

A targeted approach to medical and safety reviews

PhUSE Annual Conference
Edinburgh
October 9, 2017

Erik Doffagne
Product Manager

Agenda

Introduction

Principles of a stat approach

Guiding Safety Review

Demo

Conclusion

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CluePoints Value Chain



Risk-Based Monitoring



Inspection Readiness



Clinical Data Quality Oversight



M&A Due Diligence

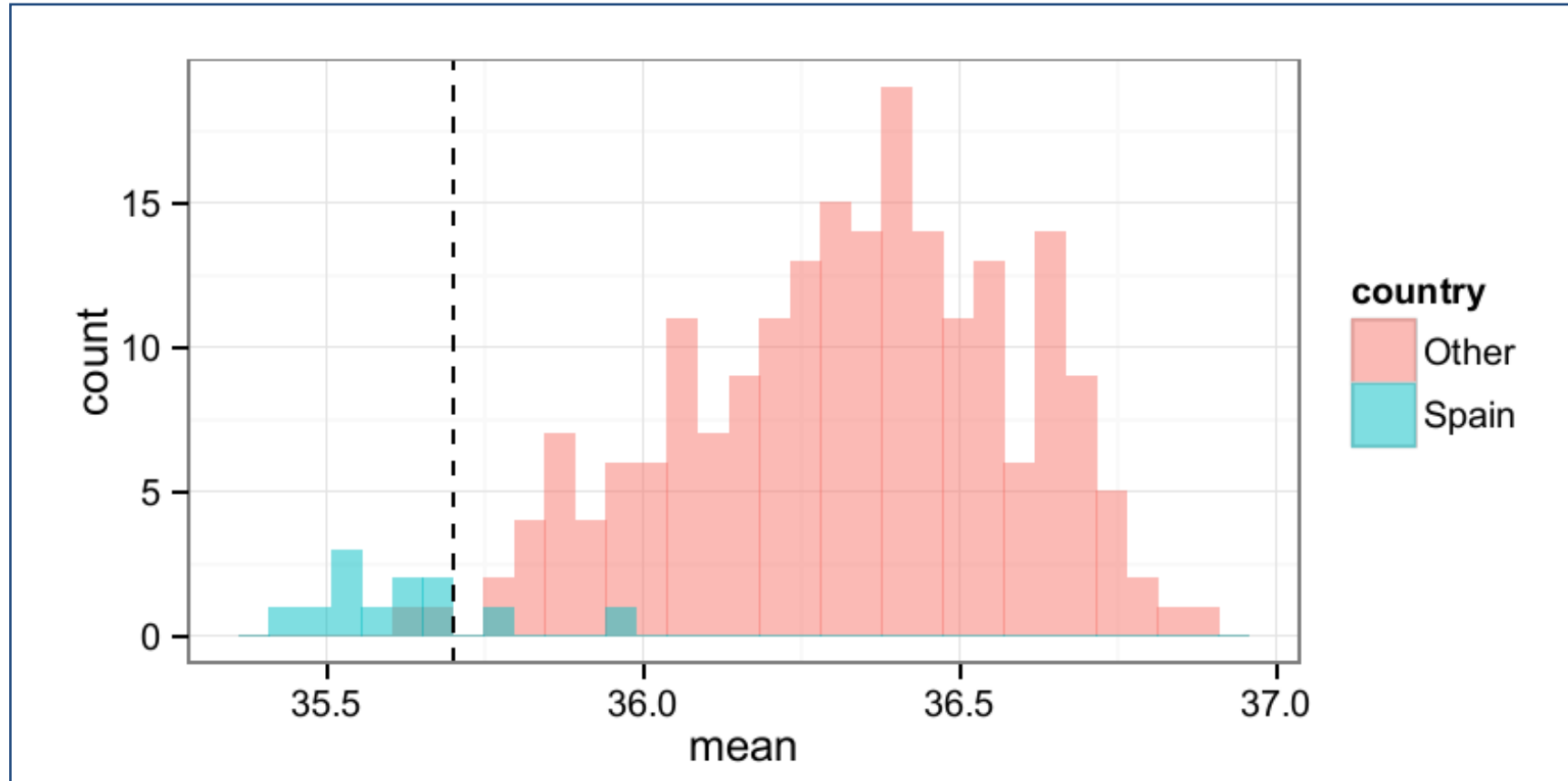
The value of CluePoints lies in its ability to identify anomalous data and site operational issues enabling pro-active and efficient management in clinical data quality & patient safety, optimization of on-site monitoring and a significant reduction in overall regulatory submission risk.

CSM: More than Just Fraud Detection in Clinical Research



- Assessment of Clinical and Operational Data Quality
- Detection of:
 - Staff Training issues
 - Misunderstanding/complexity of the protocol
 - Faulty Measuring Devices
 - Sloppiness/Laziness
- Support Monitoring Activities
 - Focused SDV (**Costs Reduction**)
 - Data 100% verified through Central Statistical Monitoring (**Quality Stamp**)

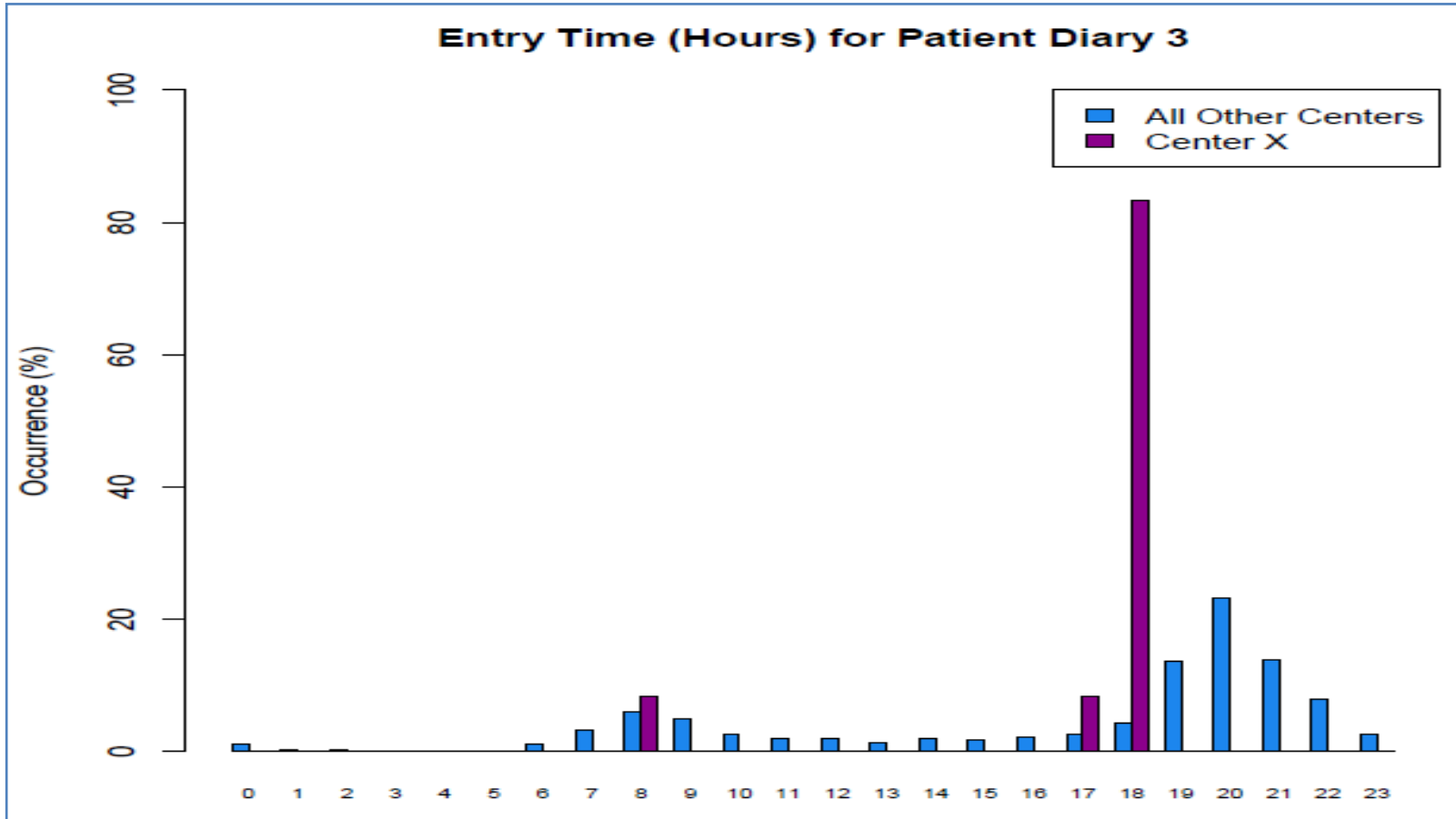
Quality Issue Example: Mis-Calibrated Equipment



Phase 3 Study –
Vaccination
200 Sites, 16000 Patients

Temperatures for all sites in Spain consistently in a lower range. Investigation revealed mis-calibrated thermometers shipped to all sites in Spain.

Quality Issue Example: Patient ePRO Diary Fraud



Phase 3 Study – Chronic Disease

Site with 15 patients – all ePRO diary entries done by site: Same time of day, same day for all patients. Sponsor removed all 15 patients from analysis.

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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

Therapeutic Innovation
& Regulatory Science
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STATISTICS IN BIOPHARMACEUTICAL RESEARCH
2016, VOL. 0, NO. 0, 1-11
<http://dx.doi.org/10.1080/19466315.2016.1164751>

Use of the Beta-Binomial Model for Central Statistical Monitoring of Multicenter Clinical Trials

Lieven Desmet, David Venet, Erik Doffagne, Catherine Timmermans, Catherine Legrand, Tomasz Burzykowski,
and Marc Buyse

Clinical Trials 20

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, Veronique Wile^h,
Catherine Legrand^h and Marc Buyse^{c,i}

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

THE ROLE OF BIOSTATISTICS IN
DETECTION AND TREATMENT OF
TRIALS[†]

STEPHEN L. GEORGE², STEPHEN L. GEORGE², STEPHEN L. GEORGE²,
BRUNO SCHERRER³, BRUNO SCHERRER³, BRUNO SCHERRER³,
JANE H. SCHERRER³, JANE H. SCHERRER³, JANE H. SCHERRER³

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

REVIEW ARTICLE

Data-driven risk identification in phase III central statistical monitoring

Catherine Timmermans¹ · David Venet² · Tomasz Burzykowski^{3,4}

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

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

L. Desmet^{a,*}, D. Venet^b, E. Doffagne^c, C. Timmermans^c, T. Burzykowski^d,
C. Legrand^a and M. Buyse^e

Statistics
in Medicine

CLINICAL
INVESTIGATION

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

STATISTICS IN MEDICINE
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THE ROLE OF BIOINFORMATICS
DETECTION AND

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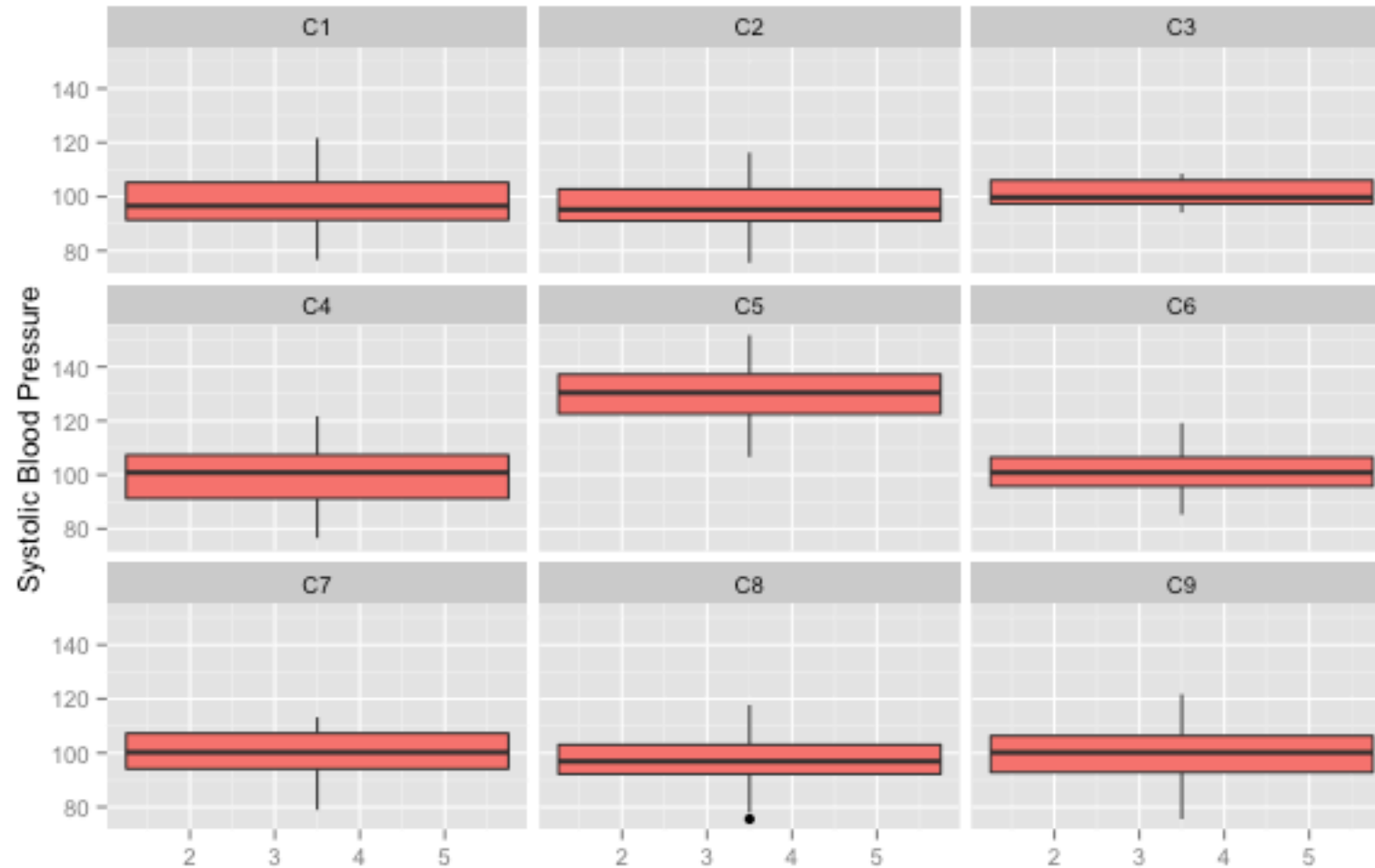
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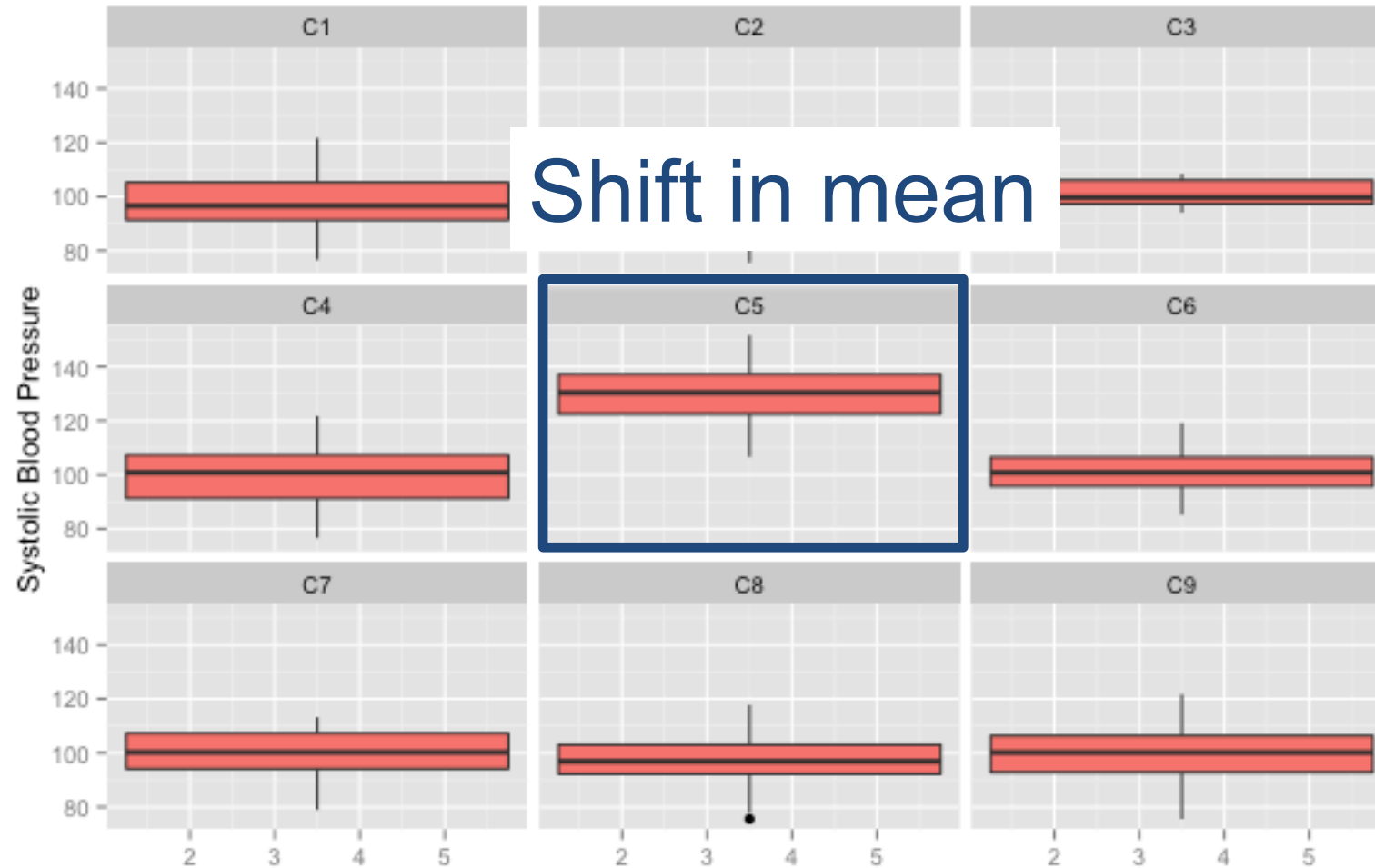
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CLINICAL
INVESTIGATION

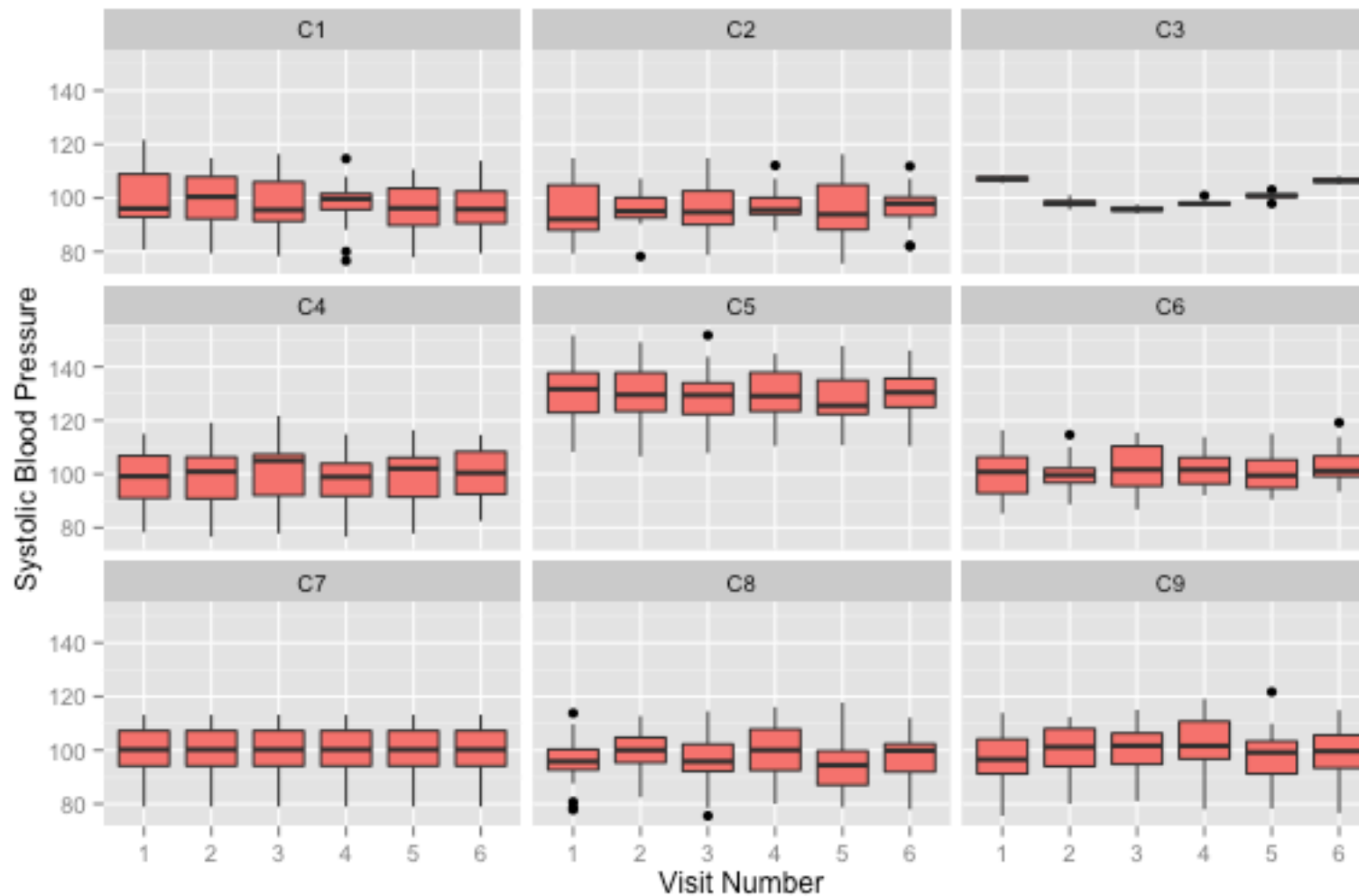
What patterns can be detected?



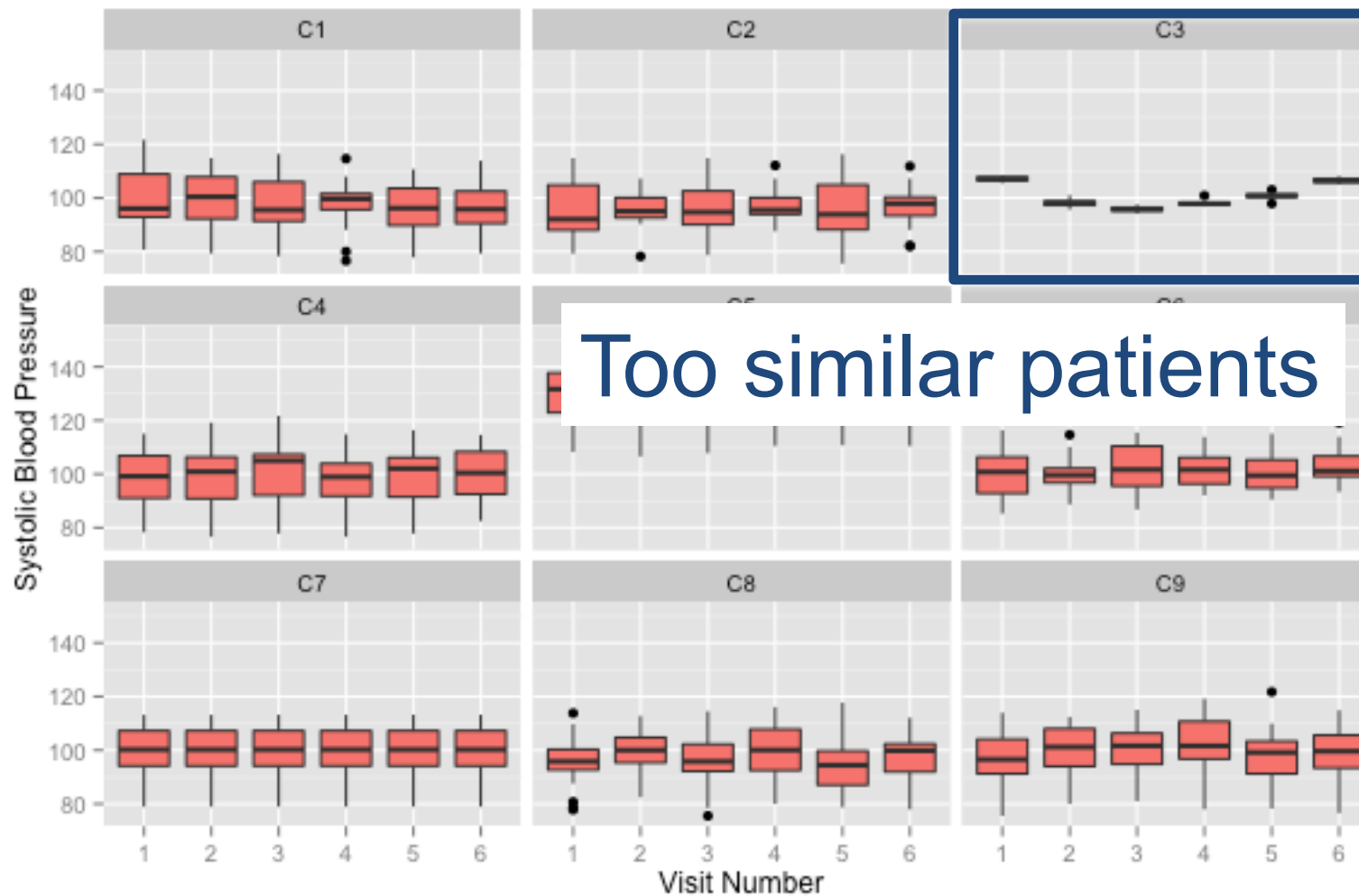
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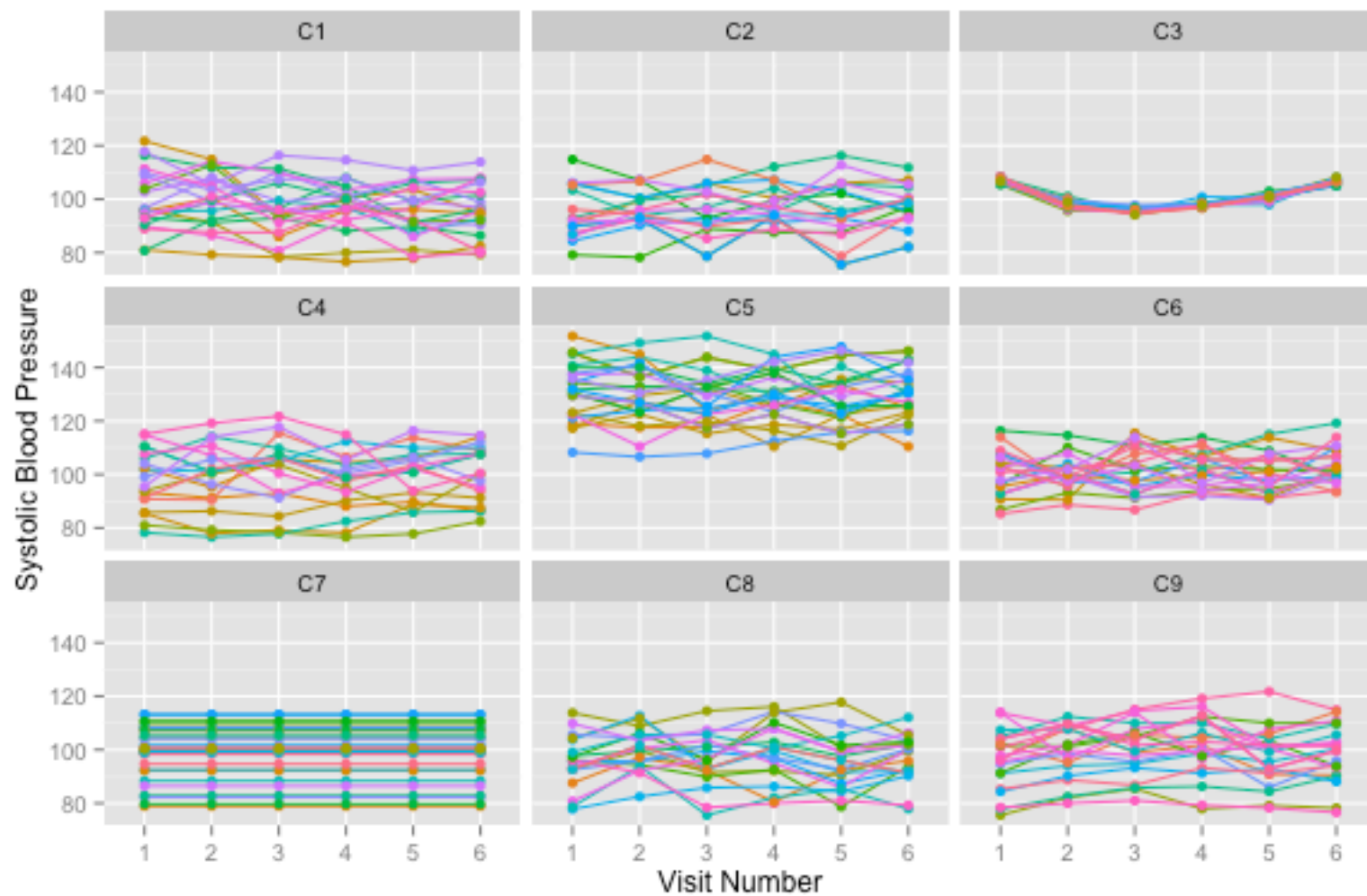
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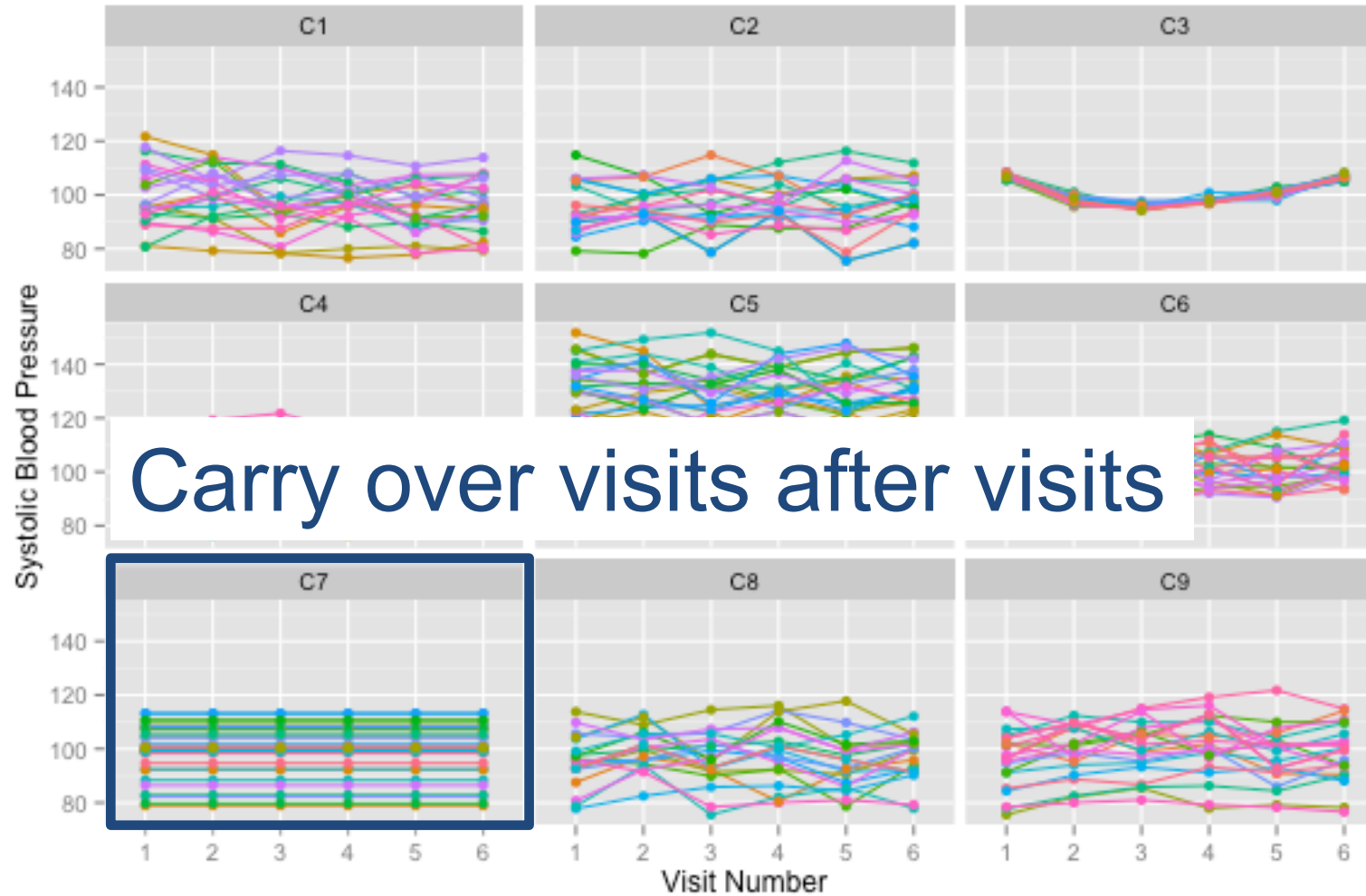
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What patterns can be detected?



What patterns can be detected?



Principles of the approach

- Compare centers against each other centers
- Use statistical models to assess significance
- Automated detection of outliers and atypical patterns

Overall Data Quality Assessment

- Perform many tests on all variables, regardless of the meaning or importance of data.
- These scores form a very large matrix with as many rows as centers and as many columns as individual tests
- Compute a single Data Inconsistency Score for each site

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Introduction

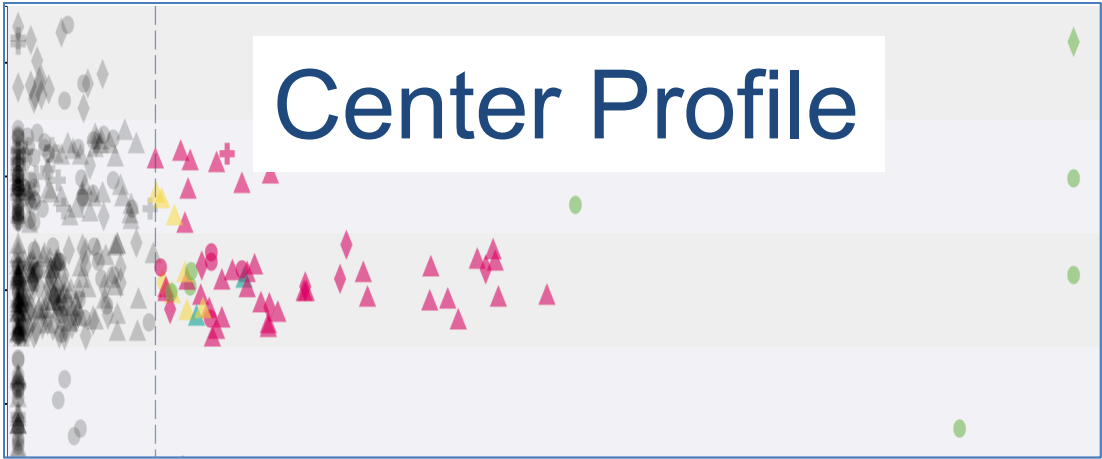
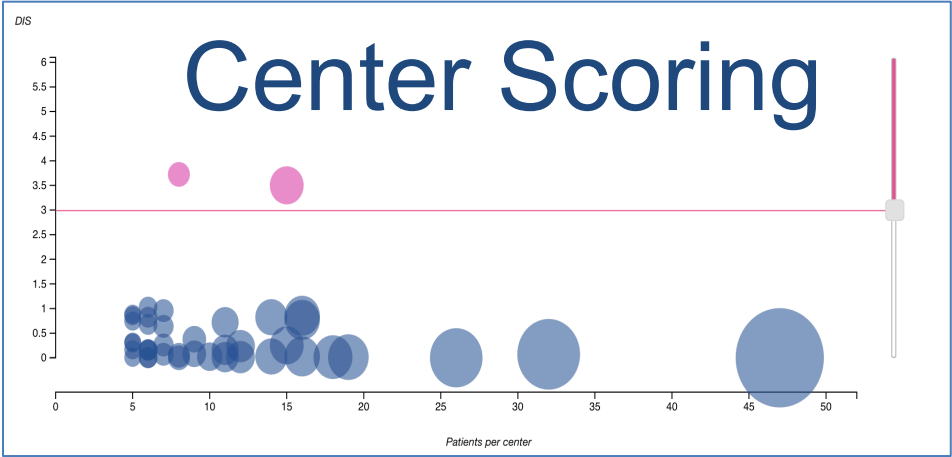
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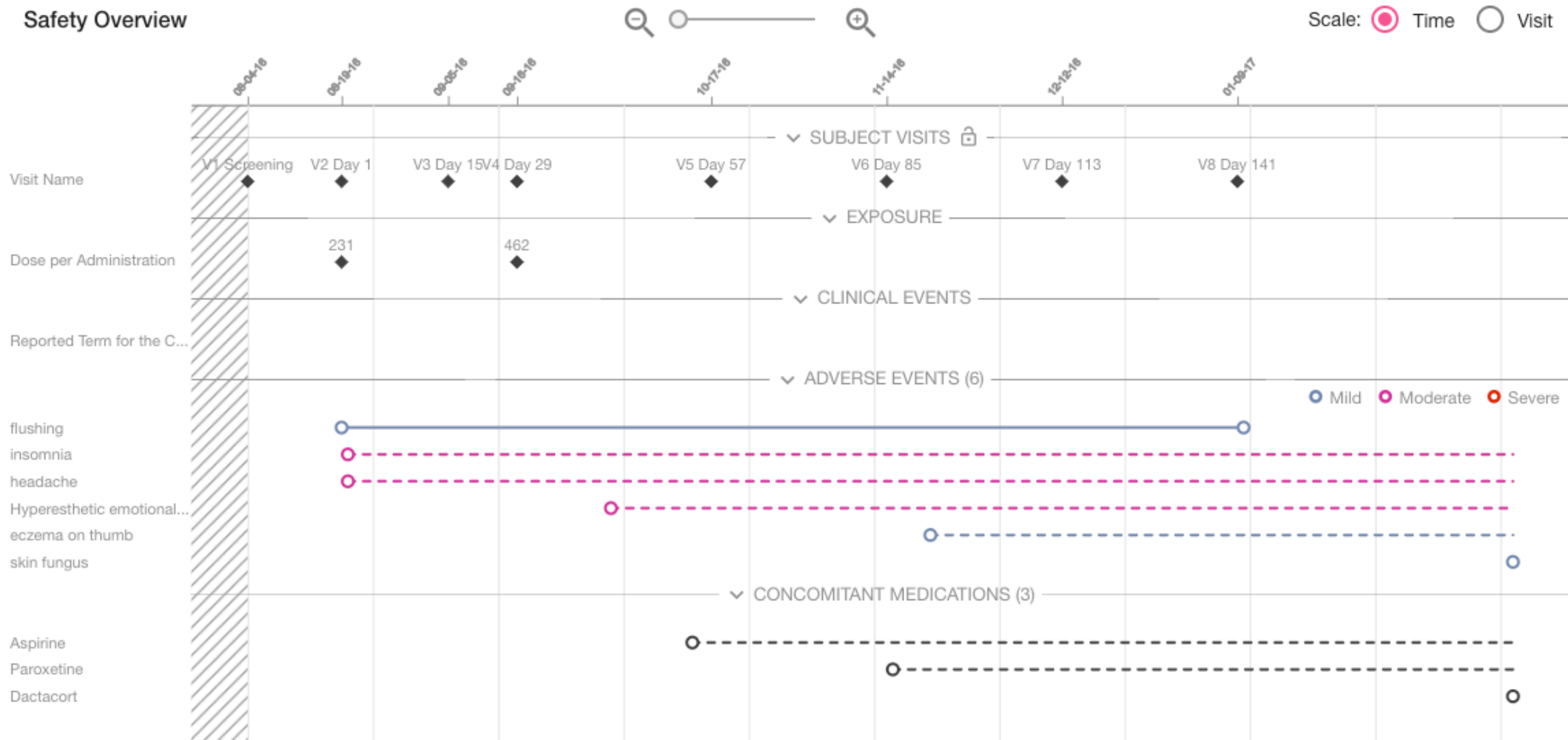
Identify patients at risk



Subjid	Center	Internal Visit Identifier	Erythrocytes_real
M0001-C302-010021	350007	5	5.06
M0001-C302-010048	350007	0	4.17
M0001-C302-010048	350007	1	4.42
M0001-C302-010048	350007	3	4.06
M0001-C302-010048	350007	5	4.09

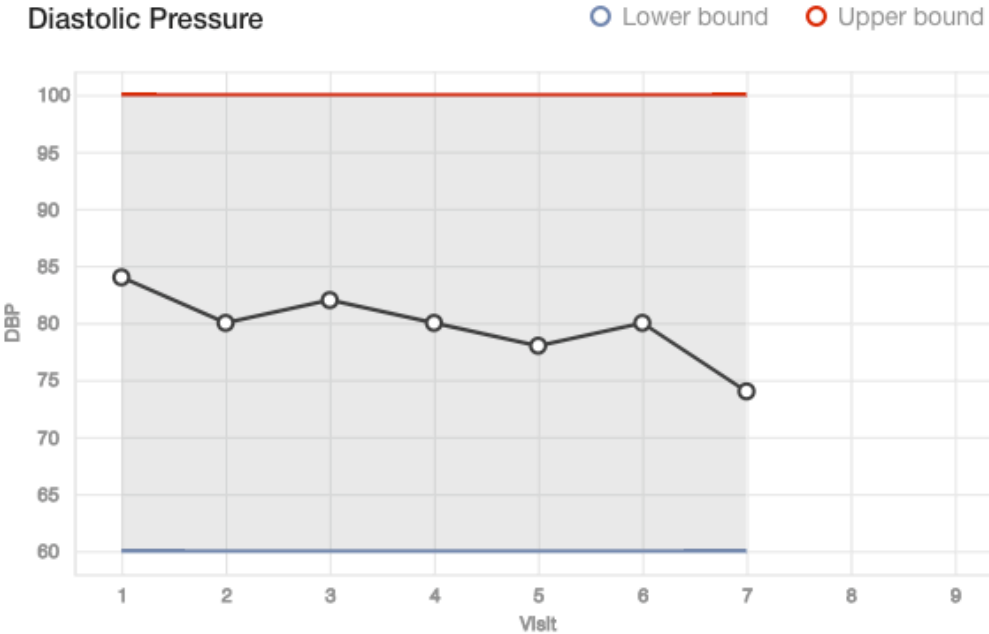
Patient Level Data

Review patients at risk

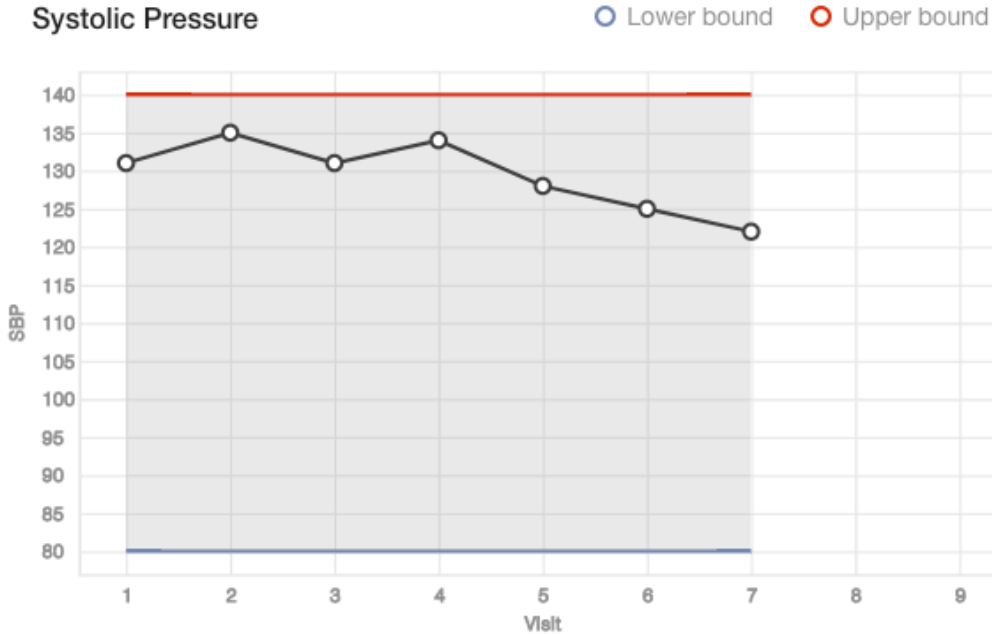


Review patients at risk

Diastolic Pressure



Systolic Pressure



Pulse Rate



Summary

Visit Number	Visit Name	DBP	SBP	Pulse
1	Visit 1.000	84	131	71
2	Visit 2.000	80	135	82
3	Visit 3.000	82	131	77
4	Visit 4.000	80	134	71
5	Visit 5.000	78	128	76
6	Visit 6.000	80	125	79
7	Visit 7.000	74	122	76

Track signals identified during patient reviews

New (1)

Ignore (0)

Watch (0)

Alert (7)

Actions (6)

Export to File

Filter

Center	Country	#Patients	Name
350007		15	Atypical lab results
350007		15	All records created around 6pm
340012		9	Test
350007		15	Constipation years - atypical
350007		15	Atypical Vital Sign
350007		15	Propagation in weight

Description

Signal ID: SIG-0004

All records created around 6pm

Mitigate

Details (1)

Actions (1)

History (1)

Display label ☒

Domain	Dataset	Variable	Test	Score	Rank	Observed	Expected
ePRO	label_bm	creation_time_h...	Proportion	0.00	1	0.68642	0.0570412

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- The combination of interactive visualization and advanced statistical methods allows medical reviewers to focus effort where it matters the most.
- Traceability is key to ensure that every action and decision are documented.



CluePoints

INTELLIGENT STATISTICAL MONITORING

| Thank You
Questions?