



SIGNAL DETECTION OF POTENTIAL MISCONDUCT ACTIVITY IN CLINICAL TRIALS



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- The definition of **signal detection** theory on Wikipedia describes “a means to quantify the ability to discern between information-bearing patterns and random patterns that distract from the information (noise)”.

INTRODUCTION

- Fraud (or misconduct) is an important subset of topics involving data quality
 - Is fraud more exciting to discuss?
 - Quality issues can be due to
 - Carelessness, such as transcription errors
 - Contamination
 - Mechanical failures
 - Poor planning, poor training
 - Fraud
- Fraud is the “Deliberate attempt to deceive” or the “intention to cheat” (Buyse et al., 1999)
- Fraud in clinical trials is difficult to diagnose
 - How to separate from carelessness?
 - Perhaps differences between sites are due to available subjects, or slight variations in technique
 - May identify unusual points indicating a quality problem, but stating that it is explicitly due to fraud may require more evidence (Evans, 2001)

INTRODUCTION

- Many authors agree fraud is uncommon in clinical trials
 - Proportion of investigators committing fraud estimated < 1% (Buyse et al., 1999)
 - Other published reports in clinical trials show few or no instances of fraud
- However!
 - Instances may be undiagnosed
 - Lack of tools
 - Hard to compare across subjects, time and sites with traditional approaches
 - Instances may go unreported (media firestorm, risk to clinical program)

INTRODUCTION

- Recommendations to minimize the incidence and effects of fraud
 - Keep study entry criteria straightforward
 - Minimize the amount of data collected
 - Sufficient and varied monitoring (Baigent et al., 2008)
 - On site
 - Centralized utilizing statistical and graphical tools
 - Randomization and blinding
 - Trials in some therapeutic areas may be open-label (Al-Marzouki et al., 2005)
- Treat fraud as a special case of data quality to examine throughout the trial

INTRODUCTION

- Why should we bother looking for fraud or quality issues?
 - Ethical to protect the patient
 - Identify problems for correction within the trial
 - Identify problematic sites to avoid in future trials
 - Minimize stress for the study team
 - Reduce risk for a clinical program
 - Besides, fraud is another quality problem
- Rest of the talk
 - Discuss graphical and statistical approaches
 - Highlight the importance of regular, centralized review of fraud and other quality concerns
 - Provide some examples of fraud (and other data quality) detection
 - Digit preference
 - Constant Findings

INTRODUCTION

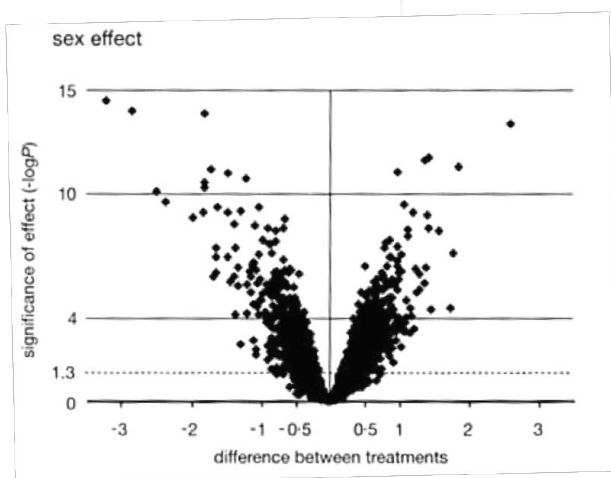
- CDISC Standard Data
 - SDTM (shown below, DM and VS)
 - ADaM

| Study Identifier | Domain Abbreviation | Unique Subject Identifier | Study Site Identifier | Subject Reference Start Date/Time | Subject Reference End Date/Time |
|------------------|---------------------|---------------------------|-----------------------|-----------------------------------|---------------------------------|
| NICSAH1 | DM | 101001 | 10 | 1988-01-21T17:15:00 | 1988-02-02T17:11:00 |
| NICSAH1 | DM | 101002 | 10 | 1988-01-26T11:30:00 | 1988-02-05T12:00:00 |
| NICSAH1 | DM | 101003 | 10 | 1988-01-26T15:10:00 | 1988-02-04T15:30:00 |

| Study Identifier | Domain Abbreviation | Unique Subject Identifier | Sequence Number | Vital Signs Test Short Name | Vital Signs Test Name | Numeric Result/Finding in ... | Standard Units | Date/Time of Measurements |
|------------------|---------------------|---------------------------|-----------------|-----------------------------|--------------------------|-------------------------------|----------------|---------------------------|
| NICSAH1 | VS | 101001 | 173 | DIABP | Diastolic Blood Pressure | 72 | mmHg | 1988-02-04T00:00:00 |
| NICSAH1 | VS | 101001 | 174 | HR | Heart Rate | 70 | BEATS/MIN | 1988-02-04T00:00:00 |
| NICSAH1 | VS | 101001 | 172 | SYSBP | Systolic Blood Pressure | 138 | mmHg | 1988-02-04T00:00:00 |
| NICSAH1 | VS | 101002 | 2 | DIABP | Diastolic Blood Pressure | 82 | mmHg | 1988-01-26T11:30:00 |

SIGNAL DETECTION OF
MISCONDUCT ACTIVITY

VOLCANO PLOT



- First described in Jin et al. (2001)
- Zink et al. (2013) for AE analysis
- X-axis is difference in LS means of \log_2 gene expression, a relative measure of RNA abundance
- Y-axis is $-\log_{10}(\text{p-value})$
 - p -value of 1 equals 0
 - p -value of 0.1 equals 1
 - p -value of 0.01 equals 2
 - p -value of 0.001 equals 3
 - p -value of 0.0001 equals 4
- Diamonds represent one of 3931 genes
- Look for large, significant differences that occur towards upper corners

ACCOUNTING FOR MULTIPLICITY

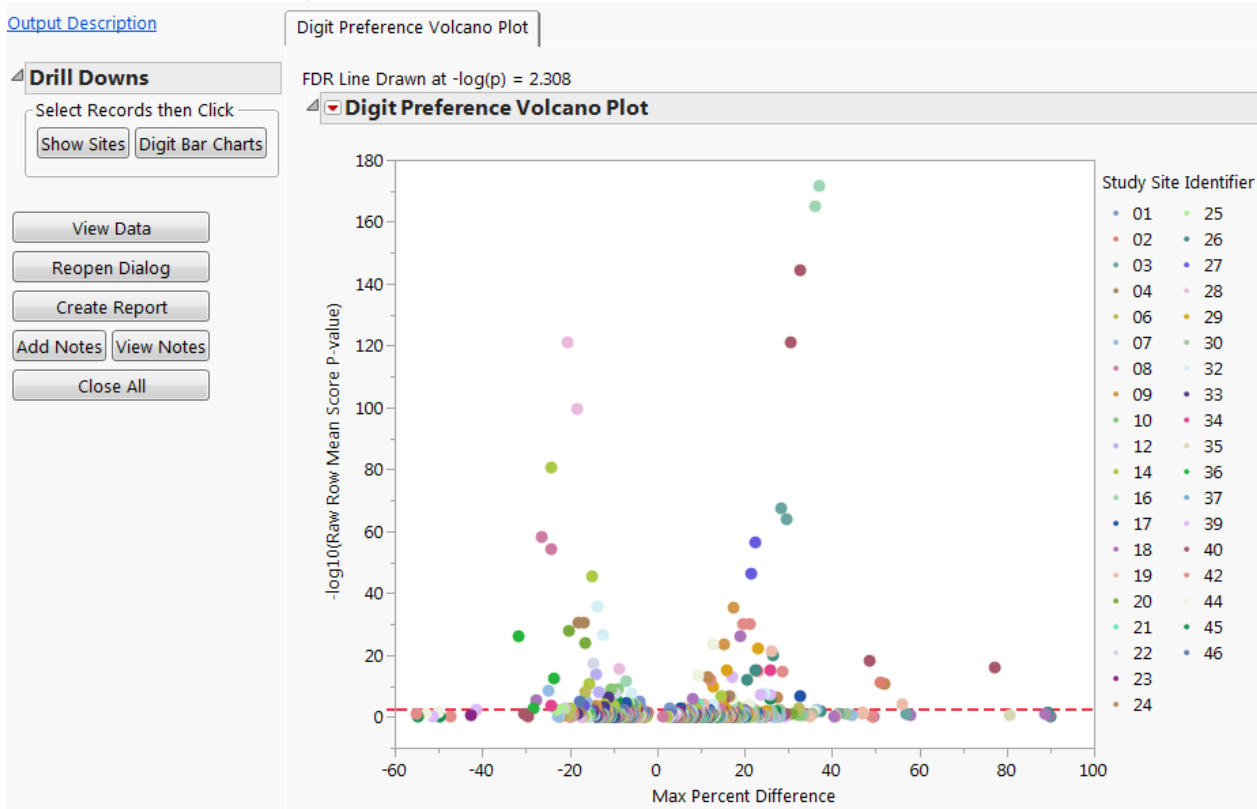
- Multiplicity adjustment to reduce false positive findings
- There are many sites and tests to consider
- How to account for this without overly affecting power?
- False Discovery Rate (FDR) multiplicity adjustment (Benjamini & Hochberg, 1995)
 - Does not control the overall familywise error
- Double FDR method considers a grouping variable (Mehrotra & Heyse, 2004; Mehrotra & Adewale, 2012)
- Provide a more balanced approach between type I error and power

- Treat each site as the suspect site
- Compare observed findings to a reference (all other sites combined)
- Summarize p-values using a volcano plot
- Review follow-up analyses for important signals to diagnose problem

EXAMPLE: DIGIT PREFERENCE

- Compare the observed distribution of leading/trailing digits of data collected from clinical site (e.g. blood pressure)
- Alternatively: Benford's Law (Hill, 1996)
 - Digits 1-9 occur with probability $\log_{10}(1+1/d)$
- Comparing digits can identify:
 - Rounding issues
 - Miscalibrated equipment
 - Protocol deviations
 - Differences in subjective interpretation
 - Duplications

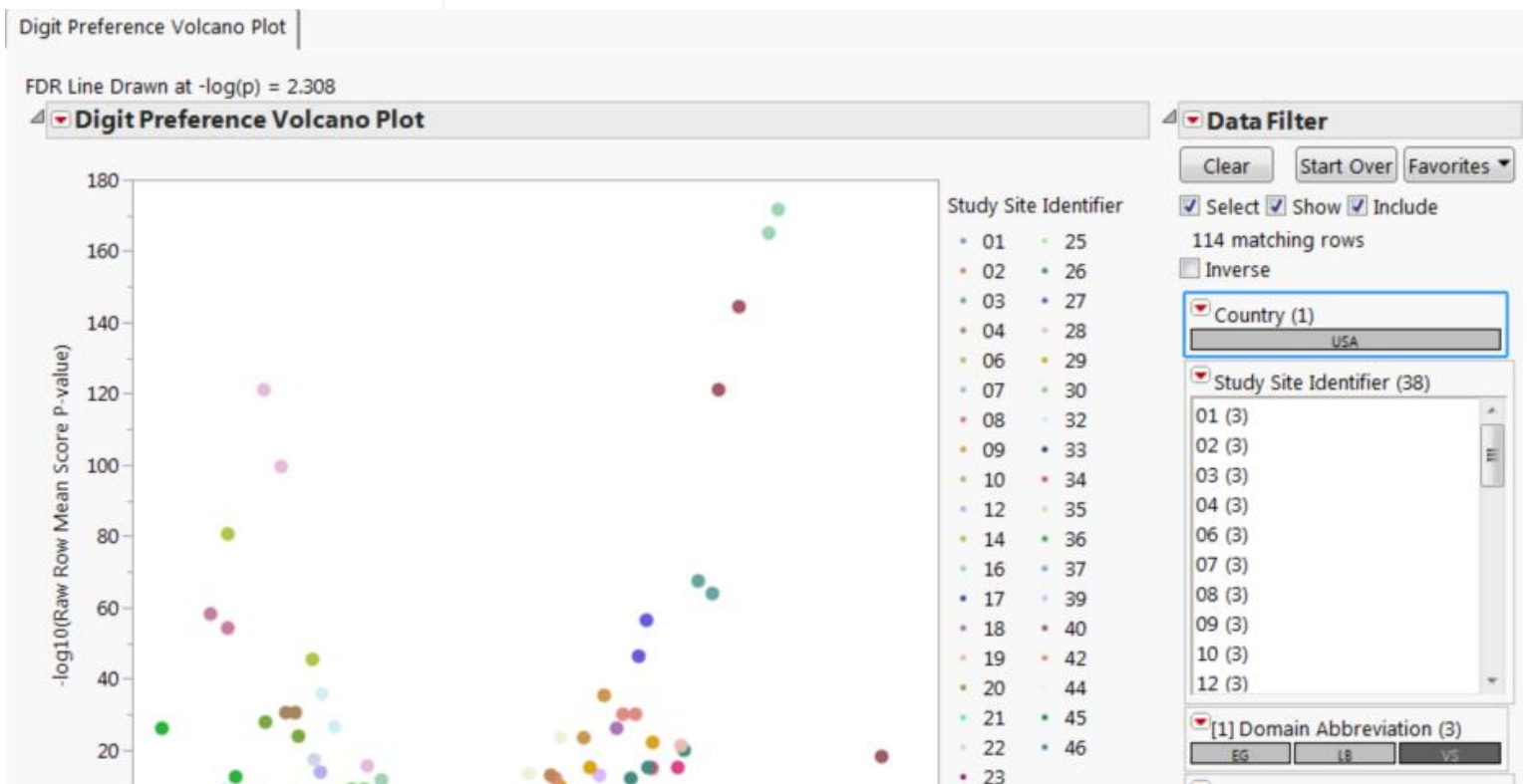
EXAMPLE: DIGIT PREFERENCE



Analysis of trailing digit preference for ECG, vital signs and laboratory measurements.

SIGNAL DETECTION OF MISCONDUCT ACTIVITY

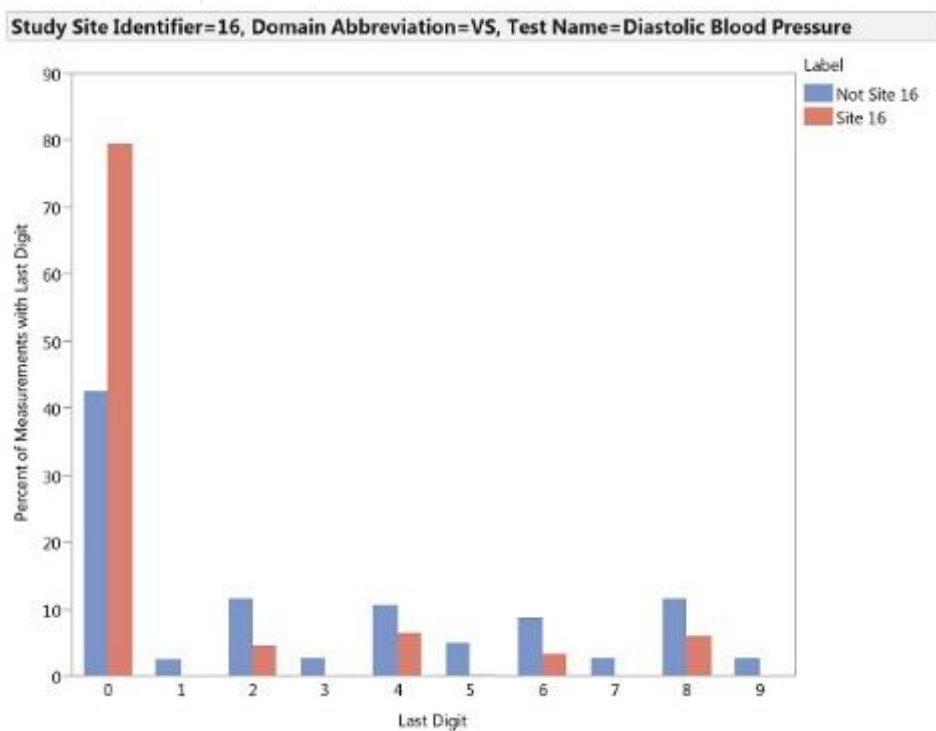
EXAMPLE: DIGIT PREFERENCE



Analysis of trailing digit preference for ECG, vital signs and laboratory measurements.

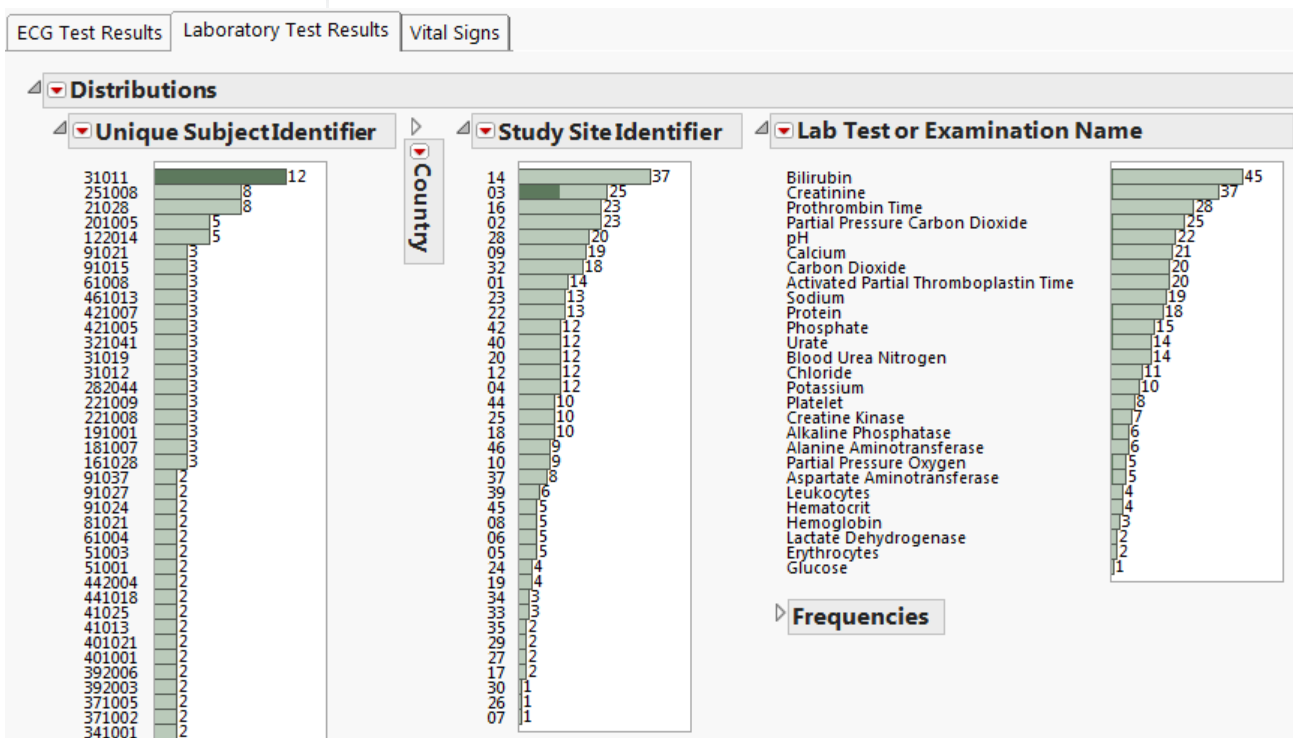
SIGNAL DETECTION OF MISCONDUCT ACTIVITY

EXAMPLE: DIGIT PREFERENCE



Trailing digit for diastolic blood pressure, Site 16 as suspect.
This site reports a 0 twice as often as reference. Perhaps not following protocol?
Systolic blood pressure has a similar same pattern.

EXAMPLE: CONSTANT FINDINGS



Display Subjects, Sites and Lab Tests with multiple constant values

Select subject 31011 with 12 constant findings

Data shown below

EXAMPLE: CONSTANT FINDINGS

| Unique Subject Identifier | Study Site Identifier | Description of Planned Arm | Country | Lab Test or Examination Name | Numeric Result/Finding in Standard Units | Freq of Standard Numeric... |
|---------------------------|-----------------------|----------------------------|---------|---------------------------------|--|-----------------------------|
| 31011 | 03 | Placebo | USA | Alkaline Phosphatase | 55 | 2 |
| 31011 | 03 | Placebo | USA | Aspartate Aminotransferase | 11 | 2 |
| 31011 | 03 | Placebo | USA | Bilirubin | 0.0006666 | 2 |
| 31011 | 03 | Placebo | USA | Calcium | 2.125 | 2 |
| 31011 | 03 | Placebo | USA | Creatine Kinase | 69 | 2 |
| 31011 | 03 | Placebo | USA | Creatinine | 0.0707200009 | 2 |
| 31011 | 03 | Placebo | USA | Partial Pressure Carbon Dioxide | 4921 | 2 |
| 31011 | 03 | Placebo | USA | Partial Pressure Oxygen | 14364 | 2 |
| 31011 | 03 | Placebo | USA | Phosphate | 1.2597000323 | 2 |
| 31011 | 03 | Placebo | USA | Protein | 6.5999999 | 2 |
| 31011 | 03 | Placebo | USA | Urate | 0.1357 | 2 |
| 31011 | 03 | Placebo | USA | pH | 7.46 | 2 |

Patient has 12 different tests with duplicates
Several are very unlikely to occur twice

SIGNAL DETECTION OF
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OTHER POSSIBILITIES

- Treatment differences at baseline
- Differences in variability
- Pairwise correlations between variables
- Proportion of duplications

CONCLUSIONS

- Important to screen database regularly for quality-fraud-misconduct
- Volcano plots are a space-constrained view which can be used to screen a large number of tests
- Quickly draws attention to the important signals for follow-up analyses
- Straightforward to incorporate multiplicity adjustment

SIGNAL DETECTION OF
MISCONDUCT ACTIVITY

Risk-Based Monitoring and Fraud Detection in Clinical Trials Using JMP® and SAS®



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jmp

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sas THE
POWER
TO KNOW.

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