RISK-BASED APPROACHES TO ASSESS DATA INTEGRITY IN MEDICAL PRODUCT DEVELOPMENT

Modern Techniques in Clinical Trial Monitoring

Richard C. Zink, Ph.D.
Principal Research Statistician Developer
JMP Life Sciences
SAS Institute, Inc.

Oct 2015

INTRODUCTION

- Where are we going today?
  - Recent history on pharmaceutical and regulatory landscapes
  - Define risk-based approaches
    - Supervised
    - Unsupervised
  - Illustrations
    - Investigator
    - Patient
  - Demonstration
  - Final thoughts

INTRODUCTION

- Clinical trials are **expensive** [1-3]
  - $1 billion USD in 2003
  - $2.6 billion USD in 2013
- If study costs continue to rise at the 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

TRADITIONAL MONITORING

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

"Monitoring refers to the methods used by sponsors of investigational studies, or CROs delegated responsibilities for the conduct of IND studies, to oversee the conduct of, and reporting of data from, clinical investigations, including appropriate CI supervision of study site staff and third party contractors. Monitoring activities include 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 to the sponsor."

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"*
- How did we get here?

TRADITIONAL MONITORING

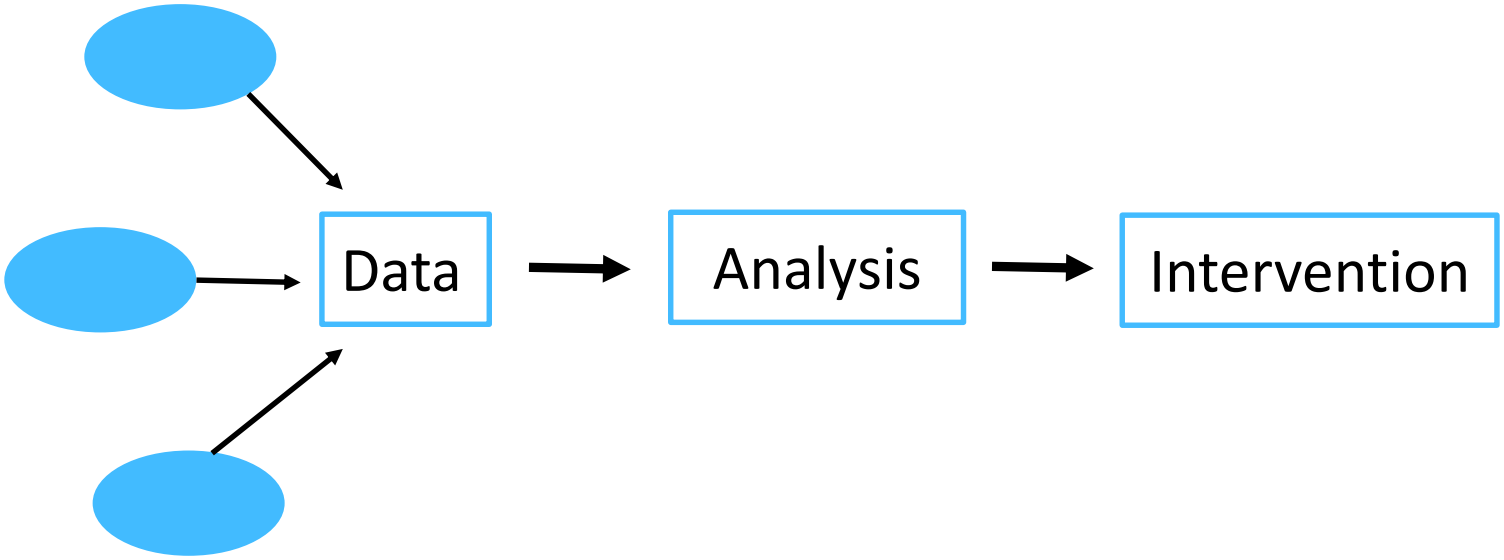
- Expensive [5-7]
- Human review is only 85% accurate [7]
- SDV generated 7.8% and 2.4% of overall queries in all and critical data, respectively [10]
- 95% of data findings were or could have been identified from database [11]
- 100% SDV not required or expected by the FDA or ICH [8,9]
- Limited in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

RISK-BASED MONITORING

- Risk-based monitoring (RBM) makes use of central computerized review of clinical trial data and site metrics
- Determine if and when clinical sites should receive more extensive quality review or intervention
- Kinds of RBM
  - Supervised (TransCelerate) [10]
  - Unsupervised (Statistical methods) [12]
  - Sampling for SDV [7, 15-16]

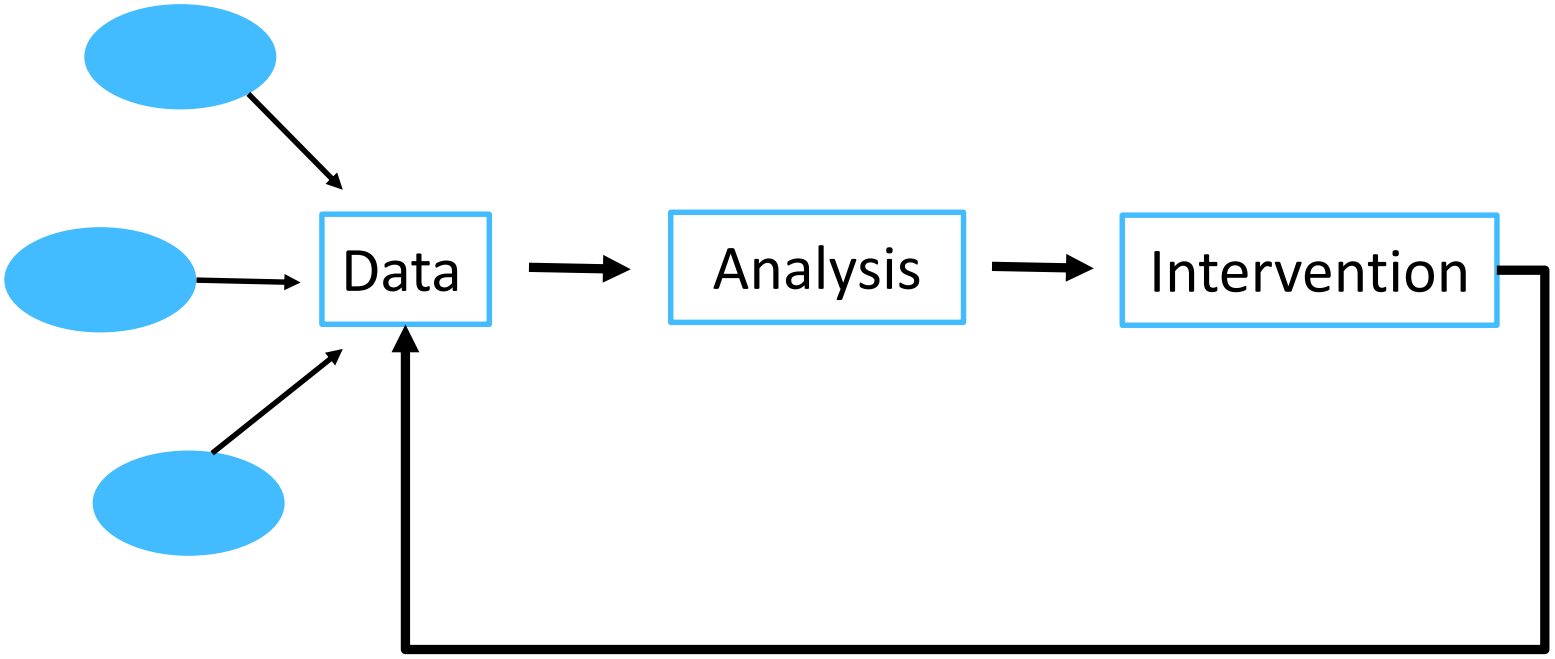
- Traditional monitoring is still important!

GRAPHICAL DISPLAY OF MONITORING PROCESS



Described in [14]

GRAPHICAL DISPLAY OF MONITORING PROCESS



How often does the cycle repeat?

DATA

- IVRS
  - Enrollment
- Study database
  - Safety such as AEs or hospitalizations
- DBMS
  - Quality (Queries, CRF entry)
- Other
  - Statistical programs (protocol deviations, eligibility violations)
  - Monitors (protocol deviations, site metrics)

SUPERVISED ANALYSES

- TransCelerate BioPharma
  - Consortium of ~20 biopharmaceutical companies
- Numerous initiatives
  - Clinical data transparency
  - Clinical trial diversification
  - Common protocol template
  - Pediatric trial efficiencies
  - Placebo and standard of care data sharing
  - Risk-based monitoring [10]
  - Many others…

SUPERVISED ANALYSES

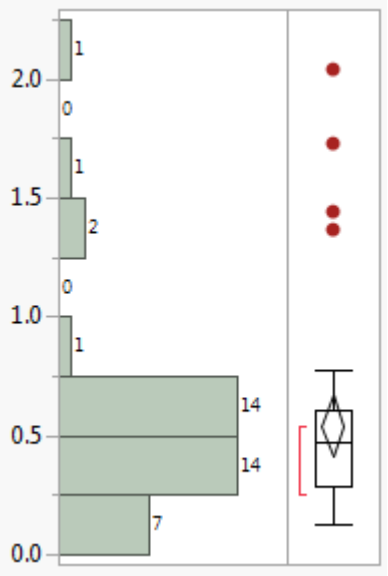
- Define risk indicators and thresholds
- Example: indicator based on the average # of AEs per randomized subject
- Compare a site to the overall average of all sites
  - **GREEN**: site AE rate ≤ 5% of overall average
  - **YELLOW**: site AE rate > 5 and ≤ 15% of overall average
  - **RED**: site AE rate > 15% of overall average
- Utilizes clinical judgment
- Everyone can understand the traffic light

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

SUPERVISED ANALYSES

- Sample size is not a barrier to identify differences
- Defining meaningful thresholds
  - Takes time
  - Differ according to therapeutic area, populations, phase...
- Graphics
  - Histograms
  - Box plots
- Example
  - 9 sites were severe (red)
  - 4 are much worse based on histogram

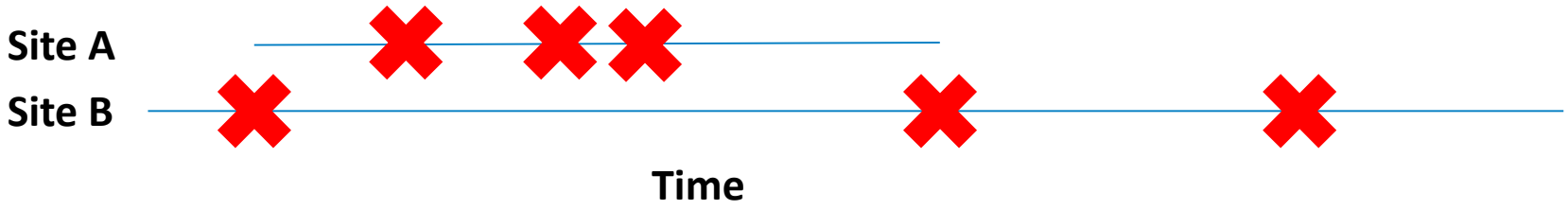
Study Site Identifier	Overall Risk Indicator
07	1.367
08	0.593
09	0.301



SUPERVISED ANALYSES

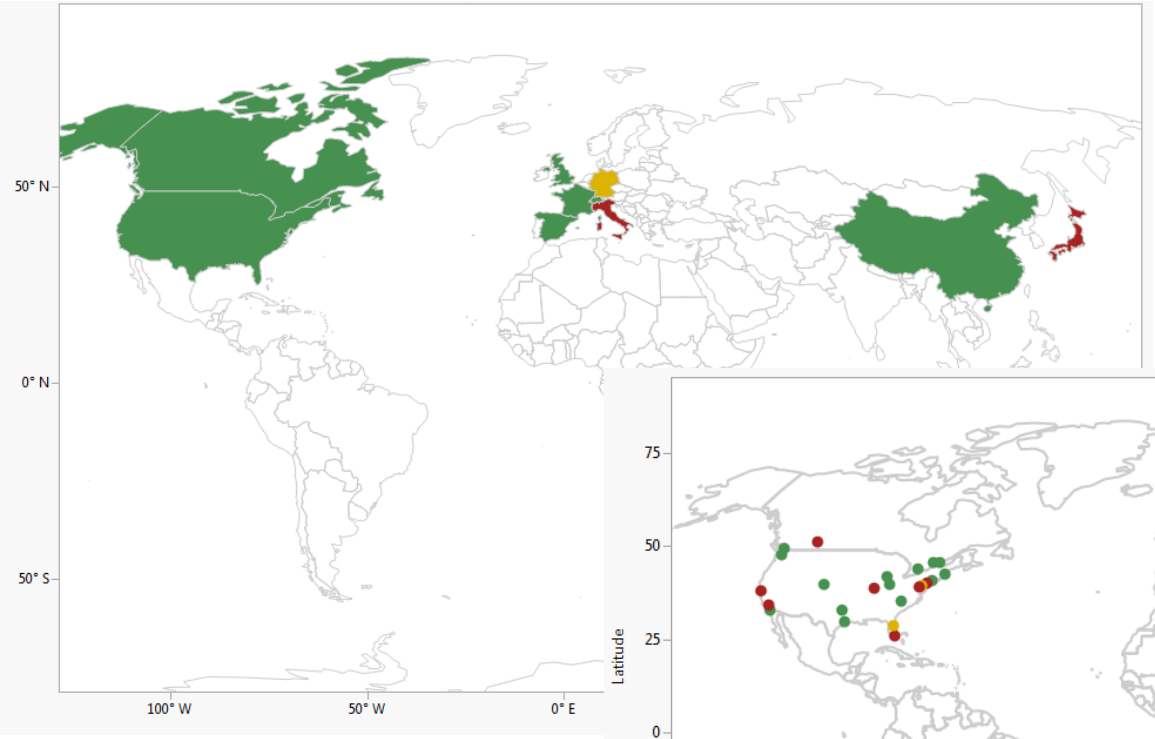
- Individual risk indicators based on
  - Number of randomized patients

    Average AEs per randomized patient
  - Number of patient weeks
    - Average AEs per patient week

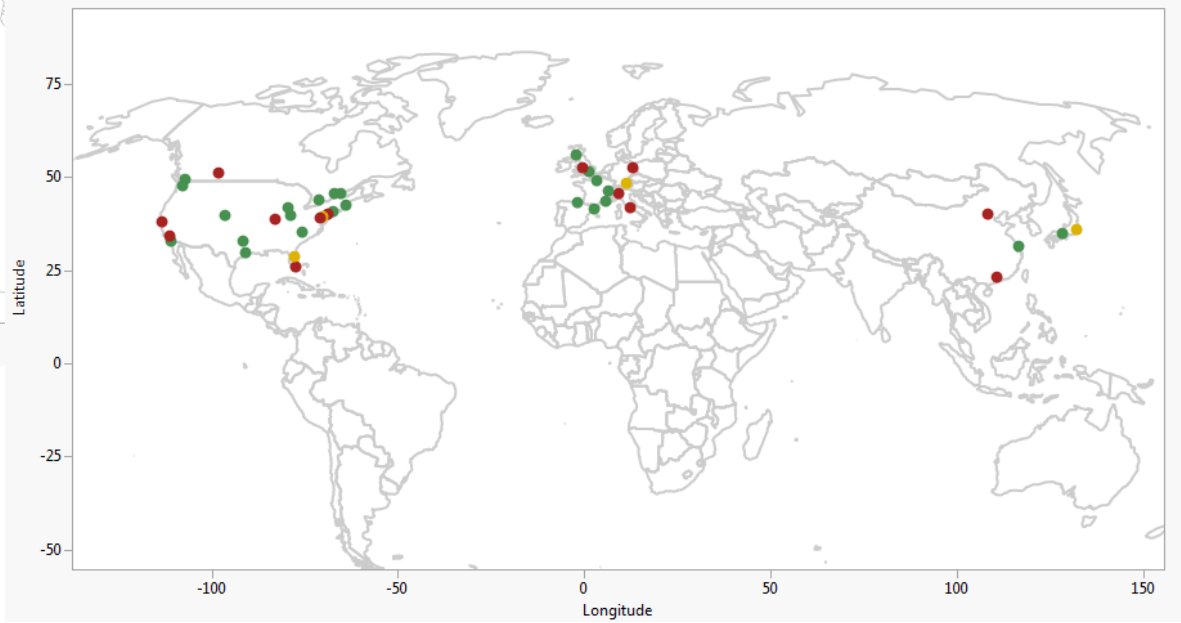


- Overall risk indicator
  - Subtypes
    - Safety
    - Disposition (screen failures or discontinuations)
    - Enrollment

SUPERVISED ANALYSES



Collapsible to different groupings



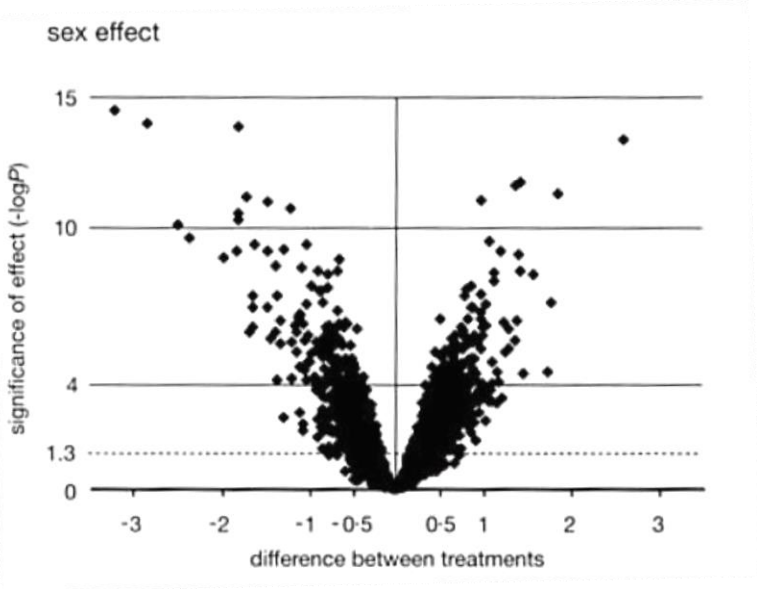
- Regulations
- Environment
- Vendors

UNSUPERVISED ANALYSES – STATISTICAL TESTING

- Fraud/misconduct/quality [4,12,13]
  - Investigator
  - Patient
  - Lab or CRO
- Statistical testing, pattern matching or clustering
- Graphical displays such as volcano plot to highlight signals and launch follow-up analyses

- A note about the “F”-word
  - Fraud (n): wrongful or criminal deception intended to result in financial or personal gain
  - Misconduct (n): unacceptable or improper behavior

VOLCANO PLOTS



- First described in [17]
- 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

UNSUPERVISED ANALYSES – SITE MISCONDUCT

- Means, variances, skewness kurtosis per visit
- Identify screening bias
- Frequency of outliers or missing data
- Duplicates or no variation across the trial
- Visits
  - Unusual scheduling (perfect or off schedule)
  - Missing visits
  - Weekends or Holidays
- Clustering for fabricated patients, misuse of samples
- Inliers and outliers
- Unusual trends, autocorrelation

UNSUPERVISED ANALYSES – PATIENT MISCONDUCT

- Patients can engage in misconduct
- Enrolling at multiple clinical sites
  - Within the same study
  - Within multiple studies of the same clinical program
- Access to additional drug, compensation, medical care
- “Professional patient”
- Independence issue, though minimal
- Mostly an accounting nightmare
  - Tracking exposure and safety
  - Could lead to a severe event
  - Potentially non-compliant to study procedures
  - Leads to additional sensitivity analyses

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
    - Money
    - Personnel
- Solutions need to account for changing systems, CROs

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**

- Appropriate model for risk-based approaches?
  - Each team monitors their studies
  - Centralized group
  - How often should reviews be conducted?

FINAL THOUGHTS

- Findings still require investigation
- Understand our role [8,12]
  - Simplify entry criteria
  - Minimize data collected
  - Build quality into the development program
    - Refine over time
    - Design the trial to limit missing data
    - Don’t “hassle” sites over missing data

FINAL THOUGHTS

- In 2013, a scientist at a pharmaceutical services company was convicted of manipulating data for preclinical studies for an anti-cancer therapy activities he had been engaged in since 2003 [18,19]
- His efforts were identified in 2009 when quality control procedures identified data irregularities, necessitating the review of hundreds of previously-conducted safety studies
  - Recent example
  - Non-clinical
  - CRO

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.
9. International Conference of Harmonisation. (1996). E6: Guideline for Good Clinical Practice. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf
10. TransCelerate BioPharma Inc. (2013). Position paper: Risk-based monitoring methodology. Available at: http://transceleratebiopharmainc.com/.

REFERENCES

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.
17. Jin W, Riley RM, Wolfinger RD, White KP, Passador-Gurgel G & Gibson G. (2001). The contributions of sex, genotype and age to transcriptional variance in Drosophila melanogaster. *Nature Genetics* 29: 389-395.
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*.