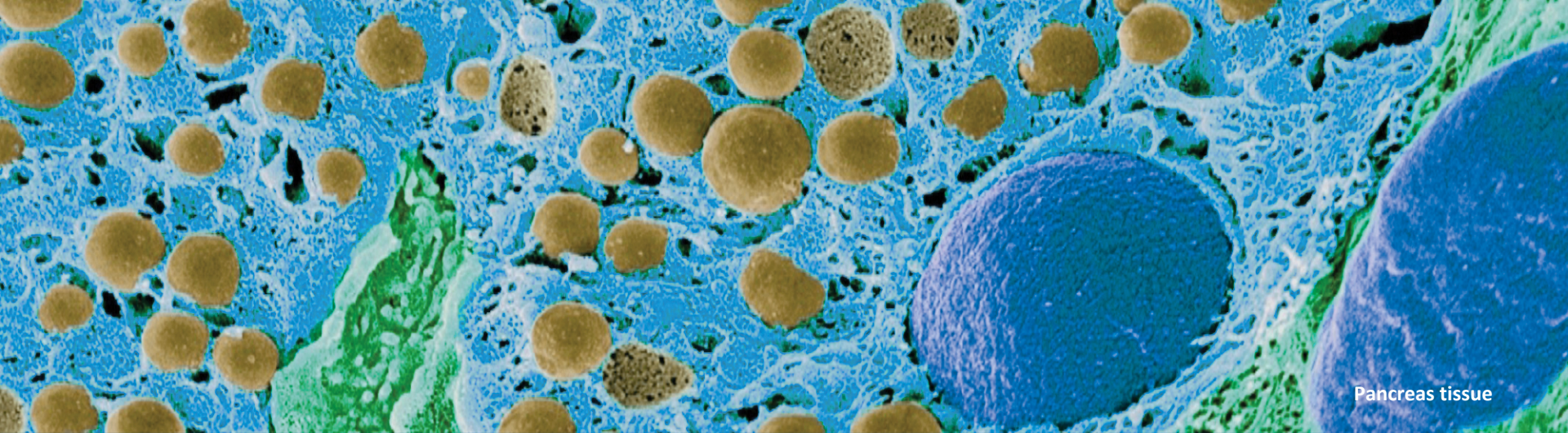




Pancreas tissue

A Three-Pronged Approach to Central Monitoring to Identify Potential Risks and Ensure Data Quality

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Marianne van de Ven, TA Lead Oncology
Risk Management & Central Monitoring
Janssen R&D, LLC | **13** November 2019

Speaker's introduction

- Marianne van de Ven is a TA lead in the Risk Management & Central Monitoring Department (RM & CM) in Janssen. In this role, she is accountable for the oversight, execution and management of the Analytical Risk-Based Monitoring (ARBM) processes for her TA (solid tumor) and its associated programs and trials. Marianne joined Janssen in 1996 as a Site Manager and held several positions in clinical R&D since then. She started in the RM & CM department at the end of 2017. Marianne holds a MSc degree in Human Nutrition at the Agricultural University of Wageningen, the Netherlands.
- Jill Ophoff is a technical data architect within the clinical research department of Janssen. Before joining Janssen, she obtained a PhD in Medical Science and worked for three years in healthcare as a scientific collaborator conducting research at the pediatric pulmonology department as well as assisting with sponsored clinical trials. Jill Joined Janssen in 2012 as reporting analyst at the business quality department where she was first involved in the data analysis and reporting of product complaints. Later she moved to the central statistical surveillance group of Janssen where she successfully implemented study specific reports for risk-based monitoring. She continues taking up this responsibility in her current role as technical data architect.

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Central Monitoring at Janssen R&D

- Quality is the absence of errors that matter.
- Group formed in 2013 with 5 employees and has expanded to 50+ employees in 2019 across multiple Therapeutic Areas and Sectors.
- Our central monitoring capabilities have expanded and enhanced our ability to detect signals indicating potential risks, which can be recognized and actioned upon in a timely manner to drive data quality.

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Case Studies

- Use of a dashboard with *standard* Key Risk Indicators to indicate potential risks in countries / sites
- Use of *Study-Specific* Reports to indicate potential risks in countries/sites related to quality of critical data
- Use of *Central Statistical Surveillance* to identify data anomalies

Centralized Monitoring

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graph TD; A[Centralized Monitoring] --- B[ ]; B --- C[KRI]; B --- D[SSR]; B --- E[CSS];
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Case Study: Key Risk Indicator Dashboard

KRI

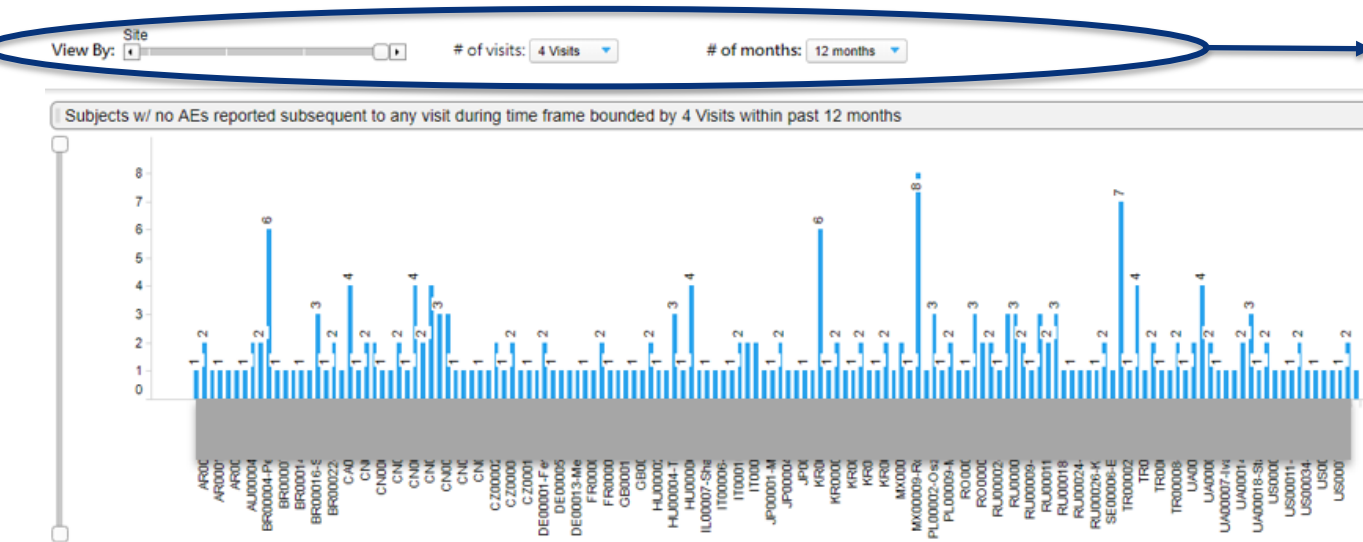
SSR

CSS

Key Risk Indicators (KRIs) available for Standard Review



Subjects with No reported AEs



View by slider:
Study, Country, Site

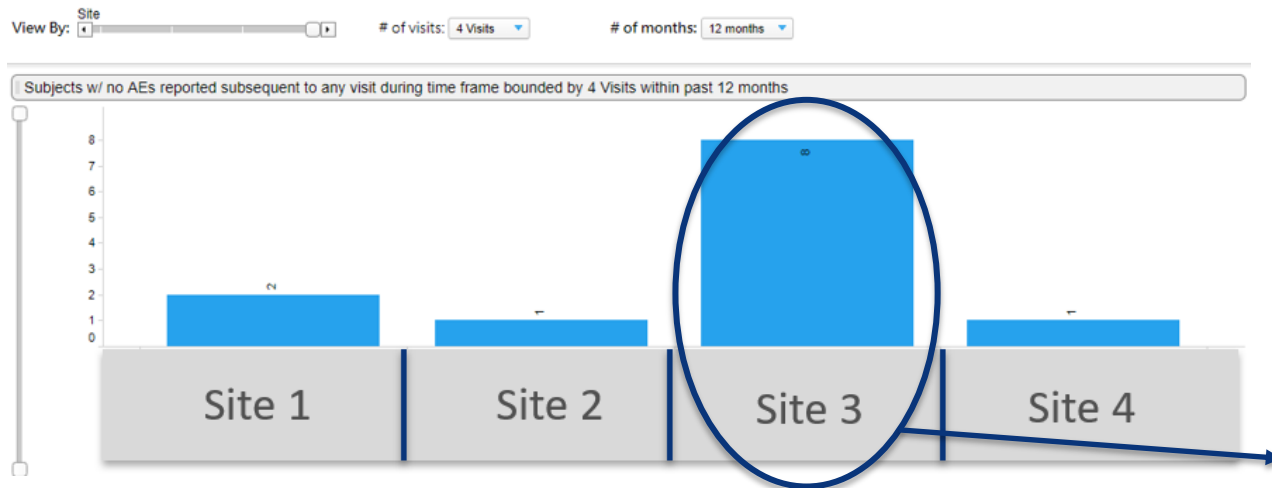
of Visit selection:
1 – 12 visits

of months selection:
6, 12, 18 months

Select based on
patient visit schedule
on site for most
effective review

Subjects with No reported AEs

Deeper dive to one country (analysis done on all countries):



Country has 4 sites with patients who have not reported AEs in their last 4 visits over 12 months

Is there a signal for site 3?

Details in table (not shown) shows 10 patients on treatment – 8 have not reported AEs

Yes, would discuss with study team at working group meeting

AE Reporting Escalation and Resolution

Escalation:

- Finding is discussed at working group meeting and documented for traceability and accountability
- Designated representative from central team contacts site:
 - Site confirmed they are knowledgeable of Janssen AE reporting requirements
 - Site reviewed patient documentation and confirmed no missed AEs

Resolution:

- Central team representative shares information with central monitor
- Finding closed with outcome documented

Centralized Monitoring

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graph TD; A[Centralized Monitoring] --> B[Case Study: Study-specific Reports]; B --> C[KRI]; B --> D[SSR]; B --> E[CSS];
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Case Study: Study-specific Reports

KRI

SSR

CSS

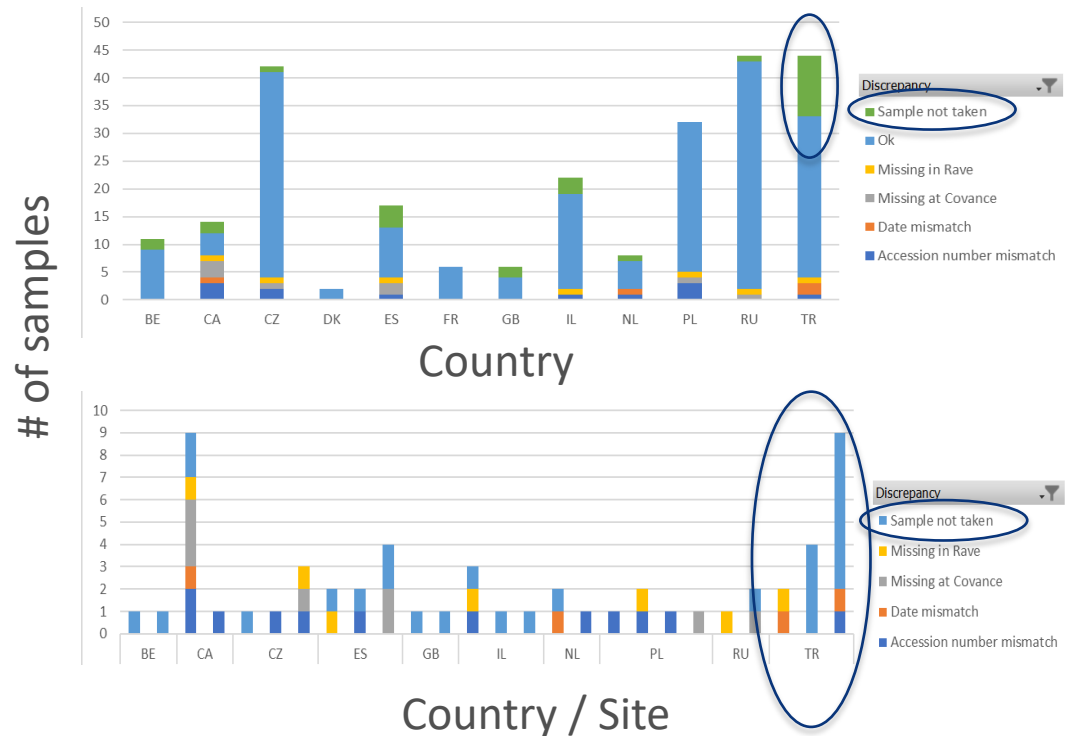
Protocol Derisking and Study Specific Reports

- Protocol Derisking:
 - Series of collaborative meetings with cross functional study team
 - Identification and mitigation of **critical to quality factors** related to the study
- Study Specific Reports (SSRs):
 - Report programmed in SAS® (Life science analytics framework)
 - Available to study team as visualizations (in Tibco Spotfire®) to identify and trend potential risks
 - Unique to each study team's needs
 - Any centrally available data can be monitored through an SSR
 - 'near' real time data is used

Critical to Quality Factor Example

- Biomarker samples taken per protocol
 - Related to study endpoint
 - Central oversight through SSR beneficial to team
- Study specific report created to identify and trend if samples weren't taken per protocol or not received at central vendor
- Any signals identified by central monitoring are discussed at working group meeting

Biomarker Sampling Study Specific Report



Central Monitor noticed for two consecutive months, biomarker samples were not taken in a specific country and raised as a signal in working group meeting

Biomarker Sampling Escalation and Resolution

Escalation:

- Finding is discussed at working group meeting, and documented for traceability and accountability
- Designated representative from central team contacts sites
 - Sites acknowledged confusion around protocol sampling requirements
- Different lab contacted Janssen in parallel

Resolution:

- Site staff retrained on protocol sampling
- No additional issues noted after sites' retraining
- Biomarker sampling continued to be reviewed in working group meetings
- Finding closed after issue resolved at site with outcome documented

Centralized Monitoring

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graph TD; A[Centralized Monitoring] --> B[KRI]; A --> C[SSR]; A --> D[CSS]
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Case Study: Central Statistical Surveillance

KRI

SSR

CSS

Central Statistical Surveillance during study conduct

- Additional layer of protection for subject safety and data quality
 - Looks at entire clinical trial data set and naturally occurring relationships in the data
 - Ability to detect otherwise hard to find data anomalies
 - Early detection of critical data issues that could jeopardize overall study data
- Central Statistical surveillance (CSS)
 - Based on SDTM data
 - Programmed in R and made available to the team through visualizations in Tibco Spotfire®
 - Study needs to meet minimum criteria of 20 sites with 3 pts & 3 visits of data
 - Performed on numerical data linked to a visit date such as Questionnaires, Lab, ECG & EDC

Central Statistical Surveillance - basics

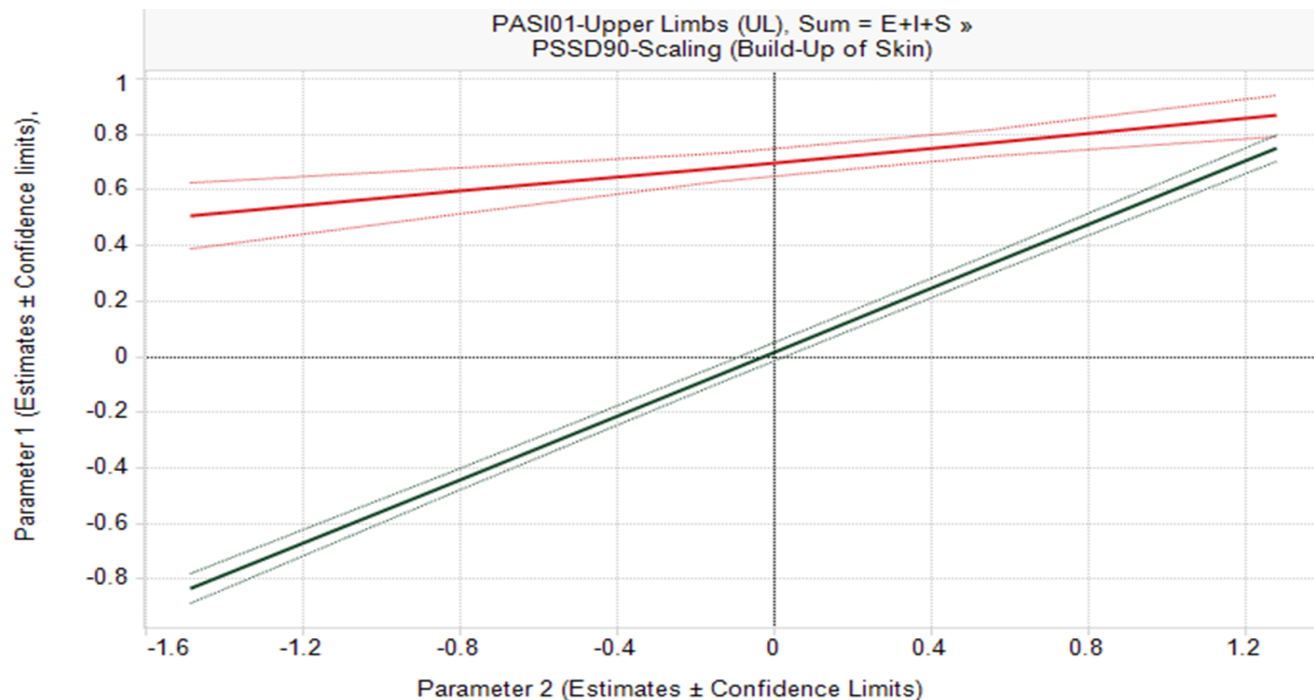
- A combination of different statistical techniques to detect abnormal patterns in the data.
- It uses the structured nature of clinical data
 - Between clinical parameters: Different measures taken from the same subject at the same time should be related to each other (to varying degrees)
 - Subject profiles over time: the same measurement from the same subject at different visits should be related
 - Between subjects: the same measurement for different subjects should NOT be related

Central Statistical Surveillance in practice

- Naturally occurring relationships are determined for all data within a trial
- The 'Naturally occurring relationships' on the study level are used as the comparator for the site level relationships to identify sites that differ
- Detect data patterns that are different from the norm, which may indicate intentional or unintentional noncompliance and significant data quality issues
- Identify sites that need further investigation or further focused monitoring

Example relationship between clinical parameters

Different relationship between questionnaire responses



LEGEND:

- **RED LINE:** Site results
- **GREEN LINE:** Study results**

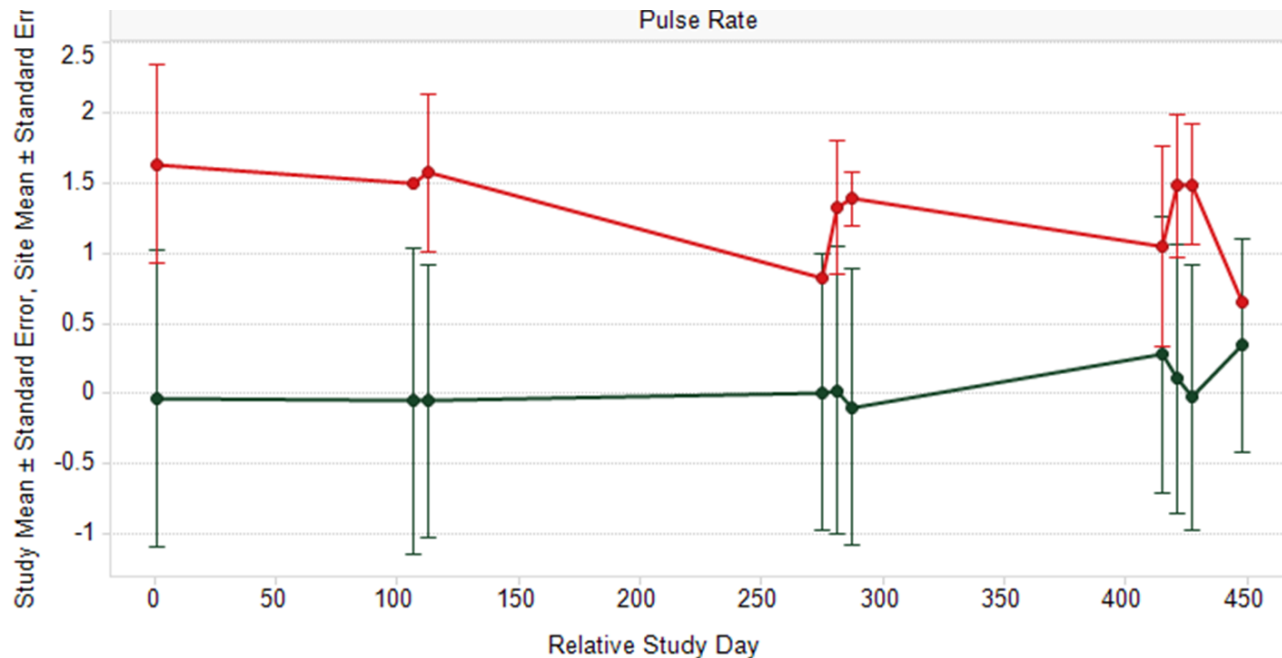
Study averages include all data with the exception of the site under review

Different relationship between questionnaire responses

- Potential root causes:
 - Misunderstanding of the question
 - Technical issues such as equipment wrongly calibrated
 - Data not accurately gathered
 - Site staff misunderstanding of assessment/protocol (cause for re-training)

Example site result changes over time

Pulse Rate test results are consistently higher than average



LEGEND:

- **RED LINE:** Site results
 - **GREEN LINE:** Study results**
- **Study averages include all data with the exception of the site under review**

Error bars represent the average difference between the test results at the respective study day

Parameter Averages v. Relative Study Day | Log-Normalized Values

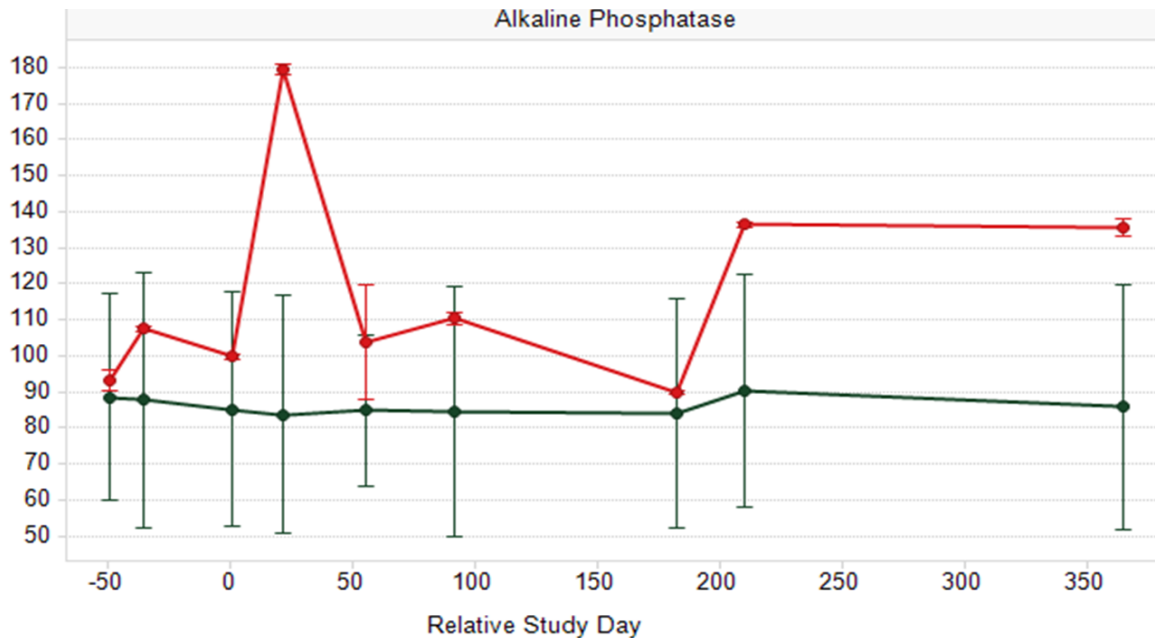
Pulse Rate test

- Potential root cause and recommendation to the study team:
 - Equipment failure or calibration issue
 - Test not administered correctly
 - Consistent demographic differences in subjects
 - Consistently poor transcription

Example between subject results

Lab results vary less than in a typical site

Study Mean $\pm$ Standard Error, Site Mean $\pm$ Standard Error



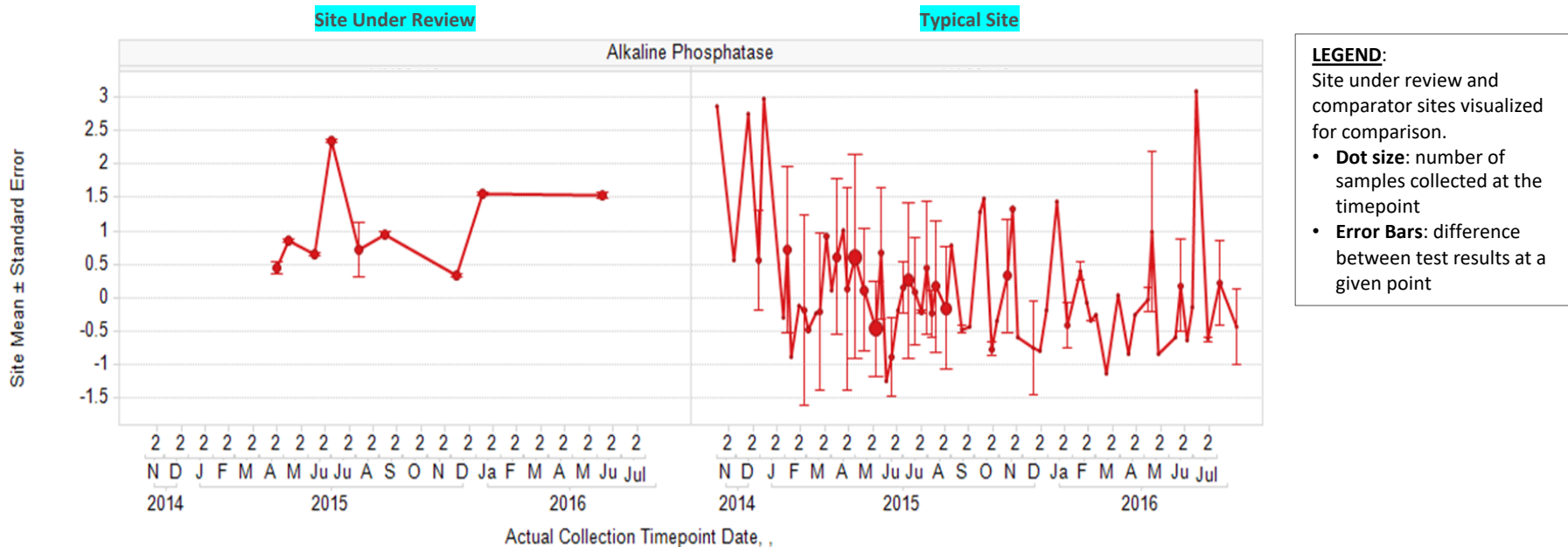
LEGEND:

- **RED LINE:** Site results
 - **GREEN LINE:** Study results**
- **Study averages include all data with the exception of the site under review**

Error bars represent the average difference between the test results at the respective study day

Example between subject results - continued

Lab results vary less than in a typical site



Similar Lab test

- Recommendation to Study Team:
 - Review site level laboratory results to determine if there are any clinical issues
 - Review source notes to ensure batching of subjects/samples was not an issue

Identification, Follow-Up & Resolution

- Dedicated team of run and analyze the CSS report outcome
- CSS analyst together with central monitoring manager discuss within study team
- Potential root causes and action items are discussed:
 - gather more information on next on site monitoring visit
 - Perform medical review of the site to determine if there are any medical anomalies that could contribute to the results differing from the norm
 - Reach out to vendors
- Escalate compliance concerns to quality group
- The follow up investigation and potential resolution actions are presented to the study team and documented
 - Potential resolution actions could include retraining of assessors or re-education of site staff

Centralized Monitoring

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graph TD; A[Centralized Monitoring] --> B[Points to consider]; B --> C[KRI]; B --> D[SSR]; B --> E[CSS]
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Points to consider

KRI

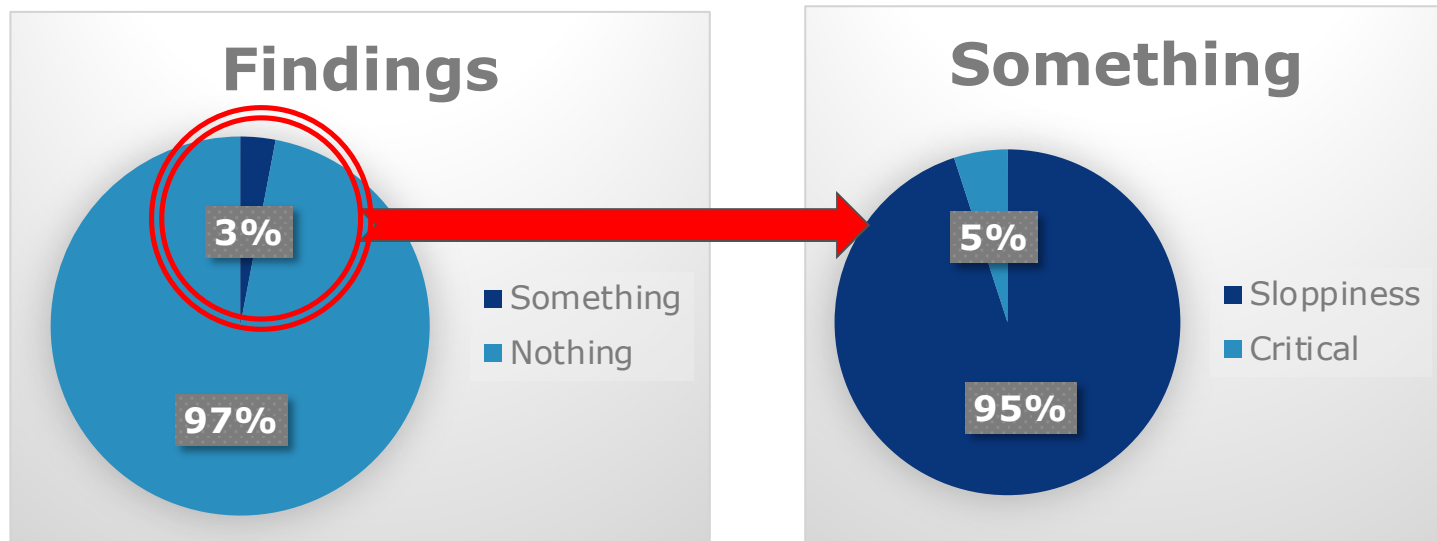
SSR

CSS

Points to consider:

- SSRs
 - Availability of vendor data early in the study
 - Standardization vs flexibility
 - Skill set needed to translate business need to requirements
- CSS
 - Amount of data available for analysis
 - Skill set needed to interpret data
 - Skill set needed to provide findings, possible root causes, and recommended follow-up actions to clinical teams

CSS Expectations



Can: Identify outliers based upon statistics using numerical data
Use human intervention to rule out obvious false positives

Can't: Take the place of Therapeutical Area expertise on the disease state and protocol nuances

Centralized Monitoring

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graph TD; A[Centralized Monitoring] --> B[Summary & Conclusion]; B --> C[KRI]; B --> D[SSR]; B --> E[CSS];
```

Summary & Conclusion

KRI

SSR

CSS

Where we've been and where we're going?

The Past

- Standard and study specific reviews were manual and time consuming

The Present

- Automation enables regular refresh of data into standard and study specific dashboards for easy analysis
- Central Statistical Surveillance is available

The Future

- Combine three types of reviews into one dashboard to allow more holistic review of site risk
- Link follow-up actions with findings to measure impact of corrective and preventive actions
- Use of predictive analytics to plan for future risk and workload at a site

Conclusion

Using this three-pronged approach to central monitoring, we are able to

- Identify:
 - Site/country risk signals
 - Critical missing and discrepant data
 - Protocol non-compliance
- Quickly conduct root cause analysis and take timely and appropriate corrective and preventive actions
- Be better prepared for database locks and inspections
- More accurately forecast resource needs
- Have clearer insights to focus attention on errors that matter

Questions?



References

Central Statistical Surveillance in Clinical Trials. Kris Lauwers, Stefan Van Yper, Giordano Lo Regio.

<https://www.lexjansen.com/phuse/2018/ar/AR04.pdf>

Thank you

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