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“Big Data” Analytics or The Fallacy Behind Risk Based Monitoring

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- Yuliya Yurova, Director Biometrics

Biorasi's Useful Sayings

The most expensive study you will ever run is the study that fails.

The only tangible thing that you receive back from the your heavy corporate R&D spend is your clinical study data.

One of the most detrimental things that you can do to a pharma company's share price is to have a NDA submission rejected.

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Big Data Analytics vs. Risk Based Monitoring

Big Data is certainly an over-hyped concept, but clinical studies do have large volumes of data that are of great value to researchers, both after study completion as well as during the study's progression. Risk Based Monitoring is but ONE utilization of this innovative technology.

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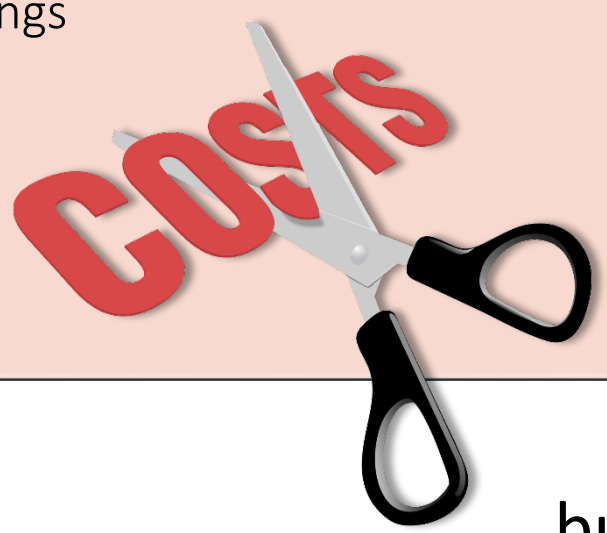
Risk Based Monitoring – Why All the Fuss?

The Key Motivating Factors:

- Monitoring Speed & Efficiency
- Best Utilization of Scarce Resources
- Cost Savings



Achieved By:

Limiting the Scope of our Monitoring Activity

- An initial risk assessment to determine what is important to the study
- Monitors doing partial SDV to only focus on what is important
- Development of custom analytics to identify when important things are going astray

…but are we missing the REAL point?

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Ramifications of Poor Monitoring

COMPLETE RESPONSE

Please refer to your New Drug Application (NDA) dated xxxx x, xxxx, received xxxx x, xxxx, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for yyyyyyyyyyyyyy xxmg tablets.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

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Ramifications of Poor Monitoring

COMPLETE RESPONSE

The report of the audit of the trial sites uncovered a broad range of irregularities and deviations from Good Clinical Practices. These include inadequate adherence to the study protocol to protect the safety of patients, poor source documentation of adverse events, numerous discrepancies between the information recorded in source documents and the Electronic Case Report Forms, and improper changes made to source documents without the ability to determine who made the changes or when they occurred. … Because of these serious deficiencies, the information from these sites cannot be used in support of your application.

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But what are sponsors really looking for?

When I ask innovative sponsors what they really want between the three key elements: Time, Cost and Quality,

Time and Quality will win every time!

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Time and Quality will win every time!

From this perspective, Risk Based Monitoring, which **myopically focuses** almost exclusively on cost savings, could be a…

RED HERRING

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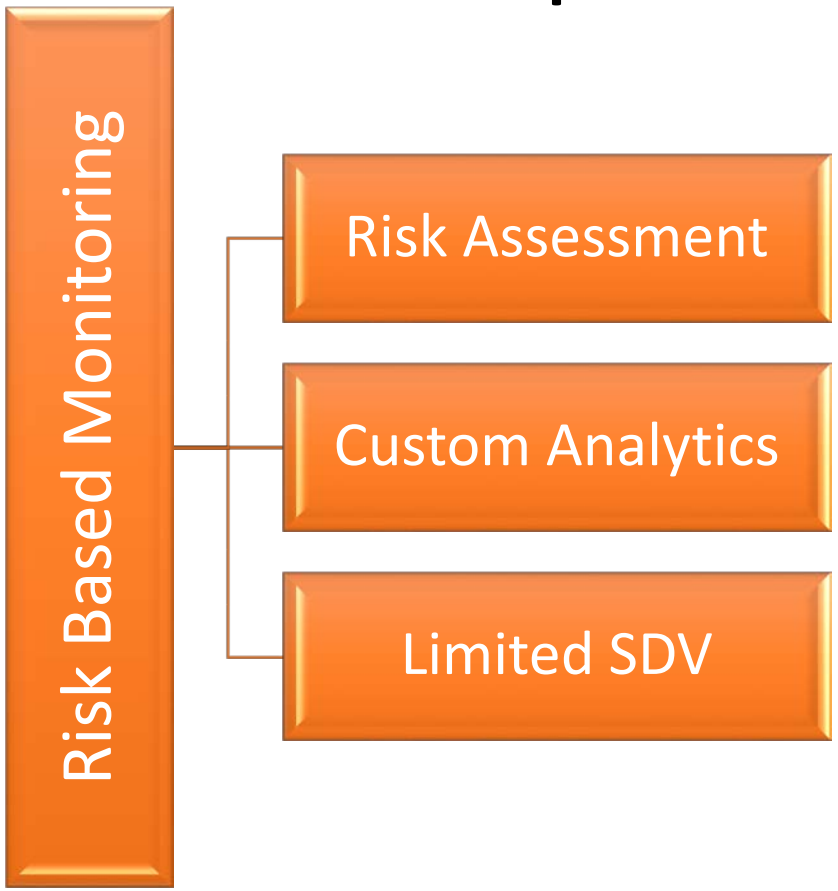
What do we really need to implement?

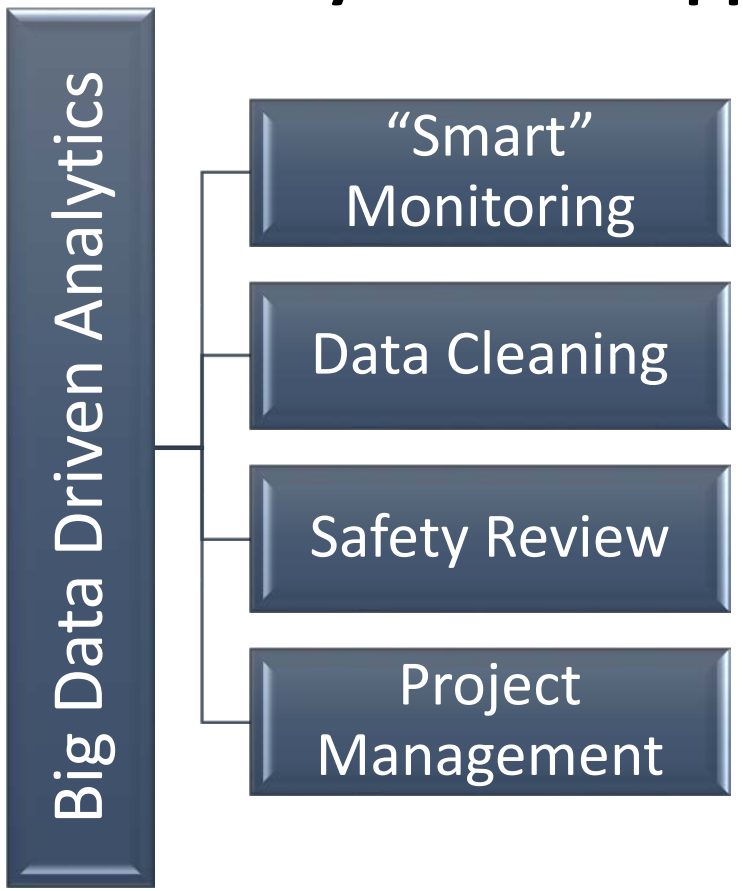
Cost Focus?

Traditional RBM Requires:



Quality Focus!

Big Data Analytics will Support:



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Big Data Approach in Clinical Trials

What is a Big Data approach to Analytics?

Big data analytics examines large amounts of data to uncover hidden patterns, correlations and other insights. (WhatIs.com)

Traditional Analysis:

Assess a change from baseline in systolic blood pressure using ANCOVA for Treatment vs. Placebo.

"Big Data" Analysis:

Look across **all** numerical and categorical data and tell me what doesn't smell right or what unusual relationships are present.

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How is this applied to Clinical Studies?

Big Data's Quality Premise in Drug Development

- Use the data itself, coupled with advanced statistical methods to identify risk areas that merit closer attention by a monitoring team or management.
- Use a blend of data sources: study metrics, metadata, and the clinical study data, as a basis of the analysis.
- As the data changes over time, becoming more complete, automatically change the sensitivity (thresholds) based on the analysis type and the variance detected.
- Lower the dependence on a pre-defined Risk Assessment
- The key focus is to identify quality issues rather than simply cutting costs. Although, one likely leads to the other.

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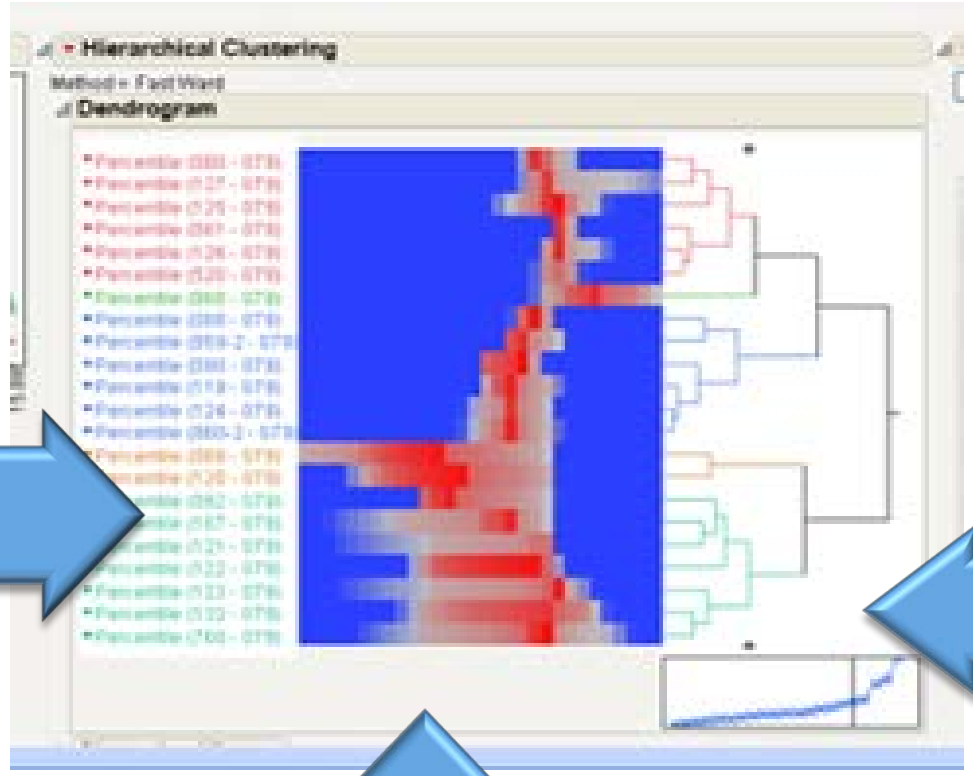
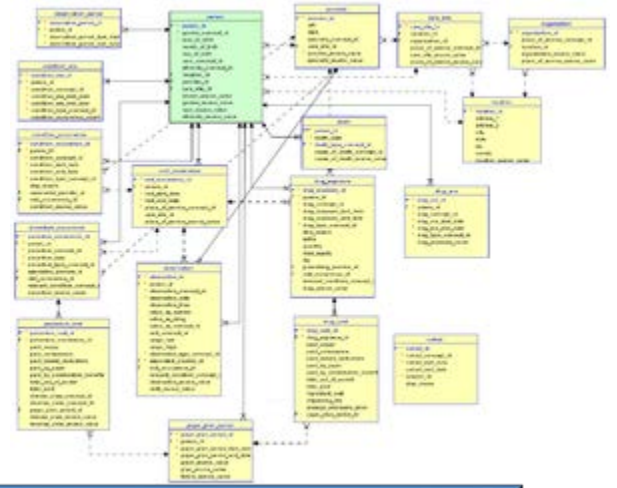
Centralized Statistical Analytics

A blend of metrics, metadata and clinical study data

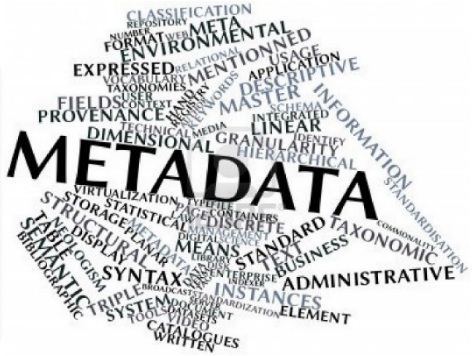
- Query rates
- Enrollment
- Data Entry Timeliness
- Protocol Deviations





- Numerical data
- Categorical data
- “Critical” data

- Data: Where is it?
- Data: What does it mean?
- CDISC Standards



Proper

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Centralized Statistical Analytics

Lower dependence on pre-defined Risk Assessment

Quality Focused, Big Data Analytics are looking for Hidden and Unexpected patterns and insights.

Risk Rating Table

Likelihood of injury or harm to health	Consequences of any injury or harm to health			
	Insignificant e.g. no harm	Moderate e.g. first aid	Major e.g. extensive injuries	Catastrophic e.g. death
Very likely	High	Extreme	Extreme	Extreme
Likely	Moderate	High	Extreme	Extreme
Moderate	Low	High	Extreme	Extreme
Unlikely	Low	Moderate	High	Extreme
Highly Unlikely	Low	Moderate	High	High

Extreme = immediate action

- By definition, hidden and unexpected data relationships cannot be pre-defined in a *risk assessed analysis plan*!

Risk assessments can play a role for determining relevance of big data analysis findings

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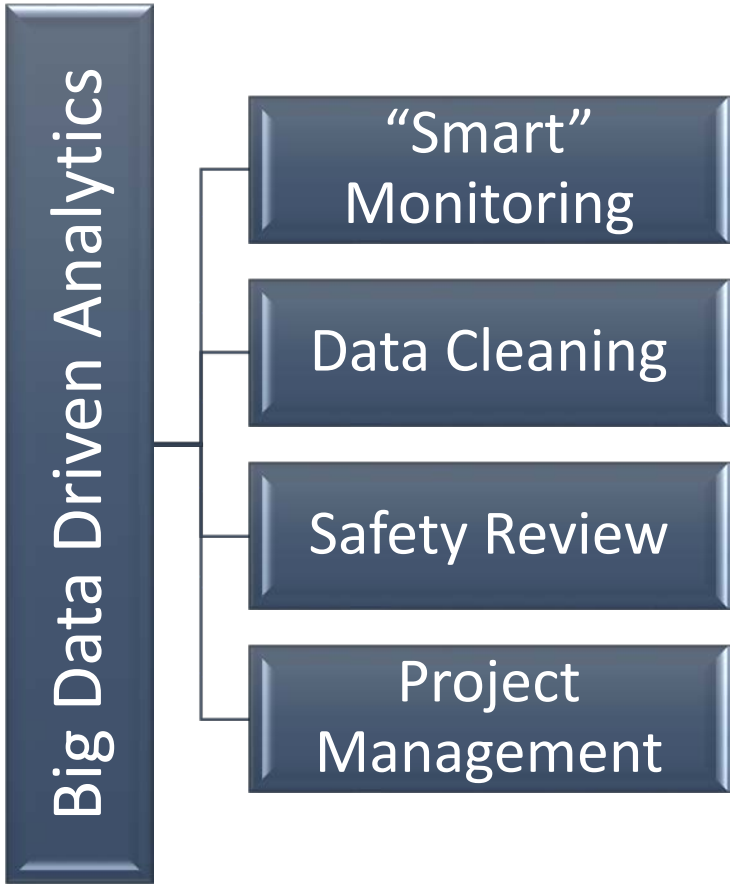
Big Data Approach in Clinical Trials

What Areas of Clinical Studies does it Support?



- **Monitoring,** by transforming RBM to "Smart Monitoring"
- **Data Management,** with analytics to support data cleaning efforts
- **Safety,** with dynamic interactive analytics to support signal detection and safety review
- **Project management,** with timely analytics on study progress, quality assessment and fraud detection

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Centralized Statistical Analytics – Provide:

Smart Monitoring

- Multi-Data Sourced RBM Analytics
- Patient Profiles of All Patients in Site
- Information on outlier and inlier datapoints
- Boxplots and Waterfall plots (change from baseline)

32/0 Cols
40/0 Rows

	Study Site Identifier	Country	Overall Risk Indicator	Overall Risk Indicator...	Overall Risk Indicator...	Overall Risk Indicator...	Total Subjects	Randomized	Screen Failure	Percent Screen Fail of Total...
1	01	USA	0.276	0.441	0.056	0.000	51	51	0	0.0
2	02	USA	0.472	0.637	0.448	0.000	32	32	0	0.0
3	03	USA	0.222	0.205	0.497	0.000	23	23	0	0.0
4	04	FRA	0.327	0.535	0.027	0.000	26	26	0	0.0
5	05	ITA	2.352	1.288	3.660	4.239	5	5	1	20.0
6	06	USA	1.747	2.481	1.289	0.000	7	7	0	0.0
7	07	CHN	1.231	1.682	1.107	0.000	5	5	0	0.0
8	08	GBR	0.900	1.149	1.052	0.000	23	23	0	0.0
9	09	CAN	0.366	0.400	0.629	0.000	40	40	0	0.0
10	10	USA	0.499	0.687	0.432	0.000	17	17	0	0.0
11	12	DEU	0.798	0.881	1.346	0.000	16	16	0	0.0
12	14	CAN	0.501	0.552	0.850	0.000	75	75	0	0.0
13	16	USA	0.614	0.597	1.282	0.000	39	39	0	0.0
14	17	USA	0.708	1.072	0.327	0.000	18	18	0	0.0
15	18	JPN	0.560	0.548	1.155	0.000	22	22	0	0.0
16	19	CAN	0.828	0.368	0.682	2.355	9	9	1	11.1
17	20	FRA	0.248	0.286	0.382	0.000	18	18	0	0.0
18	21	ESP	0.286	0.420	0.169	0.000	10	10	0	0.0
19	22	CAN	0.737	1.209	0.058	0.000	23	23	0	0.0
							29	29	0	0.0
							21	21	0	0.0
							15	15	0	0.0
							8	8	0	0.0
							24	24	0	0.0
							74	74	0	0.0

Profile

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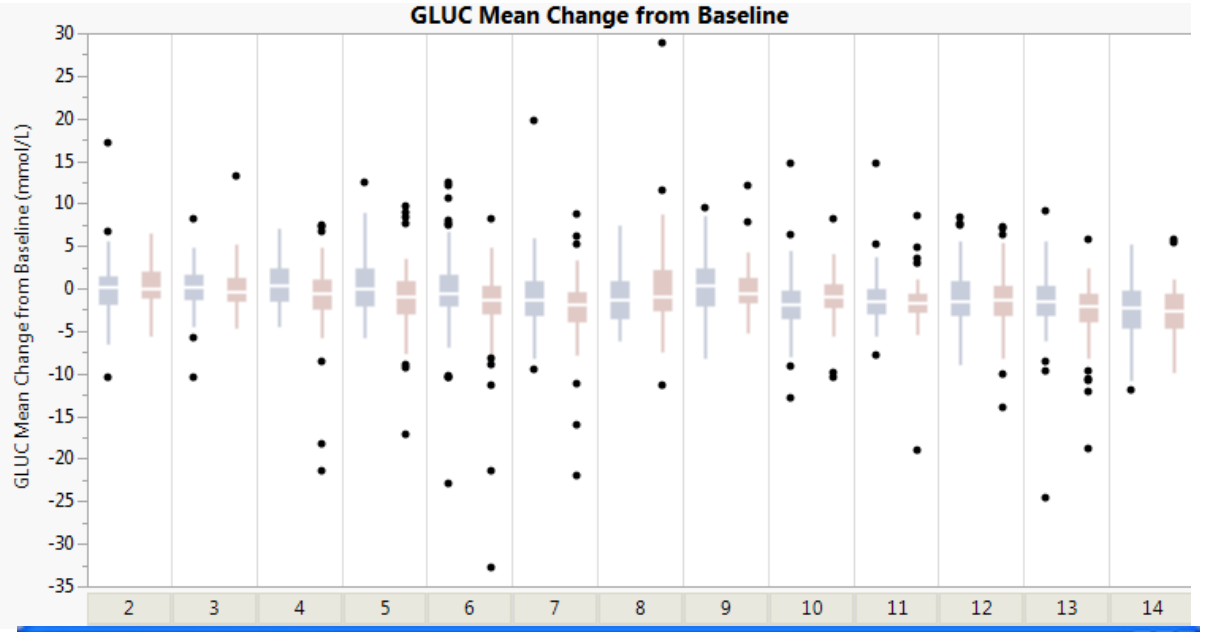
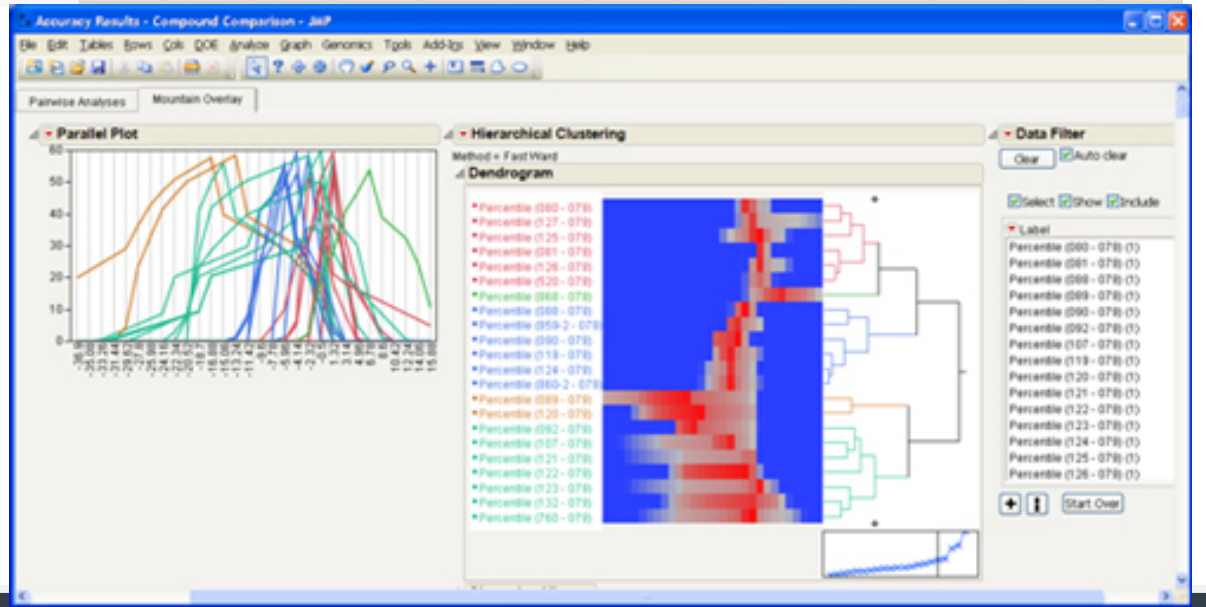
Centralized Statistical Analytics – Provide:

Data Cleaning

- Pre-defined Statistical Analyses and Standard Reports
- Subject Clustering Analyses Within and Across Sites
- Detailed on outlier and inlier analytics
- Boxplots and Waterfall plots (change from baseline)





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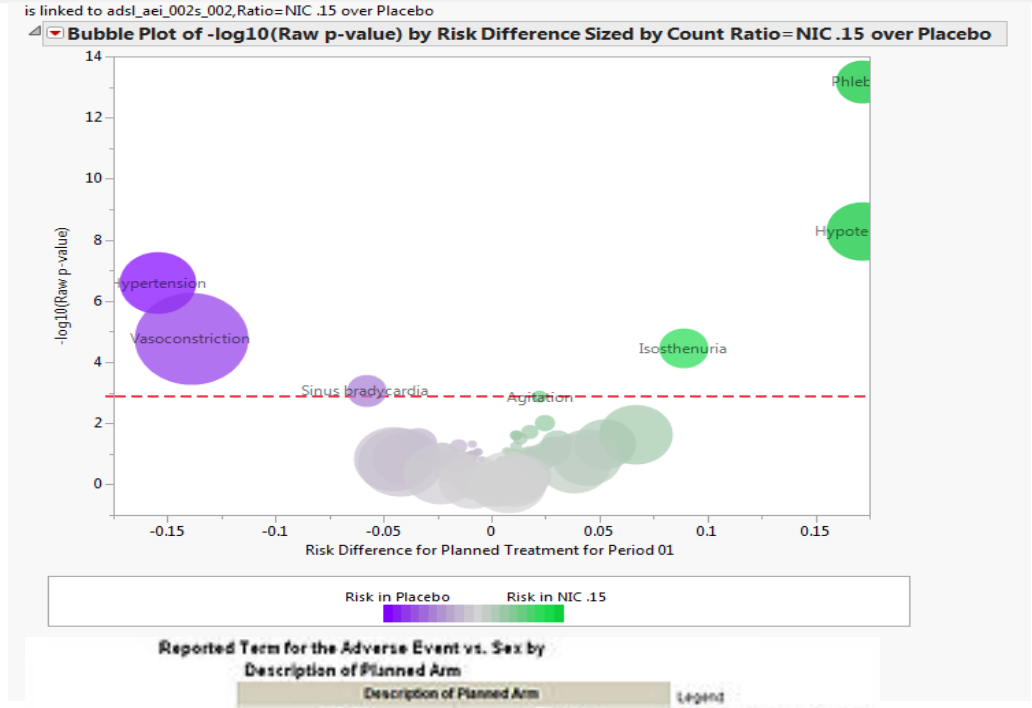
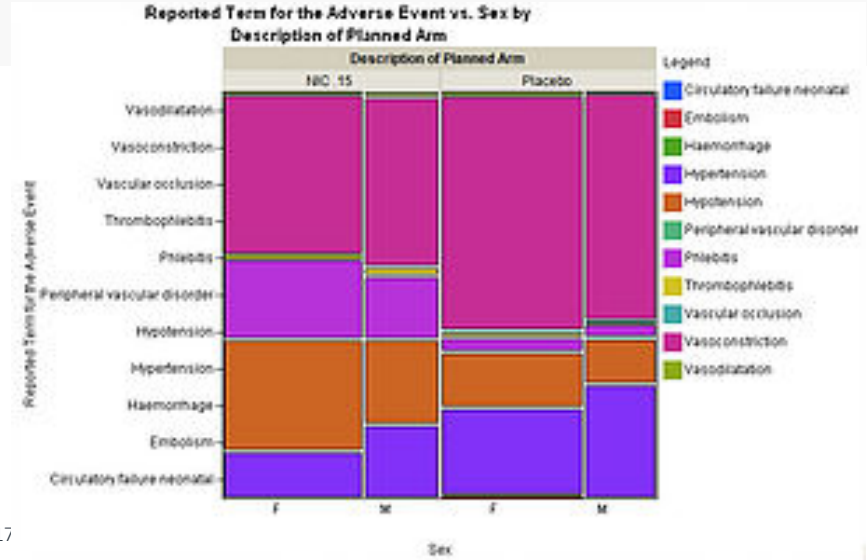
Centralized Statistical Analytics – Provide:

Safety Review

- Pre-defined Statistical Analyses and Standard Safety Reports
- Subject Clustering Analyses Within and Across Sites
- Detailed on outlier and inlier analytics
- Boxplots and Waterfall plots (change from baseline)





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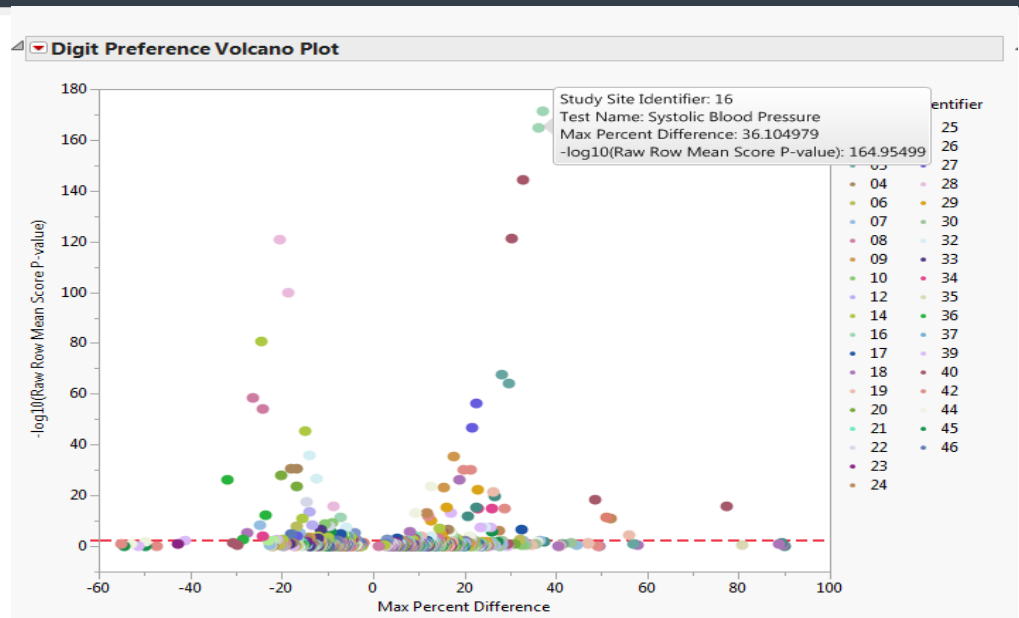
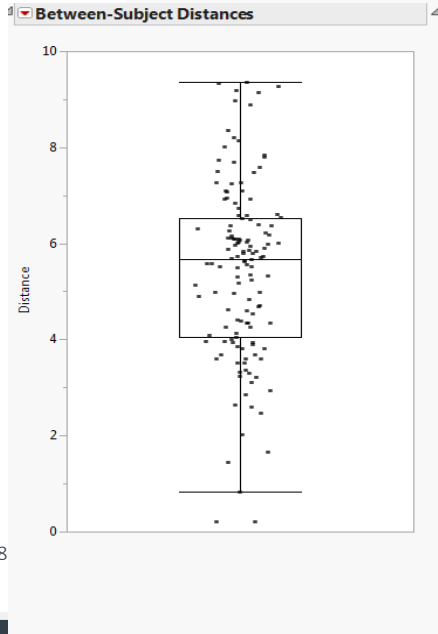
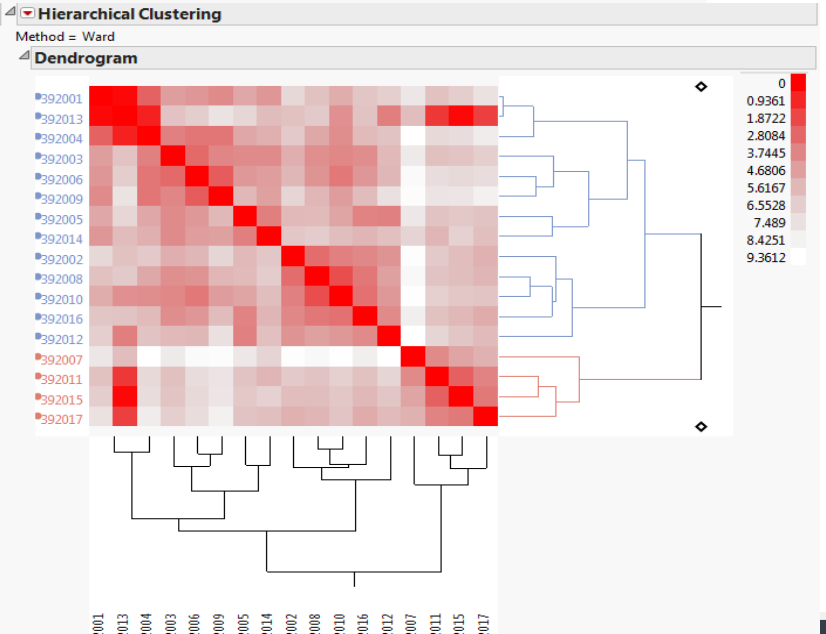
Centralized Statistical Analytics – Provide:

Fraud and Non-Compliance

- Unusual or Implausible Situations
- Multivariate Inlier and Outlier Analytics
- Constant Findings and Digit Preference
- Clustering of Patients Within Sites







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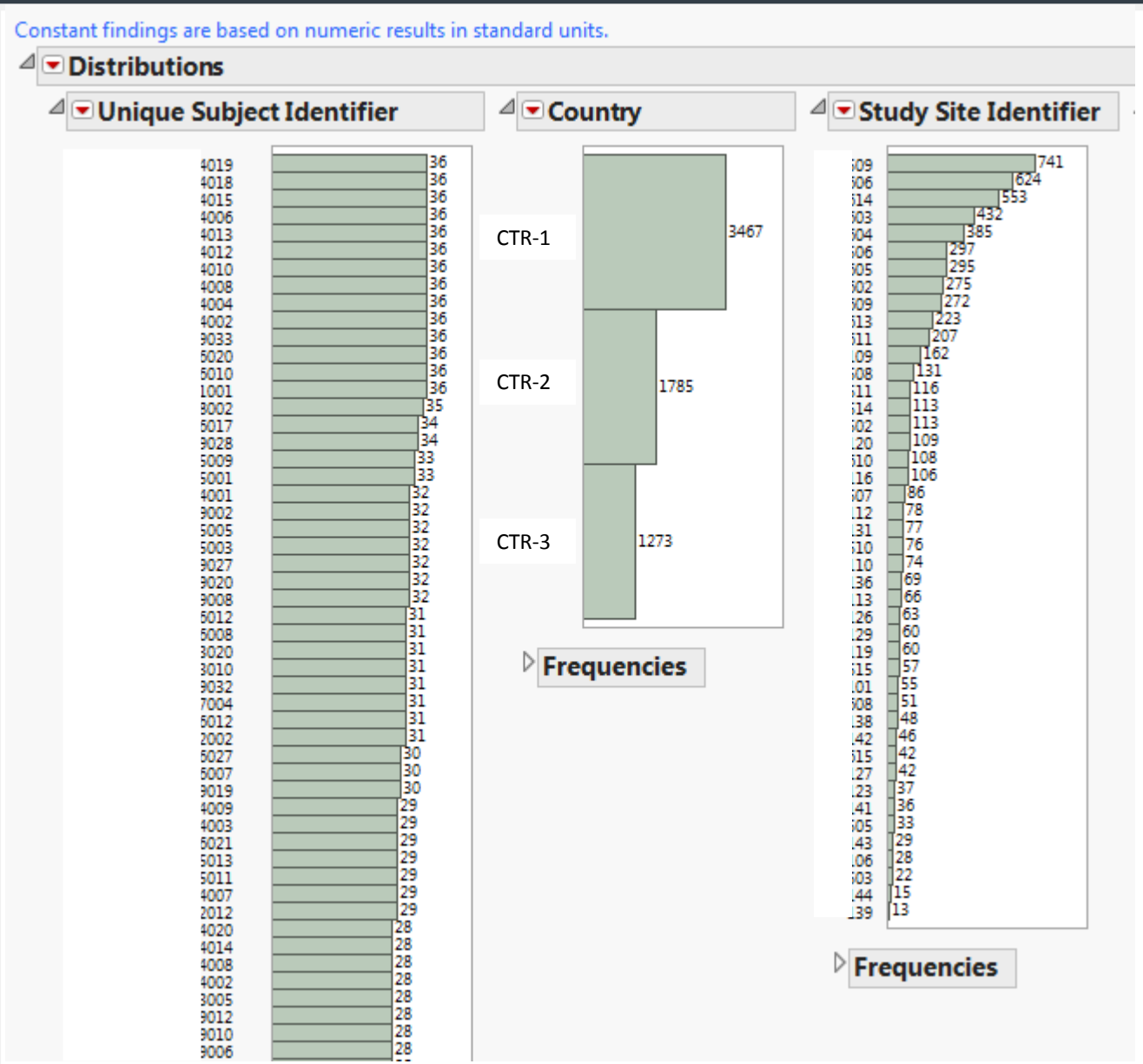
Fraud Detection: CDISC Case Study



- In this actual case study, we assess Constant Findings within individual sites. This study had subjects equally spread over three countries
- We note that CTR-1 has a much higher rate of constant findings.
- Some constant findings are expected – Height, Vitals, some rating scales like CGI, etc. Most sites have 50-70 constant findings between and within subjects.

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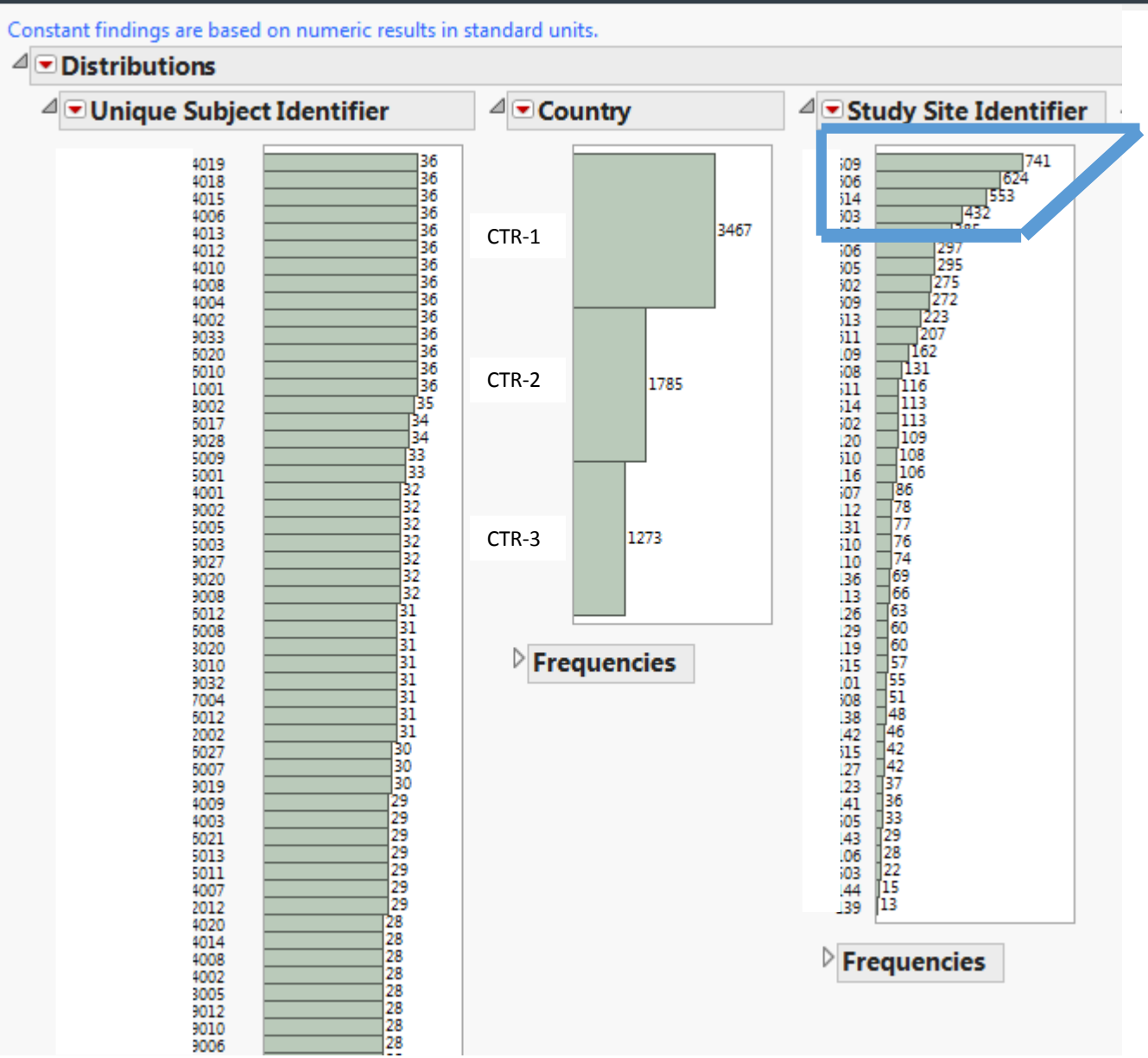
Fraud Detection: CDISC Case Study



Four sites have over 400!

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Conclusions

- Risk Based Monitoring has merits, but the objective of cost cutting seems myopic
- An integrated program of Big Data method Analytics can benefit many different areas to improve study quality, identify problem areas rapidly and possibly prevent a major catastrophe.
- Analytics performed early on, using a Big Data methodology are not necessarily labor intensive and do not require the traditional up-front planning that RBM requires.

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Conclusions

- Risk Based Monitoring has merits, but the objective of cost cutting seems myopic
- An integrated program of Big Data method Analytics can benefit many different areas to improve study quality, identify problem areas rapidly and possibly prevent a major catastrophe.
- Analytics performed early on, using a Big Data methodology are not necessarily labor intensive and do not require the traditional up-front planning that RBM requires.
- **Remember:**

The most expensive study you will ever run is the study that fails.

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Thank You!

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