Paper PH-07

Developing a Complete Picture of Patient Safety in Clinical Trials

Richard C. Zink, JMP Life Sciences, SAS Institute, Cary, NC, United States
Russell D. Wolfinger, JMP Life Sciences, SAS Institute, Cary, NC, United States

ABSTRACT

There are numerous dimensions to consider in the analysis and review of safety endpoints in clinical trials. First, a multitude of tests are regularly performed to monitor the well-being of the patients under investigation. This may include physical examinations, monitoring of vital signs and electrocardiograms, and frequent laboratory assessments. Spontaneously-occurring events of significance include deaths, study discontinuations, hospitalizations for disease progression, or other adverse events. Second, the temporal relationship of the various outcomes to one another may provide insight as to the circumstances leading to safety issues, or may highlight individuals requiring intervention. Finally, demographic characteristics, medical history and knowledge of concomitant therapies and substance use are needed to appropriately intervene without causing additional harm. Ideally, experience in the therapeutic area or within a particular drug class should inform the clinical team of safety concerns likely to arise. However, individuals studying orphan diseases or novel compounds may have little information to limit the scope of their investigation.

Summarizing this data deluge to highlight important safety concerns has traditionally been a difficult task. To gain a complete picture of the subject, data from several domains need to be combined in a clear and meaningful way to highlight any irregularities. These attempts are often cumbersome and difficult to customize, and typically require additional programming resources to manipulate and present the data. Rarely would such tools be available early in the lifetime of the trial. We highlight two subject-level views from JMP® Clinical software that can be invaluable for efficiently and comprehensively assessing patient safety: patient profiles and adverse event narratives. Automated generation of both is greatly facilitated by the Clinical Data Interchange Standards Consortium (CDISC) standard.

INTRODUCTION

Since its inception in 1997, the Clinical Data Interchange Standards Consortium (CDISC) has developed standards for data models, study designs and supporting clinical trial documents. Data standards such as the CDISC Study Data Tabulation Model (SDTM) define the specific files where individual data are located, how records stored in different file domains are related to one another, the requirements for formats and labels, and the requirements for variable inclusion for the purposes of regulatory submission. These standards enable the development of new and powerful software that facilitates analysis, review and reporting to provide greater insight into the safety of therapies under study.

Traditionally, the varying quality and standards of data submitted to the U.S. Food and Drug Administration (FDA) required new or revised tools to programmatically review each data submission, with the expertise to develop and implement these tools limited to a few key individuals. This forced many reviewers to rely on the tables and listings submitted by the sponsor. However, SDTM and other data standards make it possible for regulatory agencies to maintain a set of tools to efficiently review submissions from a multitude of pharmaceutical and medical device companies. See Zink & Mann (2012) for a summary of the benefits of CDISC standards to regulatory agencies, pharmaceutical companies and contract research organizations.

Safety analyses often involve numerous endpoints, and the temporal relationship of the various outcomes to one another provides insight into the circumstances leading to safety issues, or highlights individuals requiring intervention. To gain a complete picture of the subject, data from several domains need to be combined in a clear and meaningful way to highlight any irregularities. Too often, attempts to generate these summaries are cumbersome, difficult to customize, or require additional programming resources to manipulate and present the data. Rarely would such tools be available early in the lifetime of the trial.

Below we describe two drill-down views available in JMP® Clinical software that streamline the review of data from clinical trials through utilization of CDISC standards. These views are typically generated after statistically screening events and findings and provide critical details at the subject level. Data from a clinical trial of aneurysmal subarachnoid hemorrhage (Haley et al., 1993) provides illustration in the example figures.

PATIENT PROFILES

Figure 1 presents a patient profile for a subject experiencing an aneurysmal subarachnoid hemorrhage from a clinical trial of nicardipine (Haley et al., 1993). Data are presented by CDISC domain along the y-axis, while time is presented using Study Day along the x-axis. In a single panel, the reviewer has access to demographic

characteristics, medical history, study drug exposure, visit attendance and important disposition events. The duration of adverse events and concomitant medications are presented so that the reviewer understands which important events overlap with one another, as well as the temporal relationships with medications which either contributed to or have been used to treat each event. For adverse events, color indicates severity while symbols convey whether events meet serious adverse event (SAE) criteria.

Data from CDISC Findings domains (such as laboratory test results, ECGs and vital signs) are presented to highlight data outliers or laboratory abnormalities (high or low relative to the reference range). Symbol colors (blue to red) indicate where on the data spectrum values for an individual subject reside, with the scales corresponding to the 10th and 90th percentiles of all data in the trial. Findings measurements are grouped and sorted into functional classes for easier interpretation. Data values are viewable directly by hovering the cursor over individual symbols, with special symbols highlighting values considered to be outliers (outside of 1.5 times the Interquartile Range, the distance from the 1st to 3rd quartiles).

Data from all CDISC domains are automatically presented in the profile, including any custom domains defined for Interventions, Events, or Findings classifications. However, presenting all data domains in a patient profile may not be practical. Further, certain safety concerns may limit the data that is necessary for a thorough review, or certain reviewers may have expertise limited to specific therapeutic areas. Within JMP Clinical, it is possible to customize the patient profile to view only those data of interest. Entire domains can be excluded, or if warranted, individual laboratory tests, medications or events can be selected for review. These customized profiles can be saved as templates to be applied for the current study, or at a later time for future studies with similar endpoints. Templates are applied using a drop down menu, and they can be further refined and updated over time as data changes or additional tests, events or medications become available. Profiles can be exported as PDF or RTF files for distribution among the research group.

During the course of a safety critique, certain notable findings about a subject may require comment. Within JMP Clinical it is possible to add and save notes at the subject level for later review, such as a potential reminder to highlight certain abnormalities within the clinical study report. Further, a Review Status flag can be used to indicate which subjects have data that have yet to be studied in detail. The Review Status Distribution analytical process can be used to identify which subjects still require review, and profiles for these individuals can be generated directly from the summary display.

Additional summary reports are available from the patient profile dashboard. If available, a report of physician comments (based on the SDTM CO domain) can be generated for selected subjects. These comments often contain useful insights about study subjects that the clinician may have found difficult to summarize elsewhere within the case report form.

Adverse Event (AE) narratives are available from the patient profile**,** and summarize the details surrounding each event. When generated from the patient profile, the AE Narrative analytical process generates an editable summary report of all adverse events for selected subjects at the subject level. AE Narratives are described in greater detail in the next section.

ADVERSE EVENT NARRATIVES

The analysis of adverse events (AEs) is an important component for understanding the safety profile of any new therapy under investigation. An AE is any unfavorable experience that occurs during the course of a clinical trial that may or may not be due to the particular treatment being administered. Of particular importance, serious adverse events (SAEs) are AEs that result in death, are life threatening, require inpatient hospitalization or prolongation of hospitalization, result in disability or permanent damage, or are congenital anomalies or birth defects.

When a clinical trial subject has an SAE or other significant adverse event, such as those leading to the discontinuation of the study, a narrative is written for the clinical study report. These AE narratives summarize the details surrounding the event to enable understanding of the circumstances that may have led to the occurrence and its subsequent management. Such details may include the dose of study drug at the time of the event, the duration of the dose prior to the event, concomitant medications taken at the time of the event and used to treat the event, and other AEs that may have recently occurred. Other details include demography, medical history, lab results, the severity of the event and whether the event was related to study medication.

Narratives are written from the original SAE report faxed from the clinical site in combination with data listings that are generated as part of the study deliverables. Information contained in the typical narrative requires the medical writer to review these many disparate data sources. This is time consuming and, true for any manual effort, can require additional review and quality control. Too often, these narratives are written when the full data becomes available, which may become a rate-limiting factor in completing the study report.

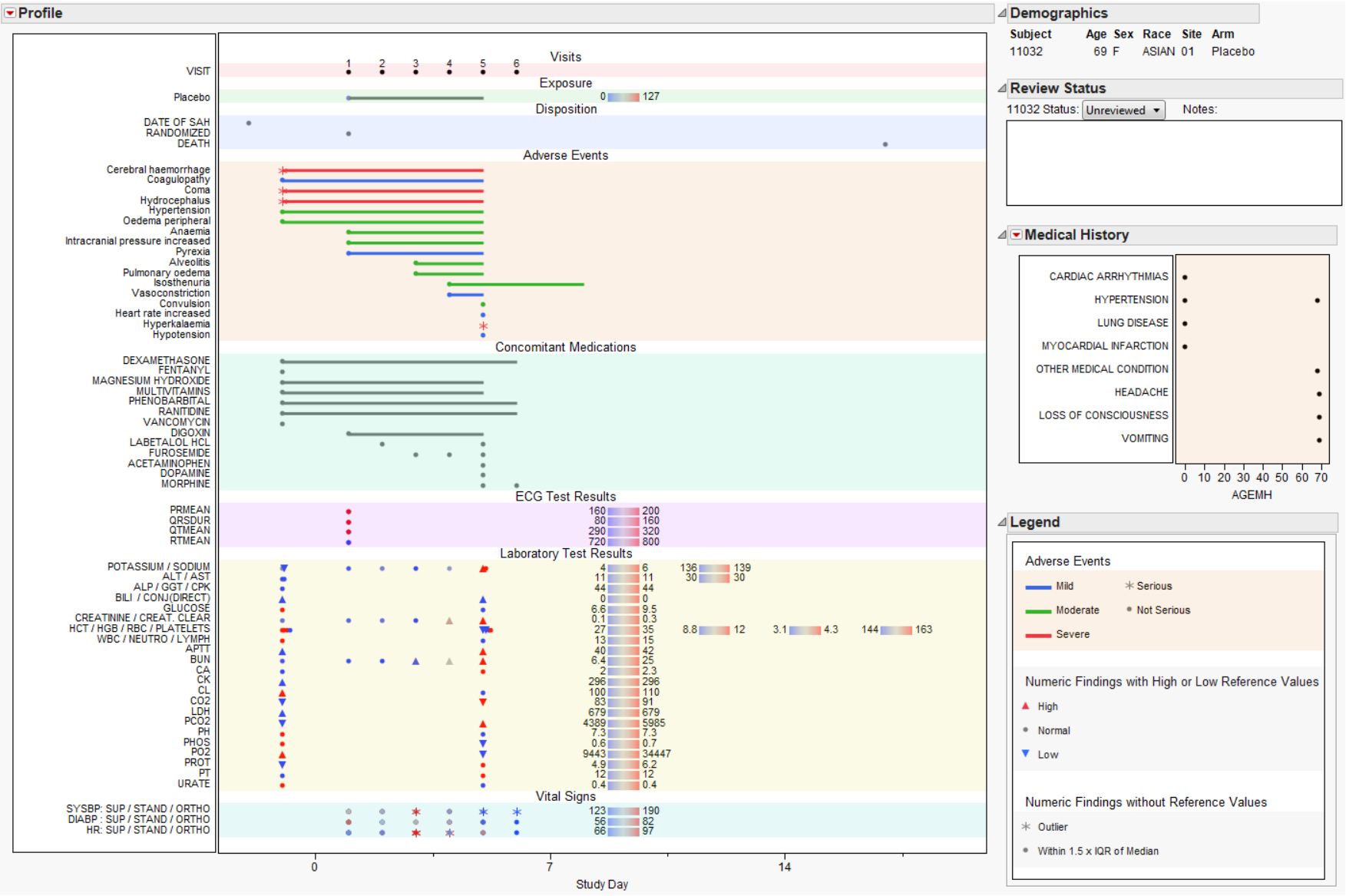

Figure 1. Sample Patient Profile

Subject: 101004
Randomized Arm: NIC .15
Investigator: 101A
Drug and Dose at Event Onset: 30 mg/h of NIC .15

Serious Adverse Event (coded term [reported term]): COMA [COMA]

Subject 101004 was a 48-year-old white female. Her medical history included focal deficit (1988), headache (1988), loss of consciousness (1988), vomiting (1988), other medical condition (1977) and allergies (start date unknown). She began dosing with 30 mg/h of nic .15 on 28JAN1988 (Day 1). The subject discontinued the trial on 31JAN1988 (Day 4) due to death.

On 28JAN1988 (Day 1) the subject experienced a coma (severe) which was considered a serious adverse event (SAE). Though the event was considered serious, no reasons were provided on the case report form. At the time of the event, the subject was taking 30 mg/h of nic .15 and had been at this dose for 1 day. The SAE occurred on the first day of dosing with any study medication. Trial medication had an action of drug withdrawn as a result of the event. It is not known from the case report form if therapeutic measures were administered to treat the event.

Adverse events that occurred within a ±3-day window of the onset of the SAE included brain oedema (mild), hydrocephalus (severe), hyperglycaemia (mild), hypotension (severe), intracranial pressure increased (severe), subarachnoid haemorrhage (severe) and vasoconstriction (severe). Concomitant medications taken at the onset of the SAE included docusate sodium (stool softner), phenobarbital (sedative), potassium supplements (fluids) and ranitidine (decrease acidity).

The subject had the following abnormal lab tests at baseline: high creatine kinase [411 U/L, range = (15 - 195)], high chloride [112 mmol/L, range = (97 - 107)], high leukocytes [21 U/L, range = (3 - 20)], low partial pressure carbon dioxide [2394 Pa, range = (4655 - 5985)] and high partial pressure oxygen [31654 Pa, range = (9975 - 13965)]. The subject had no on-study lab tests with results different than baseline on or prior to the start day of the event. On the closest lab test day subsequent to the start of the event , the subject had the following on-study lab tests with results different than baseline: low blood urea nitrogen [2.142 mmol/L, range = (2.499 - 7.497) , BL = normal], low carbon dioxide [91.308 mg/dL, range = (100.004 - 130.44) , BL = normal], low creatinine [0.053040001768 mmol/L, range = (0.05746 - 0.10608) , BL = normal] and normal leukocytes [11 U/L, range = (3 - 20) , BL = high].

The investigator considered the AE to be related to study medication. The final outcome of the event was reported as recovered/resolved on 31JAN1988 (Day 4).

Figure 2. Sample Adverse Event Narrative

JMP Clinical generates AE narratives that are written to an RTF file, which can be viewed and edited in Microsoft Word or other word-processing software. For selected adverse events, the program summarizes the contents of numerous CDISC data sets including the Analysis Data Model (ADaM) subject-level data set ADSL and the following SDTM domains: demographics (DM), adverse events (AE), medical history (MH), disposition (DS), concomitant medications (CM), exposure (EX), ECG test results (EG, not shown), laboratory test results (LB) and vital signs (VS, not shown). By default using the AE Narrative analytical process, each event is written as a separate narrative, though options exist to generate narratives at the subject-level (the default when generated from the Patient Profiler). Once generated, the narratives can be further nuanced by the medical writer or clinician to include additional details from the SAE report or additional study domains.

Various checkboxes allow the user to easily subset to events of interest, such as those events that meet SAE criteria, or those events that occur on or after the first day of dosing (so-called treatment-emergent events). SAS WHERE Statements allow additional flexibility to generate narratives for specific study subjects or events that meet specific criteria.

Numerous options allow the user to tailor narrative content to specific needs. For example, it is possible to refer to trial participants as subjects or patients, or the analyst may choose to present investigator-reported or standardized names for medications and medical history. Further, indications for concomitant medications can be included in the text, or the number of days surrounding event onset for the reporting of other related events that may have occurred within this time window may be modified (default is ± 3 days around the event of interest).

Additionally, JMP Clinical makes it possible to summarize data from several findings domains within the narrative. These domains include ECG test results (EG, not shown), laboratory test results (LB) and vital signs (VS, not shown). A user can choose whether to summarize baseline results and abnormalities, present the closest results that occur prior to or the same day as the event, or present the closest results that occur subsequent to the event. Findings reporting can be tailored using SAS WHERE Statements to subset to those tests or results that are of particular interest.

Of the 902 subjects treated with nicardipine or placebo, 310 subjects experienced 683 SAEs (Haley et al., 1993). Using the AE Narrative analytical process, 683 narratives are generated in less than one minute. A sample narrative that includes laboratory measurements is presented in **Figure 2**.

CONCLUSIONS

CDISC standards make it possible to develop flexible analysis and reporting tools. Understanding data formats, requirements and relationships within and between domains is critical for the development of easy-to-use and

powerful software. Further, the automatic generation of patient profiles and adverse event narratives illustrate the power and benefits of adopting CDISC standards to the masses, even among skeptics to the CDISC mission.

The Patient Profile and AE Narrative features of JMP Clinical quickly combine data from across multiple domains and highlight any irregularities to provide a more complete picture of patient safety. An advantage of JMP Clinical is that the output generated can be used to supplement clinical study reports, which can significantly hasten the writing process and reduce time spent in quality control.

REFERENCES

- Haley, EC, Kassell, NF & Torner, JC. 1993. "A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage." *Journal of Neurosurgery* 78: 537-47.
- Zink, RC & Mann, G. 2012. "On the importance of a single data standard." *Drug Information Journal* 46: 362-7.

RECOMMENDED READING

- CDISC SDTM Implementation Guide at http://www.cdisc.org/

CONTACT INFORMATION

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

Name: Richard C. Zink
Enterprise: SAS Institute, Inc.
Address: SAS Campus Drive
City, State ZIP: Cary, NC 27513
E-mail: richard.zink@jmp.com
Web: http://www.jmp.com/lifesciences-resources/

SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates USA registration.

Other brand and product names are trademarks of their respective companies.