

PhUSE 2014

Paper RG01

Signal Detection of Misconduct in Clinical Trials

Geoffrey Mann, JMP Division at SAS Institute, Cary North Carolina, USA

Richard Zink, JMP Division at SAS Institute, Cary North Carolina, USA

ABSTRACT

Misconduct in clinical trials may be a relatively rare phenomenon with the proportion of investigators committing fraudulent acts below one percent (Buyse et al, 1999). However, instances of fraudulent activity are likely to have gone undiagnosed due to a lack of available statistical and graphical tools, and the past over-reliance on the manual monitoring of data to assess trial quality. In this talk, we briefly review analyses to identify patient- and investigator-perpetrated fraud. We discuss the novel application of volcano plots to summarize a digit preference algorithm and drill-downs to understand their differences across sites. Further, we show how signal detection algorithms impact the safety reviews of the trials.

INTRODUCTION

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)”. This is described only slightly differently for humans and machines. Here we describe Dr. Richard Zink’s implementation of a specific signal detection method called Digit Preferences in JMP Clinical software. The results of the algorithm are communicated to the end user with a novel statistical summary visualization, a volcano plot, to discern clinical sites that are significantly different from others using data from laboratory, electrocardiogram, vital sign as well as any other findings test data (e.g. Heart Rate or Total Bilirubin).

STANDARD DATA

The use of a globally recognized standard data format in clinical trials provides numerous advantages over existing non-standard data at each separate institution engaged in medical device, biological entity and drug research. The Clinical Data Interchange Standards Consortium (CDISC) has developed standards for data models, study design, and supporting clinical trial documents. CDISC standards have made such gains that the Center for Drug Evaluation and Research strongly encourages their use and implementation for submission of drug applications. In roughly two years time their use will be required. Several papers and presentations have shown the value of the Submission Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) for safety and efficacy review and analysis. Here we describe their value discerning data quality, misconduct and fraud issues in clinical trials as the Digit Preference algorithm takes either data model as input. The SDTM model is divided into classes of data, primarily consisting of events (e.g. adverse events, disposition events, etc...), interventions (e.g. substance use, concomitant medications, etc...) and findings (e.g. laboratories, vital signs, etc...) as well as trial design and special (e.g. demographics). There are also therapeutic domains but we will ignore those for now. By combining the demographics domain with all of the different findings domains, it is possible to perform signal detection of numeric findings data for misconduct. Below we show example displays of the demographics domain and the vital signs domain that are joined to perform the Digit Preference analysis.

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

Figure 1: Demographics Domain

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	SVSBP	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

Figure 2: Vital Signs Domain

PhUSE 2014

VOLCANO PLOT

The volcano plot is a type of scatterplot used to identify changes in large datasets. This graph type is advantageous for displaying a large number of points in a spatially constrained manner (small area on the screen of a computer or paper). Initially used for display of large fold changes in genetics studies where each point represented an individual gene from a microarray experiment, it has quickly broadened to more of the –omics based high throughput sequencing technologies as well as for events, interventions and findings analyses in clinical trials. Here we describe its usage in signal detection of misconduct in clinical trials of findings data.

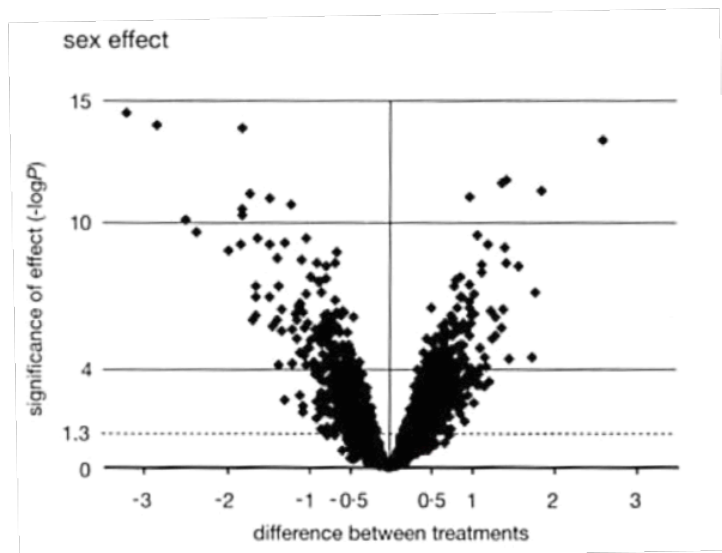


Figure 3: Volcano Plot displaying fold changes in gene expression from microarray experiments (Jin et al.)

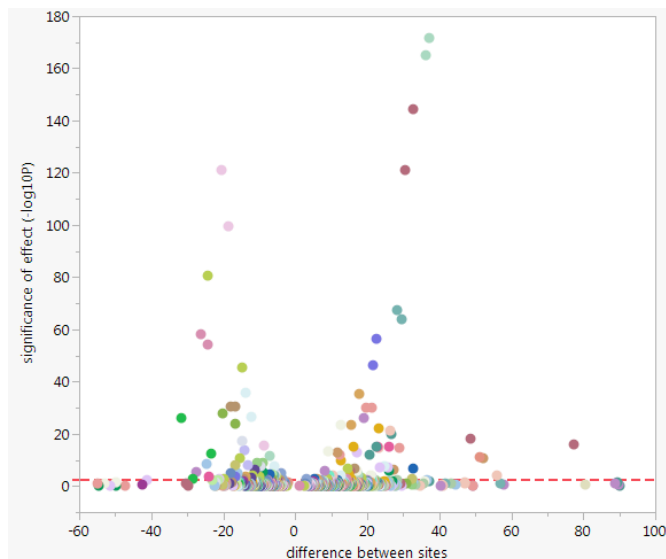


Figure 4: Volcano Plot displaying significant site differences of various findings data

MULTIPLICITY ADJUSTMENT

Signal detection theory explains how changing the “threshold” will affect the ability to discern signal from noise. In this paper, the threshold is determined by a multiplicity adjustment to reduce false positive findings, essentially reducing the noise. Simplistically, every test we perform increases the likelihood of committing type I errors. To account for this in the Frequentist paradigm, methods to adjust for multiplicity are applied. However, the downside is that these methods can adversely effect the power to detect important treatment differences, which is as important as erroneously saying a difference exists. In large clinical trials there can be many sites and tests to consider. We need to account for this without overly affecting power. Enter research on False Discovery Rate (FDR) multiplicity

PhUSE 2014

adjustment (Benjamini & Hochberg, 1995) in the 1990s as well as many other methods implemented in SAS and described by Westfall et al. In this paper a similar approach is applied to the Digit Preference algorithm to improve the signal detection of misconduct at clinical sites. The multiplicity adjustment is indicated visually using a dashed red line in the volcano plots.

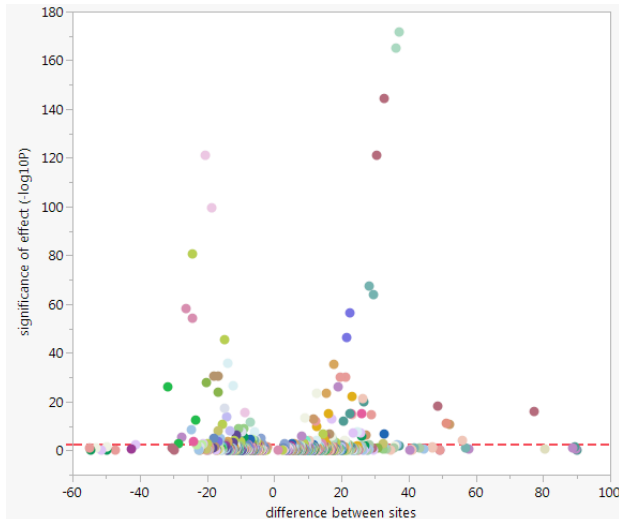


Figure 5: Dashed red line indicates multiplicity adjustment in Digit Preference analysis

DATA QUALITY / MISCONDUCT / FRAUD

Data quality issues in clinical trials can arise due to various issues such as carelessness of transcription of data, mechanical failure of equipment, poor planning, poor training and sometimes fraudulent activities. Fraud in clinical trials is a “deliberate attempt to deceive” (Buyse et al., 1999). It is indeed difficult to separate fraud from carelessness. It is possible to identify unusual points indicating a quality problem but stating that it is explicitly due to fraud may require more evidence (Evans, 2001). It is agreed by many authors that fraud is uncommon in clinical trials, where the proportion of investigators committing fraud is estimated to be below 1% (Buyse et al., 1999). Some reports show very few or no instances of fraud. However, it is very likely that many instances go undiagnosed due to a lack of tools and exploration across the disparate data sources.

GENERAL SCREENING FOR DATA QUALITY / MISCONDUCT / FRAUD

In order to perform the screening it is necessary to treat each site as the suspect site. Once selected this site is compared to a reference comprised of all other sites. It is then possible to summarize all of the p-values for each findings test at each site for display in a volcano plot allowing the end user to review follow-up analyses of significant, or important, signals to diagnose the problem.

DIGIT PREFERENCE ANALYSIS

This paper focuses on a specific signal detection algorithm called Digit Preferences. This method compares the observed distribution of trailing digits of data collected from a clinical site (e.g. blood pressure). Alternative methods, such as Benford’s Law, have not yet been implemented and tested by the authors of this paper. Comparing digits can identify rounding issues, miscalibrated equipment, protocol deviations and differences in subjective interpretation as well as duplications or constant findings data. To run the report it is as simple as choosing the study of interest and choosing the number of subjects that must be present at a site to include in the comparison. The default selection for this option is 5 subjects as can be seen in the following figure.

PhUSE 2014

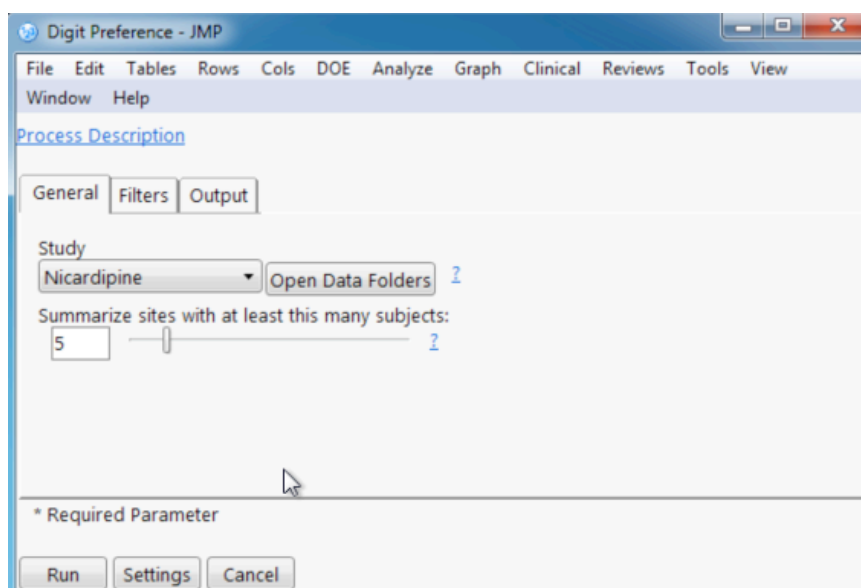


Figure 6: Digit Preferences dialog in JMP Clinical for running report

Once the user has selected the preferred options for the Digit Preferences dialog, they can simply run the report and generate the following Digit Preferences report (dashboard) with available drill down buttons, site details or add notes as well generate a pdf report or view the underlying summarized data. See the following graph for further review of the dashboard.

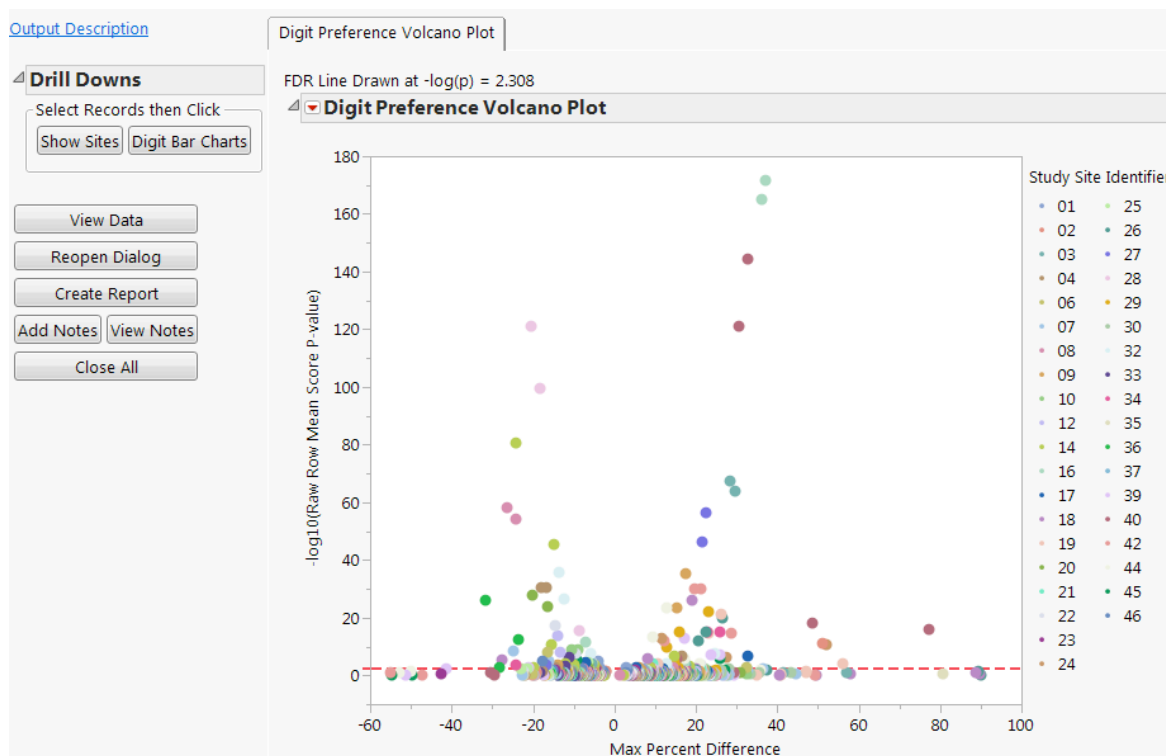


Figure 7: Digit Preferences dashboard in JMP Clinical for rapidly exploring findings tests with statistically significant site differences.

Upon reviewing the Digit Preferences results, the user may simply select the domains and tests of interest by using the data filter on the right hand side of the dashboard.

PhUSE 2014

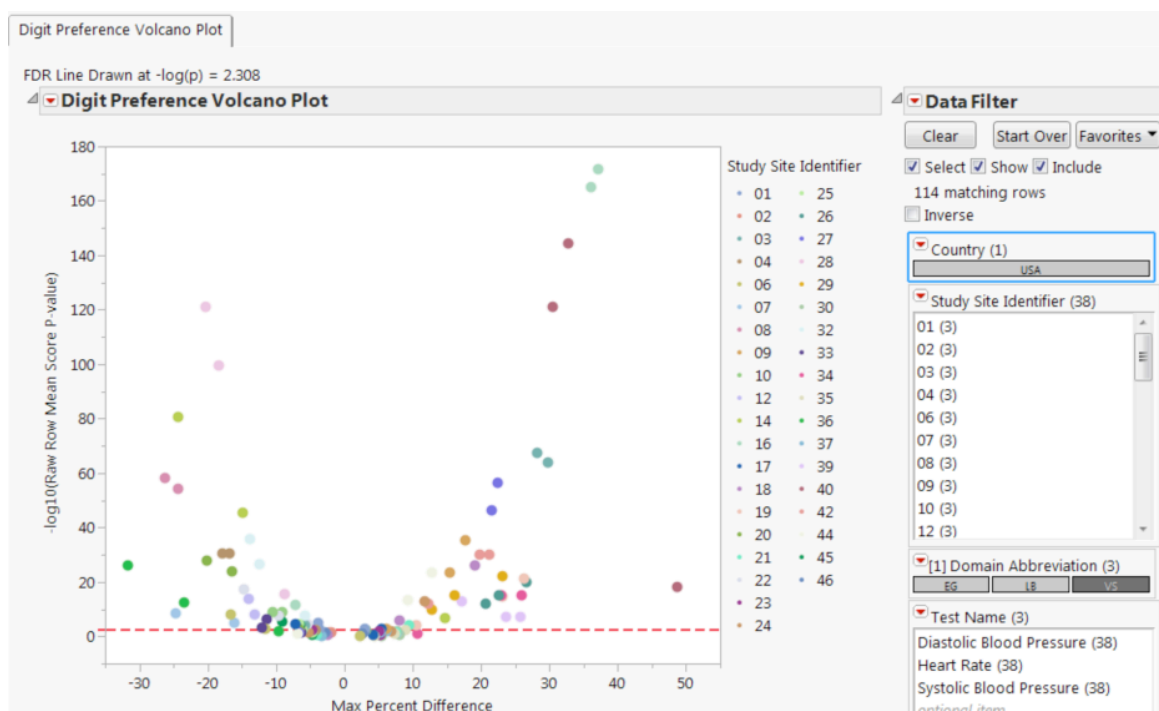


Figure 8: Use the data filter on the right side of the dashboard to restrict the view to the vital signs domain tests

By limiting the view the user can focus on fewer data points allowing comparison of a single CDISC domain rather than all findings domains at once.

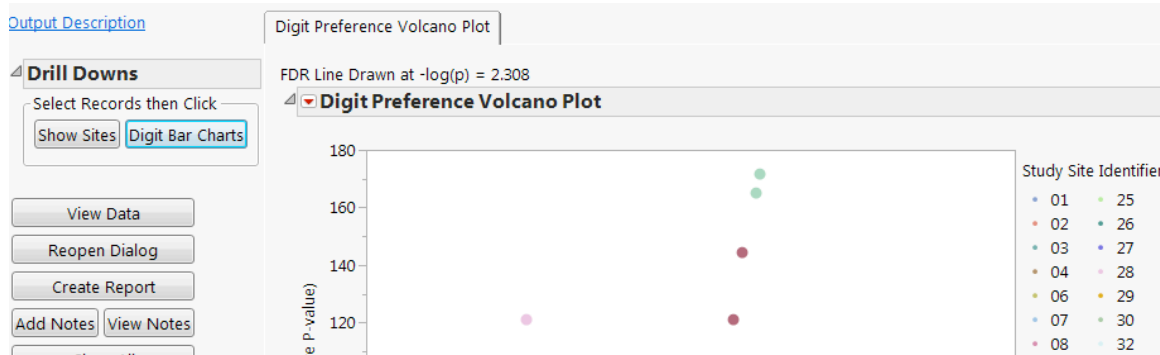


Figure 9: Select tests with significant site differences for drill down to diagnose test results

Upon selection of the significant tests of interest, in this case diastolic and systolic blood pressure for site 40 and 16, it is possible to drill down to details of the individual tests' trailing digit site distribution compared to all other sites combined. This makes it simpler to diagnose the issue as can be seen in the following figure.

PhUSE 2014

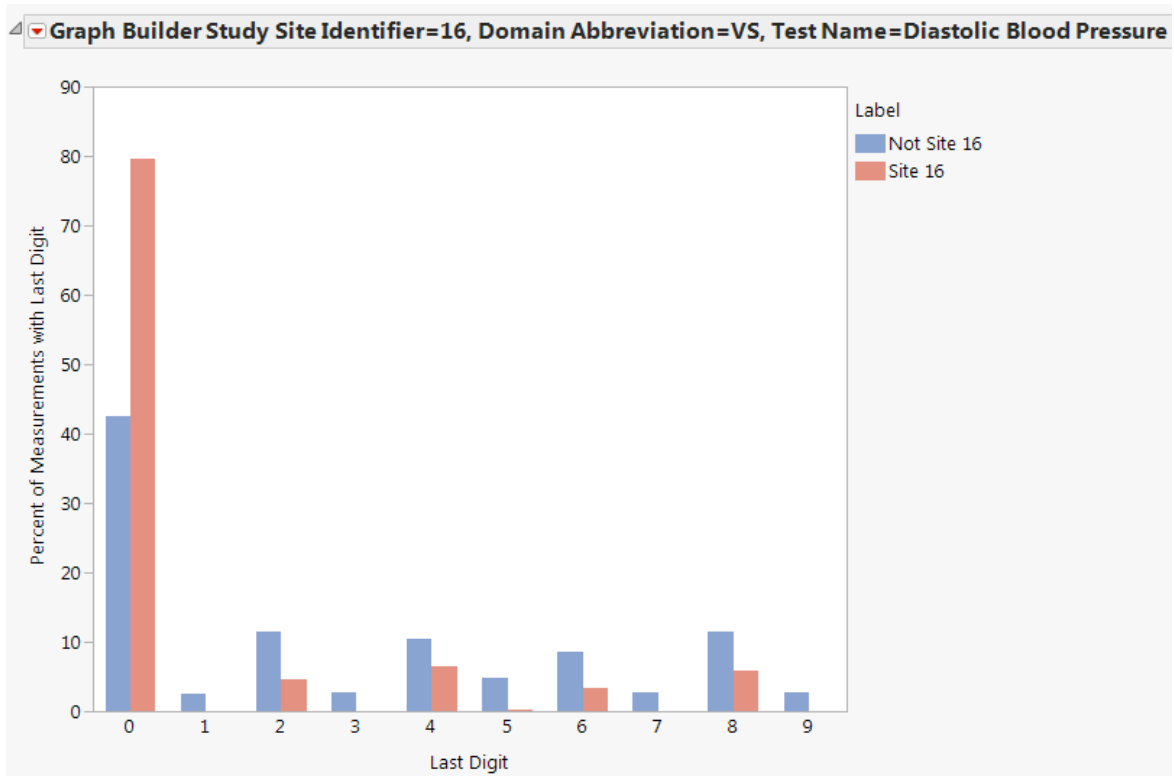


Figure 10: Drill down bar graph display of distributions of the last digit in the findings tests selected in the volcano plot

And finally after limiting subjects to the sites of concern, patient profiles or patient narratives as well as any other safety visualization in JMP Clinical can be used to investigate the overall impact of the fraud on individual subjects (figure 11).

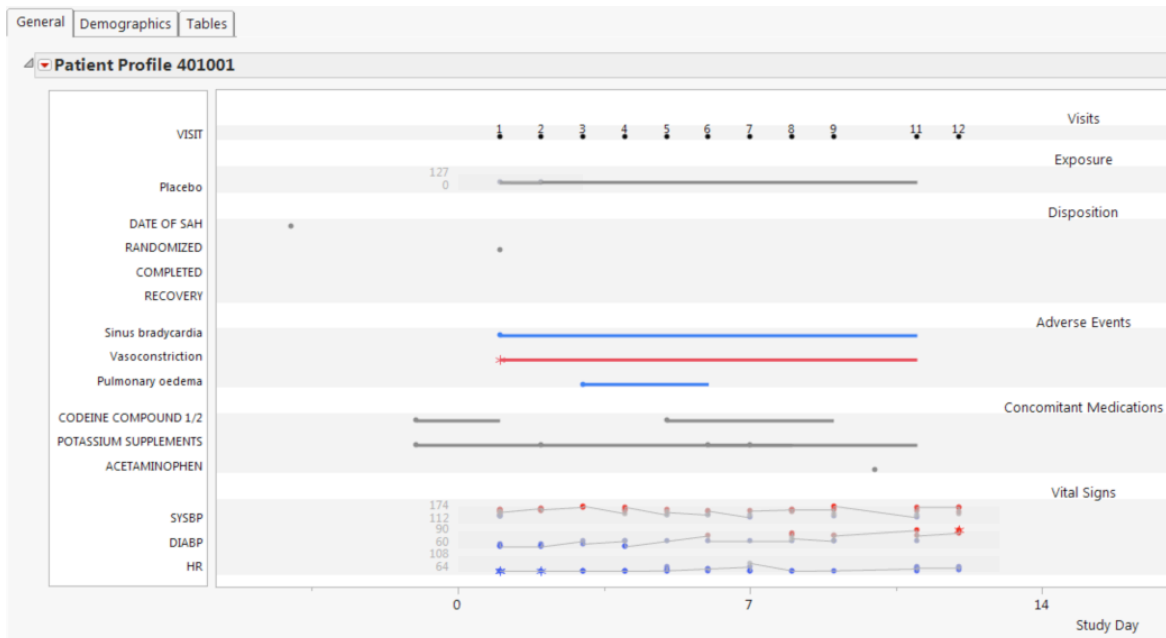


Figure 11: Patient Profile of subject in site 40 containing records with many identical trailing digits.

CONCLUSION

PhUSE 2014

The application of this signal detection algorithm to clinical trials data shows that it is necessary to screen databases regularly for data quality issues, misconduct or even fraudulent activities. A combination of volcano, a space-constrained visualization for screening a large number of tests, with drill down to bar graphs of the actual distribution of trailing digits allows for diagnosis of the findings data. This technique quickly draws attention to the important signals for follow-up analyses. By incorporating multiplicity adjustment into the analyses it is possible to reduce the noise and improve the signal detection. More signal detection algorithms in JMP Clinical to rapidly screen other aspects of the clinical trial data such as attendance records, birthdays, holidays are available. Correcting the data for quality, misconduct and/or fraud issues can have a direct impact on the safety and efficacy data. Allowing instantaneous review of this data by excluding possibly fraudulent data provides immediate insight to clinical operations, data management, medical monitors or biostatisticians alike.

REFERENCES

- Zink, RC, Mann, GA. (2012). On the Importance of a Single Data Standard. *Drug Information Journal*.
- Al-Marzouki SA, Evans S, Marshall T & Roberts I. (2005). Are these data real? Statistical methods for the detection of data fabrication in clinical trials. *British Medical Journal* 331: 267–70.
- Baigent C, Harrell FE, Buyse M, Emberson JR & Altman DG. (2008). Ensuring trial validity by data quality assurance and diversification of monitoring methods. *Clinical Trials* 5: 49–55.
- Benjamini Y & Hochberg Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society B* 57: 289–300.
- 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: 3435-51.
- Westfall, P.H., R. Tobias, D. Rom, R. Wolfinger, and Y. Hochberg (1999). Multiple Comparisons and Multiple Tests Using SAS. Cary, NC: SAS Institute, Inc.
- Evans S. (2001). Statistical aspects of the detection of fraud. In: Lock S & Wells F, eds. *Fraud and Misconduct in Biomedical Research, Third Edition*. London: BMJ Books.
- Hill T.P. (1996). A statistical derivation of the significant-digit law. *Statistical Science* 10: 354-63.
- 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: 389-95.
- Mehrotra DV & Adewale AJ. (2012). Flagging clinical adverse experiences: reducing false discoveries without materially compromising power for detecting true signals. *Statistics in Medicine* 31: 1918–30.
- Mehrotra DV & Heyse JF. (2004). Use of the false discovery rate for evaluating clinical safety data. *Statistical Methods in Medical Research* 13: 227-38.
- Zink RC, Wolfinger RD & Mann G. (2013). Summarizing the incidence of adverse events using volcano plots and time intervals. *Clinical Trials* 10: 398-406.

ACKNOWLEDGMENTS

I would like to thank Dr. Zink for his assistance in creating this paper. I would also like to thank the JMP Life Science team led by Dr. Russ Wolfinger under the direction of JMP Division founder and SAS owner John Sall for their continued support of our scientific research and software development.

RECOMMENDED READING

Risk-Based Monitoring and Fraud Detection in Clinical Trials Using JMP® and SAS®. Publisher: SAS Institute
Copyright Date: July 2014. by Dr. Richard Zink.

CONTACT INFORMATION

(In case a reader wants to get in touch with you, please put your contact information at the end of the paper.)

Your comments and questions are valued and encouraged. Contact the author at:

Author Name: Dr. Geoffrey Mann
Company: JMP Division at SAS Institute
Address: T4055, 100 SAS Campus Dr Cary NC 27513-8617
City / Postcode: Cary, NC
Work Phone: 1-919-531-1985
Fax: 1-919-677-4444
Email: Geoffrey.Mann@jmp.com
Web: www.jmp.com