MONITORING DATA AND INFORMATION QUALITY IN CLINICAL STUDIES

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QUALITY IN CLINICAL TRIALS

Safety in it's many aspects is a major concern for all stakeholders of clinical trials. Quality in a wider industrial sense is associated with the technical aspects of a trial's execution. In the specific case of clinical trial patient safety and welfare becomes an integral part of quality assessment.

- Patient Safety
  - Fit to selection criteria
  - Correct treatment
  - Thorough observation
  - No risk for health or life
  - Severe adverse events

- Study Quality
  - Correct enrollment
  - Correct treatment
  - Correct examination
  - Correct measurements
  - Correct reporting

QUALITY IN 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

MONITORING CLINICAL TRIALS

- 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…"

MONITORING CLINICAL TRIALS

- 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]
- Restricted to a pre-defined schedule
- 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]
- Completely study specific
- Detects only what is looked after

FREQUENT MONITORING

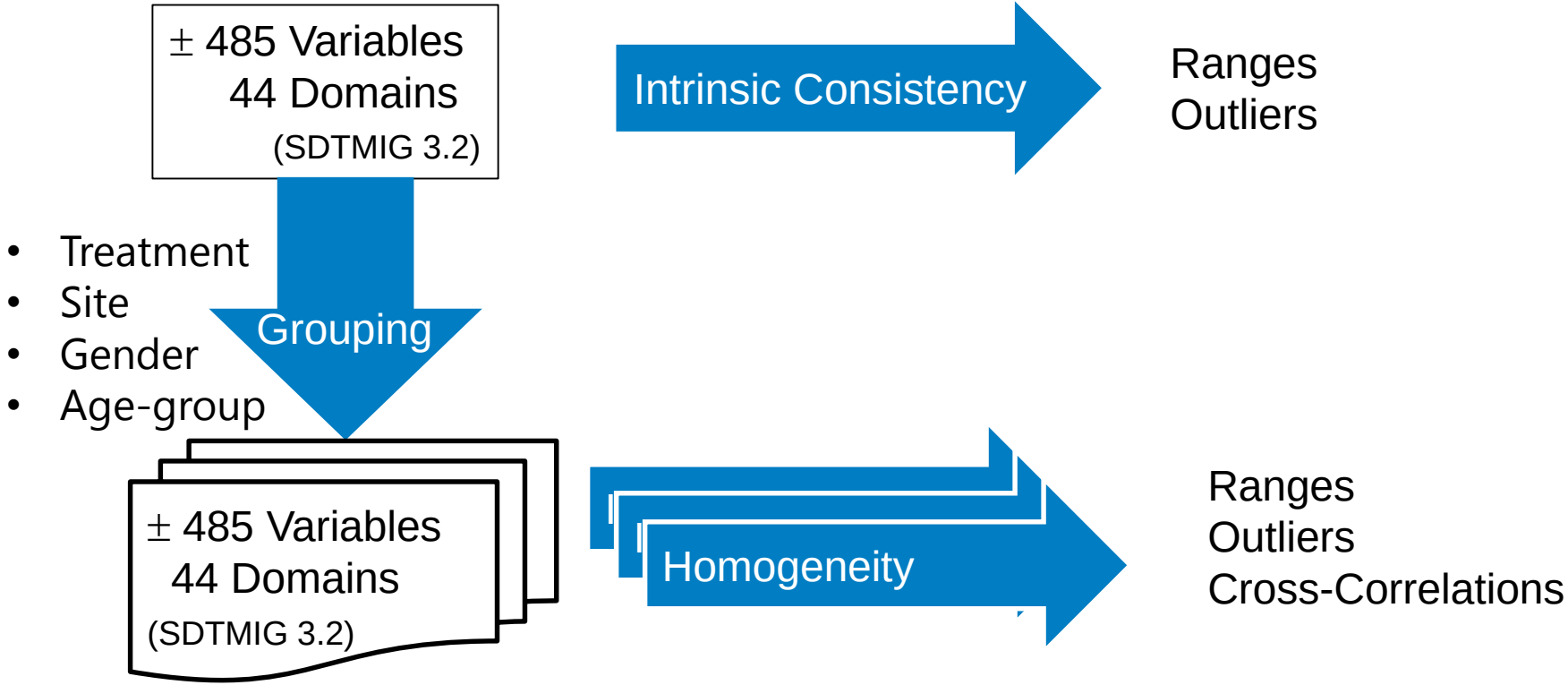
- Couldn’t be handled by human inspection
- Needs programming and statistical support
- Tigthly integrates with risk based monitoring
- Needs to reduce the need for specific programming

Risk indicators and summary statistics, good visualizations and drill-down facilities, describe the framework for a continuous monitoring process that ensures the quality of clinical trials.

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 CDISC (STDM) DATA



MONITORING APPROACHES

- Data quality and patient safety are core aspexcts of risk-based monitoring (RBM)
- RBM makes use of central computerized reviews 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	N
F	578
M	324

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

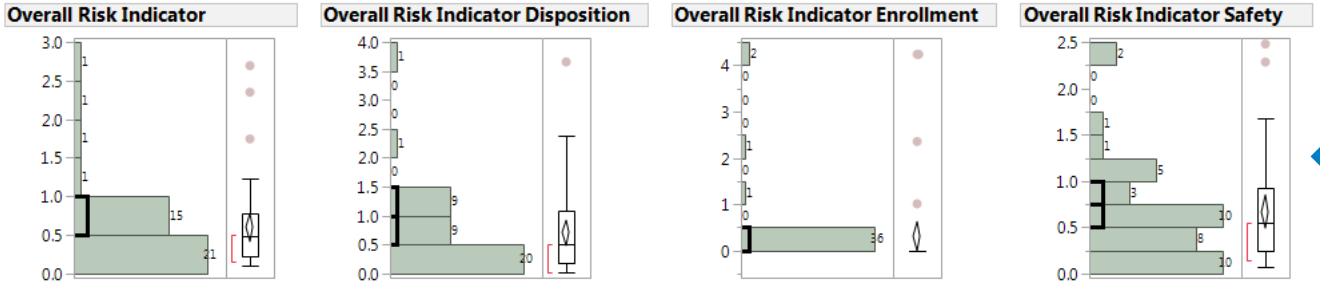
Graphs provide a much more reliable source for finding anomalies than tables. And it is easier and faster to spot unusual situations

A big step forward is the availability of software that maintains a connection to the data. Thus; if a signal pops up; the monitor has the option to drill down to lower aggregation levels and the root of indicated problems.

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

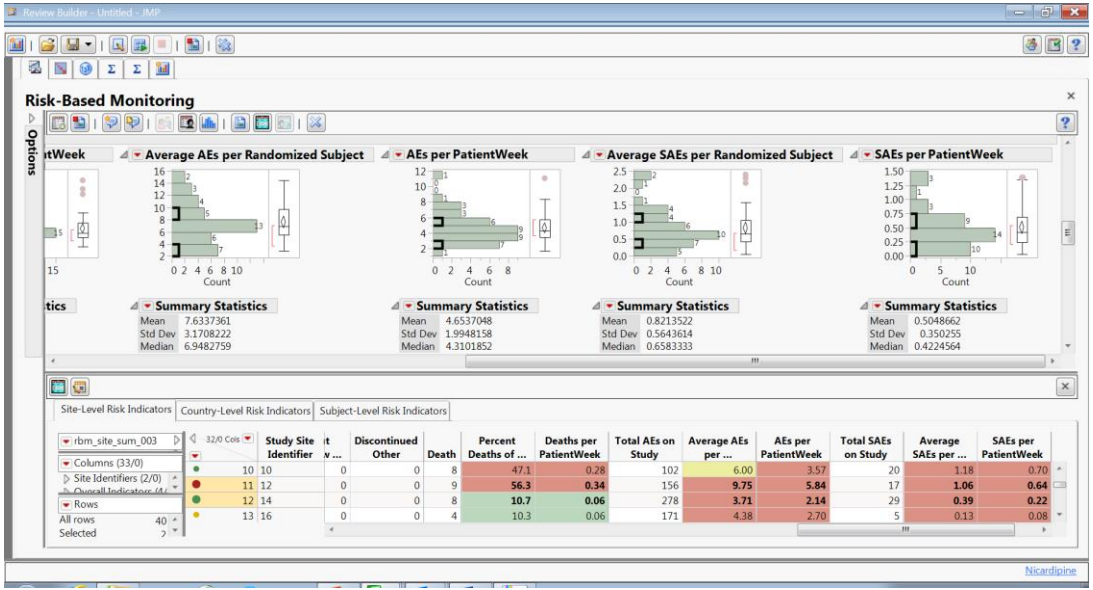
Sites 12 and 14 selected



Location in study distribution

Overall indicators show risk level per site. Color coding makes orientation easier. Highlighting selected sites allows giving additional context information and allows to assess the relative importance of the indicators.

RISK INDICATORS



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

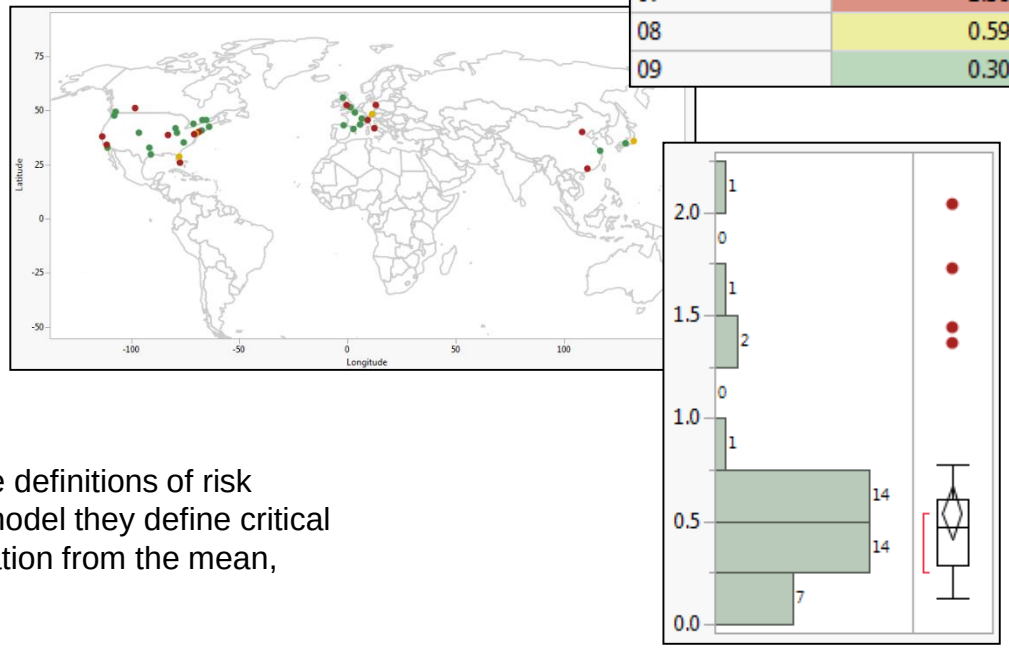
<u>Bottom level:</u> variables and their risk category

The ability to drill down to the bottom level of indicator calculation provides detailed information about the core information that contributed to the risk indicator. Overall classification let easily focus on sites that need closer monitoring. Site visits can be more thoroughly planned using the detailed variable risk classification.

SUPERVISED METHODS

- TransCelerate
- Defining Risk Thresholds and Indicators

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



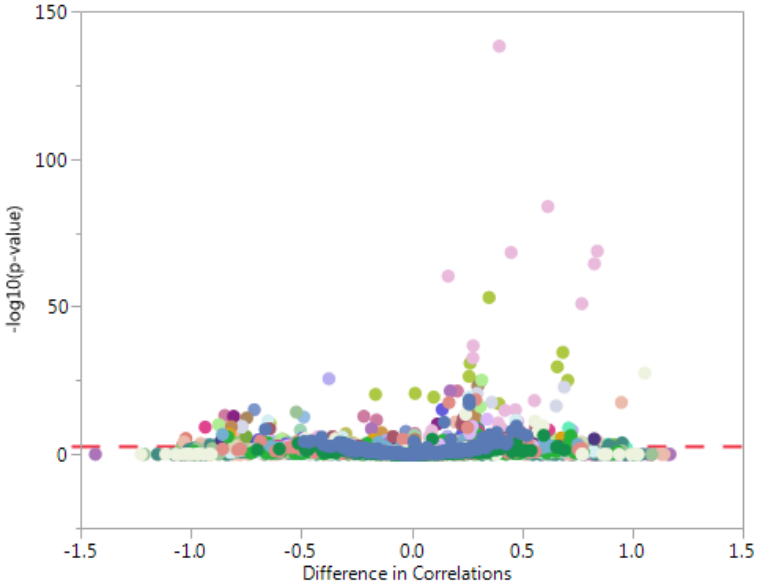
The Transcelerate Group is one of the sources where definitions of risk indicators come from. Referencing the CDISC data model they define critical signals for variables in terms of static numbers, deviation from the mean, percent of occurences and more.

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.

Two examples for supervised control of indicators. Please note „Center Flag“ and „Center Value“ which set the reference for deviation.

UNSUPERVISED METHODS

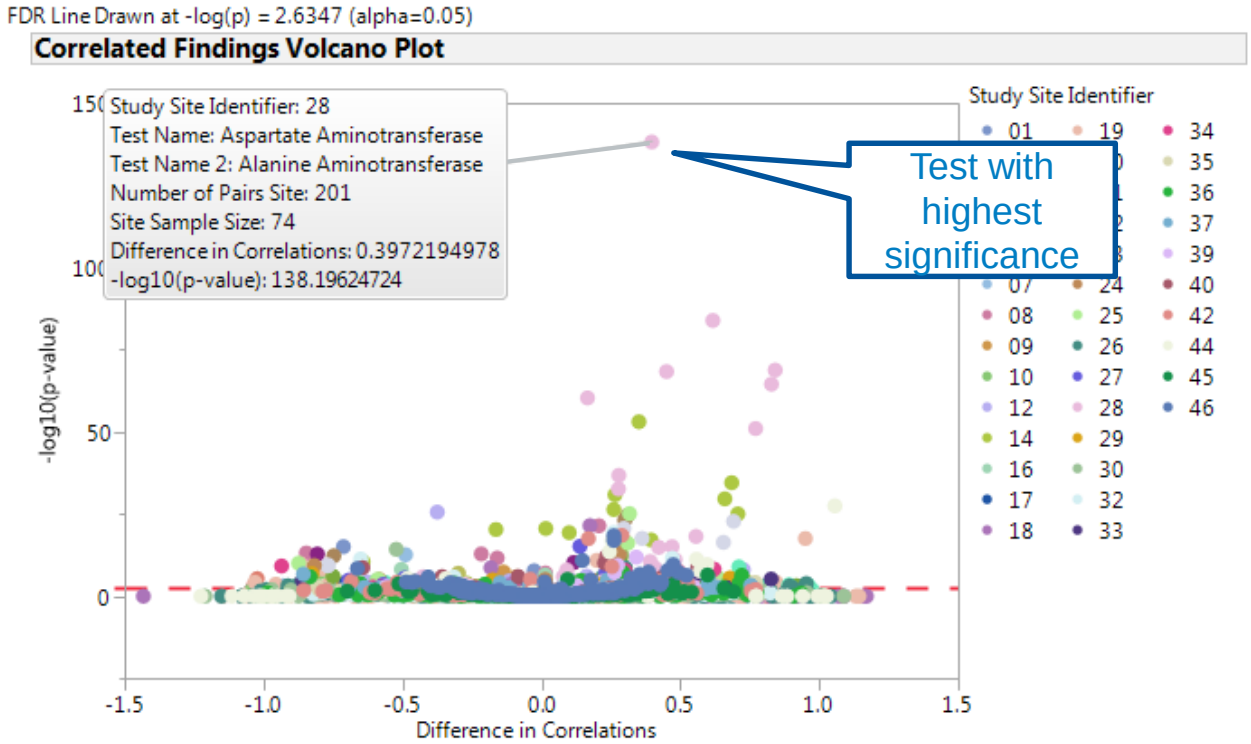


- Define some statistic of interest (mean, maximum, correlation,..).
- Calculate that statistic for each group and the respective rest of the data.
- Run a statistical test to compare both statistics for each pairing.

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 .

P-VALUE REPRESENTATION

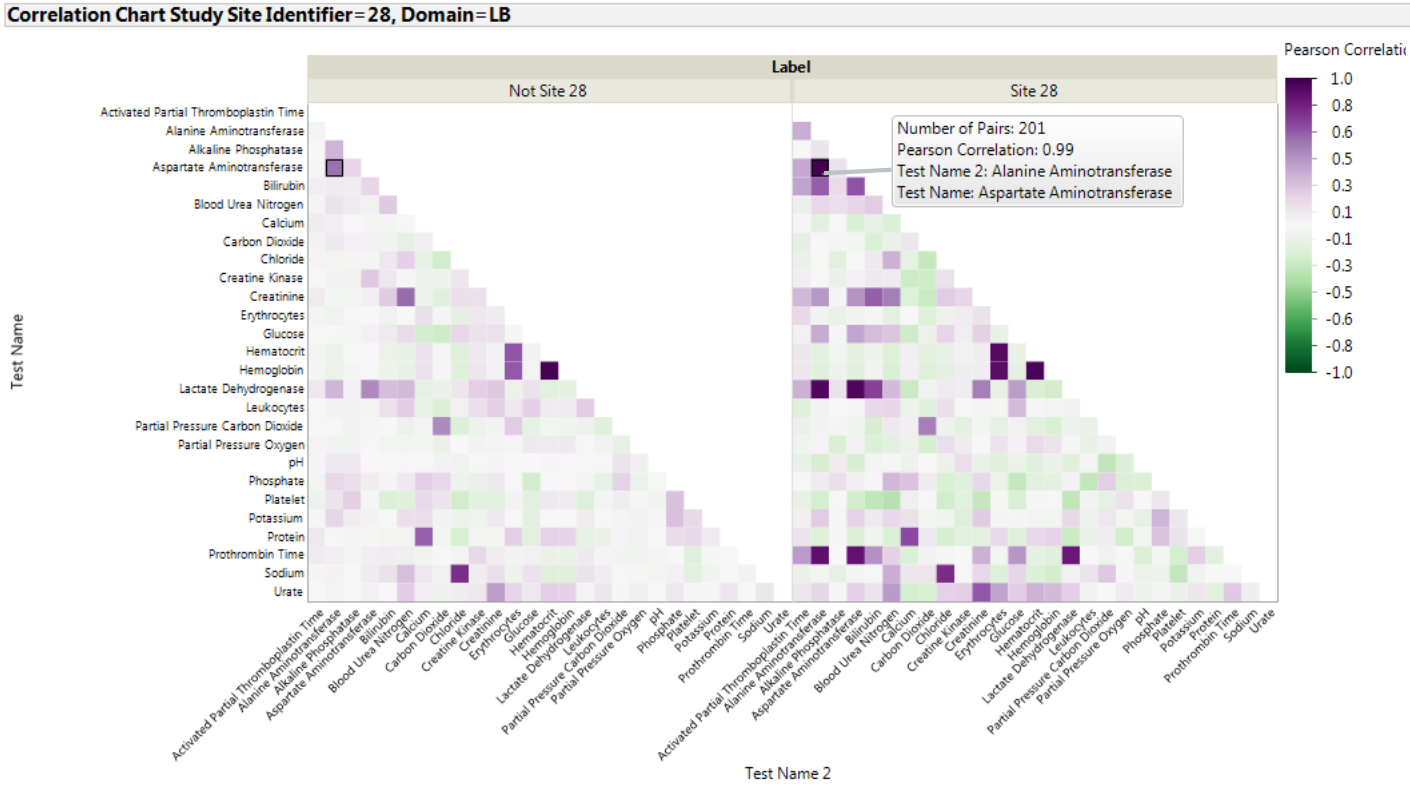


Y-axis: FDR corrected p-values after –log10 transformation

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

After having been corrected for false discovery rate a –log10 transformation is applied to the corrected p-values. Such the smallest p-values range high in the corresponding graph. On the X-axis the difference of the values of the statistics are displayed. A larger deviation to the left or right side of the graph indicates a large difference in values.

CORRELATED FINDINGS

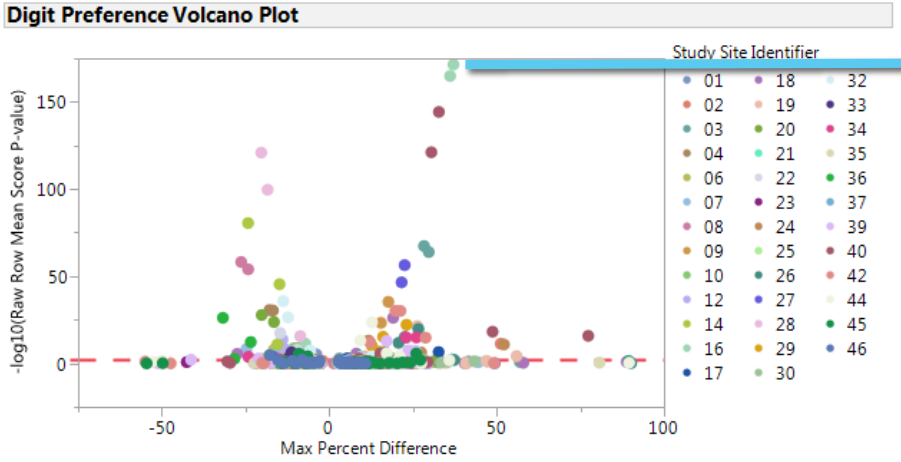


The comparison chart shows the pattern of all correlations in one domain for the selected site compared to all other sites.

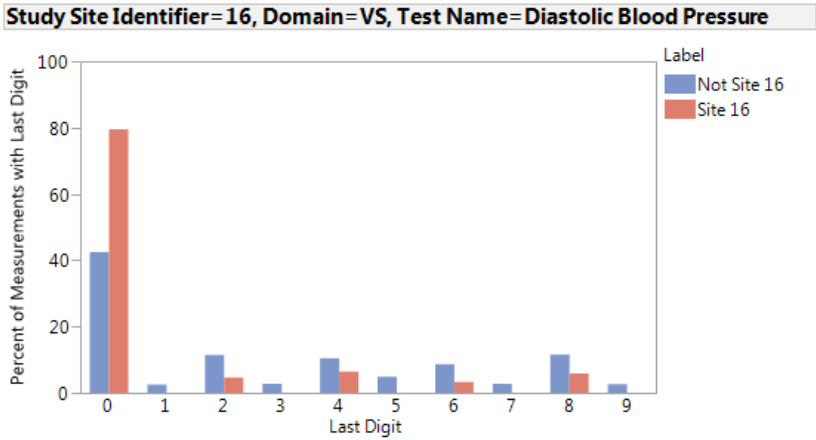
Drilling down to the site selected and the domain the test in question belongs to, shows the pattern of the current indicator. Here correlation between all pairs of tests has been calculated and displayed. So not only the test in question can be looked at; as well other lab results' correlations can be compared and patterns detected.

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.

FINAL THOUGHTS

- RBM means different things to different organizations
- Systems, partners, TA can affect implementation
- One size does not fit all…
  - Organizational structures
  - Expertise
  - Reliance on CROs and outsourcing
  - Resources
- Solutions need to account for changing systems
- CROs may play a different role

FINAL THOUGHTS

- Proactive approach to data quality and safety
- Address shortcomings while the study is ongoing
- Incorporate statistics and graphics
- Utilize supervised and unsupervised methods

Address the challenges in the conduct of clinical trials and base your inquiries on high quality data as a prerequisite for safe trials.

REFERENCES

1. Tufts Center for the Study of Drug Development. (2014). How the Tufts Center for the Study of Drug Development pegged the cost of a new drug at $2.6 billion. Boston: Tufts Center for the Study of Drug Development.
2. Zink RC & Antonijevic Z. (2015). Reduce the cost of success: Adaptive and Bayesian designs to the rescue. *DIA Global Forum* 7: 40-45.
3. Avorn J. (2015). The $2.6 Billion Pill — Methodologic and Policy Considerations. *New England Journal of Medicine* 372: 1877-1879.
4. Venet D, Doffagne E, Burzykowski T, Beckers F, Tellier Y, Genevois-Marlin E, Becker U, Bee V, Wilson V, Legrand C & Buyse M. (2012). A statistical approach to central monitoring of data quality in clinical trials. *Clinical Trials* 9: 705-713.
5. Eisenstein EL, Lemons PW, Tardiff BE, Schulman KA, Jolly MK & Califf RM. (2005). Reducing the costs of phase III cardiovascular clinical trials. *American Heart Journal* 149: 482–488.
6. Funning S, Grahnén A, Eriksson K & Kettis-Linblad A. (2009). Quality assurance within the scope of good clinical practice (GCP): what is the cost of GCP-related activities? A survey with the Swedish association of the pharmaceutical industry (LIF)'s members. *The Quality Assurance Journal* 12: 3-7.
7. Tantsyura V, Grimes I, Mitchel J, Fendt K, Sirichenko S, Waters J, Crowe J & Tardiff B. (2010). Risk-based source data verification approaches: pros and cons. *Drug Information Journal* 44: 745-756.
8. US Food & Drug Administration. (2013). Guidance for industry: Oversight of clinical investigations - a risk-based approach to monitoring.

REFERENCES

9. International Conference of Harmonisation. (1996). E6: Guideline for Good Clinical Practice.
10. TransCelerate BioPharma Inc. (2013). Position paper: Risk-based monitoring methodology.
11. Bakobaki JM, Rauchenberger M, Joffe N, McCormack S, Stenning S & Meredith S. (2012). The potential for central monitoring techniques to replace on-site monitoring: findings from an international multi centre clinical trial. *Clinical Trials* 9: 257-264.
12. Buyse M, George SL, Evans S, Geller NL, Ranstam J, Scherrer B, LeSaffre E, Murray G, Elder L, Hutton J, Colton T, Lachenbruch P & Verma BL. (1999). The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. *Statistics in Medicine* 18: 3435-3451.
13. Zink RC. (2014). *Risk-Based Monitoring and Fraud Detection in Clinical Trials Using JMP® and SAS®.* Cary, NC: SAS Institute.
14. Zink RC. (2014). Exploring the challenges, impacts and implications of risk-based monitoring. *Clinical Investigation* 4: 785-789.
15. Grieve AP. (2012). Source data verification by statistical sampling: issues in implementation. *Drug Information Journal* 46: 368-377.
16. Nielsen E, Hyder D & Deng C. (2014). A data-driven approach to risk-based source data verification. *Therapeutic Innovation and Regulatory Science* 48: 173-180.
18. Benderly BL. (2013, May 3). A prison sentence for altering data. *Science Careers*.
19. Maslen G. (2013, April 25). Scientists sent to prison for fraudulent conduct. *University World News*.
20. Fisher, R.A. (1921). On the "probable error" of a coefficient of correlation deduced from a small sample. Metron 1: 3-32.
21. Fisher, R.A. (1970). Statistical Methods for Research Workers, Fourteenth Edition. Davien, CT: Hafner Publishing Company.
22. Benjamini, Y. and Y. Hochberg. (1995). Controlling the False Discovery Rate: A practical and powerful approach to multiple testing. Journal of the Royal Statistical Society, Series B 57 : 289-300.