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)
• 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

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Domain Abbreviation</th>
<th>Unique Subject Identifier</th>
<th>Study Site Identifier</th>
<th>Subject Reference Start Date/Time</th>
<th>Subject Reference End Date/Time</th>
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<th>Unique Subject Identifier</th>
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<th>Vital Signs Test Short Name</th>
<th>Vital Signs Test Name</th>
<th>Numeric Result/Finding</th>
<th>Standard Units</th>
<th>Date/Time of Measurements</th>
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<td>Diastolic Blood Pressure</td>
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<td>mmHg</td>
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</table>
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 $-\log_{10}(p$-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
Analysis of trailing digit preference for ECG, vital signs and laboratory measurements.
Analysis of trailing digit preference for ECG, vital signs and laboratory measurements.
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.
Display Subjects, Sites and Lab Tests with multiple constant values
Select subject 31011 with 12 constant findings
Data shown below
### Example: Constant Findings

**Signal Detection of Misconduct Activity**

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

<table>
<thead>
<tr>
<th>Unique Subject Identifier</th>
<th>Study Site Identifier</th>
<th>Description of Planned Arm</th>
<th>Country</th>
<th>Lab Test or Examination Name</th>
<th>Numeric Result/Finding in Standard Units</th>
<th>Freq of Standard Numeric...</th>
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</table>
• 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
Risk-Based Monitoring and Fraud Detection in Clinical Trials Using JMP® and SAS®

Richard C. Zink
REFERENCES