CluePoints
INTELLIGENT STATISTICAL MONITORING

Central Statistical Monitoring: Insights from the analysis of a large database of trials

ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop
25 SEP 2020

Laura Trotta CluePoints S.A., Belgium
Steve Young CluePoints Inc., King of Prussia, PA
Marc Buyse CluePoints S.A., Belgium

Email: laura.trotta@cluepoints.com

ABSTRACT

Background

As part of Risk Based Monitoring, Central Statistical Monitoring (CSM) aims at detecting data anomalies in clinical trials.

Method

We analyzed all statistical scores and signals generated by use of CSM for a large database of trials and sponsors.

Goal

The goal of this research work was to assess the proportion of signals generated by use of CSM that was compelling to the study team.

Results

24% of the generated signals were mitigated as Alert by study teams, showing that CSM is an effective tool to point towards actionable interventions to improve data quality in clinical trials.

INTRODUCTION

Central Statistical Monitoring relies on the comparison of data across sites using a **wide range of statistical tests**.

One column per test x variable

One row per center

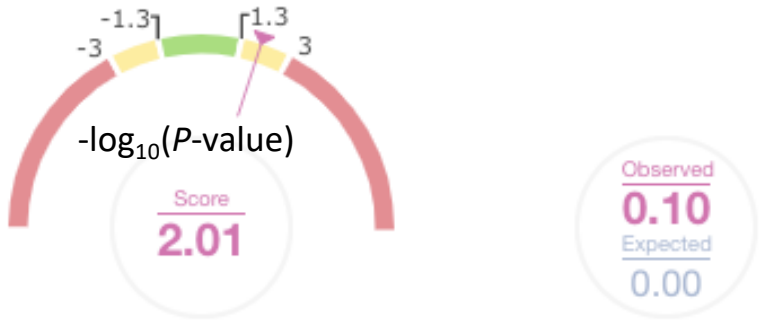
CRF Lab ECG. ePRO CTMS / IVRS

Test	Mean Var WEIGHT	Between pat. Var. WEIGHT	Within pat. Var WEIGHT	Rate Var AETERM
Center 1	0.1	1	0.1	0.9
Center 2	1	0.09	0.3	0.8
Center 3	0.5	0.2	0.4	0.2
Etc.	Etc.	Etc.	Etc.	Etc.

Matrix of *P*-values

In a **Data Quality Assessment (DQA),** the large matrix of *P*-values is summarized into **Data Inconsistency Scores (DIS)** that point towards sites with anomalies.

In addition, specific *P*-values are monitored individually as **Key Risk Indicators (KRIs).**



Description

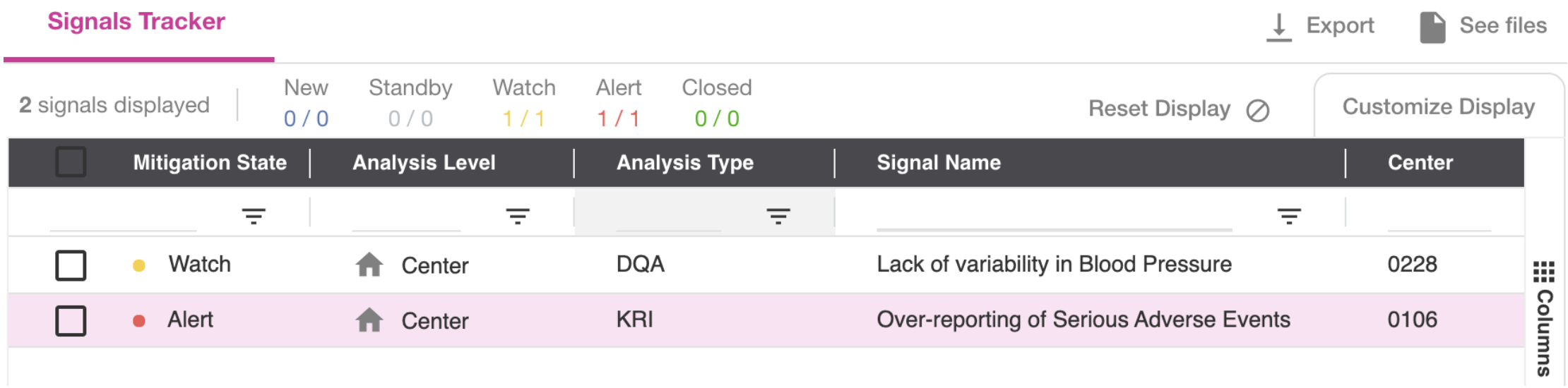
A site's number of serious AEs per patient visit - cumulative.

METHOD

CSM was applied to a **large database of trials**, generating a high number of scores, i.e. *P*-values.

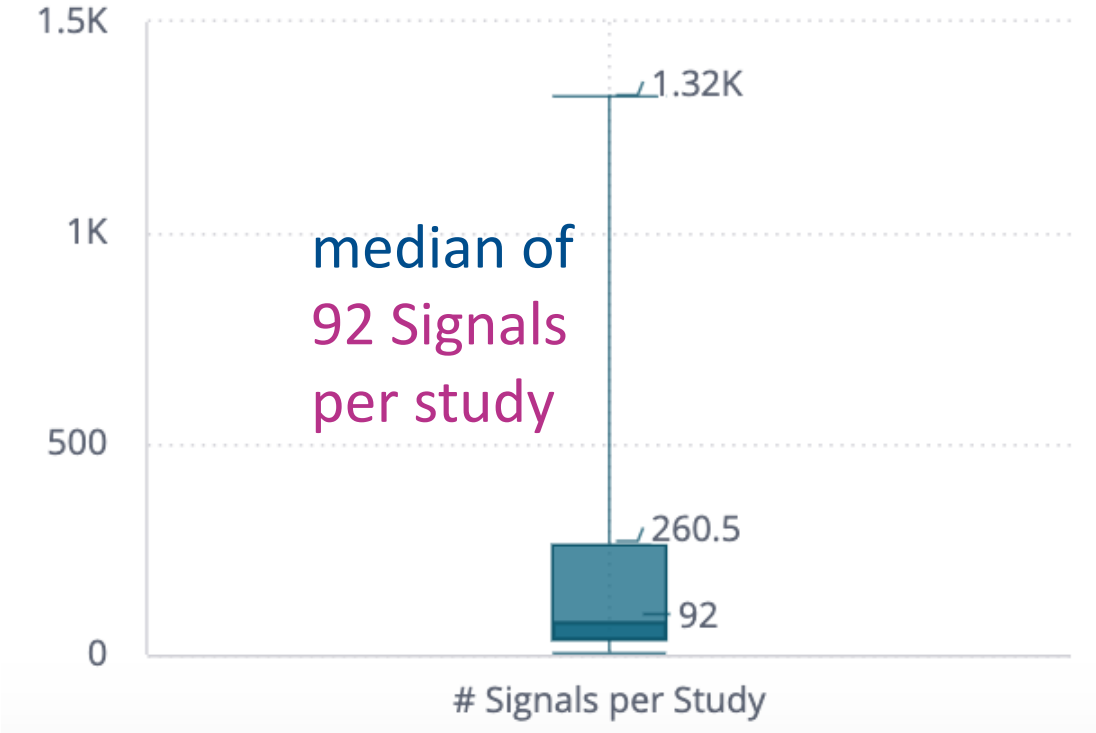
Data anomalies were **documented and mitigated** by study teams into a centralized **Signal Management System**.

Central Statistical Monitoring Platform	N
Organizations	109
Studies	621
Studies with Data Quality Assessment	244 (39%)
Studies with Key Risk Indicators	262 (42%)
Studies with Signals	262



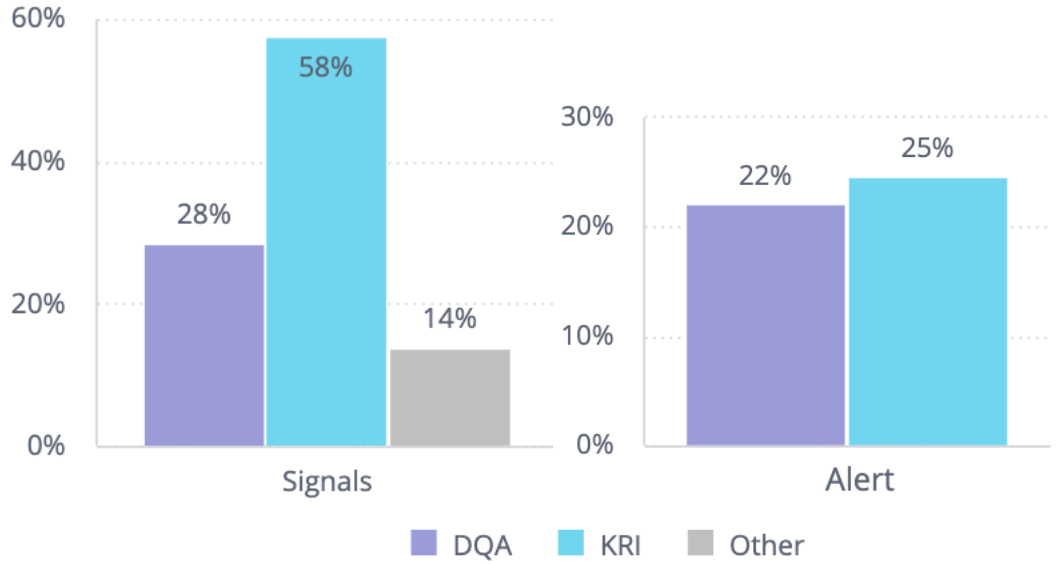
RESULTS (1/2)

Out of more than 154.6 M *P*-values, 48761 Signals were generated across all studies.



Out of all Signals, 58% were generated from KRI and 28% from DQA*.

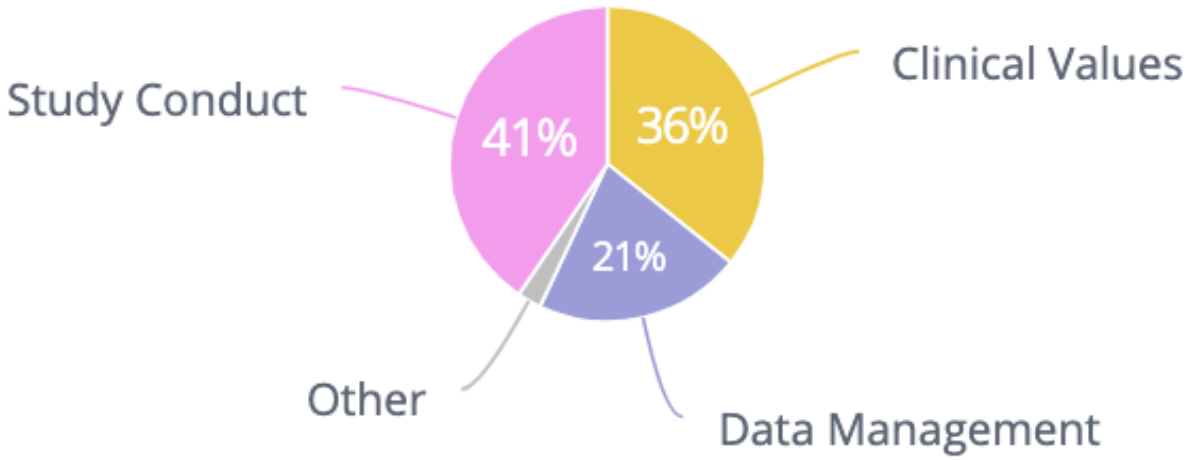
24% of Signals were mitigated as Alert with 22% for DQA and 25% for KRI.



*Other: signals generated from patient dashboard [2%] or generated prior to Q2 2018 with unknown origin [12%].

RESULTS (2/2)

41% of Signals mitigated to Alert were associated with Study Conduct



Study Conduct - Examples
Informed Consent not obtained for any patient at the site
High proportion of missing glucose tests due to the failure of new staff in delivering testing kits in time
Higher than expected number of staged procedures due to a mistake at the site

Clinical Values - Example
High number of lab tests with values outside of the standard reference range

Data Management – Example
No CRF page entered for DISPOSITION at the site

CONCLUSION

- The cost of clinical trials is huge and on-site monitoring activities represent a large fraction of total costs
- In this research work, we showed that Central Statistical Monitoring can be used to generate signals that are compelling to the study team with minimum data review
- By contrast to Source Data Verification (SDV) that mainly corrects random transcription errors in clinical data, CSM points towards systematic anomalies that are related to study conduct and for which actionable interventions can be set to improve overall data quality
- CSM is particularly relevant in the context of the Covid19 crisis, where onsite monitoring activities are suspended

BIBLIOGRAPHY

- 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
- Trotta L, Kabeya Y, Buyse M *et al.* (2019) Detection of atypical data in multicenter clinical trials using unsupervised statistical monitoring, *Clin Trials* 16: 512–522
- Brosteanu O, Schwarz G, Houben P *et al.* (2017) Risk-adapted monitoring is not inferior to extensive on-site monitoring: results of the ADAMON cluster-randomised study. *Clin Trials* 14: 584–596
- U.S. Department of Health and Human Services. (2013) Food and Drug Administration Guidance for Industry. *Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring.* National Academies Press, DC

CluePoints
INTELLIGENT STATISTICAL MONITORING

Thank You

Further Questions?

Laura Trotta
R&D Manager
laura.trotta@cluepoints.com