

Driving Quality into Clinical Trials

PhUSE Annual Conference 2015
Vienna, Austria
October 11-14, 2015

Erik Doffagne
Product Manager

Misconduct and Quality issues in Clinical Trials



Research

Original Investigation

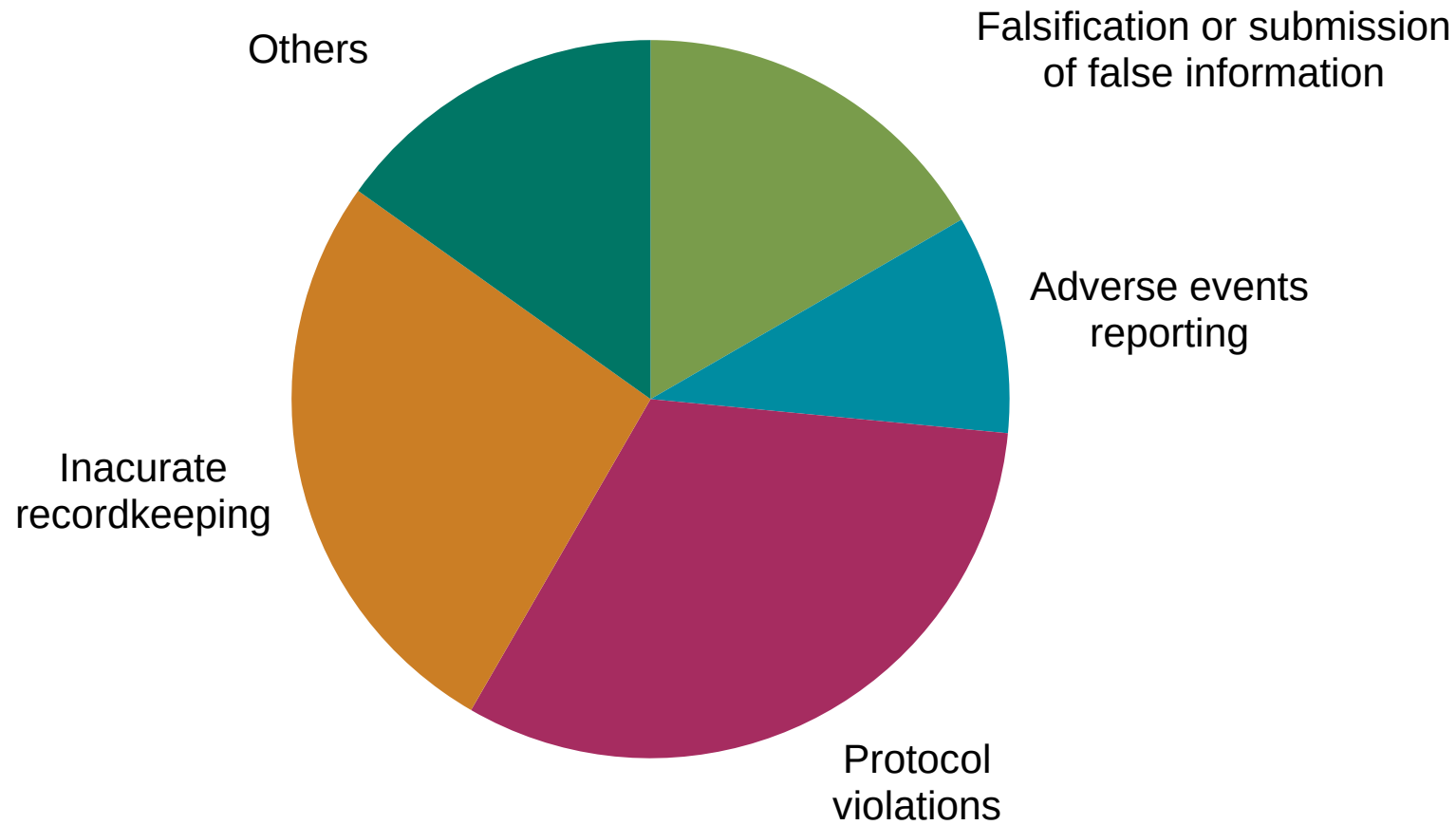
Research Misconduct Identified by the US Food and Drug Administration Out of Sight, Out of Mind, Out of the Peer-Reviewed Literature

Charles Selfe, MS

2% of the 644 inspections of trial sites carried out by the FDA's Bio-research organization were classified as OAI (Official Action Indicated)

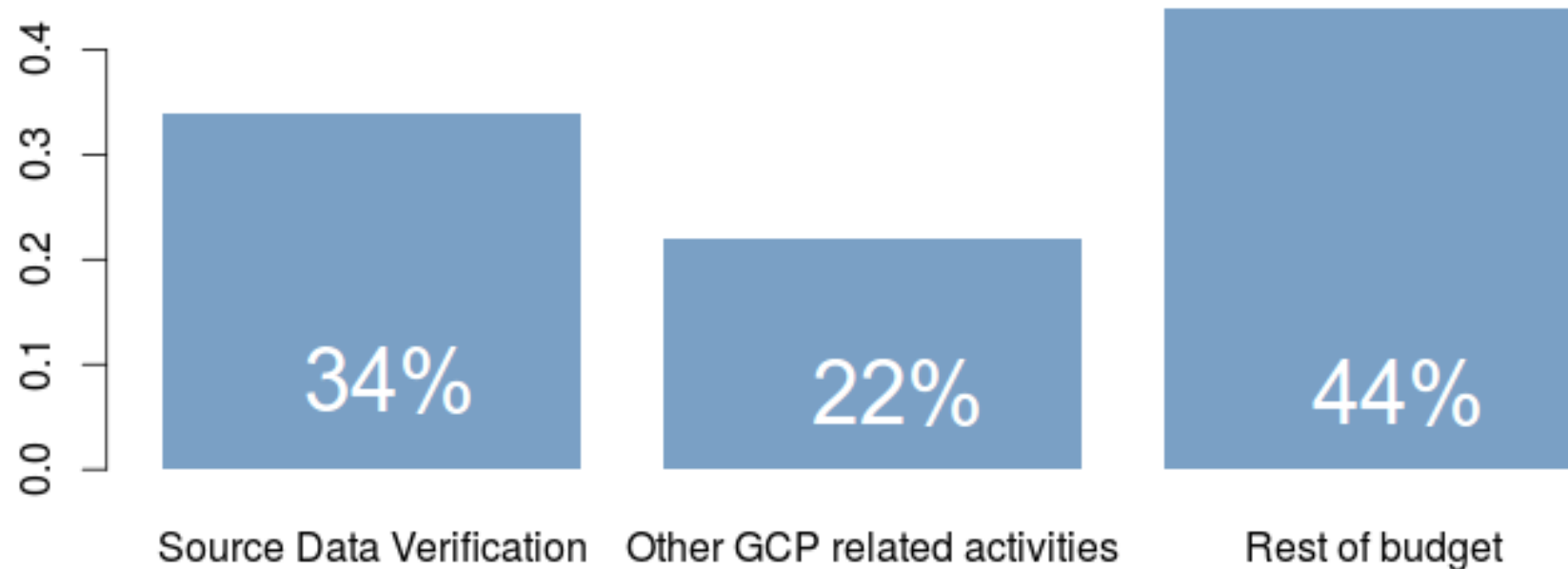
JAMA Intern Med. 2015;175(4):567-577.

Misconduct and Quality issues in Clinical Trials



JAMA Intern Med. 2015;175(4):567-577.

SDV accounts for up to 34% of the overall budget



Funning et al., Quality Assurance Journal, 2008(10)

*Sponsored Special Section by TransCelerate BioPharma:
Challenging the Value of Source Data Verification*



Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials

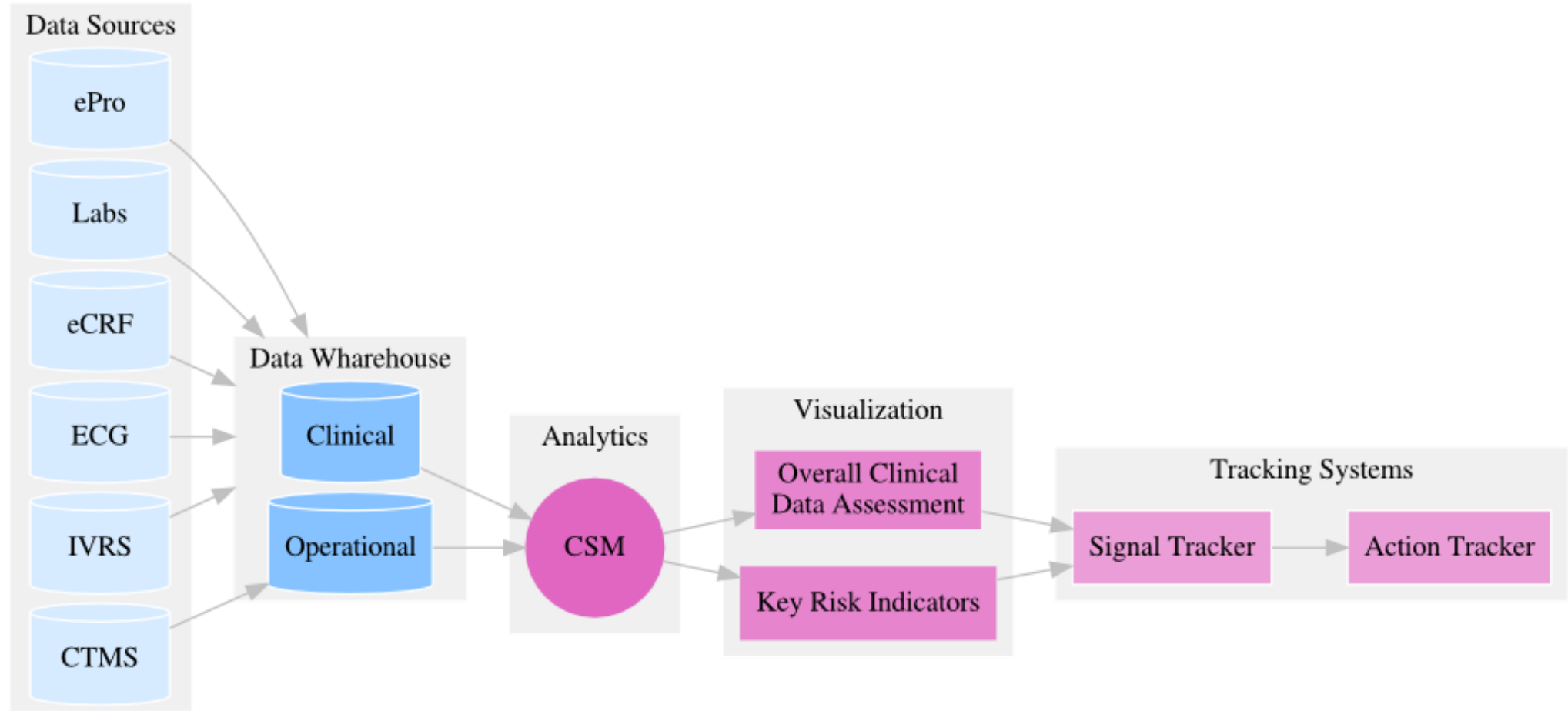
Therapeutic Innovation
& Regulatory Science
1-10
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tirs.sagepub.com

**Nicole Sheetz, PharmD¹, Brett Wilson, BSP², Joanne Benedict, MS³,
Esther Huffman, BS⁴, Andy Lawton, ASTAT⁵, Mark Travers, PhD⁶,
Patrick Nadolny, MS⁷, Stephen Young, MA⁸, Kyle Givens, MS⁹,
and Lawrence Florin, MBA¹⁰**

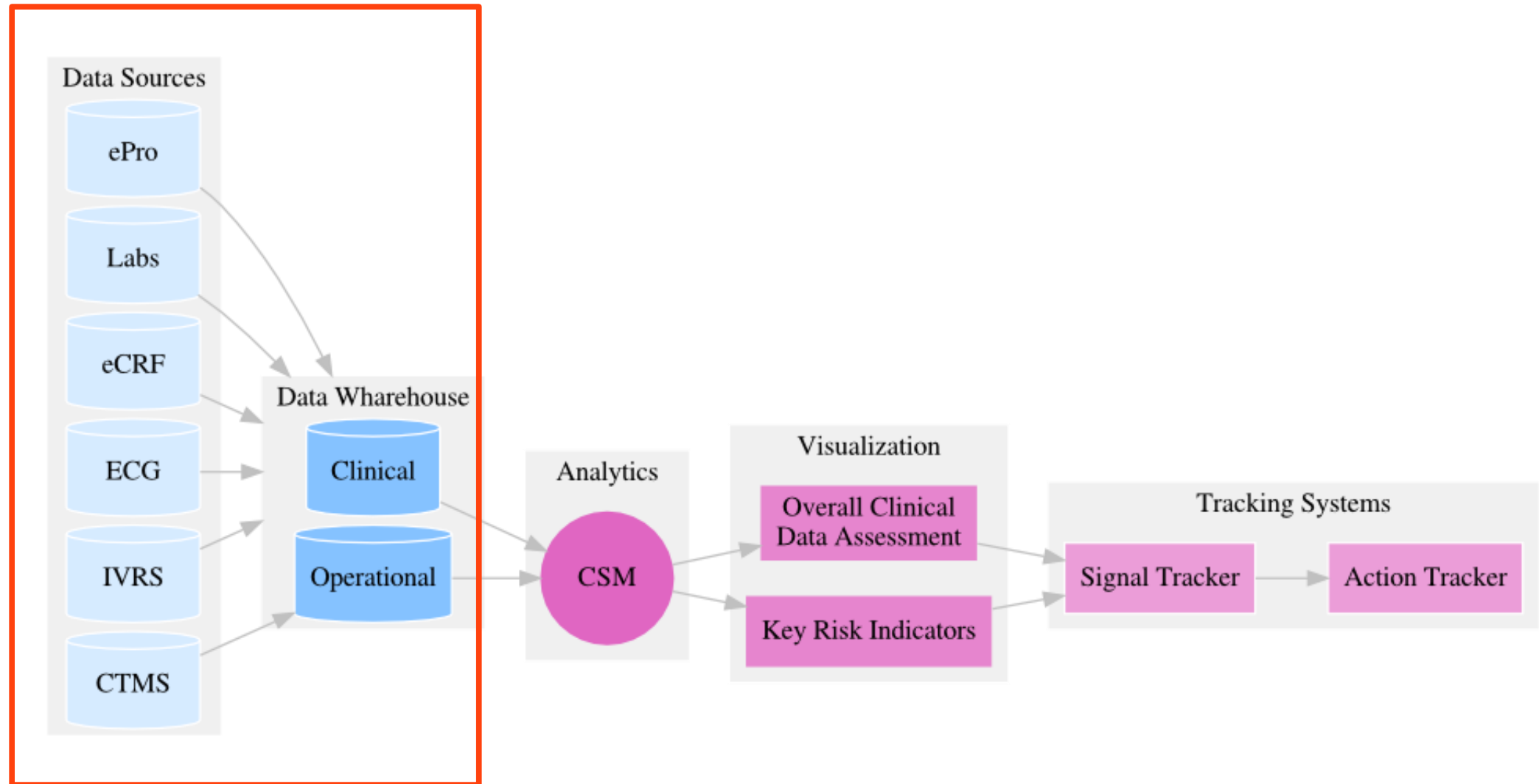
across 53 sponsors were included in the analysis. A median of 1.1% of the total eCRF data set was corrected by SDV. Some differences were observed across study phases and therapeutic areas (Table 5); these observations could benefit from further exploration.

Supporting previous findings, this analysis further indicates that only 3.7% of eCRF data was corrected by any data-cleaning method; the next results isolate the rate of those

RBM Platform Components



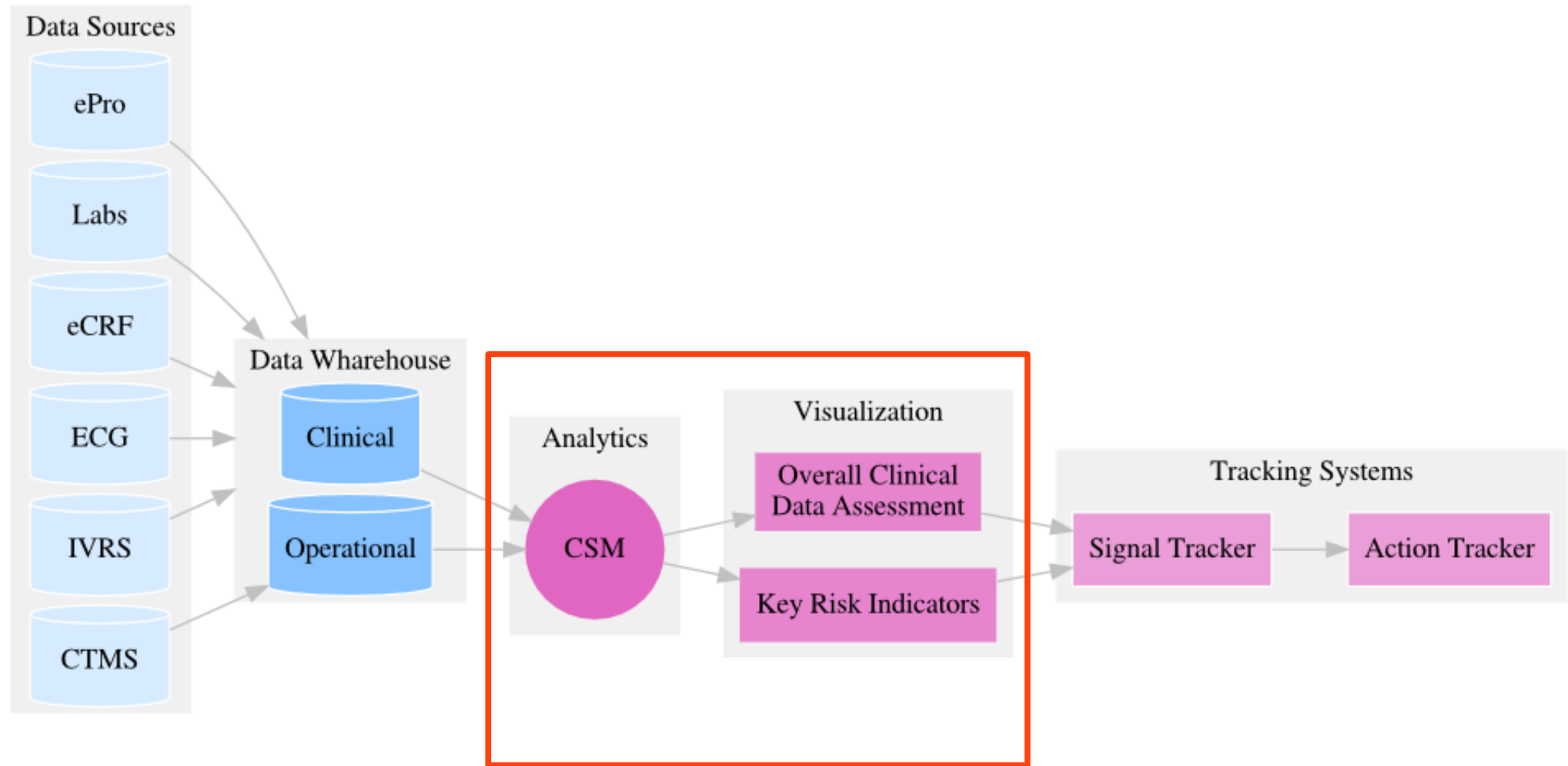
From data source to data warehouse



RBM Platform Components

- Data warehouse centralizes information from data sources
- Different ways to pull/inject data:
 - Flat files (manual upload)
 - Web Services (scheduler)
- Heterogeneity in data structure can be challenging
- Use standard formats (CDISC ODM)

Analytics and Visualization



Key Risk Indicators

Safety

SAEs

Non SAEs

SUSARs

Investigational product

Compliance

Treatment interruptions

Subjects

Recruitment

Discontinuations

Data quality

Abnormal trends

CRF completion

Discrepancies

Issue management

Protocol compliance

Data queries

Others

On-site workload triggers

Documents

Staffing, facilities, supplies

Key Risk Indicators

center	Country	#Patients	#Medium	#High	Missing pages	Missing pages >	Protocol Deviation	Queries open > 2	Discontin or Lost	# Days Open	Patient Status
		^ v	^ v	^ v	^ v	^ v	^ v	^ v	^ v	^ v	^ v
202	USA	4	0	2	🔴	🔴	🟢	🟢	⚪	⚪	🟢
80	USA	4	0	1	🟢	🟢	🟢	🔴	🟢	⚪	🟢
124	USA	25	0	1	🟢	🟢	🟢	🔴	⚪	🟢	🟢
147	USA	14	0	1	🟢	🟢	🟢	🔴	🟢	🟢	🟢
69	USA	10	2	0	🟢	🟢	🟢	🟢	⚪	⚪	🟡
123	USA	15	2	0	🟢	🟢	🟢	🟢	🟡	⚪	🟡
199	USA	7	2	0	🟢	🟢	🟡	🟢	🟢	🟢	🟡
23	USA	21	1	0	🟢	🟢	🟢	🟢	🟡	🟢	🟢
30	USA	5	1	0	🟢	🟢	🟢	🟢	🟢	🟡	🟢
33	USA	20	1	0	🟢	🟢	🟢	🟢	⚪	⚪	🟢
38	USA	9	1	0	🟢	🟢	🟢	🟡	🟢	🟢	🟢
52	USA	5	1	0	🟢	🟡	🟢	🟢	🟢	🟢	🟢

Computers are extremely good at crunching numbers



Principles of Central Statistical Monitoring

CLINICAL
TRIALS ARTICLE

Clinical Trials 2012; 0: 1–9

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 Wilson^g, Catherine Legrand^h and Marc Buyse^{c,i}

Main idea : to compare centers using all possible generic statistical tests on data from all variables.

The same approach can be used both for clinical and operational data

CSM Performs Many Tests on All Variables

Variable	Statistical Tests
Heart rate	Mean Between patient standard deviation Proportion of missing values Proportion of outliers Within patient standard deviation (repeated measures) Propagation of identical values (repeated measures) Collisions (identical values for different patients)
Serious AE	Proportion of missing values Count
Date of examination	Proportion of missing values Proportion of Saturdays/Sundays Correlation between patients
etc.	etc.

CSM Performs Many Tests on All Variables

Typical phase III clinical trial:

- 20 - 100 sites
- 250 - 1000 variables
- 2 - 10 statistical tests per item
- 10,000 to 1000,000 P-values

These P-values form a very large matrix with as many rows as centers and as many columns as individual tests

...to Produce a Matrix of P-values...

By Domains ☒ Rank ☐
By Categories ☐ Score ☒

0 10e-5 10e-3 5e-2

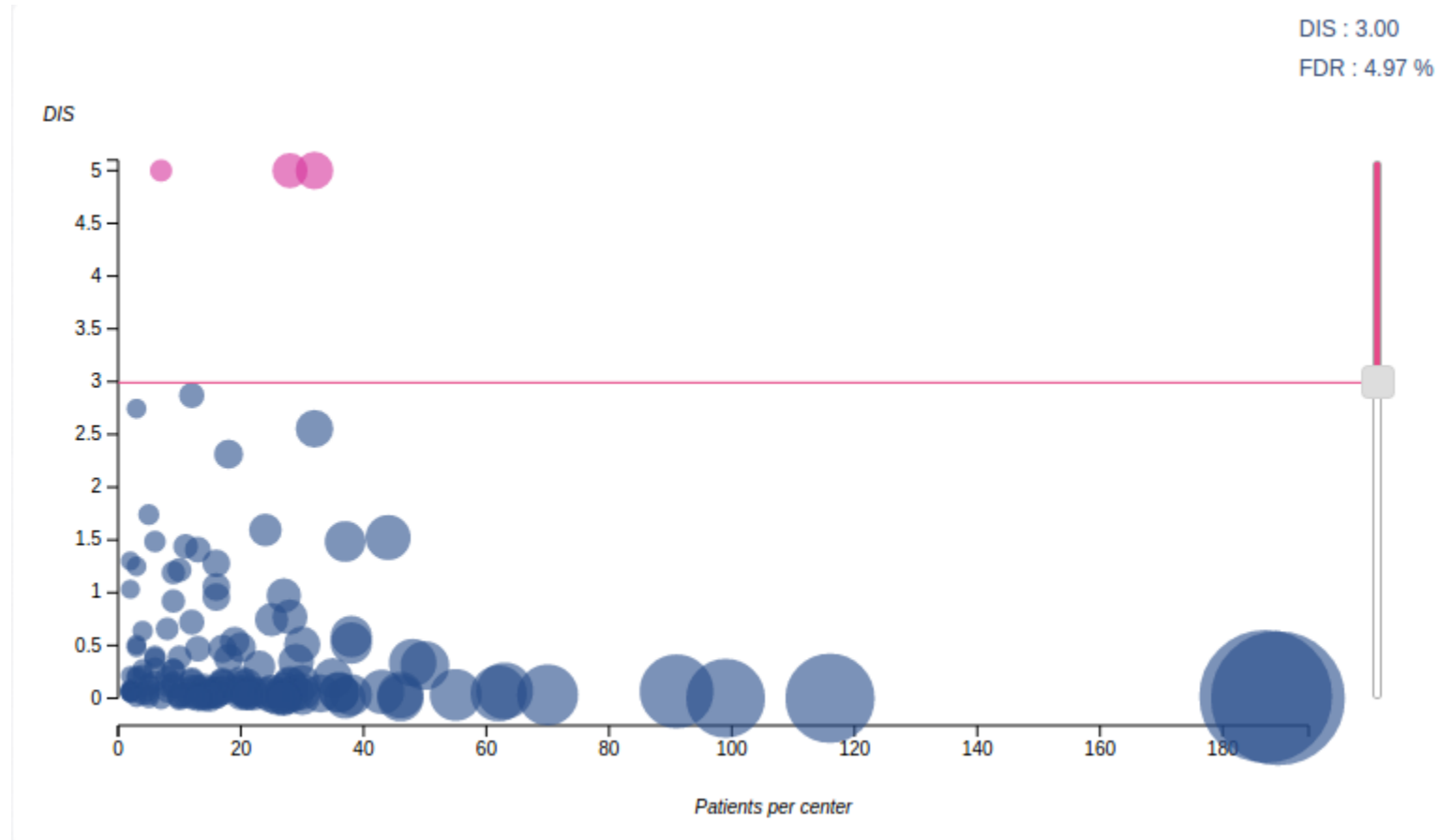
Country	Center	Score	Adbleed	Adldeath	Adlleg	Adlvent	Adlpec	Adverse Event	Ablat	Crit	Demog	Dispet	Endst	Event	Hcc	Lab	LabT	Med	Medlist	Phid	QS
POL	188	1.8e-05	0.27	0.19	0.0144	0.91	0.00189	0.3	0.34	1	0.00324	1e-05	0.0136	0.41	0.54	0.93	0.72	0.56	0.72	0.00036	0.59
POL	191	1.8e-05	0.13	0.0273	0.49	0.0618	0.46	0.68	0.21	1	0.49	0.19	0.38	0.48	0.0227	0.46	0.7	0.79	0.9	0.33	0.00018
POL	155	2.7e-05	0.0955	0.21	0.99	0.27	0.32	0.0455	0.00568	1	0.29	0.51	0.37	0.85	0.73	0.2	0.25	0.65	0.24	0.5	0.00153
USA	248	0.000342	0.28	0.00721	0.0955	0.00108	0.0373	0.16	0.4	1	0.0809	0.61	0.33	0.01	0.0555	0.96	0.0682	0.00829	0.135	0.0227	1
USA	247	0.000702	0.00297	0.0109	0.73	0.00279	0.59	0.00883	0.0382	1	0.21	0.0445	0.56	0.65	0.27	0.39	0.63	0.55	0.0318	0.0673	0.0582
POL	159	0.00306	0.37	1	0.18	0.57	0.83	0.41	0.24	1	0.108	0.3	0.63	0.4	0.15	0.51	0.98	0.11	0.76	0.21	0.00153
UKR	141	0.00992	0.15	1	0.2	0.82	0.0209	0.92	0.27	1	0.27	0.112	0.0536	0.57	0.8	0.71	0.28	0.8	0.57	0.56	0.0127
POL	156	0.0118	0.59	1	0.73	0.28	0.21	0.91	0.18	1	0.5	0.73	0.67	1	0.37	0.22	0.98	0.0382	0.75	0.47	0.00405
USA	241	0.0227	0.0791	1	0.86	0.00658	0.07	0.22	0.79	1	0.49	0.77	0.66	0.00207	0.39	0.99	0.31	0.0755	0.14	0.51	0.68
UKR	272	0.0227	0.0164	0.0545	0.19	0.123	0.27	1e-05	0.2	1	0.42	0.11	0.0455	1	0.83	0.0473	0.43	0.0945	0.75	0.98	0.8
UKR	274	0.0318	0.0509	1	0.45	0.45	0.8	0.01	0.76	1	0.61	0.61	0.56	0.76	0.99	0.0727	0.87	0.11	0.0664	0.47	0.99
USA	243	0.0436	0.0131	0.24	0.34	0.0173	0.96	0.53	0.2	1	0.69	0.63	0.7	0.75	0.61	0.12	0.2	0.0455	1e-05	0.36	0.36
UKR	302	0.0518	0.61	0.48	0.12	0.96	0.74	0.41	0.64	1	0.0345	0.63	0.59	0.7	0.39	0.16	0.11	0.51	0.26	0.67	0.29
UKR	144	0.06	0.0655	1	0.18	0.67	0.71	0.98	0.0727	1	0.102	0.85	0.15	0.46	0.34	0.00153	0.43	0.65	0.29	0.79	0.86
NLD	213	0.0655	0.67	1	0.65	0.85	0.31	0.87	0.0536	1	0.56	0.33	0.7	0.76	0.94	0.88	0.27	0.22	0.46	0.52	0.0255
GBR	134	0.0873	0.19	1	0.53	0.0245	0.95	0.16	0.42	1	0.7	0.0282	0.57	0.0773	0.27	0.99	0.0545	0.89	0.89	0.46	0.0218
UKR	142	0.11	0.56	1	0.22	0.81	0.54	0.53	0.69	1	0.14	0.0891	0.27	0.65	0.84	0.57	0.74	0.88	0.7	0.91	0.0173
USA	225	0.11	0.0509	0.0964	0.38	0.0436	0.76	0.53	0.12	1	0.15	0.63	0.0409	0.47	0.69	0.42	0.97	0.81	0.19	0.0445	0.0609
DNK	109	0.13	0.24	1e-05	0.0391	0.0482	0.19	0.0409	0.53	1	0.69	0.46	0.15	0.24	0.68	0.0509	0.68	0.71	0.64	0.15	0.49
GBR	132	0.15	0.4	1	0.66	1	0.78	0.52	0.57	1	0.0345	0.22	0.73	0.26	0.0264	0.45	0.68	0.94	0.45	0.108	1e-05
AUS	102	0.16	0.87	1	0.00027	0.98	0.11	0.19	0.12	1	0.64	0.78	0.98	1	1	0.6	0.42	0.82	0.74	0.75	1
DNK	112	0.16	0.12	0.48	0.8	0.17	0.76	0.24	0.95	1	0.0345	0.63	0.73	0.11	0.13	0.02	0.0955	0.68	0.79	0.79	1
UKR	278	0.16	0.47	0.0391	0.00739	0.69	0.93	0.6	0.0418	1	0.64	0.81	0.51	0.81	0.81	0.14	0.07	0.39	0.83	0.57	0.14
USA	233	0.17	0.107	0.11	0.15	0.82	0.89	0.105	0.94	1	0.57	0.98	0.93	1	0.3	0.54	0.28	0.0609	0.0773	0.0927	0.98
USA	242	0.17	0.54	0.11	0.49	0.05	0.54	0.35	0.66	1	0.64	0.98	0.93	0.53	0.0327	0.16	0.28	0.53	0.127	0.89	0.18
CAN	204	0.19	0.29	0.104	0.91	0.2	0.0318	0.67	0.84	1	0.76	0.0191	0.00613	0.33	0.58	0.72	0.18	0.41	0.0609	0.0627	0.46
FRA	124	0.2	0.55	1	0.29	0.96	0.66	0.0591	0.3	0.00721	0.34	0.81	0.95	1	0.68	0.39	0.74	0.42	0.14	0.52	0.22
POL	160	0.2	0.56	0.29	0.17	0.55	0.29	0.38	0.4	1	0.112	0.0209	0.2	0.92	0.6	0.51	0.63	0.26	0.22	0.74	0.25
POL	190	0.21	0.46	0.44	0.55	0.78	0.12	0.76	1	1	0.16	0.1	0.28	1	0.69	0.108	0.27	0.99	0.69	0.0318	0.0518
USA	214	0.21	0.24	1	0.86	0.109	0.58	0.1	0.135	1	0.0245	0.61	0.118	0.11	0.66	0.45	0.28	0.42	0.0182	0.21	0.81
POL	161	0.23	0.04	1	0.79	0.54	0.2	0.58	0.35	1	0.16	0.17	0.54	0.19	0.93	0.31	0.47	0.23	0.55	0.45	0.00919
NZL	153	0.24	0.37	1	0.63	0.96	0.37	0.15	0.67	1	0.0118	0.65	0.0136	0.0564	0.0964	0.53	0.64	0.34	0.25	0.19	0.52

...and a “Data Inconsistency Score”...

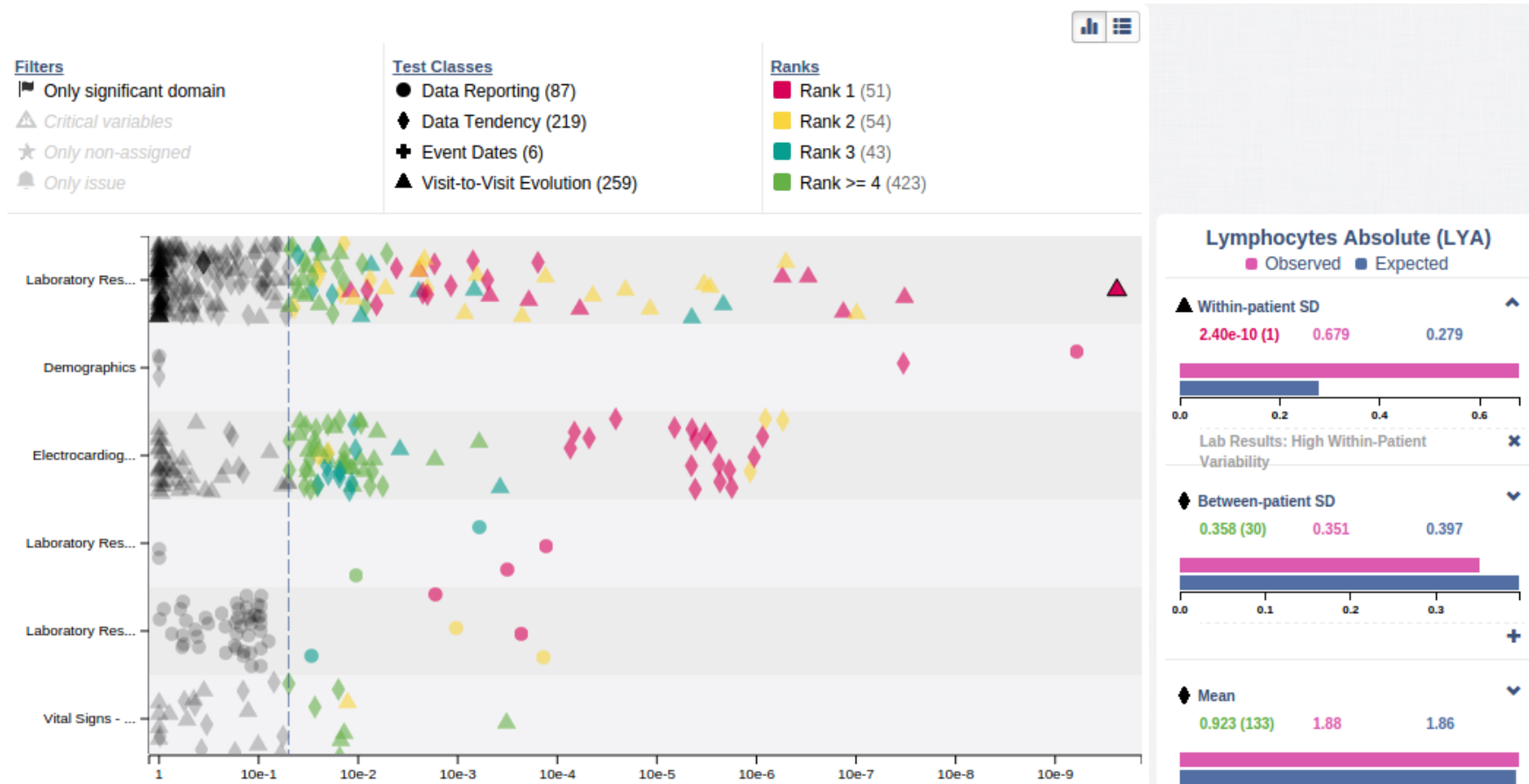
Indicates the extent to which a center differs from all other centers in terms of all available data

$$DIS_i = \exp \left(\frac{1}{N} \sum_{j=1}^N \log P_{ij} \right)$$

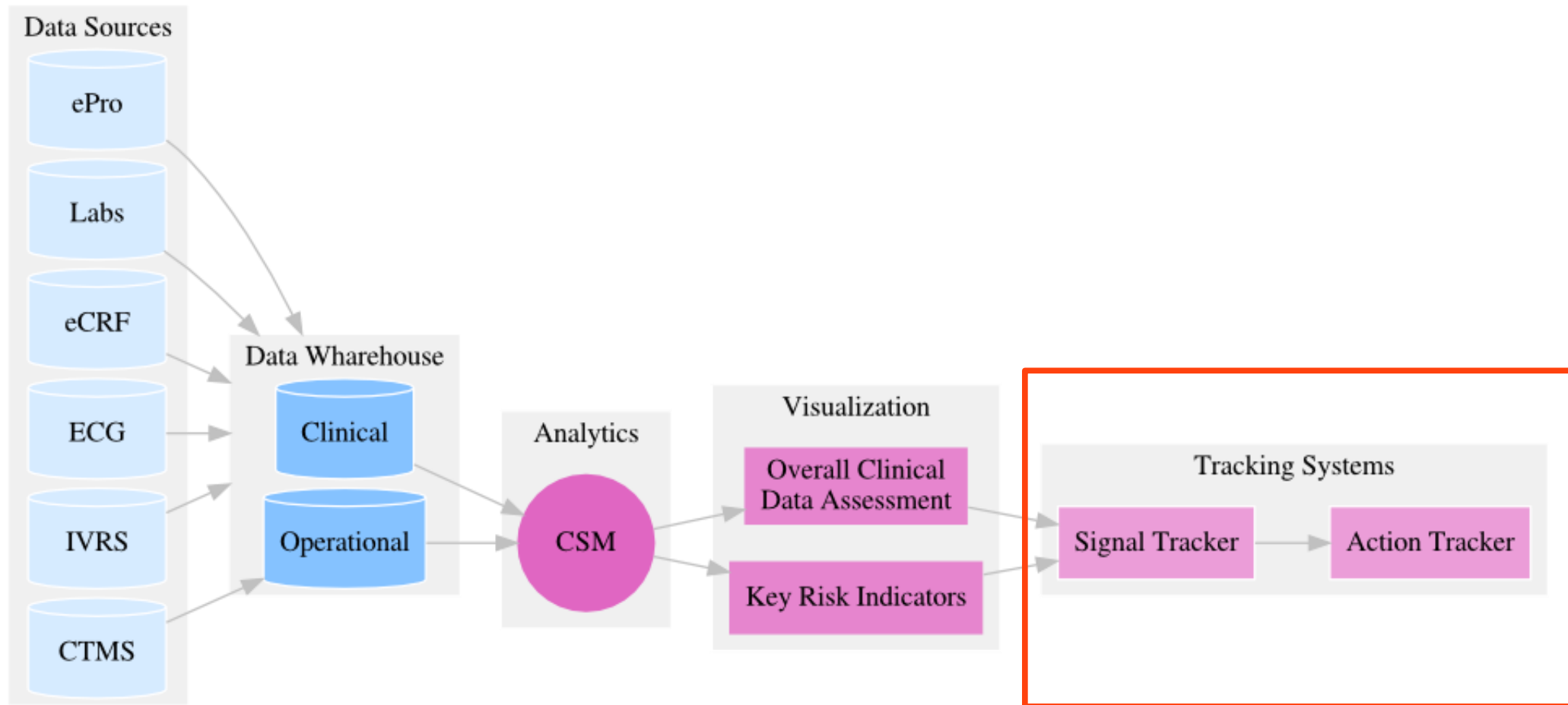
...which helps Identifying Centers at Risk...



...and Why...



Tracking Systems



List of Signals and Corrective Actions

center_all_data

Issues

413

Signal

413

Adverse Events: Under-Reporting of Data

413

ECG Results: High Within-Patient Variability

413

ECG Results: Lower Average Values

413

ECG Results: Too Similar Measurements

413

Inclusion/Exclusion: More Failures

413

Male Patients only

413

Non-Relevant Signals

413

Vital Signs: Low Within-Patient Variability

413

Vital Signs: Too Similar Measurements

413

Lab Results: Sequence Outliers

Signal

SIG-0023

413 - Male Patients only

Description

Male Patients only

Issue ?



Details

Actions

Location	Variable (domain)	Test	Pvalue (rank)	■ Observed ■ Expected
413	Childbearing Potential (Demographics)	Count	6.09e-10 (1)	Observed : 0 Expected : 0.68289
413	Sex (Demographics)	Proportion	3.34e-8 (1)	Observed : 0 Expected : 0.683192

List of Signals and Corrective Actions

Action details

CRA to go on site

Status :

open

Assignee :

Erik Doffagne

Due date :

2015-05-22

Description :

These VS are very atypical....

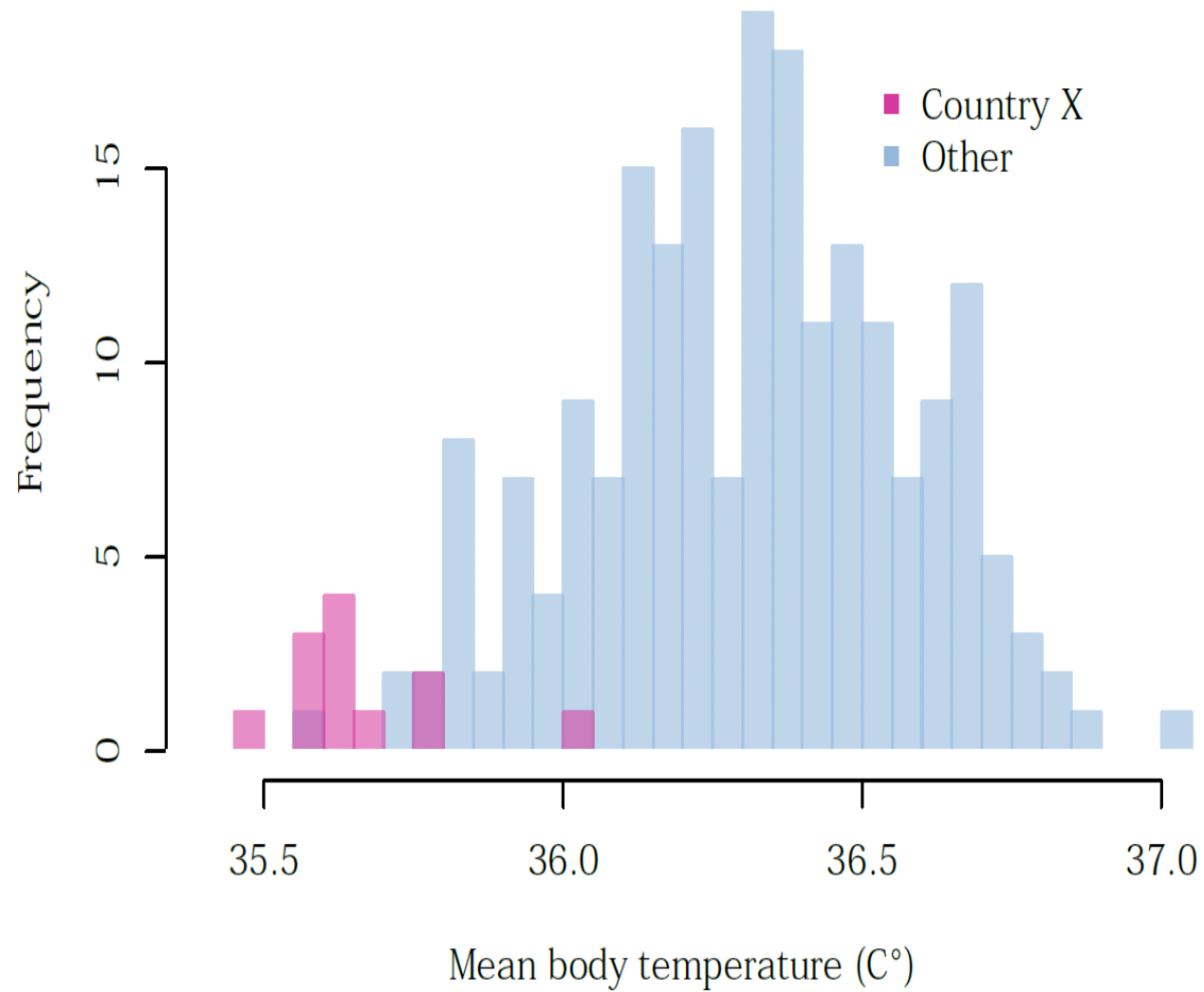
Francois Torche added a comment - 2015-05-08 15:25:21 UTC

Yes I will have a look

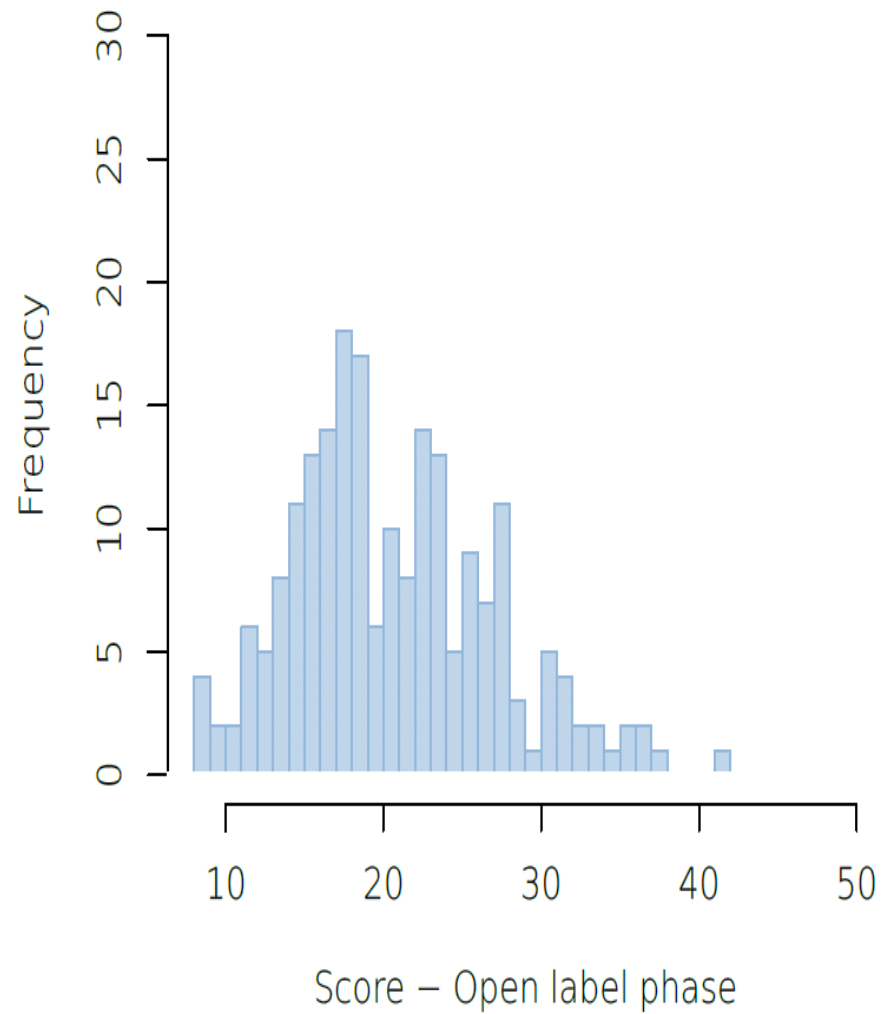
Add comment

Close

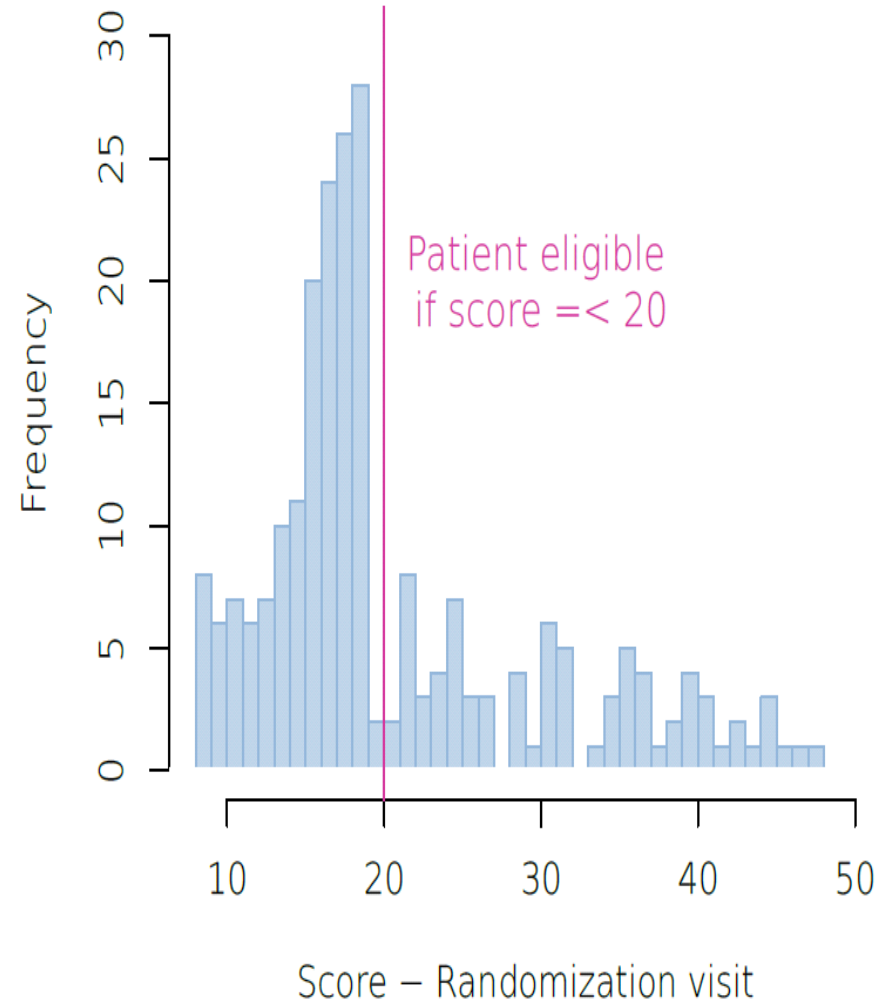
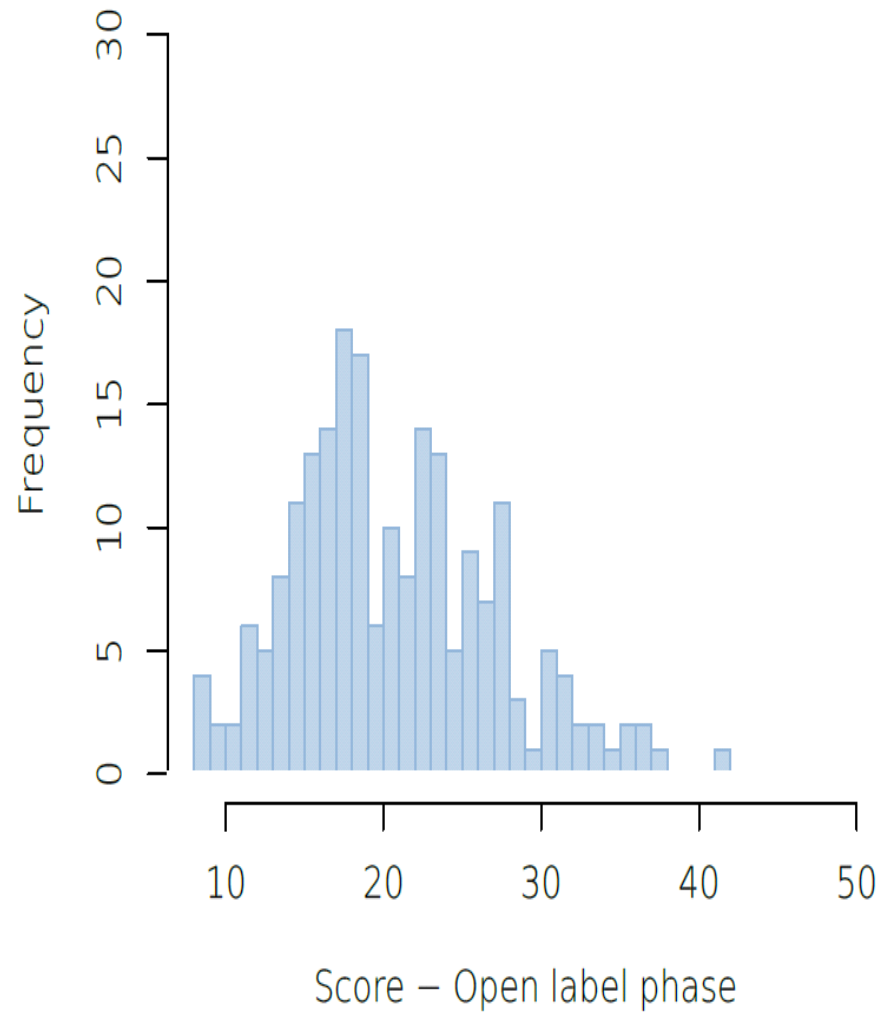
Example – Faulty Devices



Example – Fraud on inclusion criteria



Example – Fraud on inclusion criteria



Key Success Factors

- A multi-disciplinary team
 - Trial Manager, Clinicians, Monitors, Data Managers & Biostat
 - Review and discuss signals
 - Agree on corrective actions
- A central role in the organization
 - Data Analyst
 - Not necessarily a statistician
- Adapt your processes
 - Not in addition to already existing processes!
 - Documentation / Tracking

Summary

- CSM is more than just computing statistics on a subset of key variables. It's about processing all data and guiding you to where the potential issues in your data are.
- The combination of KRIs and CSM result in a powerful approach that can uncover data quality and potential fraud
- Pharma industry needs to leverage technology to be more cost effective and efficient



CluePoints
INTELLIGENT STATISTICAL MONITORING

| Thank You
Questions?