

Paper 201-2011

## Driving Clinical Safety Reviews with Data Standards

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### ABSTRACT

Data standards foster the development of software that permits informed analysis of the data, shortening the path to discovery. Emerging clinical data standards have led to the creation of JMP® Clinical, which combines the visual exploration capabilities of JMP software with the statistical rigor of SAS® Analytics. Interactive dashboard displays enable clinicians to create sophisticated visual summaries of events, findings, and interventions, and then to zoom and filter through the data to explore subject level details (e.g. patient profiles). Pattern discovery and predictive modeling techniques, used behind the scenes, enable medical reviewers to explore the study data with a visually driven user interface, lending strong evidence to the value of data standards.

### INTRODUCTION

The Clinical Data Interchange Standards Consortium (CDISC) is creating data standards for clinical trials. This work has been ongoing for more than 10 years. The development of the Submission Data Tabulation Model was a milestone for the pharmaceutical industry and the Food and Drug Administration (FDA). It allows both parties to exchange clinical trials data in a more open and transparent way. Several CDISC pilots have provided guidance for submission using SDTM and the Analysis Data Model (ADaM) along with their metadata, which is captured in the Define model. These submissions follow the Electronic Common Technical Document (eCTD) format for electronic submissions. The FDA and National Cancer Institute (NCI) are currently funding (RFP ST10-1125) the design and development of a new clinical trials repository that will receive data in the SDTM format (version 3.1.2 or later) to make it available for comparative effectiveness research. Cooperation between the NCI and FDA in development of this effort is sure to hasten the adoption of CDISC standards within the agencies and ultimately across the industry. Perhaps more important, it is enabling a faster shift from the document-centric world of clinical trials reporting to a data-centric environment.

The Submission Data Tabulation Model defines four classes – Events, Findings, Interventions and Other -- each encompassing many domains that allow classification of all of the data collected in a clinical trial. Events domains include, but are not limited to, adverse events, disposition and medical history. Examples of Findings domains are laboratory tests, electrocardiograms and vital signs. Interventions domains include both exposure and concomitant medications. Finally, the demographics domain is an example of the “Other” class. This data, with standard naming conventions, controlled terminology and metadata, supports manipulation of the data for exploration and review. The Analysis Data Model subject-level dataset (ADSL) identifies standard indicators that are useful for further, more complex, analyses of clinical trials.

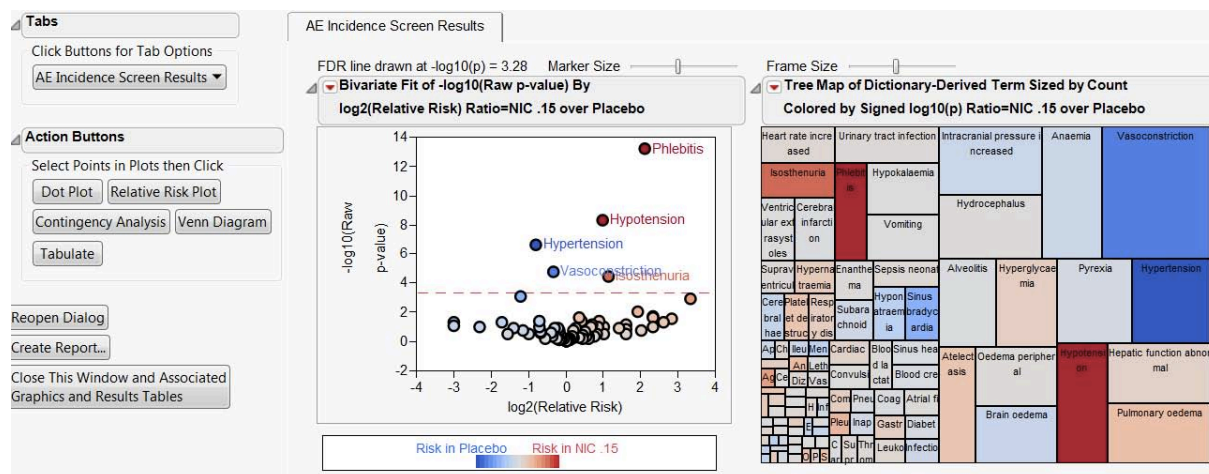
For many years the pharmaceutical industry and the FDA have been developing guidelines for standardization of the presentation of clinical trials data. Examples of these guidelines include: “Structure and Content of Clinical Study Reports” (ICH E3), “Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review” (FDA), “Clinical Review Template” (FDA) as well as the more recent “Drug-Induced Liver Injury” (DILI) document from the FDA. These guidelines provide extensive insight into the mind of a medical officer when exploring clinical trial submissions for review.

Very recently, there is gaining interest in providing standard graphs for visualization of clinical trials data. In 2008, a paper by Amit et al., “Graphical Approaches to the Analysis of Safety Data from Clinical Trials,” was written to enable medical reviewers and biostatisticians more easily consume and share the safety and efficacy results of the trials. Also in development along these lines is CTSPedia (<http://www.ctspedia.org>), a collaboration between industry, agency and academic researchers interested in clinical trials visualization and analysis. The field of data visualization is rapidly accelerating, due to fundamental research by scientists such as Edward Tufte, Ben Schneiderman and Hans Rosling. These researchers have invented small multiples (Tufte), a fundamental concept behind GraphBuilder in JMP, Tree Maps, also in JMP, are a space-constrained view which can hierarchically organize categorical information as well as color them for added dimensionality, and finally the Bubble graph, providing inspiration for JMP’s Bubble Plot.

Following Schneiderman’s Visual Information-Seeking mantra, these different visualizations are available from interactive summary dashboards with zoom and filter capabilities, to allow users to hone in on subject level details from any perspective. This technique helps JMP Clinical streamline the exploration and review of clinical trials data by leveraging the advanced statistics of SAS with the interactive visualization capabilities in JMP. This combination allows medical reviewers and biostatisticians to utilize the same tool for their distinct roles in the review of clinical trial data, facilitating communication between review groups.

## VISUALLY EXPLORE SIGNIFICANT ADVERSE EVENTS

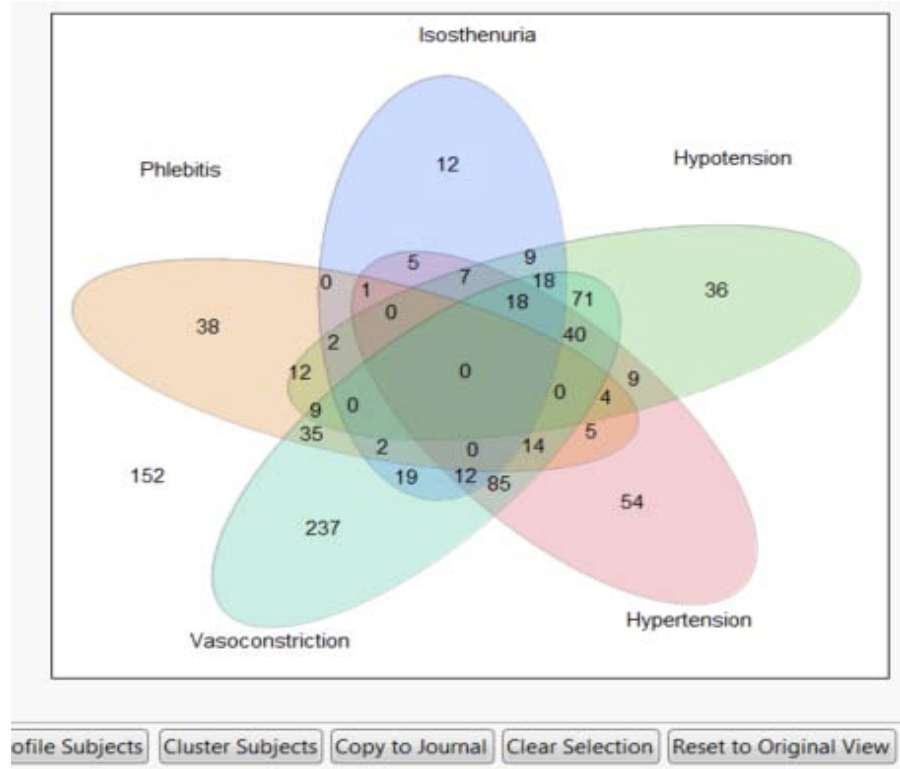
A significant focus of the safety review for clinical trials involves exploration of adverse events. This exploration is described in the reviewer guidances and plays a large role in the functionality of JMP Clinical. Creating dashboard displays, which allow interaction with the graphics and providing drill-down buttons to support user workflow are integral to the design of JMP Clinical. This exploration technique follows the philosophy of Ben Schneiderman's Visual Information-Seeking mantra: Summarize, Zoom and Filter, Details. For example, the dashboard displays of adverse event incidence screens provide an instant view of the adverse events with their relative risks. The default view is a space-constrained volcano plot allowing easy identification of relationships with treatment as well as significance. From here, the user can select a number of drill-down buttons which enable different views, such as a



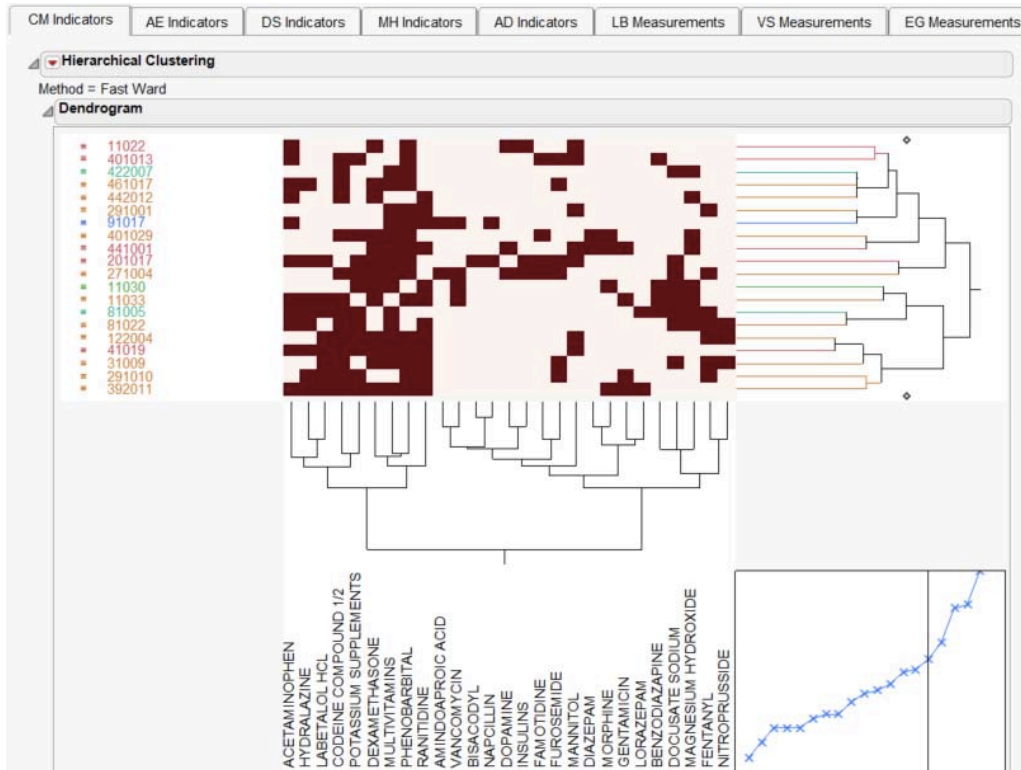
Display 1. A Volcano Plot indicating the significance (denoted by a red-dashed line which is multiplicity adjusted) by relative risk of all adverse events on the study accompanied by a Tree Map showing increased risk with frequency of occurrence. Drill-down buttons on the left allow reviewers to zoom and filter through the data to explore possible subgroups for a case study report.

more industry standard relative risk plot or a dot plot described by Amit et al. Alternatively, the user can run a contingency analysis providing more frequency and count information or use Venn diagrams or Tabulate to identify subjects with co-occurring adverse events. Exploring this type of data visually has advantages in that it is more likely to reach a broader audience without the involvement of data manipulation or programming. A Venn Diagram, containing as many as five co-occurring adverse events is perhaps the simplest user interface to interact with when dealing with intersections, or subsets, of subject selection. From here, the user can simply click on the Profile Subjects or Cluster Subjects drill-down buttons to explore more details of the subgroup. With the selection of the Cluster Subjects feature, clinically relevant patterns of different domains of data, presented on separate tabs, allow users to further subset subjects based on different clinical criteria.

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Display 2. A Venn Diagram of the most significant adverse events on the trial. Selection of the intersection(s) allows reviewers to drill down to subject details.

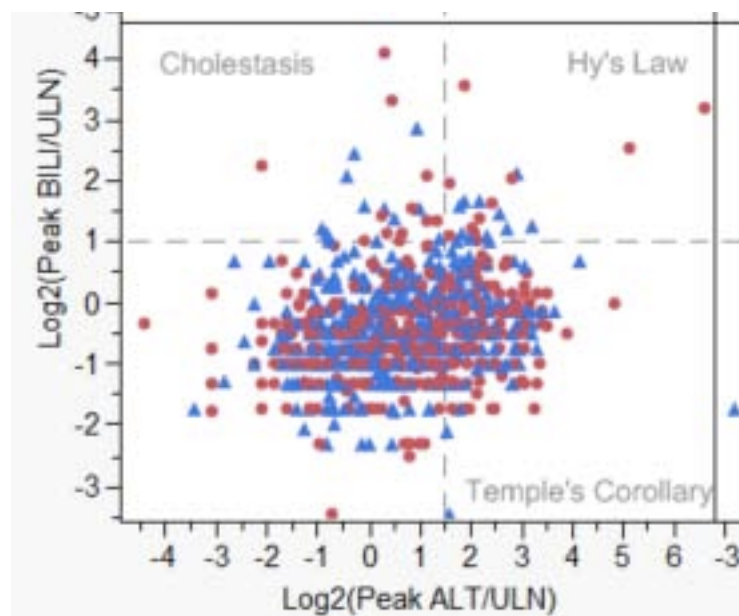


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Display 3. A Subject Cluster view for a selected subset of subjects. Tabbed panes allow reviewers to quickly discover patterns across different SDTM domains using a hierarchical clustering method.

### IDENTIFY SUBJECT OUTLIERS AT SPECIFIC STUDY DAYS (HY'S LAW)

Combining the SDTM laboratories domain (LB) with demographics (DM) provides the starting point necessary to create a liver toxicity test, called Hy's Law, which is described in detail in the Drug-Induced Liver Injury guidance. Providing the standard visualization of the peak Alanine Aminotransferase (ALT) versus peak Bilirubin is possible, so long as those lab tests are present in the LBTEST or LBTESTCD variables of the LB domain. This has become a



Display 4. Hy's Law view consisting of peak measurements of Alanine Aminotransferase vs. peak Bilirubin. The subjects in the upper right quadrant have a higher probability of death.

valuable tool to evaluate the safety of a drug. However, by utilizing the peak or maximum value for each lab test, the view lacks the ability to identify when the subjects' livers were becoming dangerously toxic and perhaps pinpoint some causal factor that occurred just before the finding presented was observed. Easy access to select other

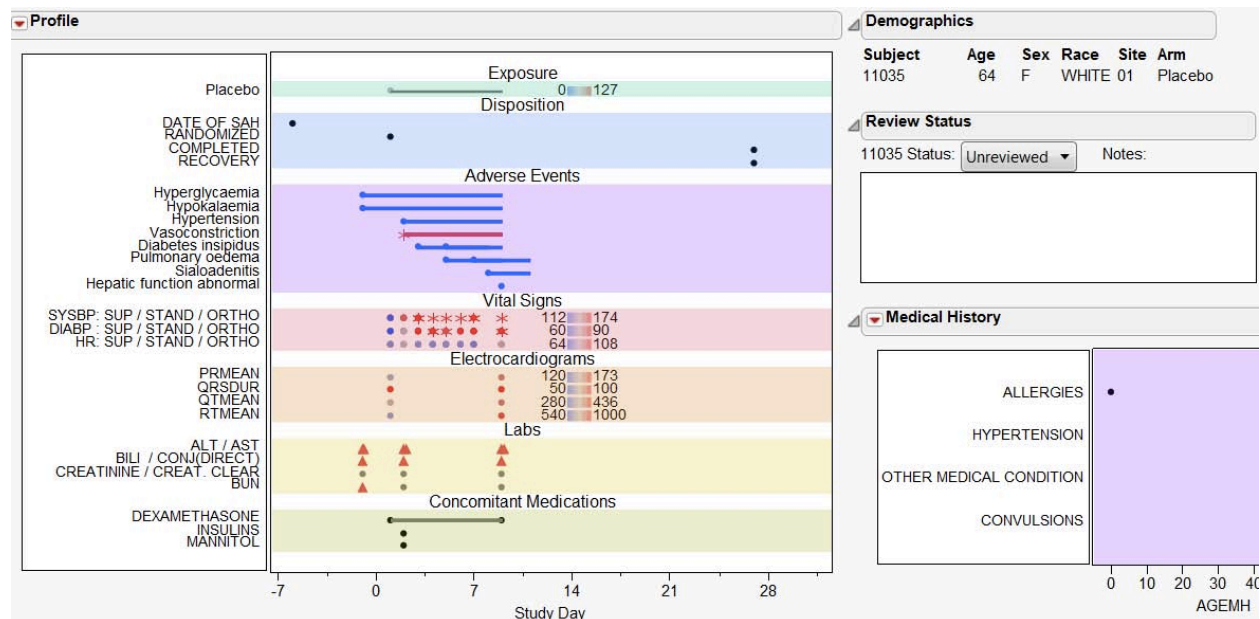




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Display 6. Trellis plot display using JMP's Graphbuilder platform to display laboratory tests indicating both liver failure (Alanine Aminotransferase and Bilirubin) and kidney failure (Blood Urea Nitrogen and Creatinine). All labs are normalized to the log 2 scale for easy comparison.

failing. At any point, users can drill-down to patient level details for a subset of subjects to generate a case study report by entering information into the Review Status text area and inform the system that the subject was reviewed by simply switching the drop-down button to reviewed.



Display 7. Patient Profile providing specific patient level detail on a single timeline. Demographic information is supplied along with medical history and a review status entry field allows medical reviewers, medical writers and others to identify specific details to capture on each subject.

Filtering down to subgroups or swimming up to summary views provides medical reviewers and biostatisticians the ability to explore hypotheses about the subject population. Patient profiles are the ultimate clinical summary view to informing clinicians of the necessary details to draw conclusions about patient outcomes.

## CONCLUSION

Combining CDISC data standards with standard clinical visualizations and reporting guidelines have given rise to JMP® Clinical, which connects the interactive visualization capabilities of JMP with the statistical rigor of SAS. With JMP as the preferred tool of medical reviewers and SAS as the standard for biostatisticians, it is possible to bring these users together in a collaborative environment in order to streamline the safety and efficacy reviews of clinical trials.

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## **ACKNOWLEDGMENTS**

I would like to thank many volunteers with the CDISC organization (ADaM, SDTM and XML Technology team members), whom I have learned so much from over the years. I would like to thank many individuals in SAS Health and Life Sciences as well as the JMP Division at SAS.

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