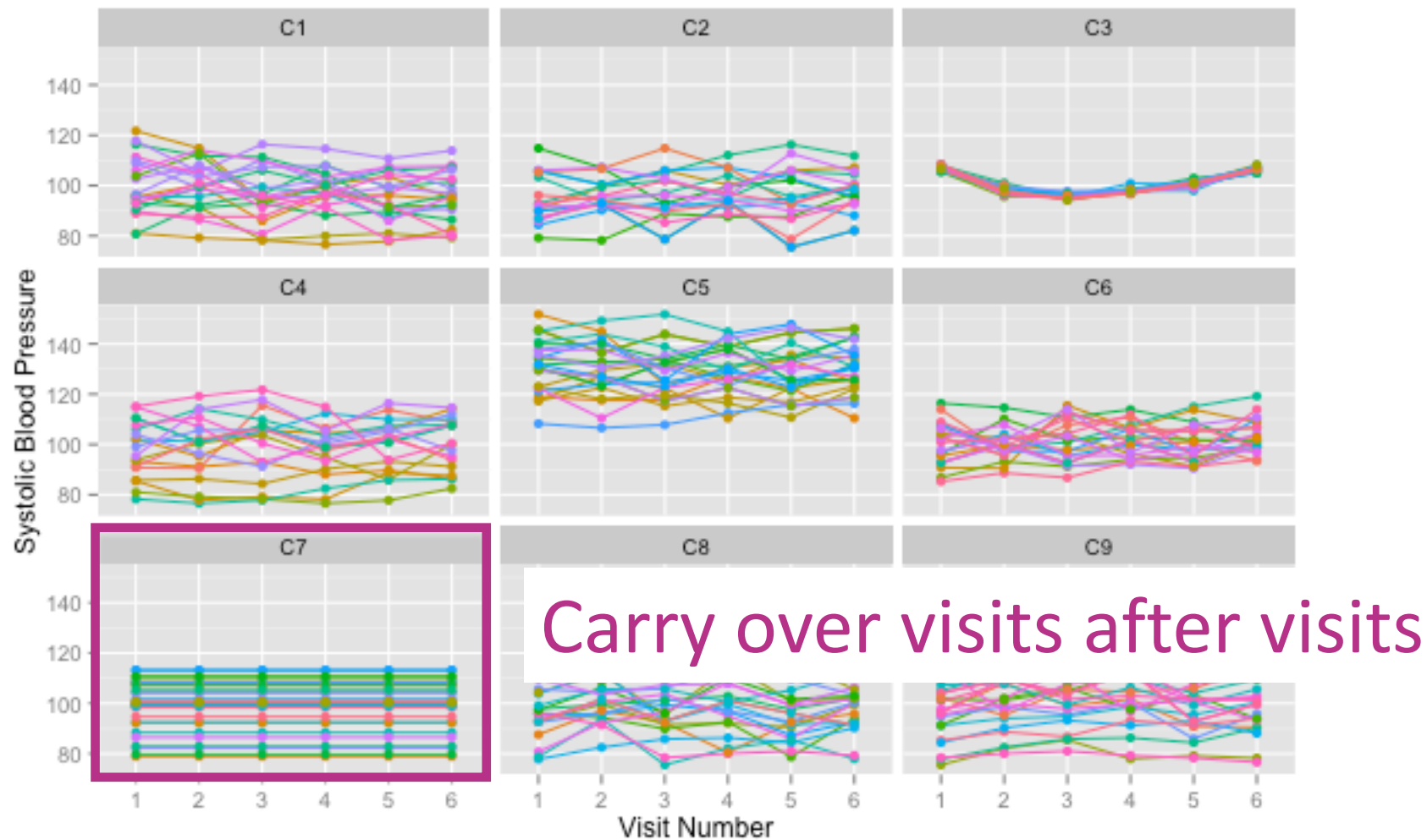
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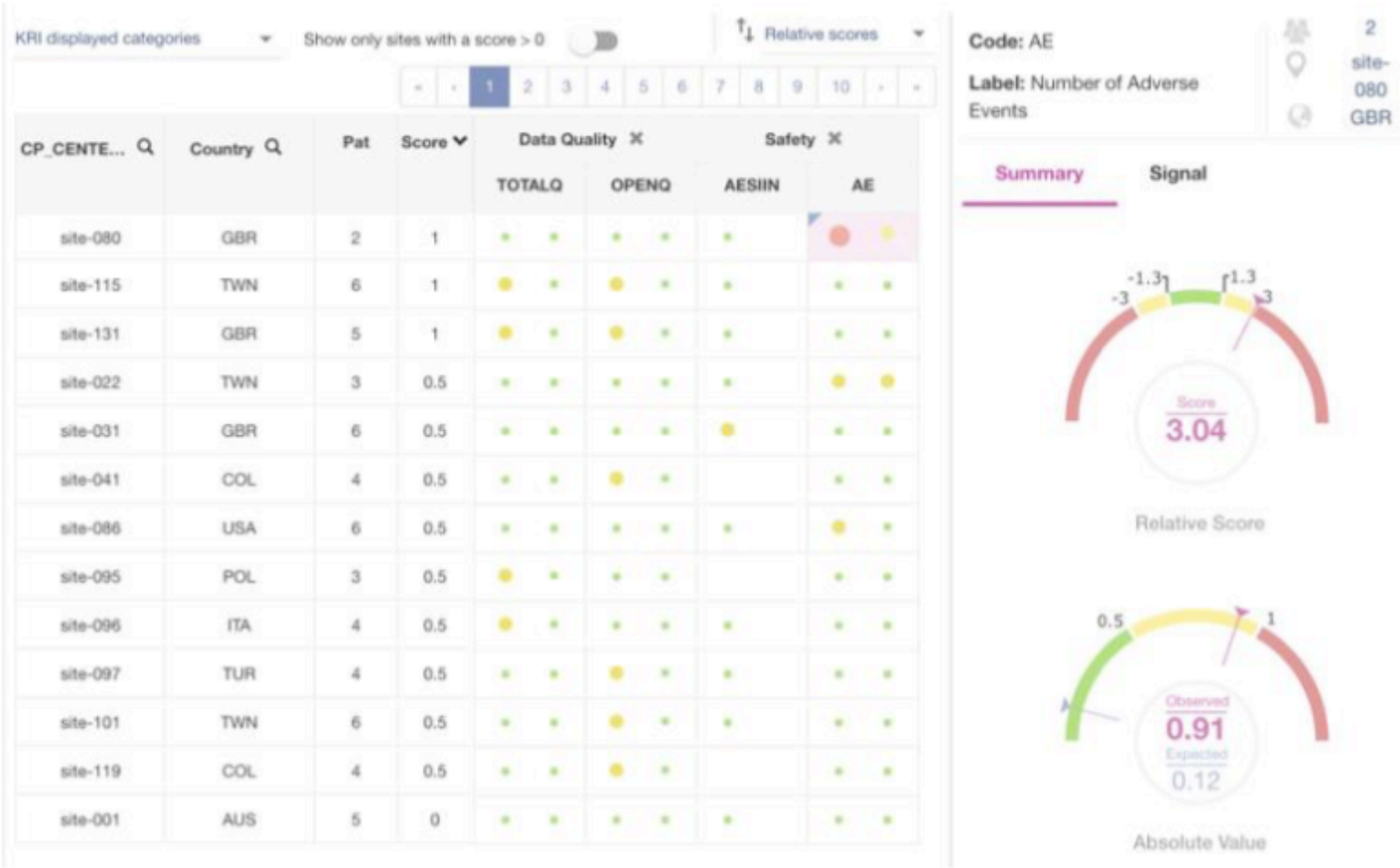
What patterns can be detected?



Key Risk Indicators

- Based on predefined metrics
- Operational and clinical metrics
 - i.e. CRF Completion, Adverse Events, Protocol compliance
- Generic vs Study Specific

Key Risk Indicators



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

- 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

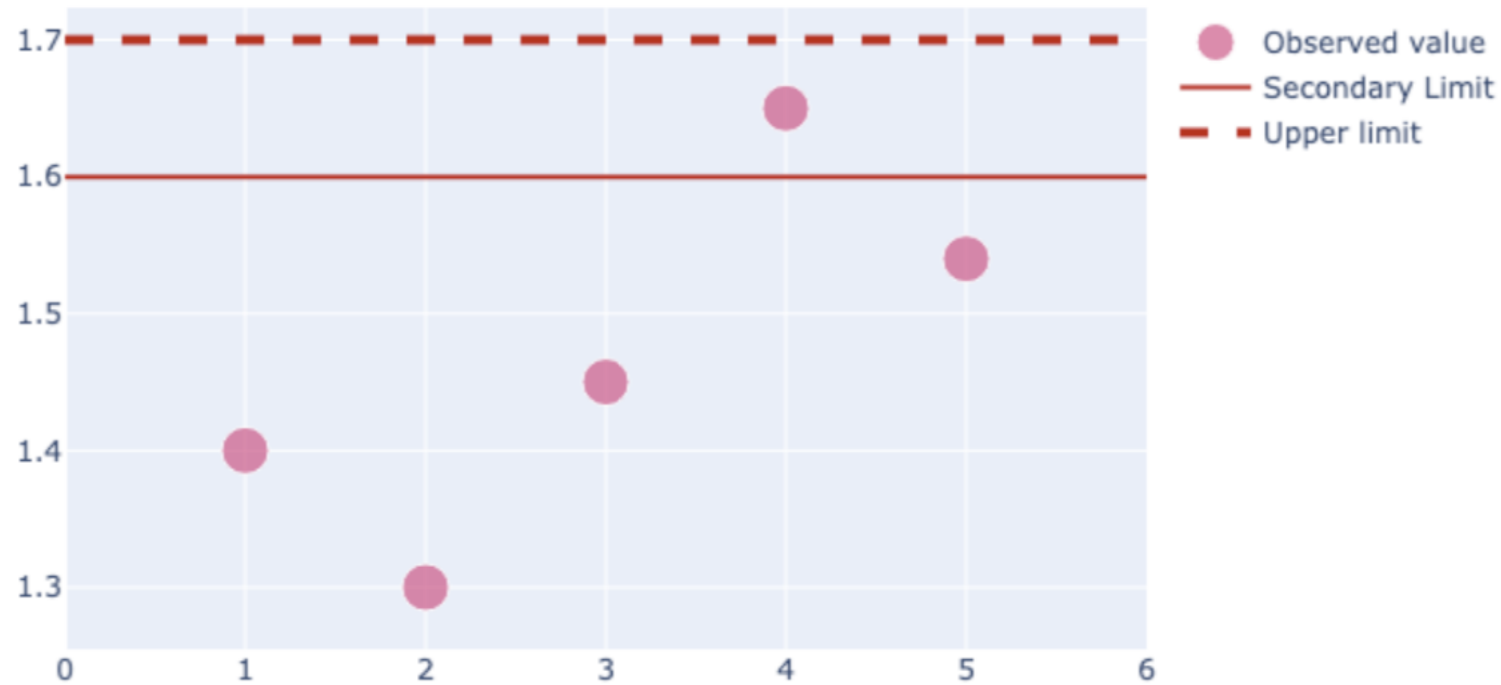
Quality Tolerance Limits

Examples of QTLs:

- % of randomized subjects not meeting per- protocol population criteria
- % of subjects with premature drug discontinuation (both arms)
- % of subjects classified as lost to follow-up in the close-out period of the trial

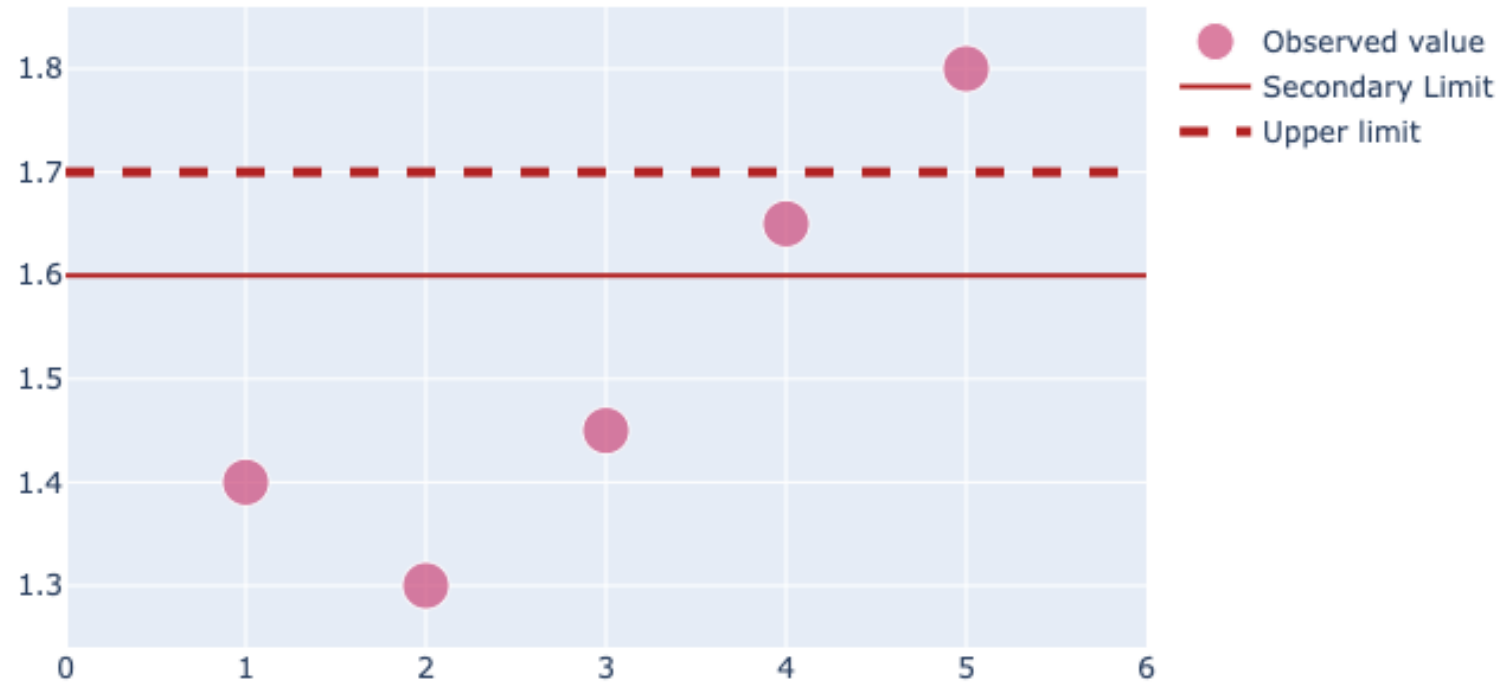
Quality Tolerance Limits

% of randomized subjects not meeting per- protocol population criteria



Quality Tolerance Limits

% of randomized subjects not meeting per- protocol population criteria





Original Research

Statistical Methods for Clinical Study Site Selection

Therapeutic Innovation
& Regulatory Science
1-9
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Abstract

Background: The US Food and Drug Administration conducts on-site inspections and data audits through Bioresearch Monitoring program for assurance of the quality and integrity of data in the pre- and postapproval processes. It is important to inspect the study sites that are different compared with other sites in clinical studies and identify the problems related to those sites. Usually one cannot inspect all the sites in a clinical study because of limited resources, and statistical tools are needed to help in selecting sites for inspection. **Methods:** We propose two technical approaches, namely Fisher combination approach and likelihood ratio test (LRT) approach, for site selection, with each approach integrating the information obtained from a *P* value matrix. The proposed approaches produce site rankings, and the sites with highest rankings may be selected for inspection. **Results:** The application of the approaches is demonstrated through a hypothetical data set reflecting the pattern of the real data in a premarket approval submission for a diagnostic device. The proposed methods are shown, through extensive simulations, to control false discovery rate, while maintaining good sensitivity. **Conclusion:** The proposed approaches will be useful for site selection process.

Take-Home Message

- ICH E6 R2 offers sponsors and CROs alike the opportunity to focus efforts on what matters most
- The change management process required for successful adoption should not be underestimated

| Thank You
Further Questions?