JMP Clinical for the Exploration of Legacy studies

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Introduction

The JMP Clinical application is explored during the CDISC conversion project of more than 150 legacy studies at Novartis Vaccines & Diagnostics. Experience with JMP Clinical on these legacy studies forms part of an evaluation for use on ongoing studies in the near future, when all NV&D trials are converted to CDISC standards. This JMP extension or add-in has been on the market for one year now and is currently in version 3, the version used for this evaluation. One issue in this evaluation is to what extent it can replace existing standard software that is currently used for submissions. Other points of interest are the benefits of the JMP Clinical interface when exploring legacy and ongoing trials for the different participants involved, and more in general what will be the impact of the shift from document-centric submissions to data-centric submissions.

JMP Clinical

JMP has been praised for its unifying approach to statistical methodology, its integration of statistical analysis and graphics and its ease of operation (1). The interactive visualizations make it a preferred tool for exploratory analysis and enable to discover more, interact more and understand more as compared to SAS, SAS/STAT and SAS/GRAPH. Statistical analysis capabilities were extended with the SAS - JMP integration starting from version 7 which can now be implemented as JMP add-ins (2, 3, 4, 5, 6) like JMP Genomics and JMP Clinical (7). JMP can connect and submit SAS code to PC SAS or a remote server, the SAS programmer can package SAS code within JSL (JMP Scripting Language) and deploy it to JMP users. SAS output is returned to JMP and converted to a JMP interactive report. Bringing SAS and JMP together in one tool creates a collaborative environment for advanced statistics and medical review (8). In JMP Clinical the interactive visualization is enhanced with dashboards that allow a drill-down into subgroups and single subjects. This advanced preprogramming of modules dealing with general clinical data, together with compliance checks and standard safety reports, is made possible by the CDISC data standardization. The available compliance checks are quite rudimentary and the 'standard' reports will need customization, both of which can be handled by the extensibility of JMP Clinical that enables programmers to access the code.

Distributions

In the domain distribution dashboards, standard JMP Distribution platform options like Bar and Mosaic graphs, together with One-way ANOVA and Contingency Analysis options are available. The default analysis is by treatment ARM variable, but the input screens allow the specification of other variables for the analyses. This is also true for the populations if available as variables in and ADSL dataset. The dynamic zooming after launching the dashboard is done with a data filter or the familiar JMP point-and-click interaction. Subject level information across domains on a single timeline is available from each distribution in Patient Profiles. This outstanding feature is an indication of the integration of the JMP Clinical application and a clear demonstration of the benefits of the CDISC standardization. No programming is required for this sub setting and basic analysis, allowing non-programming reviewers to query and analyze the data and understand how the treatment affected a subject. Customizing the domains or creating custom domains however will require both SAS and JMP Script programming skills. Storing the results is possible using the Journal facility.

For routine use, a script will probably be more convenient. A script or the combination of a workflow and a script would also be a solution for storing multiple Patient Profiles that are to be included in a document.

Events

Selection of AEs on a volcano plot on the AE Incidence Screen allows the generation of a Venn diagram and zooming in on the subject level with Patient Profiles. The interactive graphs function as a convenient point-and-click interface for selections. Relative risk plots can be sorted on relative risk for more readily appreciation of serious events by non-statisticians (9). For some graphs, e.g. the Treatment Emergent AEs, it is not immediately clear what definition is used for the generation of the plot. It is likely that certain explorations with JMP Clinical will be followed-up by dedicated programs to confirm the findings. Only a selection of all the options has been explored so far and it is to be expected that the options will not be equally relevant for different clinical trials.

Findings

Findings can be analyzed from the distribution dashboards or more specifically with an ANOVA or different plots. Modification of the plots is possible using the Graph Builder, with its drag-and-drop interface for experimentally creating graphical views of data. Certain lab measurements need a transformation of the result value (LBSTRESN) before plotting, e.g., a log transformation of the antibody titer. While this is easily done in JMP and this option is available when creating cross domain data, using these calculated variables in the predefined JMP Clinical setting without renaming them, is less straight forward.

Pooled studies

As JMP Clinical was evaluated during a legacy data conversion project, its value for the exploration of pooled studies was also considered. The SDTM datasets of the ~150 legacy studies were concatenated and stored in a study-like folder structure. The standard distribution dashboards were used to create summary views of the pooled data. Replacing the treatment variable by the studyid enabled the analysis of demographic or AE data across the legacy studies.

To evaluate more advanced Pattern Discovery techniques, subjects with a certain AE were selected using a search list. Lists of autoimmune diseases as published in the literature were consulted to identify the subjects (10, 11, 12). Individual studies are often not large enough to evaluate such rare events. SDTM datasets of these selected subjects were stored in a study like folder structure. As the classification of these autoimmune diseases is currently a matter of debate, standard Distribution dashboards as well as Clustering and PCA could be used to analyze for co-morbidities and other groupings (13, 14, 15, 16). Together with appropriate lab data these analyses could result in the identification of susceptible subject profiles (17, 18).

Conclusion

Although a limited number of the options of JMP Clinical were explored on the CDISC converted legacy studies, the graphical and interactive features make it appealing to both the SAS programmer and the non-programmer engaged in clinical trials. A large number of options for both visual exploration and statistical testing are available for routine safety analysis. If these can be performed by non-programmers, the current practice of requesting the creation of ad-hoc tables and graphs during the trial can diminish and decrease the workload of programmers. However, extending these options with, e.g., custom domains will require both SAS and JMP scripting skills. Exploring current ongoing trial data will require a connection to a remote server, a feature not tested here. More experience with, e.g., the

Journal and Log facility is required to see how the results can be documented for further use in submissions of clinical trials (19).

Literature

1. Mauromoustakos A, University of Arkansas. SAS/INSIGHT Software or JMP Software: A Comparison. Proceedings of SUGI 22 1997.

2. Borries von G, Universidade de Brasilia BB. A SAS/JMP Integration for Implementation of a Clustering Algorithm for High Dimensional Low Sample Size Data. SAS Global Forum 2009.

3. Raminez JG, W.L.Gore and Associates Inc. L. The Best of Both Worlds: Designing Complex Experiments in the JMP-SAS Environment. SAS Global Forum 2010.

4. Miclaus K, Barker C, Ge J, SAS Institute CN. JMP as an Analytical Hub: Using JMP to Build Custom Applications via SAS and R. SAS Global Forum 2011.

5. Hill E, SAS Institute Inc. CN. JMP 9 Add-Inns: Taking Visualization of SAS Data to New Heights. SAS Global Forum 2011.

6. Koprowski Jr. SP, Peng L, Dwyer J, Sanofi-Aventis US, Bridgewater N. Integrating JMP with SAS to create an automated workflow application for analyzing, processing and reporting of 96 well plate format fluorescence microplate reader data. SAS Global Forum 2010.

7. Mann G, SAS Institute, Cary, NC. Driving Clinical Safety Reviews with Data Standards. Proceedings of the SAS Global Forum 2011.

8. Nedbal V, SAS Institute, Strasbourg, France. Uncover Useful Patterns in Clinical Trials Safety Data with JMP Clinical. Phuse 2011.

9. Amit O, Heiberger RM, Lane PW. Graphical approaches to the analysis of safety data from clinical trials. Pharmaceut Statist 2008;7(1):20-35.

10. Jacobson DL, Gange SJ, Rose NR, Graham NMH. Epidemiology and Estimated Population Burden of Selected Autoimmune Diseases in the United States. Clinical Immunology and Immunopathology 1997;84(3):223-243.

11. Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. Journal of Autoimmunity 2007;29(1):1-9.

12. Cooper GS, Bynum MLK, Somers EC. Recent insights in the epidemiology of autoimmune diseases: Improved prevalence estimates and understanding of clustering of diseases. Journal of Autoimmunity 2009;33(3-4):197-207.

13. McGonagle D, McDermott MF. A Proposed Classification of the Immunological Diseases. PLoS Med 2006;3(8):e297.

14. McGonagle D, Aziz A, Dickie LJ, McDermott MF. An Integrated Classification of Pediatric Inflammatory Diseases, Based on the Concepts of Autoinflammation and the Immunological Disease Continuum. Pediatric Research 2009;65(5 Part 2):38R-45R.

15. Koenig HC, Sutherland A, Izurieta HS, McGonagle D. Application of the immunological disease continuum to study autoimmune and other inflammatory events after vaccination. Vaccine 2011;29(5):913-919.

16. Agmon-Levin N, Paz Z, Israeli E, Shoenfeld Y. Vaccines and autoimmunity. Nat Rev Rheumatol 2009;5(11):648-652.

17. Crowe JE. Genetic Predisposition for Adverse Events after Vaccination. Journal of

Infectious Diseases 2007;196(2):176-177.

18. Stanley SL, Frey SE, Taillon-Miller P et al. The Immunogenetics of Smallpox Vaccination. Journal of Infectious Diseases 2007;196(2):212-219.

19. Schlotzhauer SD. Comparing JMP and SAS for Validating Clinical Trials. Proceedings Of MWSUG 2010.

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