

Uncover Useful Patterns in Clinical Trials Safety Data with JMP® Clinical

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ABSTRACT

The conduct of clinical trials requires a complex infrastructure, and biopharmaceutical companies, CRO's and regulatory agencies are already challenged by inefficiencies in exchanging and meaningfully reviewing clinical trials data. Such difficulties negatively impact the ability to assure successful future outcomes both for patients and those involved in drug delivery, and will only become more acute as the complexity and number of therapies increase. Balanced scientific review requires close scrutiny of the patterns of variation in the data in the specific clinical context, some of which may be obvious and hoped for, some of which may be less so. There are many aspects to this but, briefly, software should make it easy for individual researchers to strengthen prior knowledge, to self-provision new, useful insights, and to simply and quickly communicate their findings with all stakeholders through appropriate dialogue. This should be possible whatever the statistical expertise of the researcher, whilst making the best use of all relevant, available data.

JMP Clinical 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), helping to both reduce risk and time to market for new therapies. It links exploratory, dynamic graphics with advanced statistics, enabling sophisticated routine and ad-hoc analyses in an easy-to-use environment. JMP Clinical creates analyses and reports from standard Clinical Data Interchange Standards Consortium (CDISC) data, facilitating communication between clinicians and biostatisticians at the sponsor organization and, subsequently, between sponsors and FDA reviewers. It also emphasizes multiple, interactive views of patient profiles and can reveal hidden patterns in drug-drug and drug-disease interactions using data from different domains.

Using CDISC data for Nicardipine as an example, this presentation shows how JMP Clinical can help researchers to discover and communicate important findings easily, making the best use of all available data.

INTRODUCTION

JMP Clinical software from SAS streamlines safety reviews of clinical trials data in 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 patient profiles can easily be constructed from CDISC data, raising the quality of the dialogue between the researcher and all stakeholders. The architecture of JMP Clinical will be briefly explained, showing the synergistic use of JMP and SAS technologies.

CHALLENGES

An ever-growing challenge to effective clinical research is how to handle the inefficiencies involved in exchanging and reviewing clinical trial data. This inefficiency is caused by the time it takes to build the requisite standard clinical report templates, to analyze the data within this framework, and to deliver and discuss the resulting reports. Moreover, if the analysis itself is not deep enough and fails to use all relevant available data, there is a risk that important findings may pass unobserved, only to surface later.

JMP CLINICAL ARCHITECTURE

JMP Clinical from SAS facilitates both internal safety reviews during clinical trials and the final evaluation of submissions by regulatory bodies such as the Food and Drug Administration (FDA). JMP Clinical uses CDISC standard data format and is a hybrid solution combining JMP, an intuitive interface for interactive and dynamic graphics and statistics, and SAS, a world-leading system for powerful and advanced data management and analytics. The JMP Clinical platform can be used by a large community of users involved in the clinical safety data review process (Figure 1).

- Statisticians benefit from SAS with its powerful and advanced data manipulation and statistics functionality. A relatively large collection of SAS programs for analysis and reports creation process is implemented in the software. However, JMP Clinical is an open architecture that enables programmers to access the code and to modify or even create routines as needed.
- Reviewers can benefit from JMP's easy-to-use interface for interactive and dynamic clinical dashboards.
- To speed up the safety review process, implementation of workflows lets users to perform a complete set of standard analyses with only a few mouse clicks.

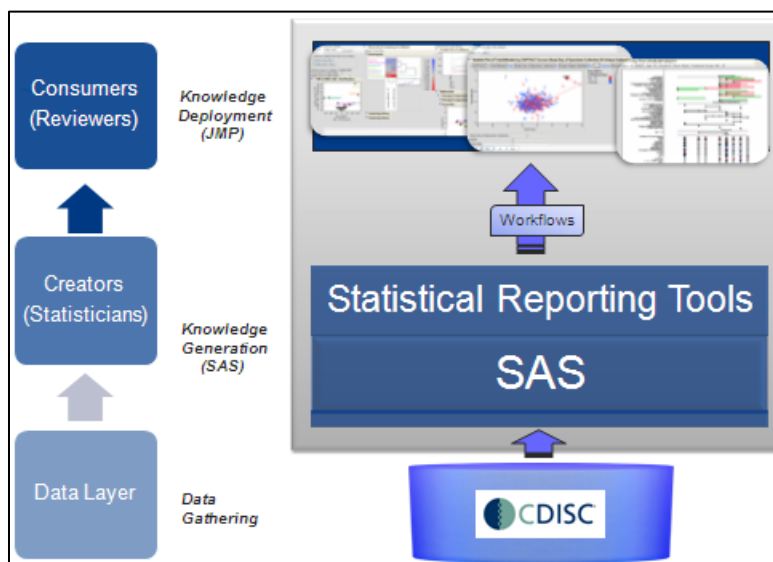


Figure 1: JMP Clinical Platform

The JMP Clinical menu organization roughly follows the order for FDA reviewer guidance (Figure 2). It provides access to more than 60 Analytical Procedures. Related processes are grouped into different submenus (Figure 2).

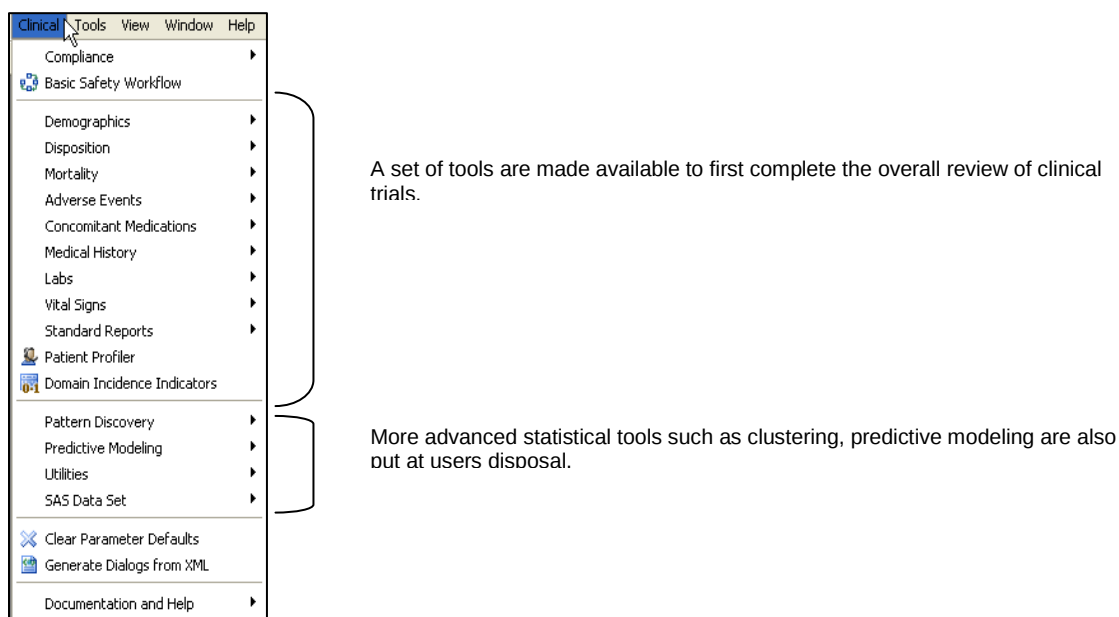


Figure 2: JMP Clinical Menu

NICARDIPINE CDISC DATA EXAMPLE

Using CDISC data from a Nicardipine study for the treatment of Subarachnoid Hemorrhage as an example, we will showcase how JMP Clinical can help researchers to discover and communicate important findings easily, making the best use of all available data.

Nicardipine or Cardene is an intravenous *dihydropyridine* calcium-channel blocking agent used for the treatment of vascular disorders such as chronic stable angina, hypertension, and Raynaud's phenomenon. The study includes Nicardipine treatment of 906 subjects that had Subarachnoid Hemorrhage. All the patients were included in a randomized double-blind placebo-controlled study; 449 patients received Nicardipine while 457 received the placebo. Patients in each group were balanced with regard to prognostic factors for overall outcome. Nicardipine and the placebo were delivered continuously at 0.15 mg/Kg/hr for up to 14 days and patients were followed for up to 120 days following administration of the drugs. Results are formatted according to the CDISC Study Data Tabulation Model (SDTM).

To track safety and efficacy issues of the drug, we will present a basic safety workflow which includes a comprehensive set of analysis resulting in intuitive dashboard reports to track safety of the drug. Many reports include drill-down functionality for exploring prominent results in more detail. More advanced statistical analysis, pattern discovery and predictive modeling methods will be applied for statistically rigorous screening of all safety domains.

1. Verify CDISC Data Consistency with JMP Clinical Compliancy Check

JMP Clinical creates analyses reports from standard Clinical Data Interchange Standards Consortium (CDISC) data. Before performing any analysis, it is necessary to check whether the CDISC data used is in accordance with the subset of standard CDISC norms used by JMP Clinical. This checks for variables or terms which are missing or do not conform to standard formatting. If there is data inconsistency, that could have a direct effect on the proper operation of JMP Clinical. JMP Clinical has implemented Compliancy Checks that checks automatically for required variables to assess compliance of the CDISC data that will be used. After this check, the safety review process itself can be started.

2. Visualize Relationships between Demographic Characteristics and Treatment Group by using Demographic Distribution Procedure

The Demographic Distribution analytical process within JMP Clinical compares distributions of demographic variables across treatment arms via a one-way ANOVA or contingency analysis. This will allow researchers to instantly see heterogeneous distributions and to check for significant variation of demographic characteristics across the different treatment cross. The addition of filters enables subsetting of the information represented on the dashboards that will be automatically updated according to the filter applied (Figure 3).

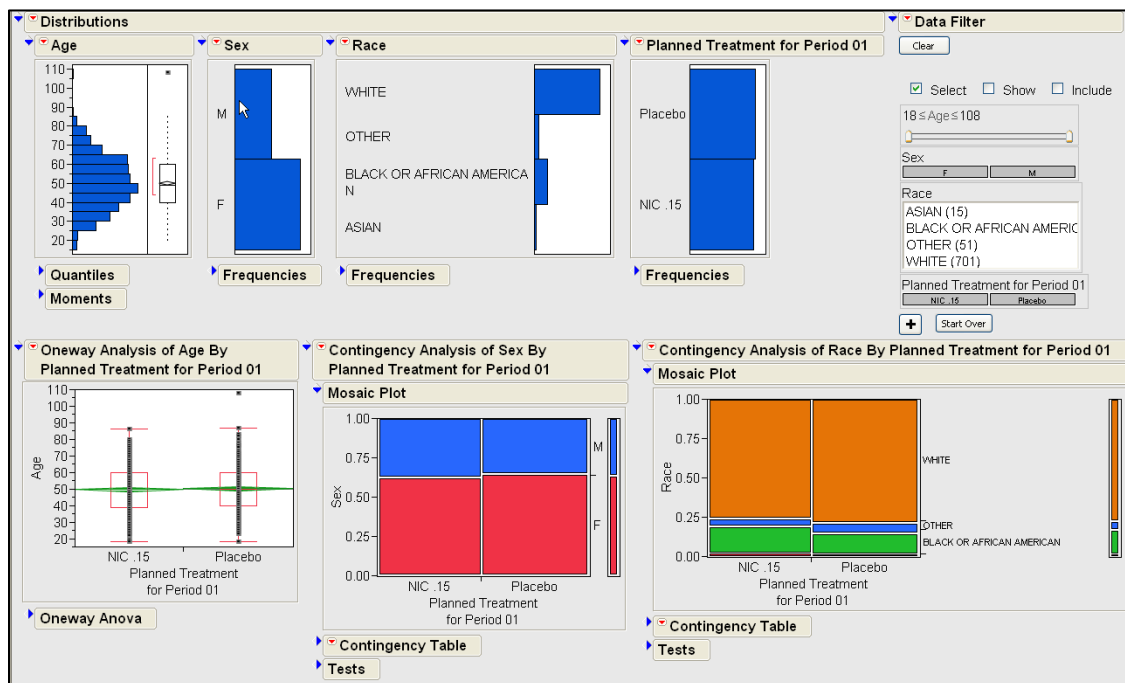


Figure 3: JMP Clinical Demographic Distribution dashboard

3. Visualize Relationships between Mortality Rate and Treatment Group by using Kaplan-Meier Curves

It is important to check for significant deviations in the mortality rates between the different treatment groups. JMP Clinical has implemented a Kaplan-Meier Curves Analytical Procedure that compares mortality results by treatment group and generates interactive Kaplan-Meier survival curves with associated statistics (not shown).

4. Visualize Significant Adverse Events analysed by Mixed Model Analysis

One crucial safety issue is to determine if any adverse events occur disproportionately across the treatment arms. JMP Clinical has implemented a variety of applications to address this issue. One powerful application uses mixed models and is called Adverse Events Severity ANOVA. This application screens all adverse events by performing a mixed-model analysis of variance, with average ranked severity score as the dependent variable and customizable fixed and random effects. A separate ANOVA is fit for each distinct adverse event. A volcano plot (left graph on Figure 4) and other output enable efficient screening of adverse event severities that differ between treatment groups (Figure 4).

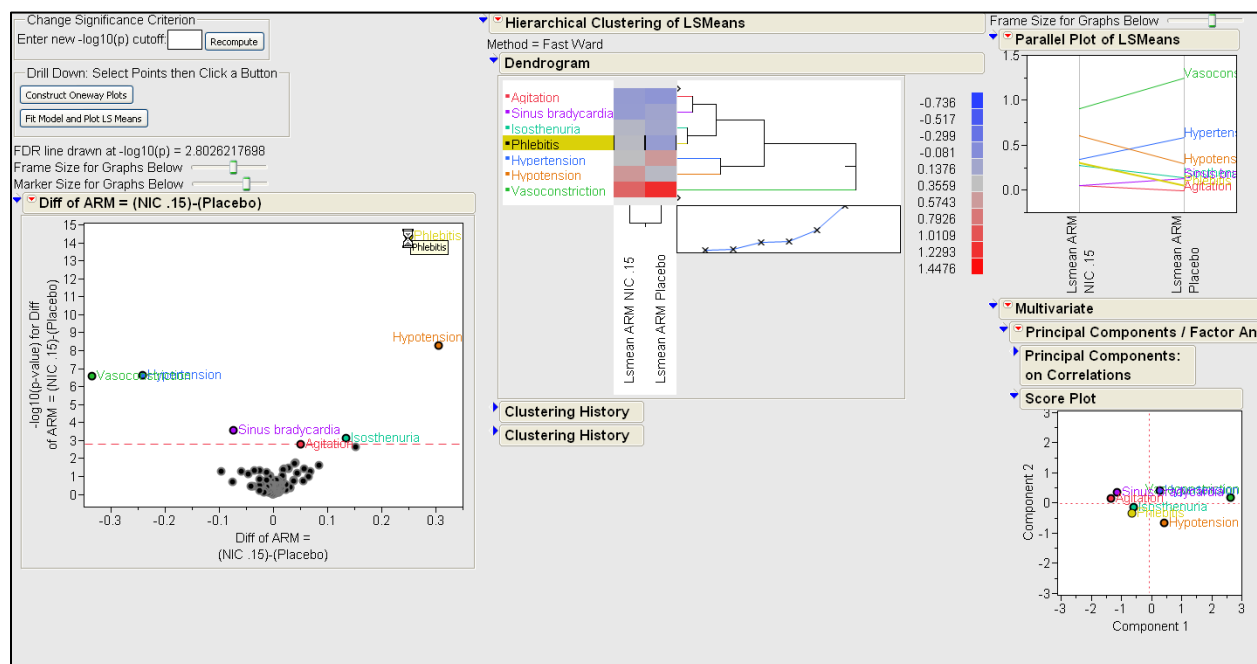


Figure 4: JMP Clinical Adverse Events Severity ANOVA dashboard

The volcano plot is a type of scatterplot that is used to quickly identify changes in large datasets. It plots significance versus effect-change on the y- and x-axes, respectively. In our study example, the events lying to the right of 0 and above the red dashed line (phlebitis, hypotension, isothermia) in the volcano plot are more severe in patients treated with Nicardipine; those lying to the left (vasoconstriction, hypertension, and sinus bradycardia) are more severe in patients treated with the placebo. This observation is supported by the clustering results, the LSMeans parallel plots and the principal components plot (Figure 4), all of which show a divergence of these events. By selecting Phlebitis in the volcano plot and clicking the "Construct One-Way Plot" drill-down button in the dashboard, JMP Clinical makes it possible to directly drill-down and to identify the number of phlebitis cases sorted by severity incidence between the different treated groups (Figure 5, left).

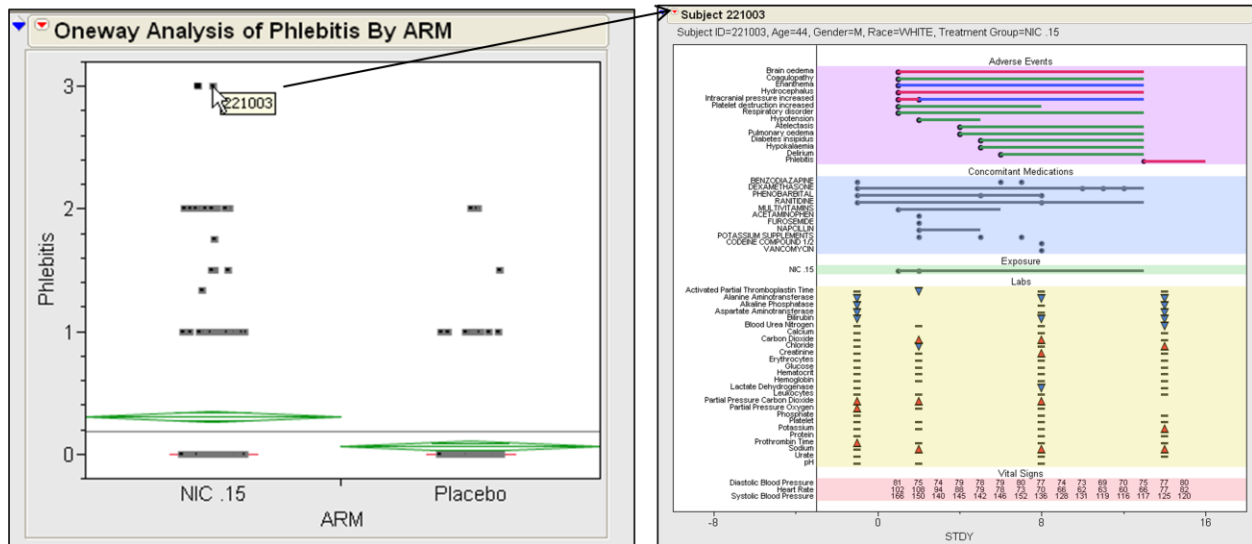


Figure 5: One Way Analysis of Phlebitis by treatment group and Patient Profiler

In the One-Way plot (Figure 5, left), more phlebitis cases of higher severity intensity occurs in the groups treated with Nicardipine. By selecting individual cases in the One-Way Plot, and select Patient Profiler, it is easy to drill down further to access more in depth patient information. The Patient Profiler process compiles information for single patients across multiple domains and displays it in a unified summary graph of all Adverse Events, Concomitant Medication, Exposure time, Lab Tests and Vital signs with time along the x-axis (Figure 5, right).

5. Analyse Laboratory Test and Monitor Animated Drug-Associated Toxic Effects

Laboratory tests are crucial in order to discover if any drug-associated toxic effects are occurring during the clinical trial. JMP Clinical has implemented a variety of applications to address this issue. One of them, Labs Bubble Plot, tracks a pair of lab measurements over time in an animated fashion. Values are linearly interpolated between days or weeks. An example in Figure 6 shows measurements of Alanine Aminotransferase (ALT) versus Bilirubin (BIL) displayed over time for all the patients. By selecting cases that revealed a higher level of both ALT and BIL, indicative of potential liver failure (Hy's Law), the progression of both lab measurements can be followed over time in an dynamic fashion (Figure 6).



Figure 6: Bubble Plot of Bilirubin by Alanine Aminotransferase across study day.

Subjects of interest can be selected to display their time profiles in a Trellis Plot via JMP's Graph Builder (Figure 7).

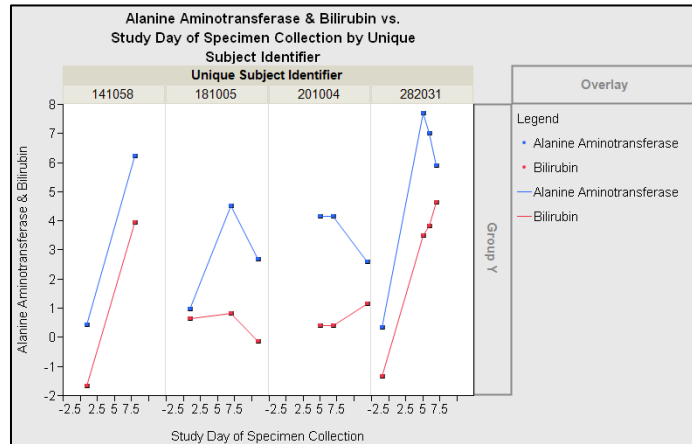


Figure 7: Trellis Plot of four cases displaying the progression over time of Alanine Aminotransferase and Bulribin.

6. Detect Relationships between Adverse Events and other Domain Variables

To find relationships of Adverse Events with other domain variables such as Medical History, Concomitant Medication, etc. JMP Clinical has implemented an Analytical Procedure called Domain Incidence Indicators. This process adds 0-1 indicator variables to the ADSL table corresponding to incidence of variables in specific domain data tables. The process also converts all character variables with values N and Y to numeric variables with values 0 and 1, respectively. The SAS output data table can be clustered to detect variables with similar patterns of appearance (Figure 8).

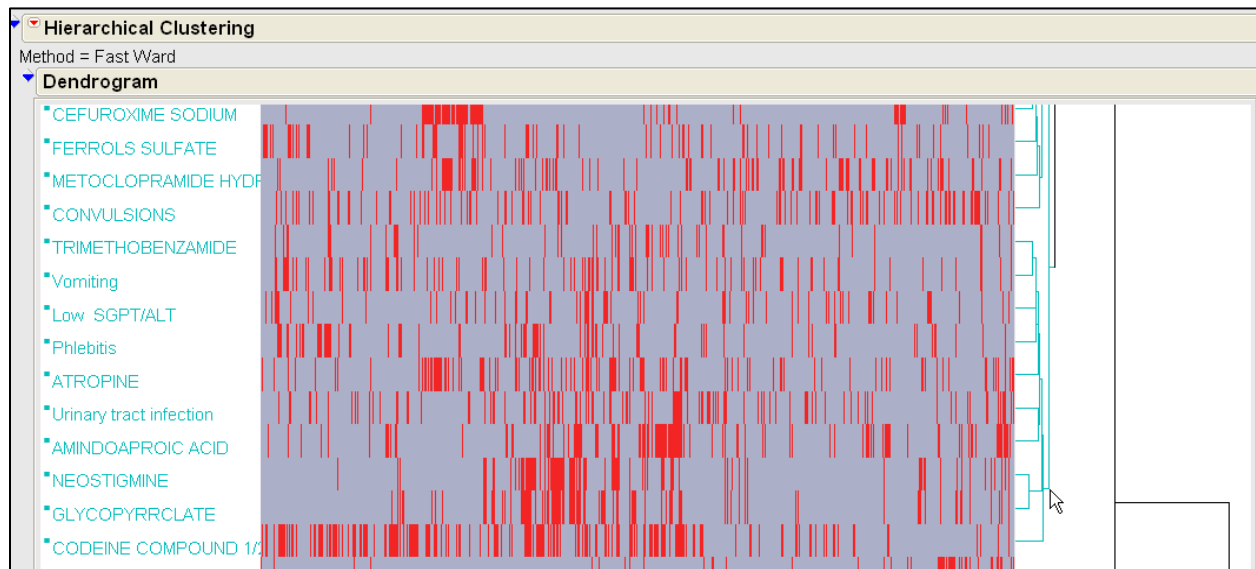


Figure 8: Hierarchical Clustering of a domain incidence indicators.

To drill down in a cluster of interest and to analyse association and potential causal relationships between the set of variables, a Partial Correlation Analytical Processes is used. This process plots each variable as a node and connects the nodes with line segments. The size and color of the segments are determined by partial correlation, which is the correlation between two variables adjusted for all other variables. The output of such an analysis is displayed in Figure 9. The output shows correlation of domain variables among Phlebitis cases.

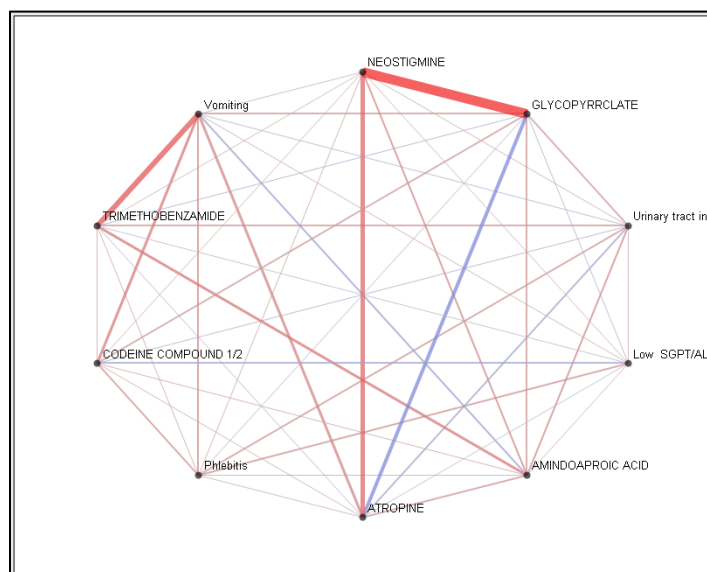


Figure 9: Partial Correlation Diagram

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
- Letting users spend time more efficiently on discovering and reviewing, less driven by data manipulation and coding
- Providing an open architecture in order to access all code, enabling users to see exactly what the application does, and to optionally modify it based on the specific clinical context and their IT environment

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