

Risk-Based Monitoring of Clinical Trials Using JMP® Clinical

Richard C. Zink, Ph.D., JMP Life Sciences, SAS Institute, Inc.

Kelci J. Miclaus, Ph.D. (Presenter), JMP Life Sciences, SAS Institute, Inc.

ABSTRACT

Guidelines from the International Conference on Harmonisation suggest that clinical trial data should be actively monitored to ensure data quality. Traditional interpretation of this guidance has often led to 100% source data verification (SDV) of respective case report forms through onsite monitoring. Such monitoring activities can also identify deficiencies in site training and uncover fraudulent behavior. However, such extensive onsite review is time consuming, expensive, and as is true for any manual effort, limited in scope and prone to error. In contrast, risk-based monitoring makes use of central computerized review of clinical trial data and site metrics to determine if sites should receive more extensive quality review through on-site monitoring visits. We will demonstrate a risk-based monitoring solution within JMP Clinical to assess clinical trial data quality. Further, we'll describe a suite of tools used for identifying potentially fraudulent data at clinical sites. Data from a clinical trial of patients who experienced an aneurysmal subarachnoid hemorrhage will provide illustration.

INTRODUCTION

Since 1990, the International Conference of Harmonisation (ICH) has brought together the regulatory bodies of the European Union, Japan and the United States. The mission of the ICH is to define a set of technical and reporting guidelines for clinical trials to minimize the testing required in humans and animals to what is absolutely necessary to establish efficacy and safety, reduce development times, and streamline the regulatory review process. In particular, ICH Guideline E6 outlines standards for Good Clinical Practice (GCP) in the design, conduct and reporting of clinical trials involving human participants [1]. GCP has two primary goals: to protect the well-being of subjects involved in a clinical trial, and to maintain a high level of data quality to ensure the validity and integrity of the final analysis results.

Guideline E6 suggests that clinical trial data should be actively monitored to ensure data quality. Despite passages that state “the sponsor should determine the appropriate extent and nature of monitoring” and “statistically controlled sampling may be an acceptable method for selecting the data to be verified,” recent practice for pharmaceutical trials has often shown a brute-force approach to source data verification (SDV) of respective case report forms (CRFs) through onsite monitoring [1-3]. The recent Food and Drug Administration (FDA) guidance document on risk-based monitoring (defined below) suggests a few reasons as to why this may have occurred [4]. First, their guidance notes that this monitoring model may have been (incorrectly) perceived as the preferred approach of the FDA. Second, the FDA document suggests that it places more emphasis on centralized monitoring than what may have been feasible at the time ICH E6 was finalized (there have been considerable technical and analytical advances in the 17 years since ICH E6 was written). While there is language in E6 referring to central monitoring, it does state a need for onsite monitoring “before, during, and after the trial.”

It is now generally accepted by industry and multiple regulatory agencies that the process for clinical trial monitoring needs to change. Such extensive onsite review is time consuming, expensive (up to a third of the cost of a clinical trial), and as is true for any manual effort, limited in scope and prone to error [5]. In contrast to on-site monitoring, risk-based monitoring (RBM) makes use of central computerized review of clinical trial data and site metrics to determine if clinical sites should receive more extensive quality review through on-site monitoring visits. There are many benefits to centralized review beyond cost: statistical and graphical checks can determine the presence of outliers or unusual patterns in the data, comparisons can be made between sites to assess performance and identify potentially fraudulent data, or mis-calibrated or faulty equipment, and issues can be identified and resolved while the trial is ongoing.

In this paper, we introduce new RBM functionality within JMP Clinical to assess data quality and the safety of trial participants. Further, we describe tools for identifying potentially fraudulent data at clinical sites. Data from a randomized placebo-controlled clinical trial of nifedipine hydrochloride in patients who experienced an aneurysmal subarachnoid hemorrhage (SAH) will provide illustration [6]. To make the data a bit more interesting, random site locations were generated across North America, Europe and Asia, and metrics for queries and CRFs were simulated.

RISK-BASED MONITORING

Recent interest in RBM is driven primarily by the increasingly unsustainable costs of conducting clinical trials. TransCelerate Biopharm Inc., a consortium of pharmaceutical and biotech companies, recently released a position paper describing the rationale for RBM and providing guidance on implementation [7]. First and foremost, trial

sponsors need to prospectively identify the areas that are critical to the success of the clinical trial and the safety of its participants. Next, sponsors should specify the extent to which these data will be reviewed, detailing the necessary steps to address and mitigate risk should problems arise. Based on these important data, risk indicators are developed (such as the average number of serious adverse events per randomized subject) and tracked to monitor progress and performance at clinical sites, and to assess whether more formal review or intervention is warranted. Important for any risk indicator is to pre-define the direction(s) of concern, the magnitudes that would exceed important thresholds of risk, and the sponsor's action should one or more thresholds be crossed. The RBM functionality of JMP Clinical was developed using the recommendations of TransCelerate Biopharm Inc. As much as possible, analyses rely on data available within the study database, such as adverse events, inclusion or exclusion criteria, protocol deviations, and important disposition events such as completing the clinical trial. Further, users may take advantage of available functionality to supplement the study database with data from other sources, such as database management systems (DBMS), summary values from statistical programs written to determine protocol deviations, or summary values from other JMP Clinical reports. In general, JMP Clinical calculates risk indicators as averages per randomized subject or PatientWeeks (the sum of the time on study for all patients within a site).

variables that contribute to overall indicators as well as the relative contribution of each variable. The colors of the row markers (filled circles) change according to the variable selected in the **Risk Indicator** drill down. Because the **Overall Risk Indicator** is highlighted, the row markers reflect the risk of this variable. Based on Figure 1, nine sites have excess overall risk.

Risk thresholds are one way of assessing risk. Risk severity based on the colors green, yellow, and red are important to understand when meaningful boundaries are crossed, but it is difficult to understand just how different sites or countries may be from one another based on the observed values presented in a data table. Figure 2 presents an alternate and perhaps complimentary approach to compare the risk among sites or countries by examining histograms and box plots to identify any outliers. For example, while nine centers are considered to have a risk severity of severe (red) for the **Overall Risk Indicator**, only four of these sites appear to be outliers according to the box plot. Outliers are colored according to the variables selected in the **Risk Indicators** drill down.

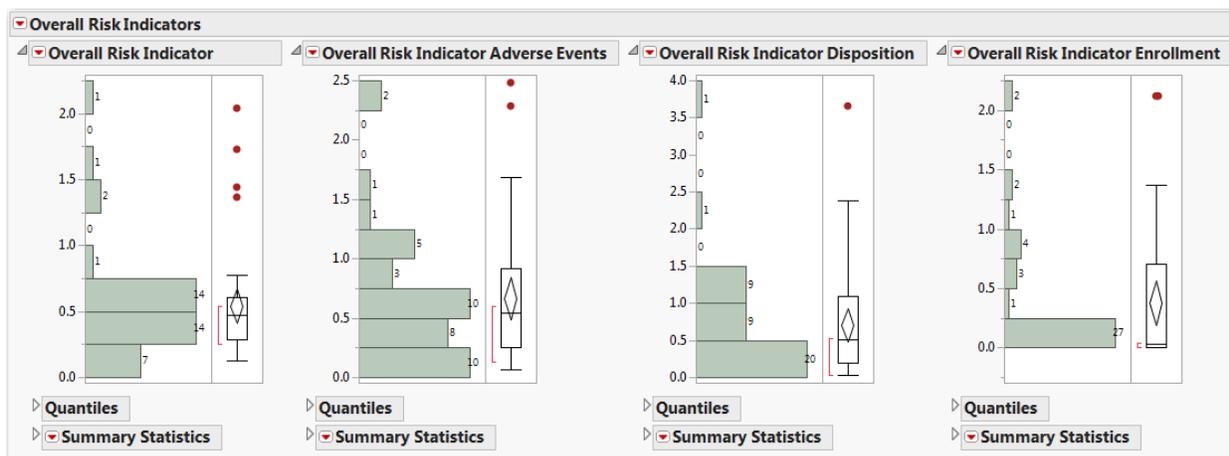


Figure 2. Histograms and Box-plots of Site-Level Risk Indicators

While a data table of site-level risk indicators is useful for understanding individual site performance, such a presentation fails to consider the role geography and location may have on the collected data and their interpretation. For example, perhaps environmental differences at certain locations lend themselves to an increased incidence of certain safety issues. Sites within certain areas may have received training from a particular vendor, and trial monitors may be responsible for different sites based on their location. Further, countries may have differing standards and regulatory obligations that can impact the findings of an RBM analysis and review. These details are important for understanding why the risk may be elevated at certain sites, particularly if such patterns are seen across multiple clinical trials.

In Figure 3, the severity for the **Overall Risk Indicator** is displayed in a global map. No obvious pattern is discernable for the United States, though eastern sites in Europe tend to be of high overall risk. Site performance in China appears to be discordant, while Japan appears to be performing well overall. Further, maps of the following countries are available if at least one clinical site is present within the country: Canada, China, France, Germany, Great Britain, Italy, Japan, Spain, and the United States (Figure 4). Country maps can be useful to distinguish between sites with close proximity to one another.

Most of the previous discussion for site-level risk indicators is applicable here for risk summarized at the country level. Why bother summarizing risk at the country level at all? For one reason, each country has its own set of rules, regulations and standards that must be followed that can impact the safety of trial subjects or the quality of data collected from clinical sites. For this reason, it is a good idea to get some assessment of the performance of sites for each country (Figure 5). Further, this country-level assessment may suggest that all sites within a particular country would benefit from an intervention, not just the one or two sites bordering on severe risk. Summarizing data at the country level also helps in the interpretation of sites with a small number of randomized subjects. The findings from these sites may be extremely variable, with summary values appearing extreme due to the small number of patients under study. Summarizing at the country level may help the sponsor ultimately decide to intervene with a site with a small number of randomized patients. However, reviewing the country-level analysis without considering the site-level analysis can be extremely misleading. If we compare the results of Figures 4 and 5, we appear to have a very unusual result. The Japanese sites when considered individually show mild risk overall, but severe risk when combined! What is going on? The **Overall Risk Indicator** for Japan is more-or-less in the same ballpark compared to the values of the individual Japanese sites. If you examine the other sites that have severe overall risk, you'll notice that a large number of these centers reside in the United States. However, when the U.S. sites are collapsed into a single unit, the extremeness of these sites is masked by the sites with mild risk. The Japanese risk that didn't

appear extreme when analyzing the sites separately now appears to be extreme! Given the Japanese sites have 20 randomized subjects a piece and mild risk at the site level, it is appropriate to interpret this country-level risk to be an anomaly.

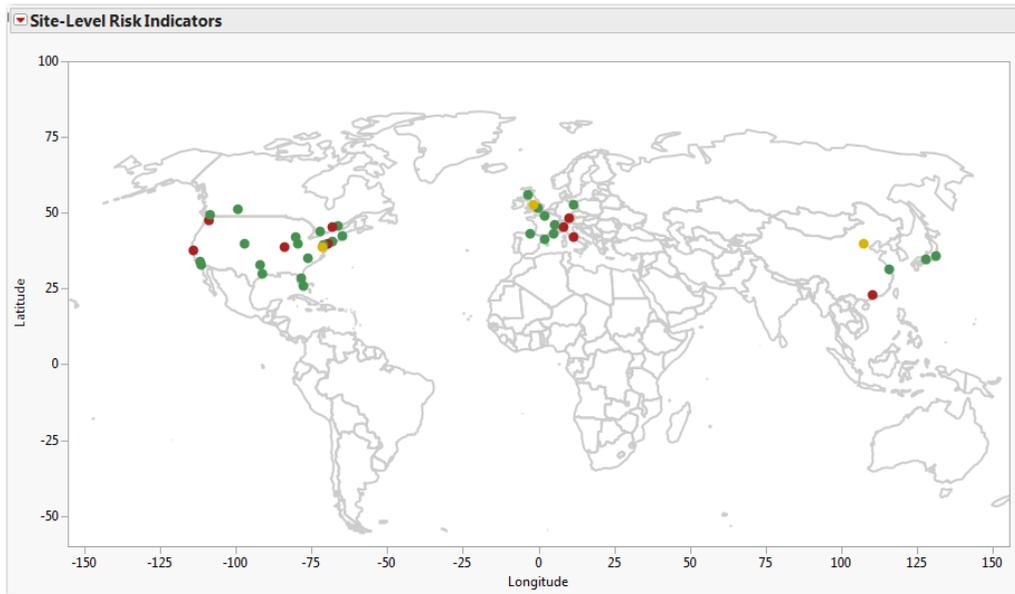


Figure 3. Global Map of Site-Level Overall Risk Indicator

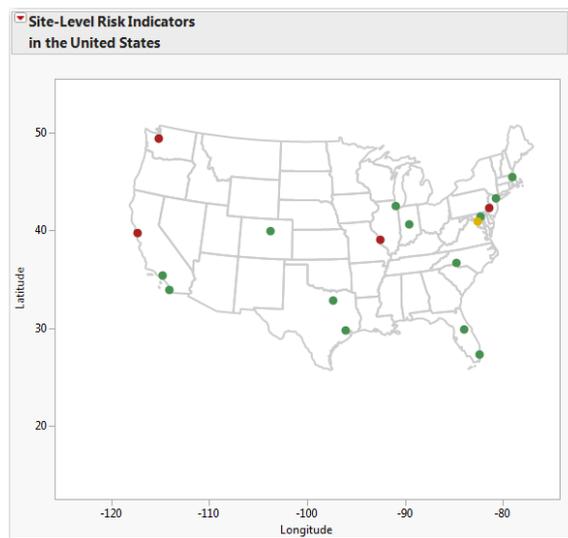


Figure 4. US Map of Site-Level Overall Risk Indicator

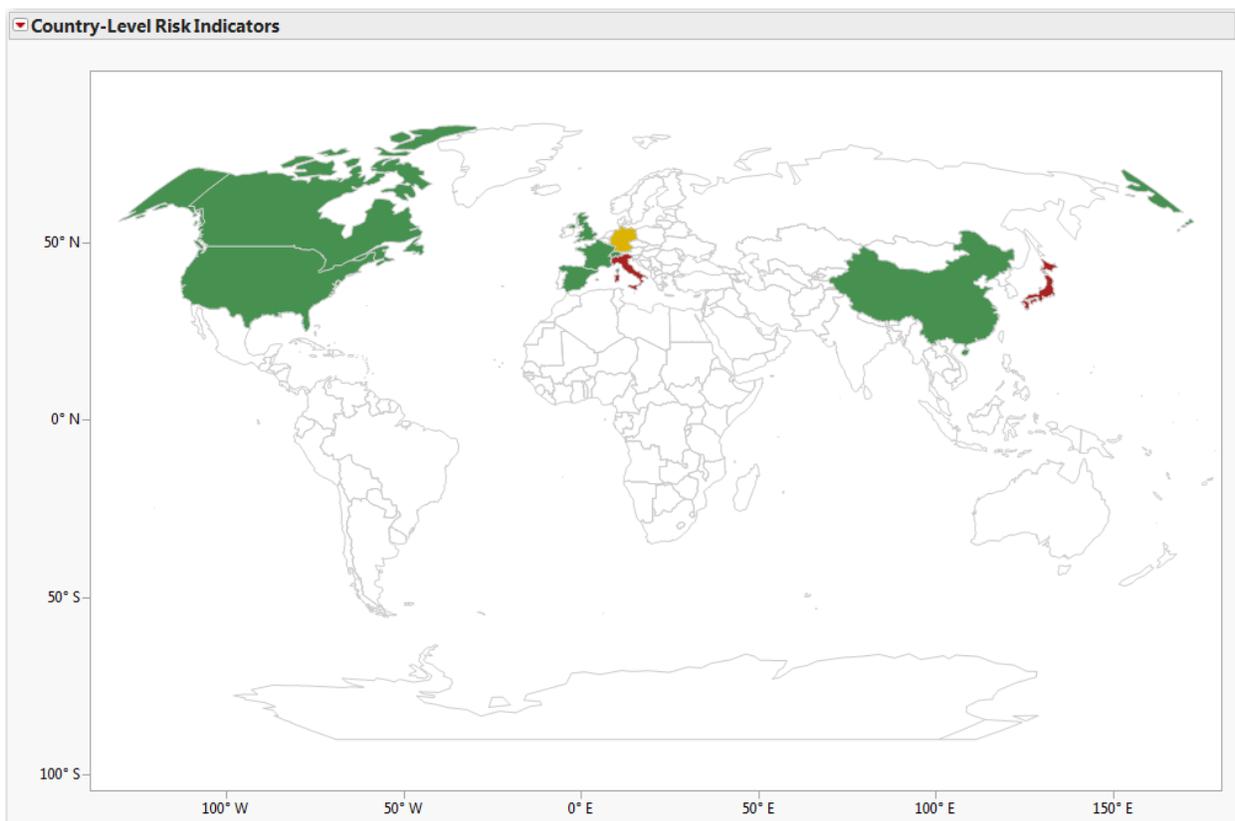


Figure 5. Global Map of Country-Level Overall Risk Indicator

The benefit of using JMP Clinical to perform RBM analysis and review is that patients from problematic sites or countries can be identified and reviewed using patient profiles or other analyses subset to this particular group of patients.

The country-, site-, and even the subject-level risk indicator data tables are of a format (each row is an independent observation) that make them employable by many if not most JMP platforms under the **Analyze** and **Graph** menus, as well as the JMP Clinical reports under **Clinical > Pattern Discovery** and **Clinical > Predictive Modeling**. Upon reviewing the Site-Level Risk Indicator data table (Figure 1), a natural question arises: which sites are similar to one another in terms of their performance? This information can be useful to identify the set of sites to utilize in future trials. More specifically, it can help distinguish which sites to approach first based upon how they are grouped according to their risk indicators and the characteristics of the upcoming study. For example, is safety of primary concern in the upcoming trial because of a particularly at-risk study population? This could suggest to the sponsor to select from those sites that neither over- or under-report adverse events or other safety issues. Further, grouping sites according to their performance can be useful in order to develop and apply training or other intervention strategies in an efficient and cost-effective manner. Given the multitude of criteria available, manually determining appropriate clusters of sites can be a challenging task. Here, we'll group sites using the hierarchical clustering methods available under **Analyze > Multivariate Methods > Cluster** (Figure 6). Here we have clustered sites based on important safety risk indicators. Sites are colored based on the **Overall Risk Indicator Adverse Events**, and risk severity matches up pretty well with suggested clustering of sites. Either reviewing the data set or a two-way clustering to examine the effects of individual covariates, we obtain some insight as to why site 36 may not be grouped with the other severe centers: this site has only one SAE.

In the next section, we'll continue to review the performance of individual sites using JMP Clinical. The focus there will be to identify potential patient- or investigator-perpetrated fraud, another important aspect of data quality.

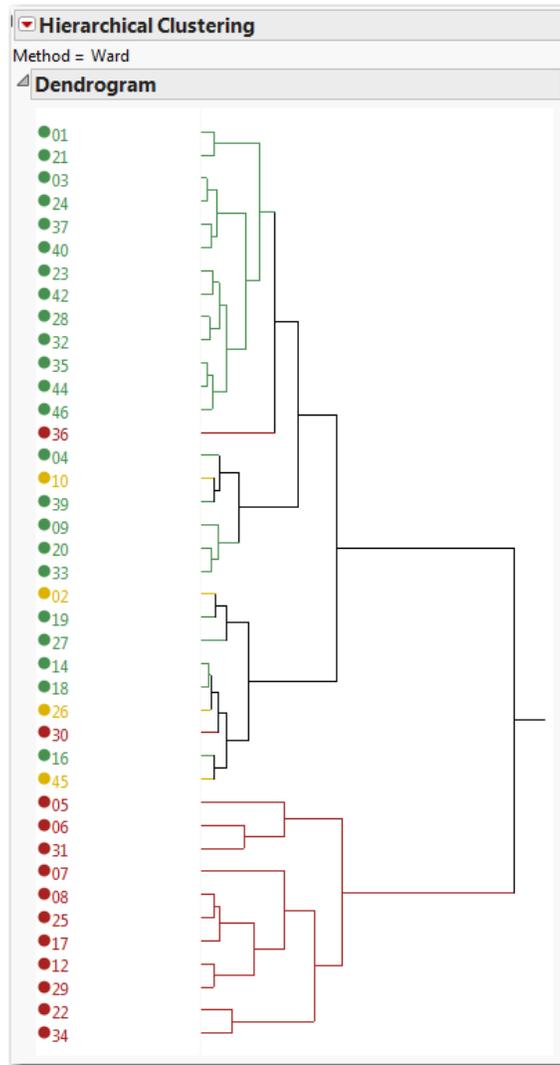


Figure 6. Hierarchical Clustering of Sites Using AEs, SAEs, and Deaths per PatientWeek

FRAUD DETECTION

Fraud is an important subset of topics involving data quality, one that perhaps conjures images of Sherlock Holmes on the hunt for clues to apprehend the “bad guy”. Quality issues in clinical trials can be due to a number of factors, among them carelessness (such as transcription errors), contamination of samples, mechanical failures or mis-calibrated equipment, poor planning (e.g. lack of appropriate back-ups or contingency planning should problems occur), poor training in trial procedures and fraud. Fraud stands out among other quality issues in that there is a “deliberate attempt to deceive” or the “intention to cheat” [8]. Here we consider both patient- and investigator-perpetrated fraud in clinical trials. For investigators, fraud is often viewed as fabricating, manipulating or deleting data. Examples of this behavior include deleting data highlighting a safety concern, propagating (carrying forward) data to avoid performing additional testing, or the wholesale manufacture of one or more patients at the site. For patients, enrolling at two or more clinical trials sites (usually for additional financial compensation, or access to additional drugs or medical services) is particularly problematic. This, of course, violates assumptions of statistical independence necessary for many statistical tests. In practice, however, multiply-enrolled subjects becomes an accounting and reporting nightmare for the clinical trial team.

Despite a bevy of statistical and graphical tools available to identify unusual data, fraud is extremely difficult to diagnose. For one, many of the methods used to identify misconduct at a center involve comparisons against other clinical trial sites. Such analyses could identify natural differences in patient population or variations in technique between the sites that wouldn’t constitute fraudulent behavior. Further, analyses motivated by a need to identify a particular type of malfeasance can detect data anomalies with perfectly reasonable explanations to describe the

unusual result. In general, stating that any unusual findings are explicitly due to fraud may require evidence beyond what's available in the clinical trial database [9].

It is believed that fraud in clinical trials is rare. Buyse and co-authors estimate the proportion of investigators engaging in misconduct below one percent, though they suggest cases may go either undiagnosed or unreported; additional cited works therein show few to no instances of fraud [8]. However, clinical trial fraud is likely underestimated for several reasons. First, instances have conceivably gone undiagnosed due to a lack of available tools and training for uncovering fraud. Part of this may be due to the past over-reliance of manual on-site monitoring techniques which made comparisons across CRF pages, subjects, time and clinical sites difficult. Further, even if unusual data are identified, going that additional step to confirm any misdoing may prove unsuccessful. Second, even if suspected fraud is detected, it may go unreported over fears that the negative publicity can severely damage the perception of an organization among regulatory agencies, patients and the general public. Even if the sponsor has behaved entirely appropriately, such attention can bring increased scrutiny and pressure to the clinical trial and larger development program [10].

Even in the presence of incorrect data due to manipulation or other quality issues, trial integrity will be preserved in most cases, most often due to randomization and blinding of study medication, or because the anomalies are limited to few sites [2,4,7,8,10]. So this begs the question: If clinical trial fraud is so uncommon, with seemingly limited potential to seriously compromise the results of the trial, why bother looking for it at all? We look for quality issues and misconduct for the second stated goal of GCP – to protect the rights and well-being of the patients enrolled in our clinical trials. Monitoring the quality of the trial ensures trial participants receive the best possible care and are protected from any potential wrong-doing. This is equally true for future patients that hope to use the new treatment to improve their quality-of-life. Below we briefly describe some fraud detection methods available in JMP Clinical.

PATIENT-PERPETRATED FRAUD

Patient behavior can greatly affect the outcome of a clinical trial. This is true if they are non-compliant in taking their study medication, or in how they complete or maintain a study diary to record various symptoms or episodes of their disease (many are familiar with the example of a patient that completes their study diary in the clinic parking lot). One particularly troublesome behavior involves a patient enrolling at two or more clinical trials sites within the same clinical study. This may be for additional access to drug, financial incentive for participating in the trial, or for continued access to high-quality healthcare. There are a number of concerns with this behavior: it can contribute to a severe safety event (particularly if the subject is enrolled in multiple sites in parallel), and it violates statistical independence often assumed for the final analysis. The practical implication is that it creates an accounting and reporting nightmare for the study team, especially if the subject happens to be randomized to different treatments. Sensitivity analyses removing these subjects may be expected by regulators for the final clinical report; the resulting loss of sample could affect the power for treatment comparisons (though any difference in the interpretation of results with or without these patients may be problematic). Ideally, these instances should be identified as early as possible to minimize the amount of data affected, avoid potential toxicity, or to enroll additional subjects to meet sample size requirements. Given that patients enrolled in the Nifedipine trial as a result of an SAH, it is extremely unlikely they would have enrolled at multiple centers. However, we can use this clinical trial to illustrate the functionality of JMP Clinical for identifying the same patient at multiple clinical sites.

Perhaps the most-straightforward means of identifying these subjects is to match patients with similar birthdates or initials (accounting for the possibility of a missing middle initial). Of course, the well-known “birthday problem” in probability states that among 50 people, there is a 97% chance that at least 2 share the same birthday. However, demographic and physical characteristics can eliminate pairs that are unlikely to be the same person (Figure 7).

However, a patient's personal information may not be available within the study database. In these scenarios, the measurements collected at the study site (such as pre-treatment blood pressure and heart rate) can be used to calculate the similarity between pairs of patients to rank order the most interesting pairs. To reduce the number of possibilities, subject pairs can be limited to those cases where, gender, race, or country match. The analyst can further reduce pairs of subjects based on age differences within the duration of enrollment (rounded up to the nearest year), height within a centimeter or two, and weight within a few kilograms (Figure 8). A hierarchical clustering of patients can help identify subsets of three or more subjects that are overly similar.

Matching Variable Value	Unique Subject Identifier	Study Site Identifier	Date/Time of Birth	Sex	Race	N
15Apr1915	141001	14	1915-04-15	M	WHITE	1
	442001	44	1915-04-15	F	WHITE	1
01Jan1917	392012	39	1917-01-01	F	OTHER	1
	41018	04	1917-01-01	M	WHITE	1
11Aug1925	221020	22	1925-08-11	M	BLACK OR AFRICAN AMERICAN	1
	282003	28	1925-08-11	F	WHITE	1
28Jul1928	241003	24	1928-07-28	F	WHITE	1
	81011	08	1928-07-28	F	WHITE	1
13Nov1935	141021	14	1935-11-13	F	OTHER	1
	231027	23	1935-11-13	F	WHITE	1
25Aug1937	31006	03	1937-08-25	M	WHITE	1
	31012	03	1937-08-25	F	WHITE	1
23Mar1938	171001	17	1938-03-23	M	WHITE	1
	271014	27	1938-03-23	F	WHITE	1
29May1939	11034	01	1939-05-29	F	WHITE	1
	161003	16	1939-05-29	F	WHITE	1
21Jan1941	282008	28	1941-01-21	F	BLACK OR AFRICAN AMERICAN	1
	351006	35	1941-01-21	M	WHITE	1
09Jul1941	11033	01	1941-07-09	F	WHITE	1
	392017	39	1941-07-09	F	WHITE	1
27Aug1943	11048	01	1943-08-27	F	WHITE	1
	291002	29	1943-08-27	F	ASIAN	1
22Feb1947	201018	20	1947-02-22	M	WHITE	1
	81023	08	1947-02-22	M	WHITE	1
23Jan1949	141013	14	1949-01-23	F	ASIAN	1
	461023	46	1949-01-23	M	WHITE	1
09Feb1954	161016	16	1954-02-09	F	WHITE	1
	241011	24	1954-02-09	F	WHITE	1
15Oct1955	141054	14	1955-10-15	F	WHITE	1
	231020	23	1955-10-15	F	WHITE	1
18Oct1956	91038	09	1956-10-18	F	BLACK OR AFRICAN AMERICAN	1
	91040	09	1956-10-18	F	BLACK OR AFRICAN AMERICAN	1

Figure 7. Patients Matched According to Birth Date

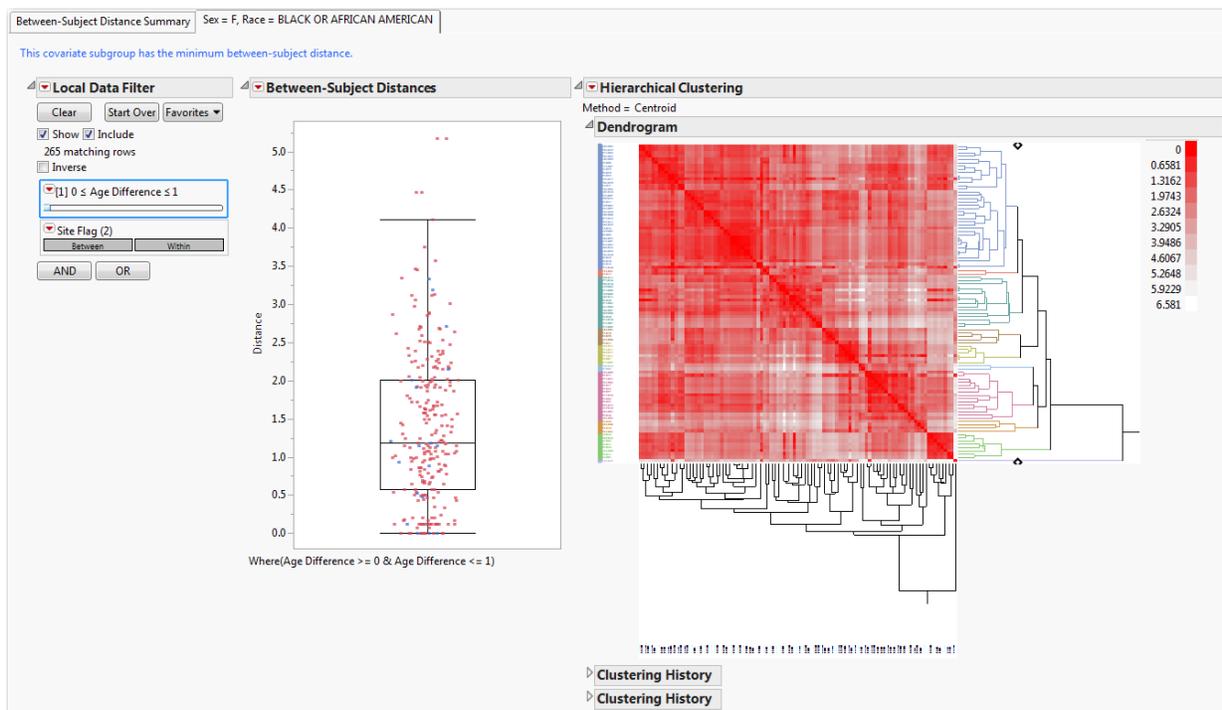


Figure 8. Pairwise Comparisons of Trial Patients Using Blood Pressure and Heart Rate

INVESTIGATOR-PERPETRATED FRAUD

In this section, we'll detail some analyses to identify fraudulent behavior at the clinical site by the investigator or his or her staff. For our purposes, fraud is defined as the fabrication of data, modification of data, or the deletion of data [8]. Why would anyone engage in such activities in the clinical trial? Perhaps the investigator is having difficulty identifying suitable patients for the study. In order to enroll the patient, they may modify study entry criteria, changing dates or altering test results so that the patient appears to meet eligibility criteria. In some extreme cases, entire subjects may be fabricated from the CRF of an actual patient. For fear of additional scrutiny from the trial sponsor, safety issues may be down-played or go unreported altogether. Missed procedures may be copied from the results collected during earlier visits. Even a well-intentioned act, such as manipulating a randomization scheme so that a particular patient receives a novel medication is problematic since this may bias the final treatment estimate from the study. In general, fraud can occur to obtain some benefit whether fame or financial, to cover up neglect or carelessness (perceived or otherwise), to silence nagging sponsors (at the thought that any data could be missing), or in the hope of bringing any new therapy to patients. Below we describe some specific examples.

Clinical Visits

For some therapeutic areas, the clinic door is always open. However, instances of visits taking place on weekends or major holidays may raise red flags for other diseases (Figure 9). Further, other unexpected events, such as extreme weather (e.g., hurricane or snowstorm), may disrupt normal operations so that patients cannot attend scheduled visits. JMP Clinical identifies the weekday on which study visits occur, as well as any major U.S. or Canadian holidays. In addition, the analyst can pre-define holidays for clinical sites in other countries, as well as important events that may prevent patients from reaching the clinic.

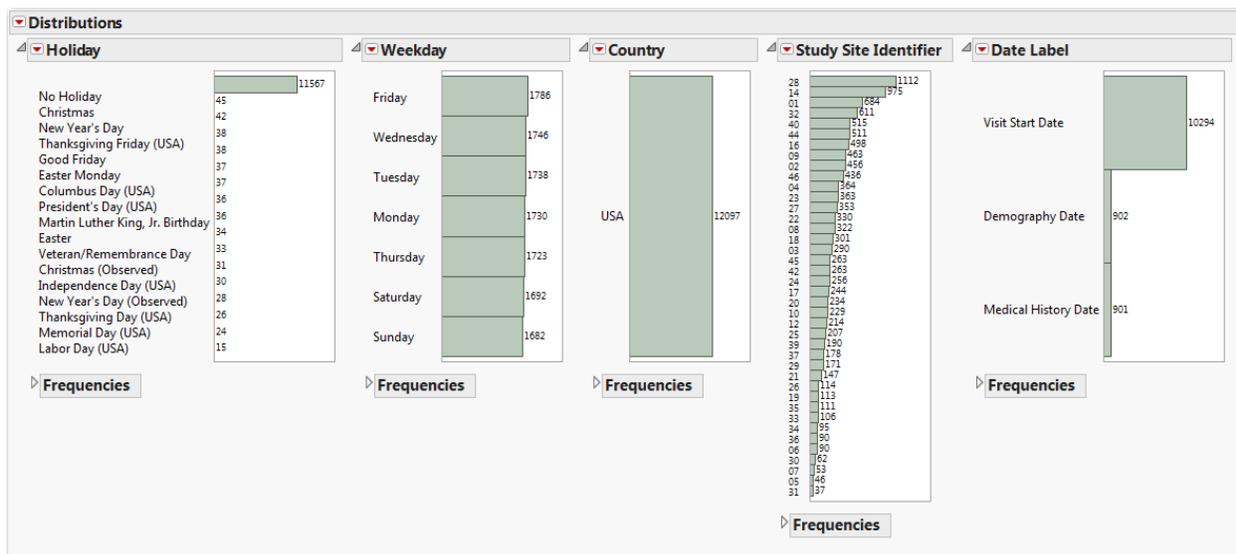


Figure 9. Weekdays and Holidays on which Study Visits Occurred

Visit attendance can appear too perfect (Figure 10). This figure shows a suspect site where the patients arrived on the day when expected considerably more often when compared to the other sites [8,10]. Such analyses can also identify sites that are extremely off schedule. For studies with multiple centers and visits, there are numerous site-visit combinations to screen to identify unusual patterns. Summary results of these site-visit combinations can be displayed using a volcano plot to detect any problematic pairs, similar to the description presented below for digit preference.

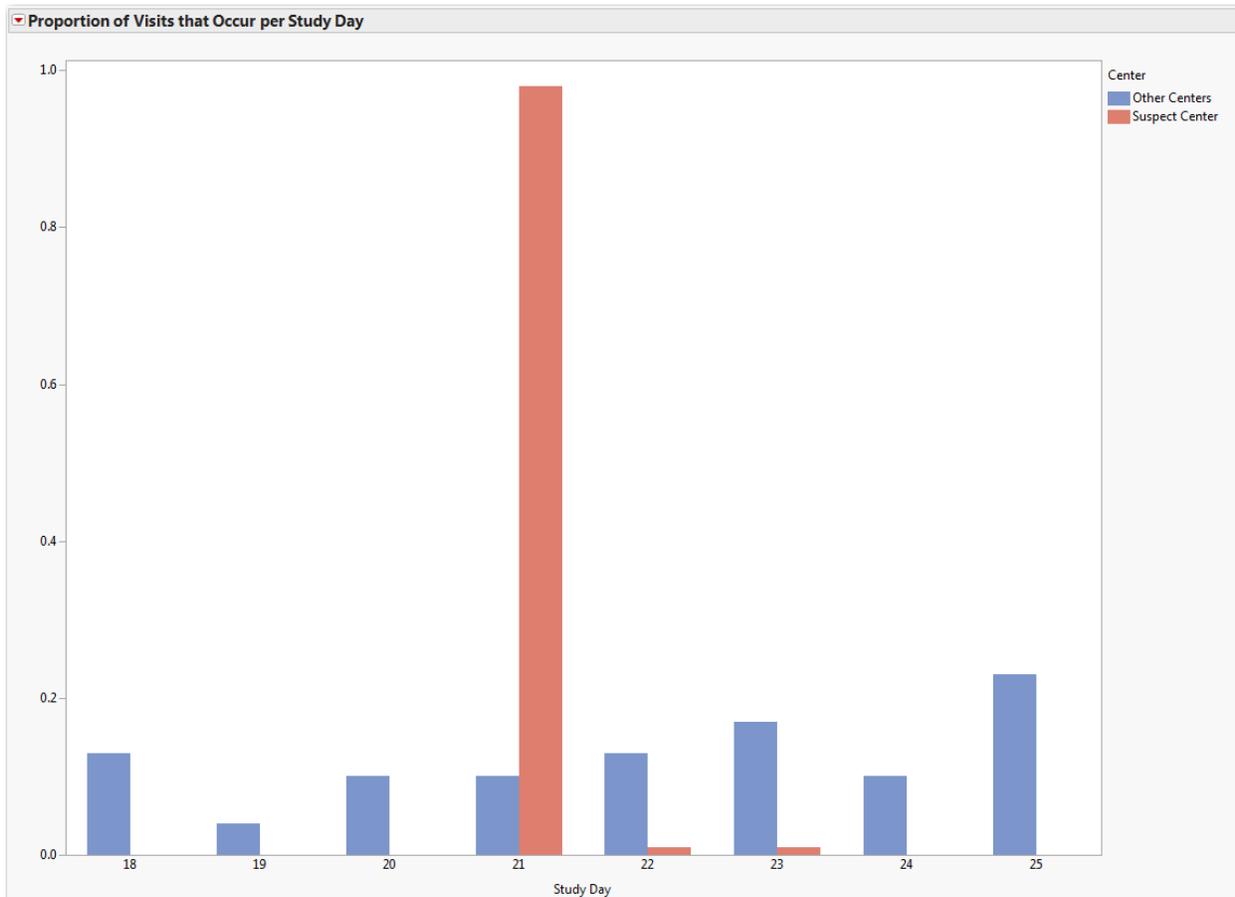


Figure 10. Distribution of Visit Attendance for Suspect Site Versus All Other Sites

Measurements Collected at Clinical Sites

There are many unusual patterns that can be identified from the data collected as the study site (such as vital signs, laboratory test, and ECGs). For example, we can identify findings where there is no variability over the course of the clinical trial (Figure 11). This is extremely unusual, as the measurements taken from human beings are subject to variability based on any number of factors: temperature, medication, nervousness, time of last meal, time of day etc. Such findings may be acceptable if assays reach lower- or upper-limits of detection.

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 Findings
81010	08	NIC .15	USA	Bilirubin	0.0009999	4
101012	10	Placebo	USA	Bilirubin	0.0016665	3
11042	01	Placebo	USA	Bilirubin	0.0016665	3
141022	14	Placebo	USA	Bilirubin	0.0013332	3

Figure 11. Constant Results of Bilirubin

Given the variability of measurements as described above, it would be unusual to observe sets of measurements repeated with identical values on different occasions, especially for sets of measurements of increasing size. For example, Figure 12 shows a set of blood pressure and heart rate results that are identical when measured at 6 hour intervals at Visit 10 for subject 421007. This may be a situation where vital signs were not collected at later times, and imputed by the investigator to provide complete data. Observing multiple duplications between subjects could indicate pages that were copied between CRFs.

Unique Subject Identifier	Study Site Identifier	Description of Planned Arm	Country	Date	Time	Visit Number	Diastolic Blood Pressure	Heart Rate	Systolic Blood Pressure
421007	42	NIC .15	USA	14Aug1989	:0:06:00:00	10	70	78	120
421007	42	NIC .15	USA	14Aug1989	:0:12:00:00	10	70	78	120
421007	42	NIC .15	USA	14Aug1989	:0:18:00:00	10	70	78	120
422004	42	Placebo	USA	11Jun1988	:0:16:00:00	10	70	78	120

Figure 12. Duplicate Vital Sign Records

Comparisons of the distribution of the terminal digit for study measurements between each site versus all others can identify numerous problems. For example, it can identify instances of rounding, mis-calibrated equipment, investigators using varying technique than what is specified in the protocol (manual blood pressure measurements versus a machine), or important differences in subjective measurements (which may suggest training is needed). The volcano plot in Figure 13 examines all site-test combinations to identify instances when the distribution of a site differs from the reference (all other sites). The x-axis summarizes the maximum percentage difference in the digit distribution, while the y-axis is the $-\log_{10}$ p-value for the comparisons. Markers towards the upper corners highlight meaningful differences which can be explored further using drill downs. For example, Figure 14 shows that Site 16 tends to report diastolic blood pressure with a zero digit more often than the other sites.

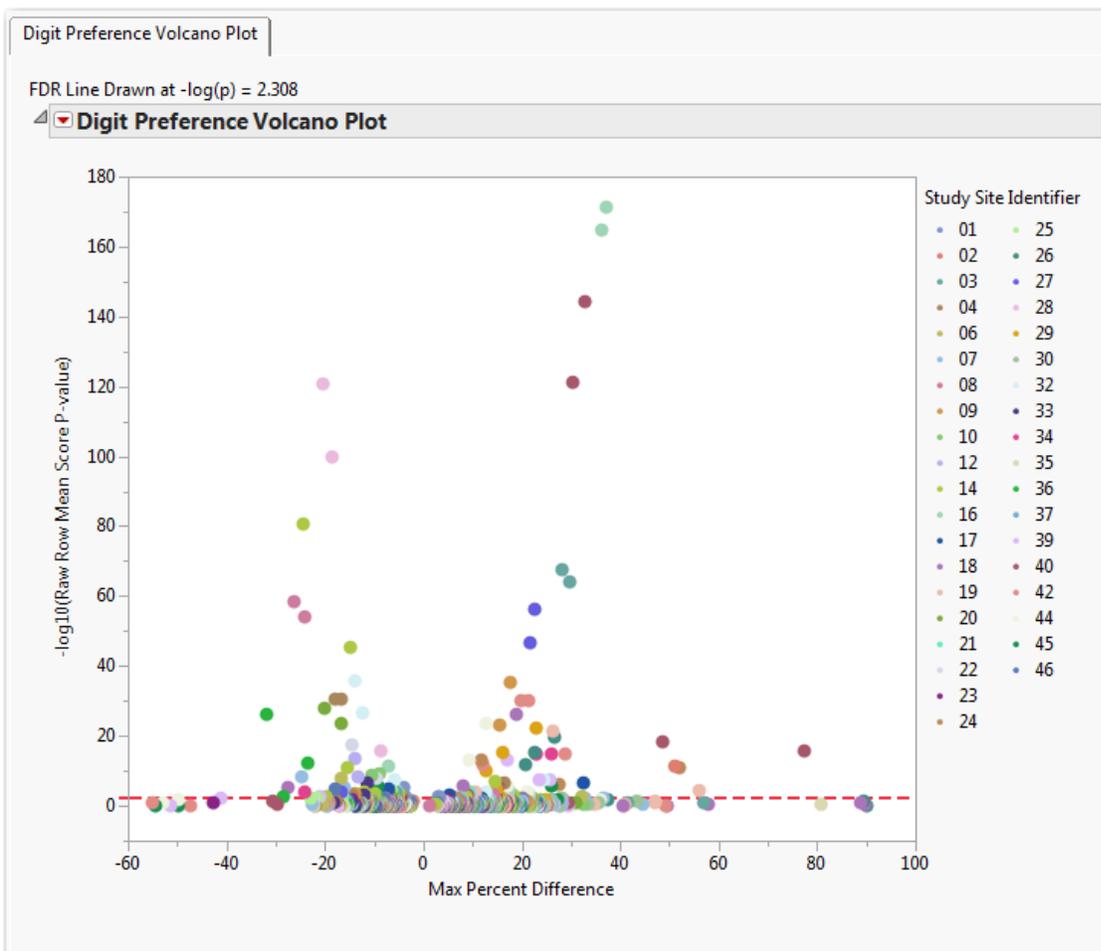


Figure 13. Volcano Plot of Digit Preference.

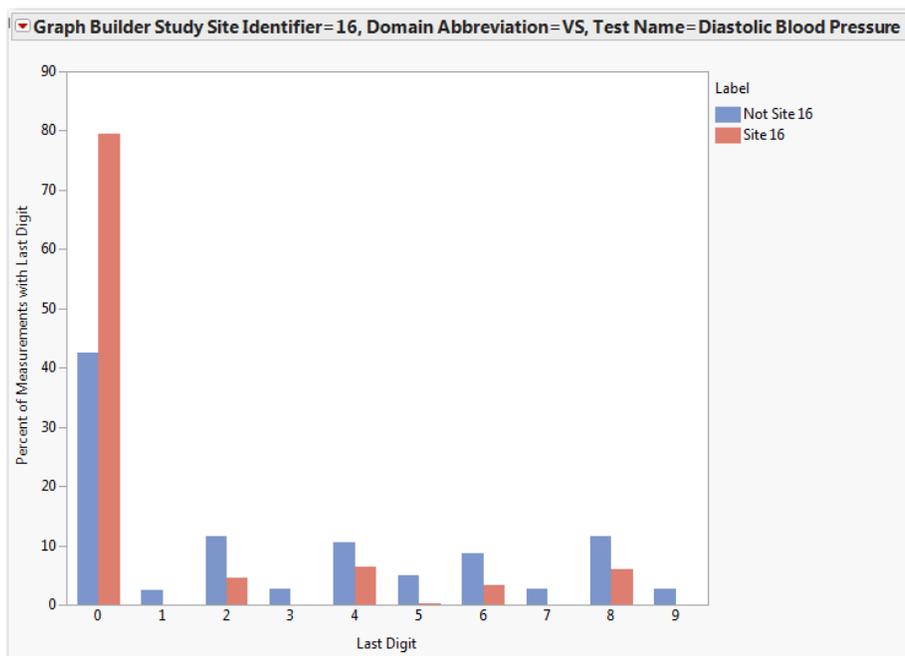


Figure 14. Distribution of Diastolic Blood Pressure Terminal Digit for Site 16

The final sets of analyses attempt to use as much of the trial data as possible to identify unusual subjects. While it is straightforward to identify outliers for each individual variable, examining outliers in the multivariate space of all variables may identify subjects with unusual combinations of results. This results in a large distance from the centroid, or multivariate mean. Further, inliers are points that lie close to the multivariate mean and suggest patients that are perhaps “too good to be true”. To get an idea of distances that may be considered too large or too small, we can plot box plots by site (Figure 15). This can also help identify sites that may be considered extreme; there may be important differences in patient populations or techniques at these clinical sites.

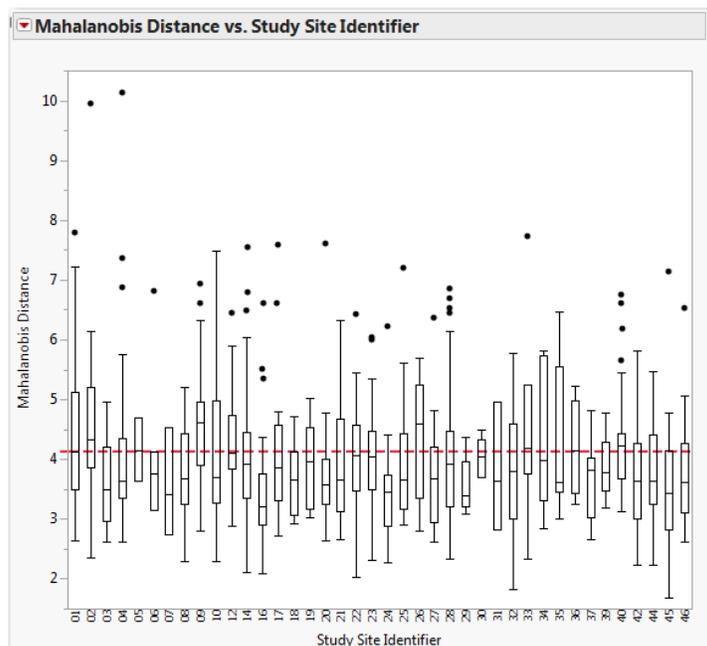


Figure 15. Box Plots of Mahalanobis Distance by Study Site Identifier

This goal of this last analysis is to use as much data as possible to identify subjects that are “too” similar. While the analysis above was used to identify subjects that had enrolled at two or more clinical sites, the purpose of this analysis is to identify fabricated patients that are slightly-modified copies of other patients within the site. Here, we’ll limit all pairwise comparisons to subjects within the same site, and plot results by site so we can assess how similar is too similar (Figure 16); the most similar pair of subjects from each site are summarized as well. Site 39 has the most-similar pair of subjects (Figure 17).

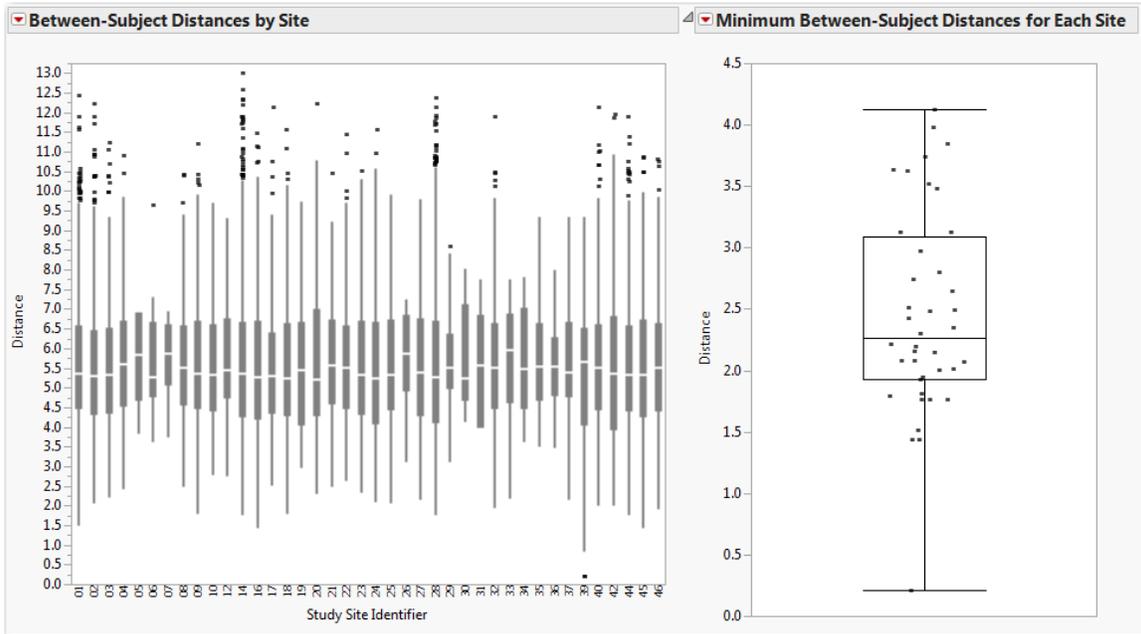


Figure 16. Box Plots of Between-Subject Distances by Study Site Identifier

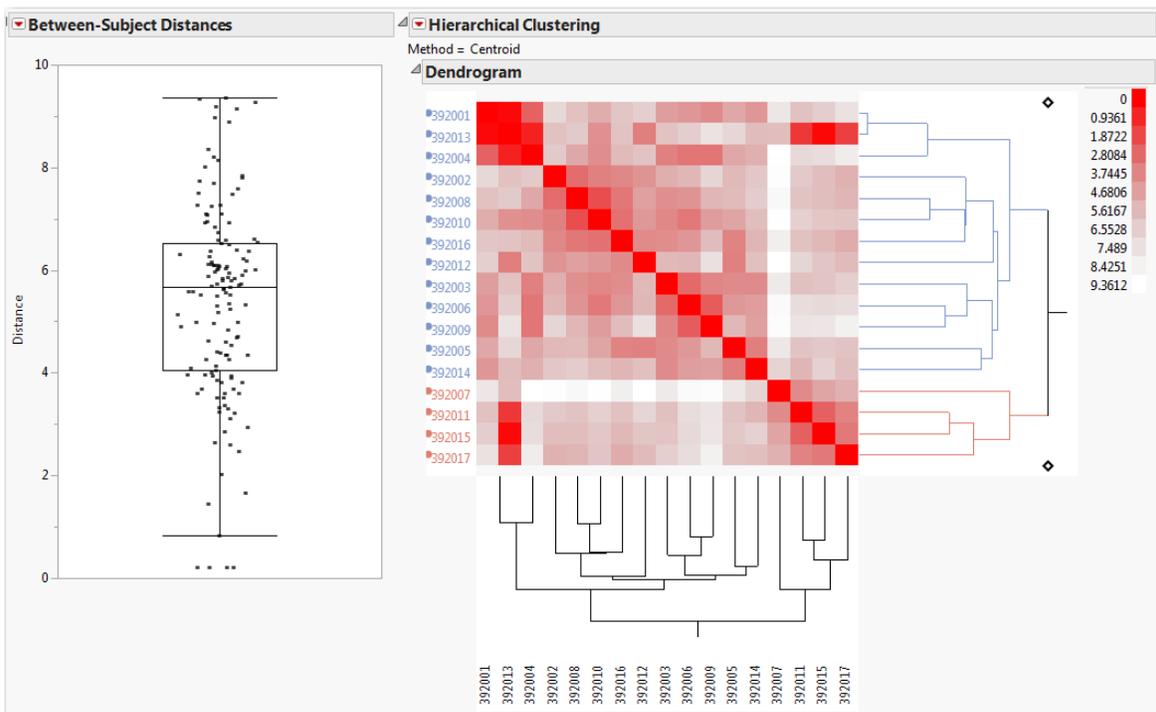


Figure 17. Box Plot of Between-Subject Distances at Site 39

CONCLUSIONS

In this paper, we have reviewed numerous features available in JMP Clinical to assess data quality in clinical trials. These straightforward tools enable the clinical trial team to review data remotely to protect the well-being of patients and ensure the integrity of final study results. An additional benefit of centralized monitoring is the potential to significantly reduce clinical trial costs, freeing valuable resources to further explore areas of unmet medical need. Additional examples and methodological details will be available in the forthcoming SAS book tentatively titled *Risk-Based Monitoring and Fraud Detection in Clinical Trials Using JMP and SAS* (expected Fall 2014).

REFERENCES

1. 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.
2. 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.
3. Morrison BW, Cochran CJ, White JG, Harley J, Kleppinger CF, Liu A, Mitchel JT, Nickerson DF, Zacharias CR, Kramer JM, Neaton JD. (2011). Monitoring the quality of conduct of clinical trials: a survey of current practices. *Clinical Trials* 8: 342-349.
4. US Food & Drug Administration. (2013). Guidance for industry: Oversight of clinical investigations - a risk-based approach to monitoring. Available at: <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf>.
5. 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.
6. Haley EC, Kassell NF and Torner JC. (1993). A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage. *Journal of Neurosurgery* 78: 537-547.
7. TransCelerate BioPharma Inc. (2013). Position paper: Risk-based monitoring methodology. Available at: <http://transceleratebiopharmainc.com/>.
8. 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.
9. 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.
10. Weir C. & Murray G. (2011). Fraud in clinical trials: detecting it and preventing it. *Significance* 8: 164-168.

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CONTACT INFORMATION

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

Name: Richard C. Zink, Ph.D.
Enterprise: JMP Life Sciences, SAS Institute Inc.
Address: SAS Campus Drive
City, State ZIP: Cary, North Carolina 27513
E-mail: richard.zink@jmp.com
Web: <http://www.jmp.com/lifesciences-resources/>
Blog: <http://blogs.sas.com/content/jmp/author/rizink/>
Twitter: [@rczink](https://twitter.com/rczink)

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