Efficient data reviews and Quality in clinical trials using CDISC Data Standards

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ABSTRACT

Comprehensive and efficient assessment of drug safety is a critical component of ethical clinical trials. Safety reviews have been greatly aided in recent years by dynamically interactive graphics of various domains of safety data. During this presentation, we will demonstrate how integrating powerful analytical methods with well-ordered visual displays and drill-downs enhances the clinical trial review process using CDISC data standards. Further, we describe how statistical and graphical techniques can help diagnose fraudulent behavior and support risk-based monitoring at investigator sites. The interplay between statistics and graphics affords insights into the data inaccessible by either approach alone. Data from a clinical trial of patients who experienced an aneurysmal subarachnoid hemorrhage will provide illustration for most of the presentation. Analyses from JMP Clinical®, software that combines the analytical power of SAS with the elegant user interface and dynamic graphics of JMP, will demonstrate key concepts.

INTRODUCTION

JMP Clinical software from SAS streamlines safety reviews of clinical trials data in a user-friendly environment. Through standardized analytical processes, this ease of use can promote the exploitation of all relevant, available data in any clinical context. Using a study on Nicardipine as an example, this presentation will show how intuitive and intelligible preset graphical dashboards can easily be constructed from CDISC data, raising the quality of the dialogue between the researcher and all stakeholders. Coupling statistical analysis with effective data visualization is a key component for an effective data review process. Recent cases of fraud in clinical trials have attracted considerable media attention, but relatively little reaction from the biostatistical community. The presentation will also address how to detect fraudulent behavior and assess Risk Based Monitoring in clinical trials.

FRAUD DETECTION

Fraud is an important subset of topics involving data quality. Quality issues can be due to carelessness, such as transcription errors; contamination; mechanical failures; poor planning, poor training or fraud. Fraud is the “Deliberate attempt to deceive” or the “intention to cheat” (Buyse et al. (ISCB), 1999). In clinical trials, fraud is difficult to diagnose. If unusual values are identified, how do we separate fraud from carelessness? Perhaps differences between sites are

due to available subjects, or slight variations in technique. We may identify unusual points indicating a quality problem, but stating that it is explicitly due to fraud may require more evidence (Evans, 2001). In the presentation, we will show how JMP Clinical can be used to identify unusual and potentially fraudulent data from clinical trials.

A simple example: Patients in clinical trials receive excellent medical care, sometimes with the addition of financial reimbursement. Sometimes the need to maintain this treatment or receive additional financial incentives may cause subjects to re-enroll in the trial at another participating study center. These duplicate-enrolled subjects are problematic. From a statistical perspective, the assumption of independence among study subjects is violated. Not considering this violation has the potential to underestimate the standard error for the effect of treatment. Alternatively, if these errors are identified after the trial has completed enrollment, this can result in a loss of power since a straightforward way to handle duplicated data is to include efficacy data only for the first instance of each subject participating in the trial (resulting in a loss of sample size). Sensitivity analyses may include these duplicated subjects. In any event, the analysis and study reporting becomes much more difficult with the presence of duplicate subjects.

How is it possible to identify subjects that have participated more than once? Straightforward ways of identifying potential re-enrollers include matching subject IDs by birth date or initials. See Figure 1. This output is from the **Birthdays and Initials** JMP Clinical process using data from a clinical trial. Subjects are matched either by birth date, with options to allow for windows around a birth date (in case dates are entered into the database incorrectly); or by initials accounting for the possibility that a previously reported middle initial may go unreported at another site. Here, differing sex and race within a match can quickly identify pairs that do not require further attention. If available, JMP Clinical will also summarize ethnicity, height and weight in this table.

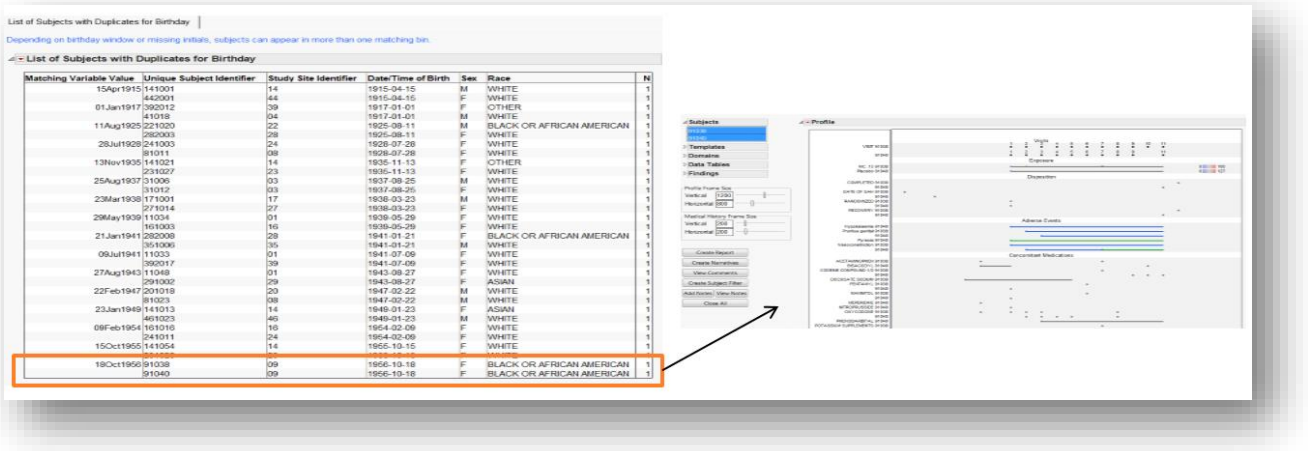

Figure 1: Subjects matched on date of birth, drill down to associated duplicated subject patient profiles.

Other aspects of fraud are analysis of constant laboratory values. JMP Clinical contains the **Constant Findings** Analytical Process (AP). This AP searches for any tests where there is no variability within a subject, which could be an indication that results were copied throughout the CRF. In Figure 2, we have summarized the occurrence of constant lab tests from the Nicardipine trial. For Bilirubin, it appears that 45 subjects had no change in their values from the time they entered the trial until the time they exited.

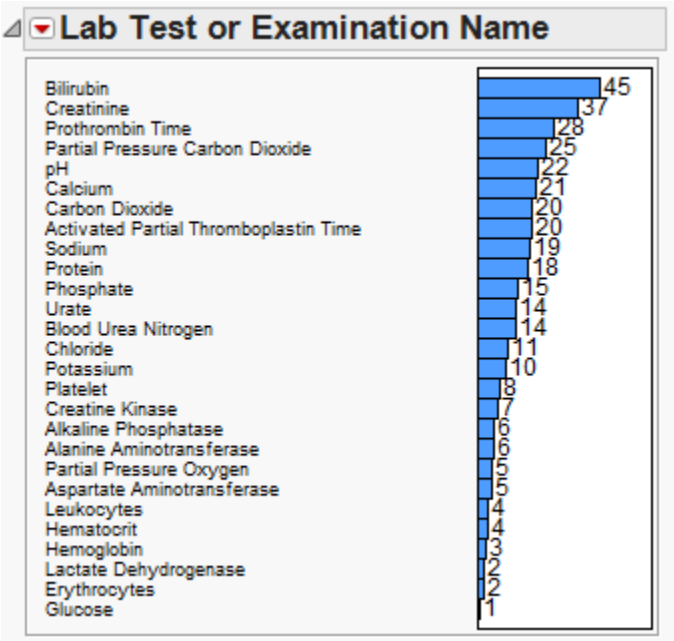

Figure 2: Distribution of Constant Lab Tests

While unusual, these results may not necessarily indicate that fraudulent behavior is occurring. Some laboratory tests may show little variability across time (particularly when hitting an upper or lower limit of detection). Further, for subjects who discontinue the trial early, there may only be a handful of repeated measurements.

One other example: The **Digital Preference** AP analyzes the frequency of use of the last/first digit in a test at a site against the average value of use across this other sites.

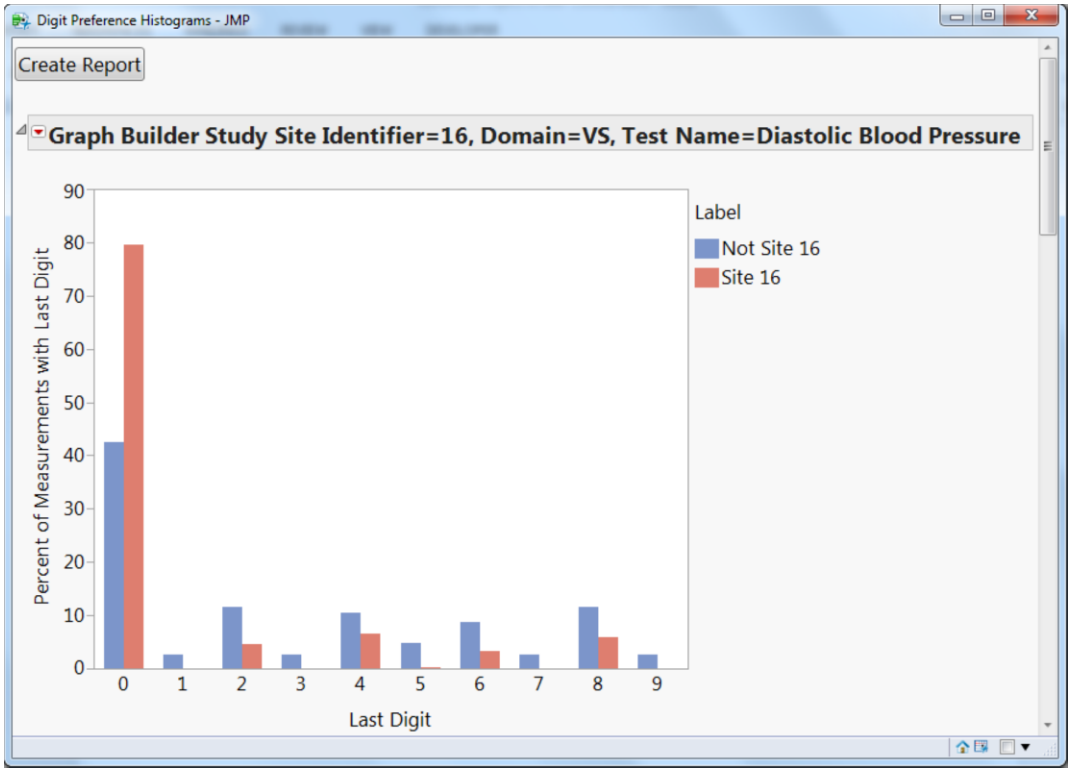

Figure 3: Digital Preference for Site 16

On Figure 3, the Last Digit is on the x-axis, and the percent is on the y-axis. The blue bars represent the average values of all sites but 16, and the red represents site 16. We can see that site 16 ends with 0 nearly 80 percent of the time, and if not 0, then 2, 4, 6, or 8. The other 4 charts are similar.

The **Duplicate Records** AP identifies sets of variables that may occur more than once. What does “record” mean? A record will refer to a set of tests reported at the same visit and time (if applicable) number from the same domain. This will often encompass a single panel on a CRF page. For example, a set of vital sign measurements (stored in the SDTM VS domain) may be

collected for a subject. It would be extremely unusual to find the same exact set of measurements within the subject or across subjects within the same clinical site. Multiple hits between two subjects can possibly indicate that CRF pages were copied between these subjects. Even worse, a large number of multiple hits may identify a fictitious subject. Hits within a subject can identify "carried-forward" problems similar to those described above, or it may indicate visits that did not actually occur for the subject. Figure 4 identifies the triplicate above among two subjects within the same clinical site.

Unique Subject Identifier	Study Site Identifier	Description of Planned Arm	Country	Date	Time	VISITNUM	Diastolic Blood Pressure	Heart Rate	Systolic Blood Pressure	Duplicate ID
461002	46	NIC .15	USA	05Oct1988	:0:21:00:00	9	80	80	130	453
461017	46	Placebo	USA	14Mar1989	:0:06:00:00	9	80	80	130	453

Figure 4: Record Duplication for Vital Signs

While unusual, it is possible for a record (i.e., a set of measurements) to occur between or within subjects. However, if this same record is repeated among multiple subjects within a clinical site, or repeated across multiple visits or time points, or there are a large number of tests that make up the record, this would warrant additional investigation.

JMP Clinical's **Multivariate Inliers and Outliers** analytical process (AP) creates a data set comprising one row per subject from a set of CDISC formatted data sets. Variables for lab tests, vital signs, symptoms and other findings data are generated by visit number and time point. Variables representing frequencies of adverse events, medications and medical history terms are computed. Based on dialog options, variables exceeding a certain percentage of missing data (default 5%) are excluded from the analysis, since subjects with any missing data for the variables of interest cannot have Mahalanobis distance computed. Inliers are more indicative of fraud since it is extremely unlikely for a subject to be average for a large set of variables (Evans, 2001).

The resulting data set computed above will then be used to compute Mahalanobis distance. Figure 5 shows a box plot of distance measures for each subject compared to the centroid of the multivariate distribution. The distance measure is computed from 268 of 744 possible variables. The remaining variables had missing data rates exceeding 5% and were removed from analysis. Fifty-two subjects did not have distance measures computed due to 15 variables with some missing data. This figure can identify outliers (large distances) or inliers (small distances). The dotted red reference line is derived from a chi-square distribution with k (number of variables in the analysis) degrees of freedom. The square of Mahalanobis distance follows this distribution.

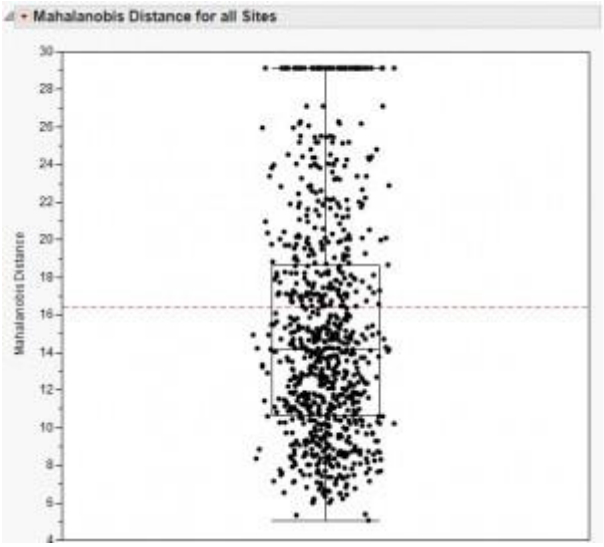

Figure 5: Box plot of Mahalanobis distance for all sites

Figure 6 presents Mahalanobis distance by study site to identify if any particular site is extreme. This may uncover possible data errors among the analyzed variables, but it may also describe key differences in study population across the sites. The length of the box plots indicates how variable subjects are within a given site around the multivariate mean. Large variability can reflect a diverse study population or a site that may benefit from additional training. Low variability may reflect a particularly homogeneous population. In any event, any site that "stands out" may require greater scrutiny.

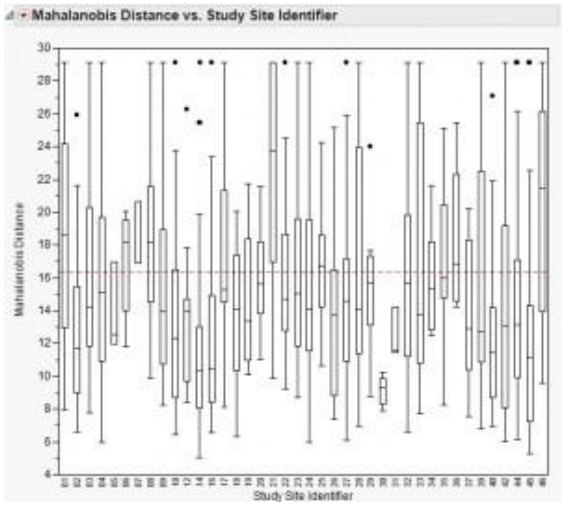

Figure 6: Box plots of Mahalanobis distance by site

The **Cluster Subjects within Study Site** AP performs the analyses described in the preceding paragraph. Similar to the **Multivariate Inliers and Outliers** AP, data from CDISC findings, Events and Interventions domains are used to generate a data set comprising one row per study subject. However, rather than compute Mahalanobis distance to the centroid of all subjects, an Euclidian distance (with each covariate centered and scaled) matrix for each center is generated to assess the similarity of all subjects within that center. We use Euclidian distance for this application since PROC DISTANCE of SAS is capable of computing distance in the presence of missing values for covariates. Users can, however, delete variables with high rates of missing data from the analysis.

Figure 7 summarizes the pairwise distances at each site using box plots. The plot to the left allows us to compare subject-similarity across the study centers. This is an important plot since we need to first answer the question “How similar is similar?" Of course, a distance of 0 between any two subjects would indicate an exact copy, but as analysts we need to have some idea of what is reasonable to expect between subjects among the different sites.

Recall, fraud is likely occurring at one or a small number of sites, so this figure should help to identify sites that are “different.” The plot on the right summarizes the distribution of the most similar pair of subjects from each site. While it may be motivated to identify duplicated subjects, such an analysis also helps describe the study population that may be available at the clinical site. Small or large boxes would indicate centers with a more homogenous or heterogeneous population, respectively.

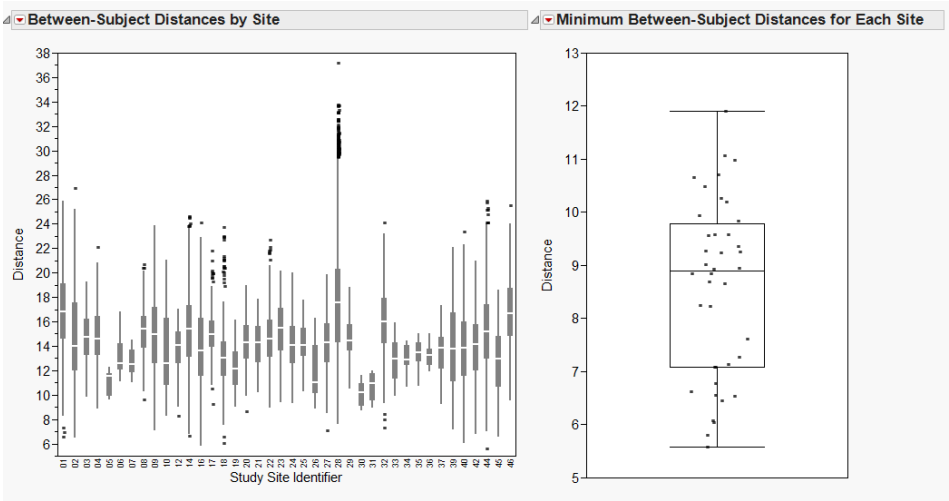

Figure 7: Comparison of between-subject distances across sites

Though an analysis is performed for each site, by default JMP Clinical only presents the analysis for the center with the minimum overall between-subject distances (Figure 8). Results from

analyses of other sites are available using drill-downs. The plot in the left summarizes the distribution of all pairwise distances for subjects available at Site 44 from a clinical trial of Nicardipine. The heat map and dendogram summarize the distance matrix and hierarchical clustering analysis for subjects within the site. From the box plot, we can select the minimum pairwise distance and highlight these individuals within the heat map to identify and further explore subjects with whom they may be clustered. Further, using additional features, we can open the data table to examine the covariates of these two subjects (or a larger cluster to which they belong) side-by-side.

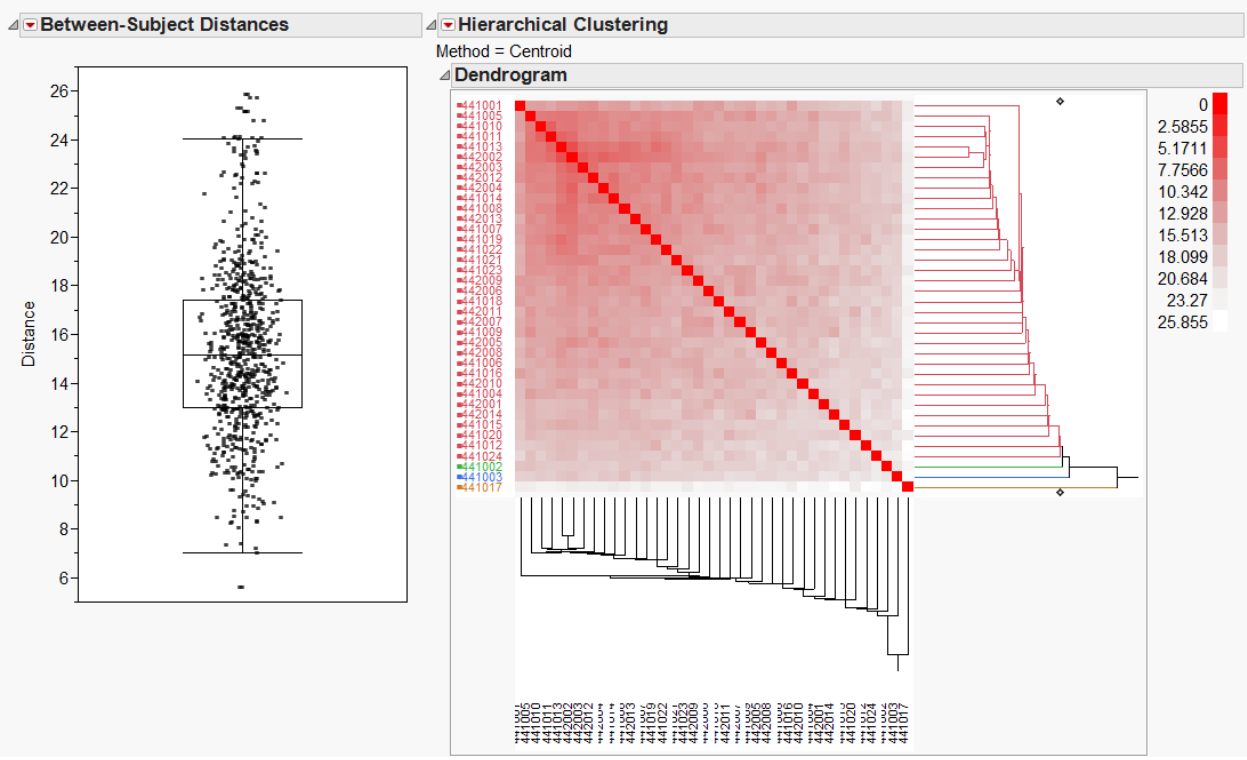

Figure 8: Analysis of Subjects at Site 44

RISK BASED MONITORING

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. 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 on-site monitoring. 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. First, its 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 on-site 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 on-site 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. 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.

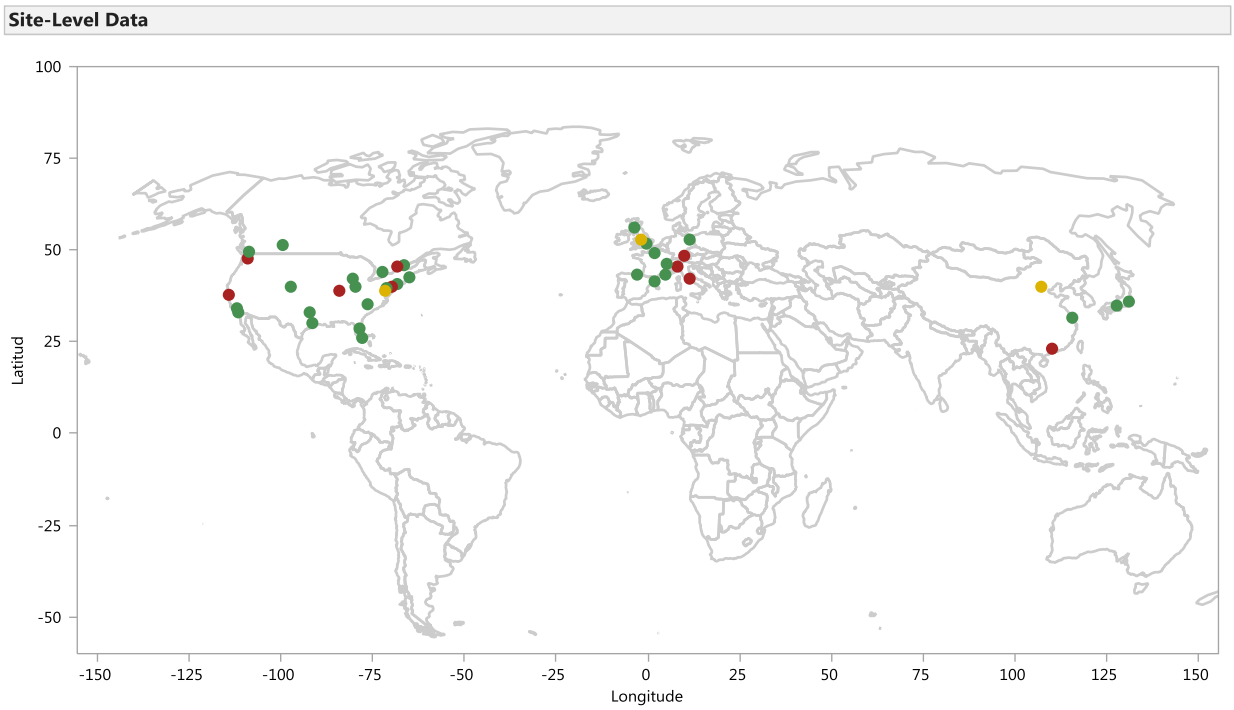

Figure 9: Risk Based Monitoring site level indicator

In this presentation, we introduce the new RBM functionality (Figure 9) within JMP Clinical to assess data quality and the safety of trial participants

CONCLUSION

JMP Clinical, a solution from SAS streamlines both internal safety reviews during clinical trials and the final evaluation of submissions by regulatory bodies such as the Food and Drug Administration (FDA), by

- Combining dynamic graphics and powerful advanced statistical analysis
- Using CDISC and ADaM standard data formats, making user interfaces very simple
- Generating a series of innovative, easy-to-understand visual dashboards
- Delivering unparalleled flexibility, point and click, and drill-down functionalities for exploring prominent results in more detail
- Detecting easily fraudulent behavior in clinical trials
- Displaying data quality issues with Risk Based Monitoring

REFERENCES

Evans, S. (2001). Statistical aspects of the detection of fraud. In: Lock, S, Wells, F & Farthing, M, eds. *Fraud and Misconduct: in Biomedical Research, Third Edition*. BMJ Books.

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