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USING RISK INDICATORS FOR VISUALIZING HIGH-DIMENSIONAL SAFETY DATA

sas

THE POWER TO KNOW.

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RISK IN CLINICAL TRIALS

Developing, producing and selling in the pharmaceutical industry is a risky business. Brainstorming in this audience would reveal many risks but today we clearly focus on clinical trials and primarily on phase III trials.

- Patient Risk
  - Fit to selection criteria
  - Correct treatment
  - Thorough observation
  - No risk for health or life
  - Severe adverse events
- Study Risk
  - Correct enrollment
  - Correct treatment
  - Correct examination
  - Correct measurements
  - Correct reporting

RISK FOR CLINICAL TRIALS

- Clinical trials are expensive [1-3]
  - $1 billion USD in 2003
  - $2.6 billion USD in 2013
- If Study costs continue to rise at current pace, clinical trials to establish efficacy and tolerability will become impossible to conduct [4]
  - Making drugs unavailable for areas of unmet need
  - Stifling innovation in established treatment areas
  - Placing an extreme price burden on consumers and health care systems

Kenneth Getz, Director of Sponsored Research at the Tufts Center for the Study of Drug Development

TRADITIONAL MONITORING

- A large source of Clinical trial costs?
- Clinical trial monitoring practices (including 100% SDV)
- Estimated at 25-30% of trial cost [5-7]
- But what is monitoring? FDA Guidance [8]:

"… methods used by sponsors… or CROs… to oversee the conduct of, and reporting of data from, clinical investigations... include[s] communication with the CI and study site staff; review of the study site's processes, procedures, and records; and verification of the accuracy of data submitted…"

TRADITIONAL MONITORING

- Why do we do this? ICH Guidance E6 [9]
- Good Clinical Practice (GCP)
  - Protect the well-being of study participants
  - Maintain a high level of data quality to ensure the validity and integrity of the final analysis results
- Interesting tidbits
  - *“sponsor should ensure trials are adequately monitored”*
  - *“sponsor should determine the appropriate extent and nature of monitoring”*
  - *“statistically controlled sampling may be an acceptable method for selecting the data to be verified”*

TRADITIONAL MONITORING

- Expensive [5-7]
- Human review is only 85% accurate [7]
- SDV generated 7.8% and 2.4% of overall queries in all and critical data, respectively [10]
- 95% of data findings were or could have been identified from database [11]
- 100% SDV not required or expected by the FDA or ICH [8,9]
- Limited in its ability to provide insight for data trends across time, patients, and clinical sites [4,12-14]
- Completely study specific
- Detects only what is looked after

RISK-BASED MONITORING

- Determine if and when clinical sites should receive more extensive quality review or intervention
- Reduce the need for specific programming

Risk based monitoring requires risk indicators.

THE POWER OF STANDARDIZATION

- Authorities recommend/request CDISC data transmission
- CDISC is easy and flexible
- CDISC is extendible
- Standard products can be developed for CDISC data management/analysis

MONITORING APPROACHES

- Risk-based monitoring (RBM) makes use of central computerized review of clinical trial data and site metrics
- Kinds of RBM
  - Supervised (TransCelerate) [10] and most traditional approaches
    - Completely study specific
    - Detects only what is looked after
  - Unsupervised (Statistical methods) [12]
  - Sampling for SDV [7, 15-16]

MONITORING APPROACHES

- Monitoring makes use of central clinical trial data
- Performance (or risk) indicators constitute the fundamental information
- Indicators are compared against
  - Time trends
  - Like indicators in other populations
  - Fixed thresholds
- Two different types of monitoring
  - Supervised monitoring
  - Unsupervised monitoring

SUPERVISED MONITORING

Upfront definition of critical criteria

- TransCelerate[10] and most traditional approaches
- completely study specific
- detects exactly what is looked after
- may identify “signals” that may not be considered anomalous from a statistical perspective
- no requirements for sample size (may identify potential issues for sites that are small)

- Hy’s Law Screening for liver toxicity
- Number of drop outs
- Percentage of adverse events

UNSUPERVISED MONITORING

Determine critical signals after analysis has been done

Apply statistical methods on (all) variables and subgroups

- finds statistically significant aberrations (not neccessarily relevant)
- requires greater level of interpretation
- May reveal unexpected signals

- Digit Preference
- Pairwise Correlation
- Significant Deviations

WATCH OUT FOR SIGNALS

Midpoint Age	N
20	18
30	115
40	195
50	232
60	211
70	92
80	36
90	2
110	1

Sex	
F	578
M	324

Race	
ASIAN	15
BLACK OR AFRICAN AMERICAN	138
OTHER	50
WHITE	699

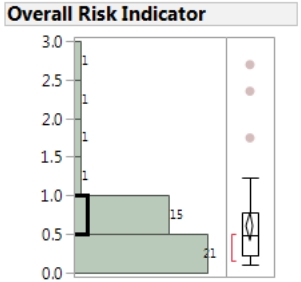
WATCH OUT FOR SIGNALS

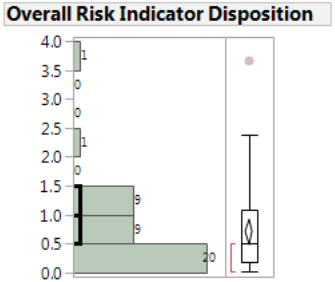
RISK INDICATORS

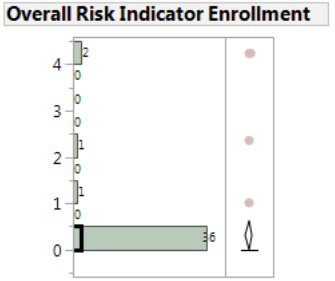
	Study Site Identifier	Country	Overall Risk Indicator	Overall Risk Indicator Disposition	Overall Risk Indicator Enrollment	Overall Risk Indicator Safety
●	12	DEU	0.798	1.346	0.000	0.881
●	14	CAN	0.501	0.850	0.000	0.552
●	16	USA	0.614	1.282	0.000	0.597

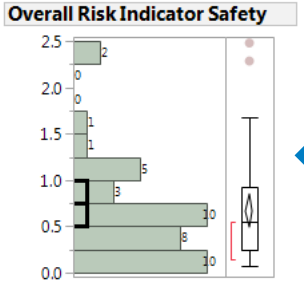
Sites 12 and 14 selected

Location in study distribution

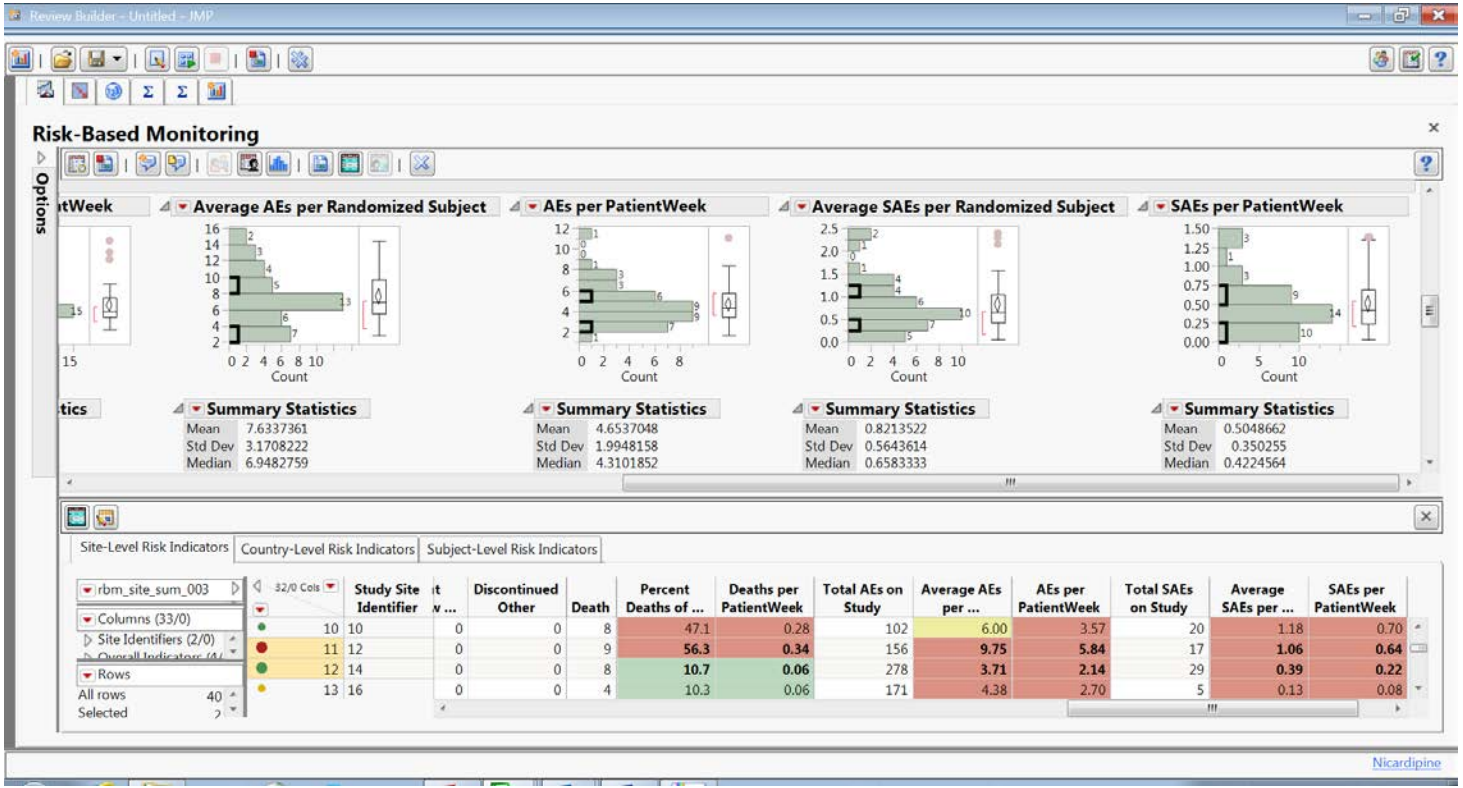








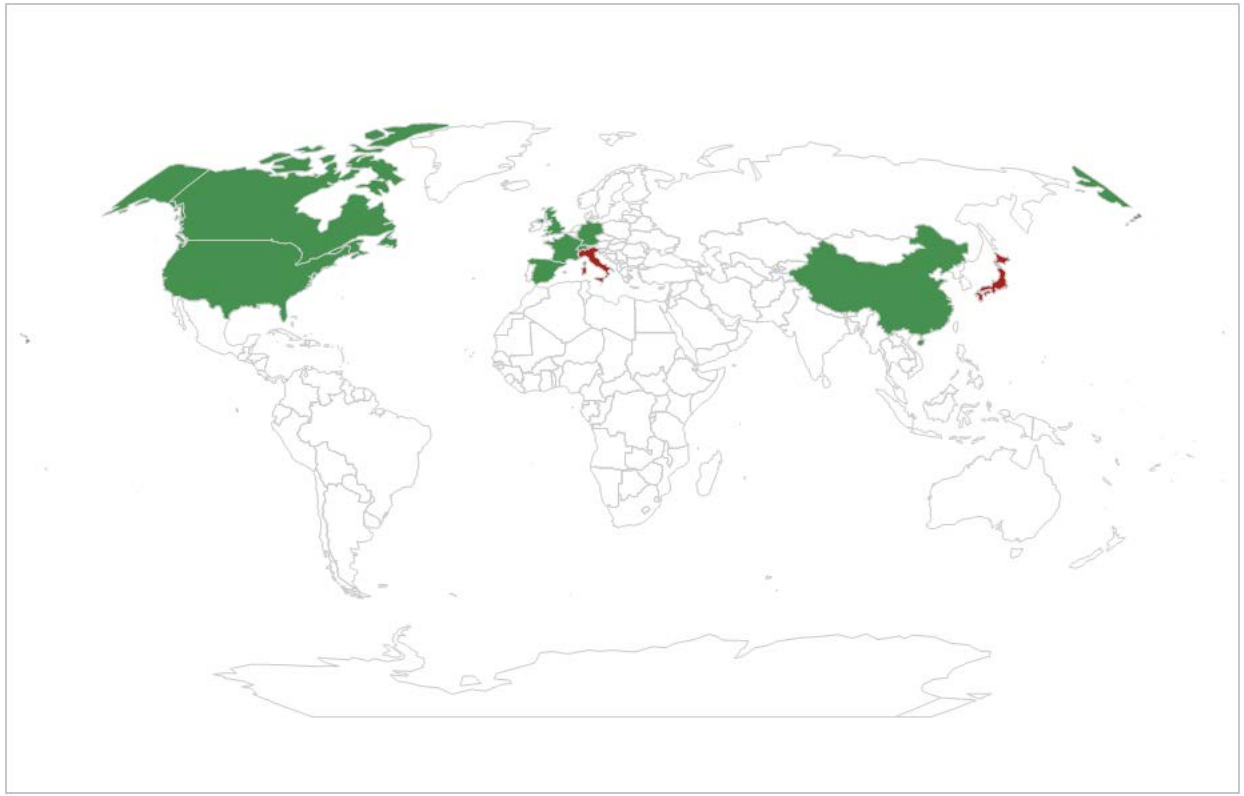
RISK INDICATORS



Location of the variable‘s values for selected sites within the study population

<u>Bottom level:</u> variables and their risk category

RISK INDICATORS

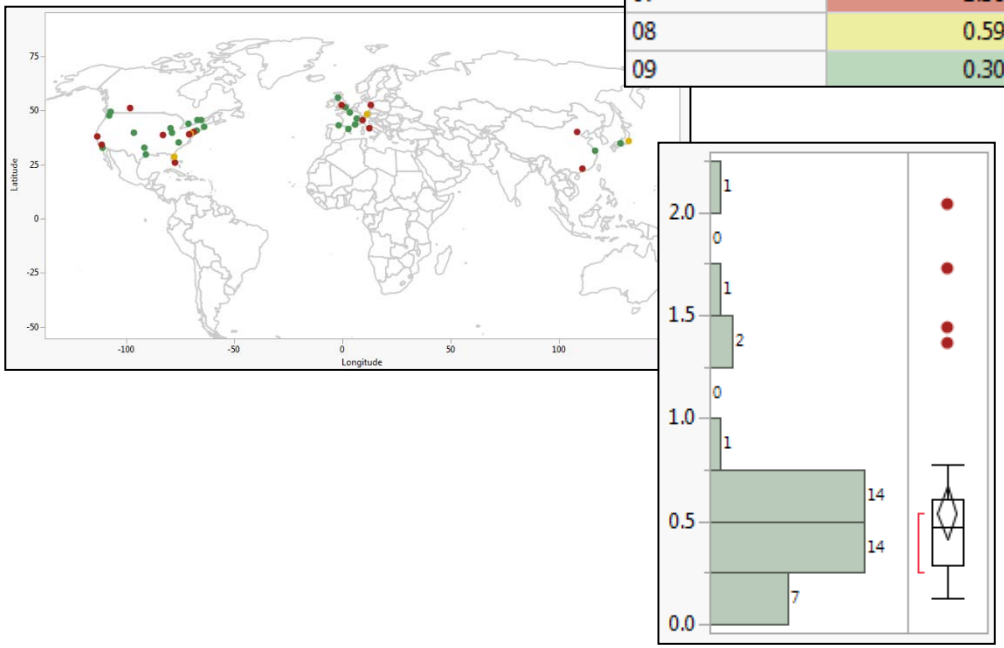


(Risk) indicators can be looked at in variuos combinations or levels of aggregation

SUPERVISED METHODS

- TransCelerate
- Defining Risk Thresholds and Indicators

Study Site Identifier	Overall Risk Indicator
07	1.367
08	0.593
09	0.301



INDICATOR CONTROL TABLE

Variable	SITERATE	MISSCONSENT
Label	Randomized per Week Active	Missing Informed Consent
Category	Enrollment	Enrollment
Yellow Percent of Center	5	
Yellow Magnitude	0	
Red Percent of Center	15	
Red Magnitude	0	1
Weight for Overall Risk Indicator	1	1
Center Flag	Median	Fixed
Center Value		0
Direction for Risk Signals	U	U
Yellow Recommended Action		
Red Recommended Action		Contact Site principal investigator for missing informed consent.
Comment	Poor performing versus potentially going easy on entry criteria. Used Fixed to compare against a specified target enrollment rate.	A single instance of missing informed consent is a huge red flag.

INDICATORS ARE GROUPED

Variable	Explanation	Indicator Group
DEATH	Death	Safety
PCTDEATH	Percent Deaths of Randomized Subjects	Safety
PWDEATH	Deaths per PatientWeek	Safety
TOTAE	Total AEs on Study	Safety
AVGAE	Average AEs per Randomized Subject	Safety
PWAE	AEs per PatientWeek	Safety
TOTSAE	Total SAEs on Study	Safety
AVGSAE	Average SAEs per Randomized Subject	Safety
PWSAE	SAEs per PatientWeek	Safety
TOTHO	Total Healthcare Encounters on Study	Safety
AVGHO	Average Healthcare Encounters per Randomized Subject	Safety
PWHO	Healthcare Encounters per PatientWeek	Safety

Indicators of the same group are averaged to derive an overall group indicator

RISK INDICATOR CALCULATION

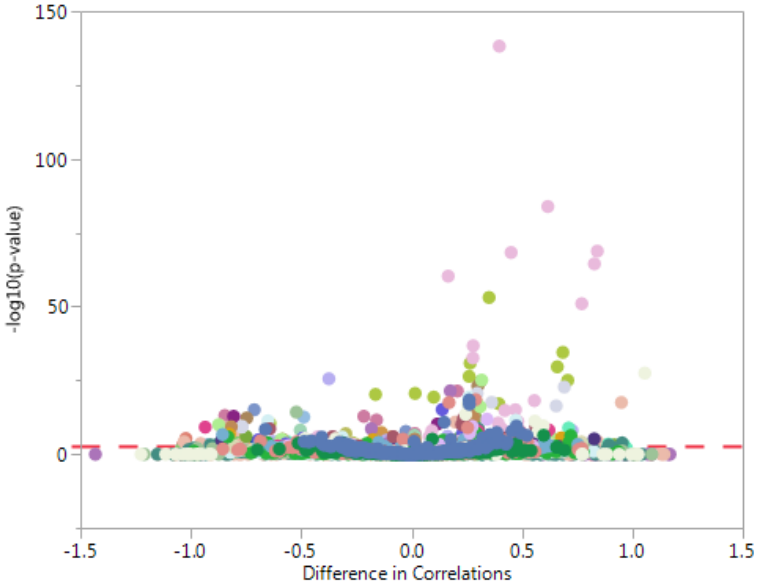
Risk Indicator j for group i $= \frac{c_{ij}}{\mu_{j,}}$ where

$$c_{ij} = \begin{cases} |x_{ij} - \mu_j| & \text{B (both)} \\ (x_{ij} - \mu_j) & \text{U (upper)} \\ -(x_{ij} - \mu_j) & \text{L (lower)} \end{cases}$$

If „Direction“ equals

$$\mu_j = \text{“Center Value”} = \begin{cases} \text{Median} \\ \text{Mean} \\ \text{User supplied value} \end{cases}$$

UNSUPERVISED METHODS



- Define some statistic of interest (mean, maximum, correlation,..).
- Calculate that statistic for each group and the respective rest of the data.
- Run a statistical test to compare both statistics for each pairing.

The indicator to look at is the **p-value of the statistical test**.

The reference line is drawn at the -log10 transformation of the maximum raw p-value where the corresponding FDR *p* -value is less than or equal to α .

EXAMPLE: TEST OF CORRELATION COEFFICIENTS

Fisher's transformation (Fisher, 1921 [20], 1970 [21])

$$r_i^* = \frac{1}{2}\log_e\left(\frac{1+r_i}{1-r_i}\right)$$

$$Z = \frac{r_s^* - r_o^*}{\sqrt{\frac{1}{n_s - 3} + \frac{1}{n_o - 3}}}$$

Indices:

s	site under test
o	all other sites

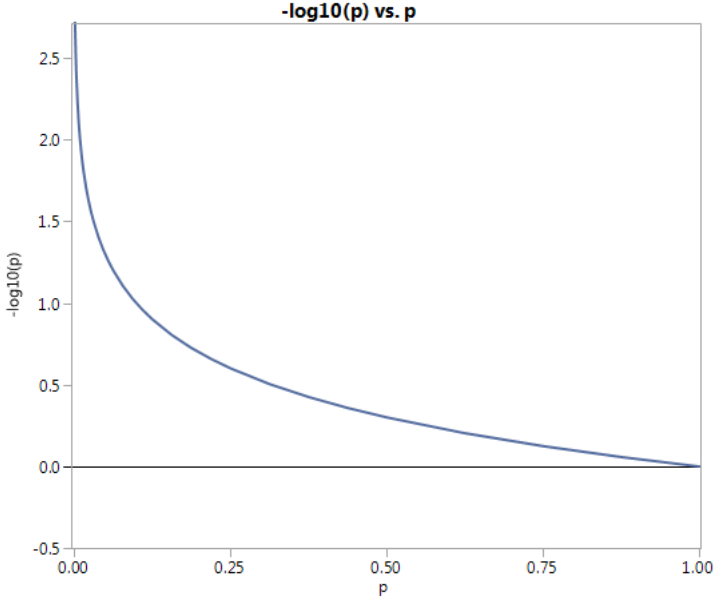
PROTECT AGAINST FALSE DISCOVERY RATE

With *J* treatment comparisons of ordered (smallest to largest) *p* -values $p_{(j)}$, the FDR *p* -value (Benjamini & Hochberg, 1995 [22]) for the j^{th} hypothesis is:

$$p^*_{(j)} = \begin{cases} p_{(J)} & \text{for } j = J \\ \min\left(p^*_{(j)}, \dfrac{j}{(j-1)} p_{(j-1)}\right) & \text{for } j = 1, 2, \ldots (J-1) \end{cases}$$

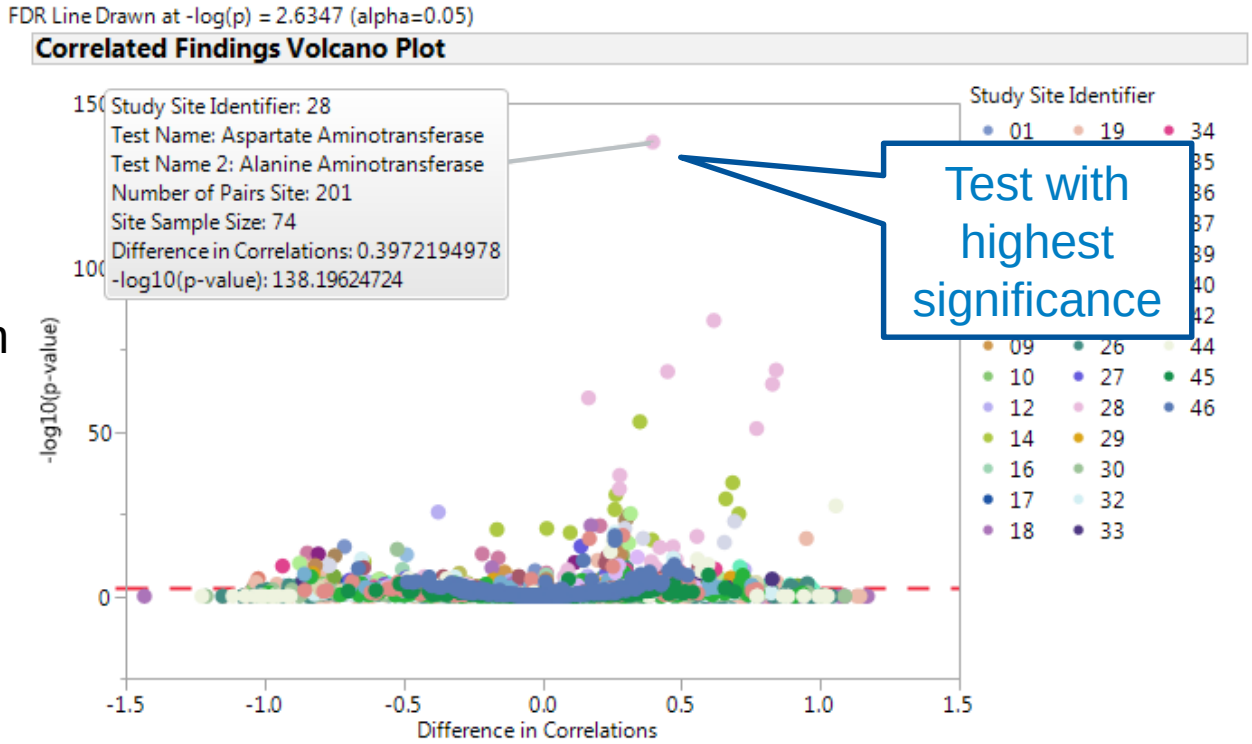
FOCUS ON HIGHLY SIGNIFICANT TESTS

- The statistic to look at is the p-value of statistical tests
- Many tests shall be looked at so a „p < 0.001“ notation is obsolete
- It‘s difficult to spot differences in very small numbers
- A –log10 transformation reverses the order and lets small values stand out prominent.



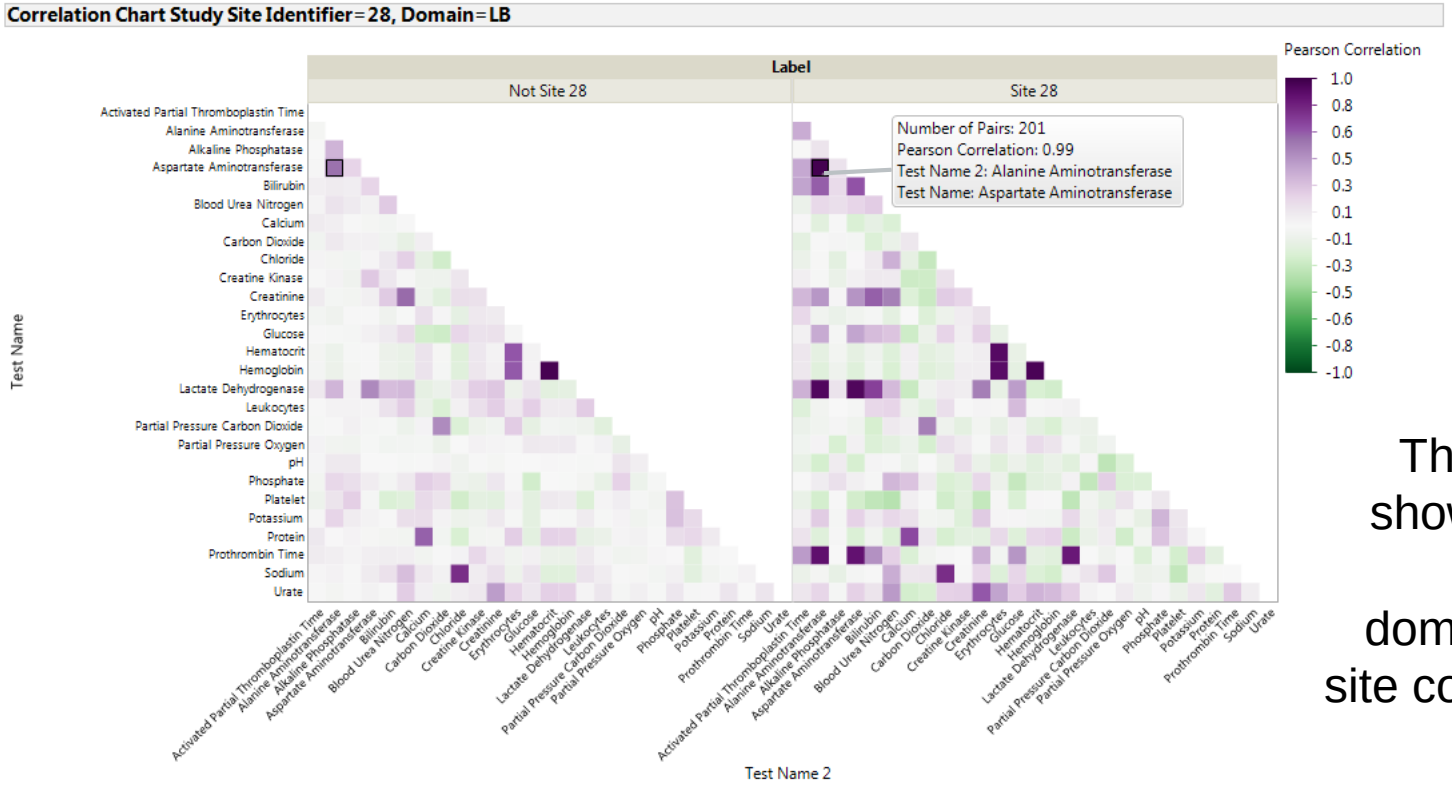
P-VALUE REPRESENTATION

Y-axis: FDR corrected p-values after –log10 transformation



X-axis: difference between statistics (here: correlations)

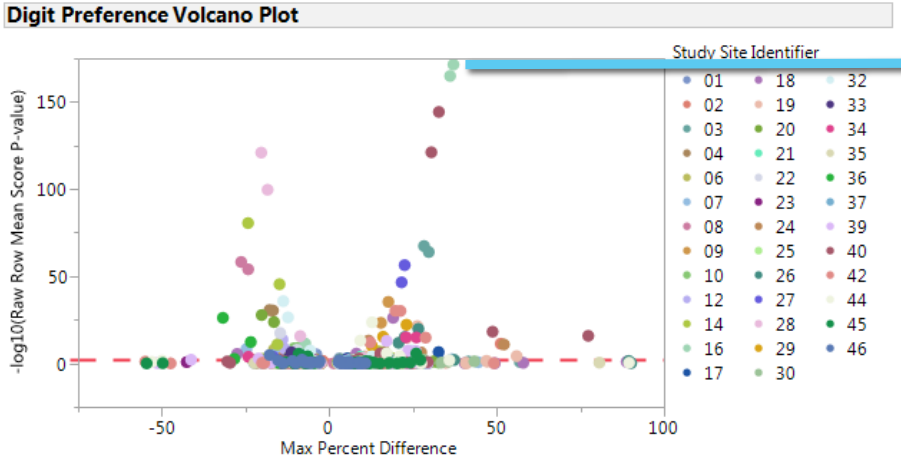
CORRELATED FINDINGS



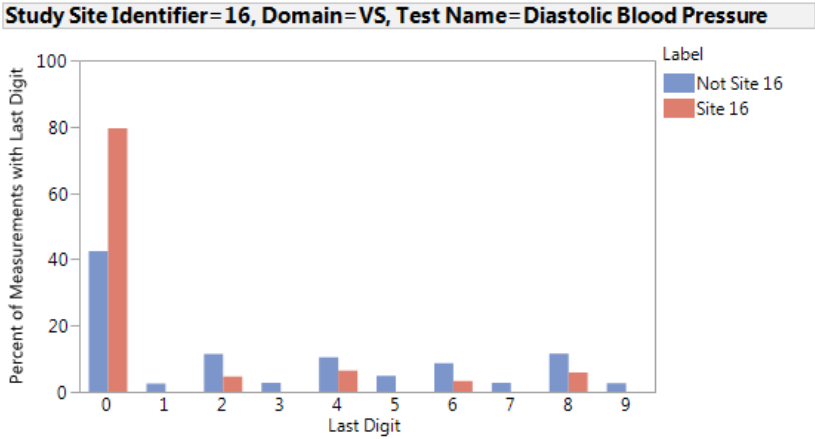
The comparison chart shows the pattern of all correlations in one domain for the selected site compared to all other sites

DIGIT PREFERENCE

Analysis performed using last digit.
FDR Line Drawn at -log(p) = 2.3076 (alpha=0.05)



Drill Down

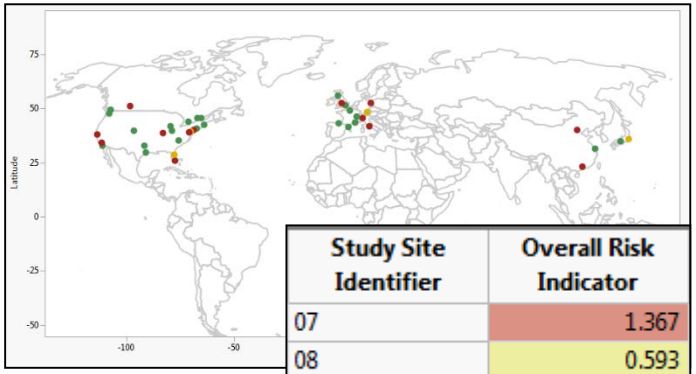


- Statistic of interest: the maximum difference of the frequency of usage of the different last digits of measurements.
- Volcano plot lets find the largest deviations.
- Bar chart for single group (site) reveals the reason for the outstanding result.

RISK INDICATOR SUMMARY

Risk indicators can be built following

supervised



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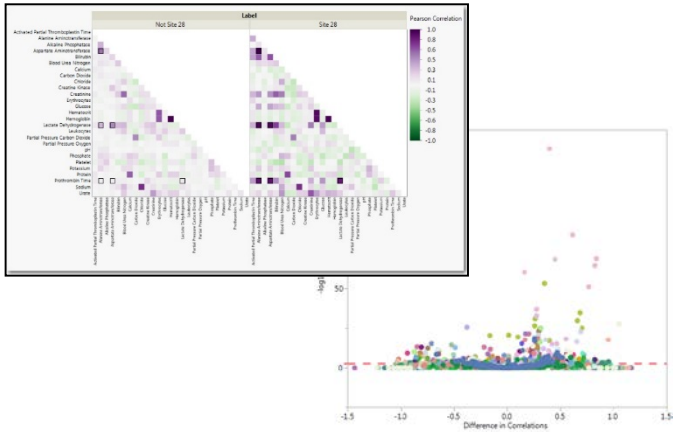
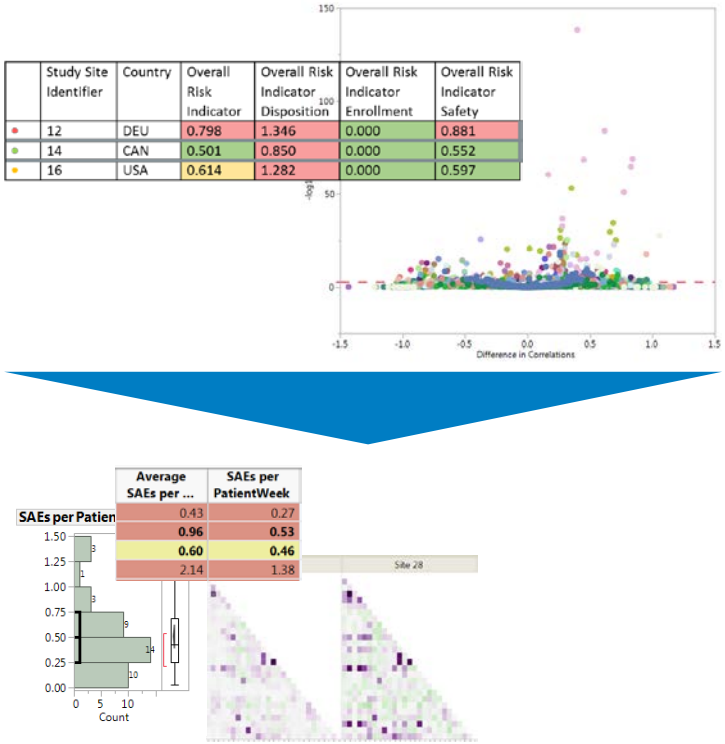
or

unsupervised



Methods

RISK INDICATOR SUMMARY



Color-coding, aggregation and transformation allow for an easy overview in a highly complex environment

Drill-down abilities help keeping track of the details involved

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