

Efficient Safety Assessment in Clinical Trials using the Computer-generated AE Narratives of JMP® Clinical

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ABSTRACT

ICH Guideline E3 recommends that sponsors provide written narratives describing each death, serious adverse event (SAE), and other significant AE of special interest to the disease under investigation. Narratives summarize the details surrounding these events to enable understanding of the circumstances that may have led to the occurrence and its subsequent management and outcome. Ultimately, narratives may shed light on factors associated with severe events, or describe effective means for managing patients for appropriate recovery. Narratives are written from the original SAE report in combination with summary tables and 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 sources. This is time consuming and often requires additional review and quality control. Too often, narratives may not be composed until the full data for a patient becomes available. This may cause narratives to become a rate-limiting factor in completing the CSR. Further, while changes to the study database are easily reflected in statistical tables by re-running programs, changes to narratives occur manually which may result in incorrect reporting. Finally, patients in therapeutic areas for severe conditions likely experience numerous SAEs; the volume of events to summarize can consume a great deal of resources. In this talk, we describe how AE narratives can be generated directly from study data sets using JMP Clinical. Further, we discuss the importance of standards and templates for narrative text, as well as utilizing CDISC data submission standards for narrative content.

INTRODUCTION

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 that which is necessary to establish efficacy and safety, reduce development times, and streamline the regulatory review process. Despite the intent of this guidance, there has been a great deal of recent interest in Guideline E6: Good Clinical Practice, particularly in regards to the excessive resources devoted to clinical monitoring [1]. In retrospect, traditional monitoring practices, including 100% source data verification and frequent visits to clinical sites, can be viewed as a mis- or over-interpretation of these guidelines. Currently, industry is moving towards risk-based approaches to assess data integrity.

One resource-intensive part of the ICH guidance has yet to receive the same level of scrutiny as Guideline E6 for clinical monitoring. Specifically, Section 12.3.2 of Guideline E3: Structure and Content of Clinical Study Reports recommends that sponsors provide written narratives describing each death, serious adverse event (SAE), and other significant AEs of special interest to the disease under investigation [2]. Narratives summarize the details surrounding important events to enable understanding of the circumstances that may have led to the occurrence and its subsequent management and outcome. Ultimately, these narratives may shed light on factors associated with severe events, or describe effective means for managing patients for appropriate recovery.

Narratives are written from the original SAE report in combination with summary tables and listings that are generated as part of the study deliverables. Other source files may include CIOMS, MedWatch and Data Clarification forms. Information that must be 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, narratives may not be composed until the full data becomes available, which may cause them to become a rate-limiting factor in completing the study report. Further, while changes to the study database are easily reflected in tables, listings and figures by re-running statistical programs, changes to narratives have to occur manually and may result in incorrect reporting. Finally, patients in therapeutic areas for severe conditions such as oncology, likely experience numerous SAEs or other significant events. The volume of events to summarize, even as patients complete the trial, can consume a great deal of resources available for the trial.

The goal of this paper is to improve upon the current practice of generating adverse event narratives for understanding patient safety in clinical trials. This includes the development of standards and templates for narrative text, as well as utilizing current data submission standards in developing narratives. In addition, we describe how AE narratives can be computer-generated directly from study data sets using JMP® Clinical to accelerate the medical writing process, and enable new possibilities for quality control. Finally, we argue that computer-generated narratives provide a more complete picture of the subject details surrounding SAEs and other events of interest, which in turn

provides a better understanding of patient risk.

METHODS

DATA

The 902 treated patients in the nicardipine clinical trial experienced a total of 6471 adverse events, 5963 of which occurred on or after the first day of dosing [3]. Of these 902 patients treated with either nicardipine or placebo, 310 patients experienced a total of 683 SAEs. Nicardipine has the following domains: adverse events (AE), concomitant medications (CM), demographics (DM), disposition (DS), ECG test results (EG), study medication exposure (EX), laboratory test results (LB), medical history (MH), study visits (SV) and vital signs (VS).

SAS® CODE

Narratives are written using clinical trial data sets adhering to standards developed by the Clinical Data Interchange Standards Consortium (CDISC). CDISC is a global, non-profit organization started in 1997. It develops standards for data models (SDTM, ADaM), study design and support of clinical trial documents [4,5]. The FDA encourages their use and implementation for the submission of new drug applications (NDAs). CDISC data standards can be useful for statistics, programming and data management. For example, the JMP Clinical software system provides easy to use, interactive displays for many facets of clinical trial analysis and reporting.

A SAS program (approximately 3000 lines in length) available as part of JMP Clinical generates AE narratives directly from CDISC data sets that are written to a rich text format (RTF) file. This file type can be viewed and edited in Microsoft Word or other word-processing packages. The program summarizes the contents of the ADaM subject-level analysis data set (ADSL) and several SDTM domains: adverse events (AE), concomitant medications (CM), demographics (DM), disposition (DS), study medication exposure (EX), healthcare encounters (HO, not shown below), medical history (MH) and up to three findings domains, typically ECG test results (EG, not shown below), laboratory test results (LB) and vital signs (VS, not shown below). By default, each event is written as a separate narrative, though templates (described below) can support narratives at the patient level. Extensive logic is in place to modify text strings based on the presence or absence of certain information.

Study Identifier	Domain Abbreviation	Unique Subject Identifier	Sequence Number	Lab Test or Examination Short Name	Lab Test or Examination Name	Numeric Result/Finding in Standard Units	Standard Units	Reference Range Lower Limit-Std Units	Reference Range Upper Limit-Std Units	Reference Range Indicator	Date/Time of Specimen Collection
NICSAH1	LB	101004	7	CK	Creatine Kinase	411	U/L	15	195	HIGH	1988-01-27T13:04:00
NICSAH1	LB	101004	8	CL	Chloride	112	mmol/L	97	107	HIGH	1988-01-27T13:04:00
NICSAH1	LB	101004	16	PCO2	Partial Pressure Carbon Dioxide	3990	Pa	4655	5985	LOW	1988-01-27T13:04:00
NICSAH1	LB	101004	20	PO2	Partial Pressure Oxygen	15295	Pa	9975	13965	HIGH	1988-01-27T13:04:00
NICSAH1	LB	101004	25	WBC	Leukocytes	21	U/L	3	20	HIGH	1988-01-27T13:04:00
NICSAH1	LB	101004	26	PCO2	Partial Pressure Carbon Dioxide	4522	Pa	4655	5985	LOW	1988-01-28T16:46:00
NICSAH1	LB	101004	27	PCO2	Partial Pressure Carbon Dioxide	2394	Pa	4655	5985	LOW	1988-01-28T19:34:00
NICSAH1	LB	101004	30	PO2	Partial Pressure Oxygen	14630	Pa	9975	13965	HIGH	1988-01-28T16:46:00
NICSAH1	LB	101004	31	PO2	Partial Pressure Oxygen	31654	Pa	9975	13965	HIGH	1988-01-28T19:34:00
NICSAH1	LB	101004	33	BUN	Blood Urea Nitrogen	2.142	mmol/L	2.499	7.497	LOW	1988-01-29T02:55:00
NICSAH1	LB	101004	34	CL	Chloride	113	mmol/L	97	107	HIGH	1988-01-29T02:55:00
NICSAH1	LB	101004	35	CO2	Carbon Dioxide	91.308	mg/dL	100.004	130.44	LOW	1988-01-29T02:55:00
NICSAH1	LB	101004	36	CREAT	Creatinine	0.0530400018	mmol/L	0.05746	0.10608	LOW	1988-01-29T02:55:00
NICSAH1	LB	101004	41	PCO2	Partial Pressure Carbon Dioxide	3724	Pa	4655	5985	LOW	1988-01-29T02:55:00
NICSAH1	LB	101004	44	PO2	Partial Pressure Oxygen	23694	Pa	9975	13965	HIGH	1988-01-29T02:55:00
NICSAH1	LB	101004	50	CL	Chloride	111	mmol/L	97	107	HIGH	1988-01-30T02:32:00
NICSAH1	LB	101004	51	CO2	Carbon Dioxide	82.612	mg/dL	100.004	130.44	LOW	1988-01-30T02:32:00
NICSAH1	LB	101004	56	PCO2	Partial Pressure Carbon Dioxide	3325	Pa	4655	5985	LOW	1988-01-30T02:32:00
NICSAH1	LB	101004	59	PO2	Partial Pressure Oxygen	20216	Pa	9975	13965	HIGH	1988-01-30T02:32:00
NICSAH1	LB	101004	62	SODIUM	Sodium	133	mmol/L	136	144	LOW	1988-01-30T02:32:00

Figure 1. Abnormal laboratory records for subject 101004 from the LB domain

For building the narrative, most parts of the program operate in a similar manner. For example, Figure 1 contains the laboratory records that exhibited an abnormality from the CDISC SDTM LB domain for subject 101004, with lab results either below the lower limit of normal (LLN) or above the upper limit of normal (ULN). The trick is to associate these data with each adverse event that a subject may experience. For individuals familiar with SAS, a merge within a data step will not suffice since the unique subject identifier (USUBJID) is the only criteria available to match records between the AE and LB domain. Performing a merge using USUBJID as a by variable would associate the first lab record to the first event, the second lab record to the second event and so on resulting in an improper merge -- every LB record should be considered against every adverse event to determine which lab records meet the appropriate criteria in terms of their timing relative to the event (as well as other characteristics).

To perform the appropriate join between the AE and LB domains, our macro makes use of the structured query language (SQL) through SAS proc sql to join each record of interest from the LB domain with each record of AE where USUBJID matches (referred to as an outer join).

```
proc sql;
  create table AELB(drop = usubjid1 usubjid2) as
  select coalesce(AE.USUBJID1, LB. USUBJID2)as usubjid, AE.*, LB.*
  from AE(rename=(USUBJID=USUBJID1)) left join LB(rename=( USUBJID=USUBJID2))
  on AE.USUBJID1 = LB. USUBJID2
  order by USUBJID, AEDECOD, AESTDTC, LBTEST, LBDMTC;
quit;
```

For example, if the AE and LB domains contained 4 and 20 records, respectively, for subject 101004, the resulting data set AELB would contain $4 \times 20 = 80$ records. This data set could be further reduced to records of interest, say to those laboratory tests that occurred just prior or subsequent to the adverse event, which would require comparing the date field of the laboratory tests to the date field of the adverse events.

Once the appropriate records are identified, a text string can be constructed from the available SDTM variables. For example, the text string “low blood urea nitrogen [2.142 mmol/L, range = (2.499 - 7.497)]” available in the sample narrative in Figure 7 can be created from row 10 of Figure 1 by concatenating the contents of 6 variables along with some additional characters to achieve the appropriate formatting. Next, these text strings are accumulated for all relevant LB records for each event, resulting in a single text string that represents a list of all lab tests meeting the appropriate criteria, such as those that occurred subsequent to the event with an outcome that differed from baseline (which would first require defining the baseline records).

While the above description details the algorithm for laboratory measurements, similar approaches are taken to summarize medical history terms, study or concomitant medications, and even other adverse events that occur within a close proximity to the events of interest. The goal is to use as much of the data available in the SDTM domains to write the narrative. Certain data are obviously required for the macro to work, and these data often fall in line with the domain requirements of CDISC. However, some variables are optional and in these cases, the code alters the text appropriately. For example, if lab test units were not provided in the LB domain (usually a bad idea), the generated string would have been “low blood urea nitrogen [2.142, range = (2.499 - 7.497)]”. In this scenario, the appropriate units can be added later on as part of the manual writing process.

Knowledge of the contents of each CDISC variable is important to consider so that the narrative can be appropriately written without various codes more appropriate for programming entering the text. The SDTM standards are very clear about which variables contain codes and which contain text. Some coded fields may have straightforward values that can be translated. For example, yes/no response variables are typically captured as Y or N and can be written as “yes” or “no” in the narrative; gender is coded as M, F, U or UN for “male”, “female”, “unknown” or “undifferentiated”. Other SDTM fields rely on controlled terminology which can suggest appropriate sentence structure. For example, AE outcome (AEOUT) has the controlled terminology of FATAL, NOT RECOVERED/NOT RESOLVED, RECOVERED/RESOLVED, RECOVERED/RESOLVED WITH SEQUELAE, RECOVERING/RESOLVING and UNKNOWN.

The required variables in CDISC are actually quite minimal. Though some information may be provided using SDTM variables (e.g., baseline or study day), there is no guarantee that these variables will be available for a given study. However, the information of interest can often be derived using variables that are typically more common or required. The determination of baseline values for each test performed (i.e. the last values prior to dosing), or the calculation of study day from the reference date in DM (to provide an idea of when different events occur relative to the start of the study) are examples where data derivations can provide a more informative AE narrative.

Once text strings containing the appropriate data are built, the full narrative is generated using Velocity Templates.

VELOCITY TEMPLATES

The narrative document generation utilizes the Velocity Template Engine, an open source project which is hosted by the Apache Software Foundation. The Velocity engine enables a clean separation between the presentation and organization of content and the data being presented. As such, an array of templates may be created with each template tailoring the narrative in a variety of layouts, styles and/or content. The templates are read by JMP Clinical at run-time and available for selection when creating the final document. The result of this design enables very customizable output which may be altered and/or extended as appropriate for different types of studies or specific regulatory requests.

The template language itself has a simple syntax that not only supports substituting values for variables, but additionally supports conditional logic, looping constructs, and string manipulation and arithmetic functions. The full details of the template syntax are available from the Apache Foundation [6].

Specifically for JMP Clinical, the narrative generation process starts by first generating a table of metadata values and a table of the adverse event data. The selected template is then merged with these data sets to produce the narrative document. The template content is a mixture of the static sentence information and snippets of substitution variables and logic for controlling which sentences are displayed, the order in which they are displayed, and which specific words/phrases/tables/etc. should make up the narrative. This enables templates to be created that support any language and still adhere to the appropriate grammar rules of that language.

JMP CLINICAL DIALOG OPTIONS

Below, we detail the options available in the dialog of the Adverse Events Narrative report in JMP Clinical 6.0.

General (Figure 2)

1. **AE Narrative Template** allows the user to choose a specific narrative template. A template includes non-CDISC domain text to include in the narrative, rules for how to print information obtained from the CDISC domains, as well as logic for printing specific sentences when certain conditions are met. The **Default** template shipped with JMP Clinical is used for the narrative presented in Figure 7.
2. Check **Include serious adverse events only** to only print narratives for SAEs. When selected, works with the intersection of **Event Type** and **Filter to Include Adverse Events** (described below)
3. **Event Type** works with the intersection of **Event Type** and **Filter to Include Adverse Events** and is one of
 - **All event types** includes all events regardless of timing with dosing
 - **Pre treatment events** includes events that occur prior to the first dose of study drug
 - **Treatment emergent events** includes events that occur on or after the first dose of study drug
 - **On treatment events** includes events that occur on or after the first dose of study drug and at or before the last dose of drug (plus the offset specified in **Offset for End of Dosing**)
 - **Off treatment follow up events** includes events that occur after the last dose of drug (plus the offset specified in **Offset for End of Dosing**)
4. **Offset for End of Dosing** allows for changing the treatment phase duration for drugs with long half-lives
5. **Number of days around Adverse Event start date for reported related events** will summarize other events that occur within a window around the event being summarized. The default is ± 3 days
6. Check **Include subject-level table of contents** to include a table of contents with entries for each USUBJID (or SUBJID) to easily navigate the resulting RTF file

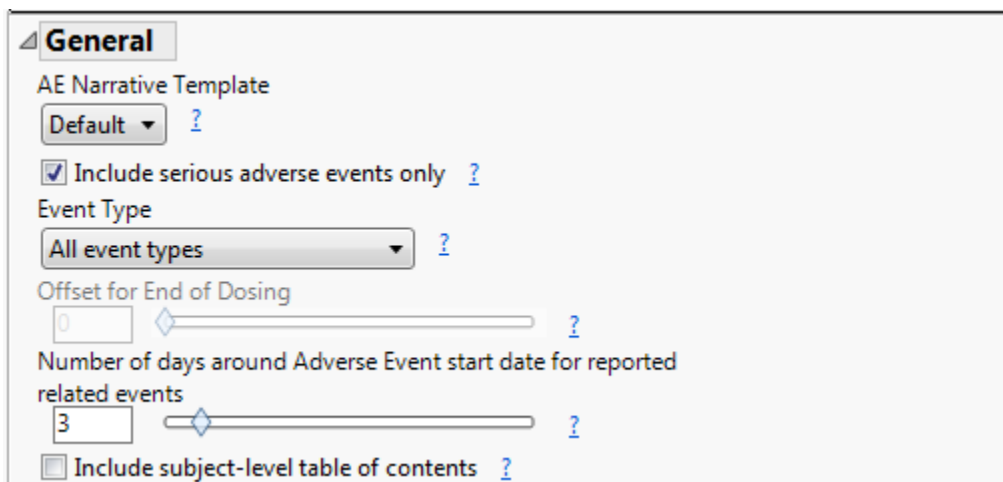


Figure 2. General Section in JMP Clinical Adverse Events Narrative Dialog

Filters (Figure 3)

1. **Subject Filter** will display any filters created by the user while exploring their study in JMP Clinical. Each filter is a list of patients summarized by USUBJID. Selecting a filter will limit summarized events to those experienced by patients included in the filter. When a filter is applied, it works with the intersection of **Additional Filter to Include Subjects** and **Select Analysis Population**
2. **Additional Filter to Include Subjects** is in the form of a SAS *where* statement and subsets patients according to variables available in ADSL (or DM, if not available). Works with the intersection of **Subject Filter** and **Select Analysis Population**
3. **Filter to Include Adverse Events** is in the form of a SAS *where* statement and subsets events using variables within the ADAE or AE domain. When provided, works with the intersection of **Event Type** and **Include serious adverse events only**
4. **Filter to Choose Appropriate Disposition Event for Completion Status** is in the form of a SAS *where* statement to appropriately select records from the DS domain to determine whether a patient completed or discontinued the trial. If missing, the program chooses the most recent DS record for each subject where DSEPOCH = "TREATMENT" (if available) and DSCAT = "DISPOSITION EVENT" (if available)
5. **Select Analysis Population** works with the intersection of **Subject Filter** and **Additional Filter to Include Subjects**. All choices (save the first two below) are determined according to the population indicators available in ADSL (or DM, if not available)
 - All Subjects Excluding Screen Failures
 - All Subjects
 - Full Analysis Set
 - Intent-to-Treat
 - Per-Protocol
 - Completers
 - Randomized
 - Enrolled

The screenshot shows a dialog box titled "Filters" with a collapse icon on the left. It contains the following elements:

- Subject Filter:** A dropdown menu with a question mark icon to its right.
- Additional Filter to Include Subjects:** A text input field starting with "where", a "Clear" button, and a question mark icon.
- Filter to Include Adverse Events:** A text input field starting with "where", a "Clear" button, and a question mark icon.
- Filter to Choose Appropriate Disposition Event for Completion Status:** A text input field starting with "where", a "Clear" button, and a question mark icon.
- Select Analysis Population:** A section with the instruction "Select the population to include in the analysis" and a dropdown menu currently showing "Safety", with a question mark icon to its right.

Figure 3. Filters in JMP Clinical Adverse Events Narrative Dialog

Findings A (Figure 4). Similar options are available for **Findings B** and **Findings C** which are not shown

1. Check **Include a findings domain in the narrative** to include paragraphs for the domain listed in **Findings domain to include**
2. **Use result or finding in**
 - **Original units** will summarize the values available in xx.xxORRES
 - **Standard units** will summarize the values available in xx.xxSTRESN first using xx.xxSTRESC when xx.xxSTRESN is missing
3. Check **Round numeric findings results** to round values to a precision specified in **Number of decimals for numeric findings** when the number of decimal places is greater than specified. Otherwise, values are printed with all digits
4. **Include summary of baseline findings** will print baseline results for all xx.xxTEST values for non-LB findings domains. For laboratory results (LB), only results that are abnormal (LB.LBNRIND not in ("NORMAL", "N", "NORM")) will be printed
5. **Include closest on-study findings test dates**
 - **Prior to or same day of event** includes findings that occur just prior to an event to see if these findings results may have been predictive of the event occurring
 - **Subsequent to event** includes findings that occur just after an event to see if these unusual findings results resolved after the event
 - **Both** includes findings before and after the event as described above
 - **Neither** prevents any on-study findings from being printed
6. For laboratory results (LB), **Include on-study lab tests where reference range indicator is**
 - **Abnormal with a normal baseline** prints on-study labs that got worse from baseline
 - **Abnormal regardless of baseline** prints all abnormal on-study lab results
 - **Different compared to baseline** prints all abnormal on-study lab results when they were normal at baseline, or prints normal on-study lab results when they were abnormal at baseline. Will also print on-study lab results when the direction of the abnormality is different from baseline (e.g., LOW versus HIGH)
7. **Refer to findings tests using** will print either **Test Code** (xx.xxTESTCD) or **Test Name** (xx.xxTEST) in the narrative text
8. **Filter to include findings tests** is in the form of a SAS *where* statement and subsets findings using variables within the **Findings domain to include**. For example, to only present laboratory results related to liver enzymes, specify LBTESTCD in ("AST","ALT","BILI","ASP").

Healthcare Encounters (Figure 5).

1. Check **Include healthcare encounters (HO) in the narrative** to include paragraphs for the HO domain
2. **Healthcare encounters are reported using** will print either **Reported term for the healthcare encounter** (HO.HOTERM) or the **Dictionary derived term** (HO.HODECOD) in the narrative text
3. **Report the following healthcare encounters** works with the intersection of **Filter to include healthcare encounters**
 - **All** will include all healthcare encounters regardless of timing to the summarized event
 - **Start within a window around the AE** include all healthcare encounters that occur within a window around the event being summarized. The default is ± 3 days which is specified in **Report healthcare encounters this many days around Adverse Event start date**
4. **Filter to include healthcare encounters** is in the form of a SAS *where* statement and subsets records using variables within the ADHO or HO domain. When provided, works with the intersection of **Report the following healthcare encounters**

Options (Figure 6).

1. Check **Use subject identifier for study in lieu of unique subject identifier, if available** to write narratives using DM.SUBJID in lieu of DM.USUBJID
2. Check **Include exposure (EX) in the narrative** to include paragraphs for the EX domain
3. Check **Treatment end date is equivalent to the start date** when EX.EXENDTC is not available. Both EX.EXSTDTC and EX.EXENDTC are required to summarize the EX domain in the narrative
4. Check **All study treatments are to be taken at least once per day** when true. This tailors narrative text to describe whether the event happens during a dosing interruption or how long the patient had been at the particular dose of the study medication when the event occurred
5. Check **A 0 dose for placebo or vehicle indicates a dose interruption** when true. Used when non-zero doses of placebo are provided to indicate that a subject did in fact take placebo (compared to the case when dose is always 0 since no study drug is available)
6. Specify **Number of days prior to Adverse Event start date for reporting concomitant medications** to include medications within a window prior to the event. A value of 0 includes medications that were taken the same day as the event onset. A value of X includes concomitant medications that were taken at the onset of the AE and up to X days prior to AE onset.
7. **Concomitant medications are reported using** will print either **Reported name of drug** (CM.CMTRT) or the **Standardized medication name** (CM.CMDECOD) in the narrative text
8. Check **Include concomitant medication indication in narrative** to include indication (CM.CMINDC) in the narrative text
9. **Medical history terms are reported using** will print either **Reported term for the medical history** (HO.HOTERM) or the **Dictionary derived term** (HO.HODECOD) in the narrative text

Findings A

Include a findings domain in the narrative ?

Findings domain to include
 ?

Use result or finding in: ?

Original units
 Standard units

Round numeric findings results ?

Number of decimals for numeric findings
 ?

Include summary of baseline findings ?

Include closest on-study findings test dates: ?

Prior to or same day of event
 Subsequent to event
 Both
 Neither

Include on-study lab tests where reference range indicator is: ?

Abnormal with a normal baseline
 Abnormal regardless of baseline
 Different compared to baseline

Refer to findings tests using: ?

Test code
 Test name

Filter to include findings tests
 where ?

Figure 4. Findings A in JMP Clinical Adverse Events Narrative Dialog

Healthcare Encounters

Include healthcare encounters (HO) in the narrative ?

Healthcare encounters are reported using: ?

Reported term for the healthcare encounter

Dictionary derived term

Report the following healthcare encounters: ?

All

Start within a window around the AE

Report healthcare encounters this many days around Adverse Event start date

3 ?

Filter to include healthcare encounters where ?

Figure 5. Healthcare Encounters in JMP Clinical Adverse Events Narrative Dialog

Options

Use subject identifier for study in lieu of unique subject identifier, if available ?

Exposure

Include exposure (EX) in the narrative ?

Treatment end date is equivalent to the start date ?

All study treatments are to be taken at least once per day ?

A 0 dose for placebo or vehicle indicates a dose interruption ?

Concomitant Medications

Number of days prior to Adverse Event start date for reporting concomitant medications

0 ?

Concomitant medications are reported using: ?

Reported name of drug

Standardized medication name

Include concomitant medication indication in narrative ?

Medical History

Medical history terms are reported using: ?

Reported term for the medical history

Dictionary derived term

Figure 6. Options in JMP Clinical Adverse Events Narrative Dialog

RESULTS

DEFAULT NARRATIVE TEMPLATE

Here, we present an SAE narrative using investigator WHO-Drug coded terms for concomitant medications and include their indications, summarize medical history using MedDRA coded terms, and include a ± 3 day window around event onset date for reporting of additional potentially-related events that recently occurred.

Using JMP Clinical, 683 narratives for SAEs were generated in less than one minute. A sample narrative that includes laboratory measurements is presented in Figure 7. The initial paragraph provides a summary of patient demographics and medical history and describes when the subject began dosing (if applicable) and whether the subject completed the trial. The second paragraph details the event itself, describing the dose and duration of study drug at the time of the event and criterion for seriousness (if applicable). Details that describe whether study drug was interrupted and whether any medications were used to treat the event are included. Paragraph three lists any AEs that occur within a ± 3 day window as well as any concomitant medications the subject was taking on the day of the event

The fourth paragraph includes a summary of all laboratory abnormalities that occurred at baseline, providing available units and reference ranges from the LB SDTM domain. Laboratory findings that differ from baselines are summarized using the closest lab tests prior to and subsequent to the event. These paragraphs summarize baseline results and abnormalities, or present on-study findings such as the closest results that occurred prior to or on the same day as the event, or 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, for example, on laboratory tests associated with normal liver function (i.e., alanine and aspartate aminotransferase, alkaline phosphatase and bilirubin). In this way, we can gain insight into whether certain lab test results foreshadow the particular event or return to normal after the event.

While not shown in the example narrative, summary details on up to two more findings domains, such as electrocardiogram results or vital signs, can also be added to this section. In a similar fashion to laboratory tests, we can ascertain whether these findings are possibly connected to the particular event. The last paragraph in the narrative details whether the investigator found the event to be related to study medication and states the final outcome of the event.

Additional software options allow for tailored narrative content based on a user's specific needs. For example, investigator-reported or standardized names for medications and medical history can be reported, or the indication for concomitant medications can be included within the narrative text. The number of days surrounding event onset can be modified for reporting of other related events that may have occurred within this time window. Also, SAS `where` statements allow additional flexibility to generate narratives for specific study patients or events that meet specific criteria.

Subject 101004 experienced 8 adverse events, had 6 concomitant medications, 3 disposition events (including randomization, death and discontinuation), 63 laboratory results and 6 medical history terms and 1 record of uninterrupted dosing of study medication lasting one day. In our practical experience, the medical writer was provided a set of paper or pdf data listings detailing the study database (such as the lab data in Figure 1). In order to manually write the narratives for these 8 events similar to what was provided in Figure 2, the writer would need to manually identify which laboratory tests occurred at baseline by comparing the dosing and laboratory information; manually identify the temporal order of study medication dosing, the adverse event, concomitant medications and laboratory tests; and manually determine from available variables if any medications were used to treat the event or if the event may be due to a medication. This requires comparing data fields across multiple pages or files to determine the records to present, as well as retyping the information in an appropriate format or manually cutting and pasting to a separate narrative file. This is labor intensive with the potential to introduce numerous errors -- even for a subject that was on trial for 4 days. More informative data listings beyond a dump of the database would be helpful to develop narratives, but the macro takes this a step further by generating the narrative itself from the informative listings.

Subject: 101004

Randomized Arm: NIC .15

Investigator Name: 101A

Drugs and Doses on Day of Event: On Treatment

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

Subject 101004 was a 48-year-old white female. Her medical history included focal deficit associated with sah (1988), headache associated with sah (1988), loss of consciousness associated with sah (1988), vomiting associated with sah (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. The subject was on treatment when the event occurred. 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, phenobarbital, potassium supplements, and ranitidine.

The subject had the following abnormal laboratory test results at baseline: high chloride [112 mmol/L, range = (97 - 107)], high creatine kinase [411 U/L, range = (15 - 195)], 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)]. On the closest laboratory test results day on or prior to the start of the event, the subject had no on-study laboratory test results with results different than baseline. On the closest laboratory test results day subsequent to the start of the event (29JAN1988, Day 2), the subject had the following on-study laboratory test results 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 [0.053 mmol/L, range = (0.057 - 0.106), 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 event ended on 31JAN1988 (Day 4) with a final outcome of recovered/resolved.

Figure 7. Adverse Event Narrative Using Default Template

NARRATIVE TEMPLATE WITH TABLES

Selecting a different template using **AE Narrative Template** (Figure 2) generates an alternate presentation of the narrative (Figure 8). This template was designed for the purposes of this paper to illustrate how different changes can be applied to the narrative. Differences include:

1. Header presentation and information, including the addition of study ID and country and the modification of text to read “Study Phase”
2. Referring the to study participant as “patient” in lieu of “subject” throughout the narrative text
3. Presenting medical history and start date of medical history in Table 1
4. Presenting concomitant medications and indication in Table 2
5. Changing last sentence of paragraph 2 from “It is not known from the case report form if therapeutic measures were administered to treat the event” to “It is not known if any medications were used to treat the event”

DISCUSSION

For therapeutic areas, such as oncology, where multiple SAEs per subject are common, the writing process can be significantly time-consuming. Allowing a program to generate initial AE narratives can afford the medical writer or clinician additional time to focus on the science rather than spending time sifting through source data to generate narratives de novo. Their efforts may then be more focused on analyzing the scientific, clinical and statistical data to provide guidance to the team.

Computer-generated narratives provide several other additional benefits. Firstly, such narratives can reduce errors that occur through inadvertent misinterpretation or omission of study data. These potential oversights or lack of detail can be present in the original SAE form received from the study site, or they could be introduced while manually trying to piece together a narrative from the SAE report and study data listings. Secondly, less time can be spent in quality control of the narrative text. Thirdly, a more complete picture of the circumstances surrounding an SAE or other significant event can be detailed. While we have programmed some reasonable defaults into our narrative code, there is always the potential to ask more complex questions to better understand the temporal relationships of the event with medications, hospitalizations or other important study findings.

When using a program, writing can be performed in stages prior to database lock as subjects complete the study. Because the narratives are provided as RTF files, the medical writer can edit or add detail to the narrative from additional study sources. The **Compare Documents** functionality of Microsoft Word (Figure 9) may be used to compare edited narratives to those generated on the final locked database to highlight any database changes that should be incorporated into the final narratives. This step will also uncover any manually generated results that should receive additional scrutiny during the quality control process.

Finally, computer-generated AE narratives allow for new possibilities in the analysis and review of safety data. Because narratives can be generated so quickly, they can easily be provided to supplement analyses for the interim meetings of data monitoring committees (DMCs). This additional detail can allow the DMC to make quicker, more-informed decisions regarding patient safety for ongoing trials.

Study: NICSAH1**Patient: 101004****Randomized Arm: NIC .15****Investigator Name: 101A****Country: USA****Study Phase: On Treatment****Serious Adverse Event (coded term [reported term]): COMA [COMA]**

Patient 101004 was a 48-year-old white female. Her medical history is reported in Table 1. The patient discontinued the trial on 31JAN1988 (Day 4) due to death.

Table 1	
Medical History	Start Date
<i>focal deficit associated with sah</i>	1988
<i>headache associated with sah</i>	1988
<i>loss of consciousness associated with sah</i>	1988
<i>vomiting associated with sah</i>	1988
<i>other medical condition</i>	1977
<i>allergies</i>	<i>start date unknown</i>

On 28JAN1988 (Day 1) the patient 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. The patient was on treatment when the event occurred. Trial medication had an action of drug withdrawn as a result of the event. It is not known if any medications were used 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 are reported in Table 2.

Table 2	
Concomitant Medications	Indication
<i>docusate sodium</i>	<i>stool softner</i>
<i>phenobarbital</i>	<i>sedative</i>
<i>potassium supplements</i>	<i>fluids</i>
<i>ranitidine</i>	<i>decrease acidity</i>

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

Figure 8. Adverse Event Narrative Using Template with Tables

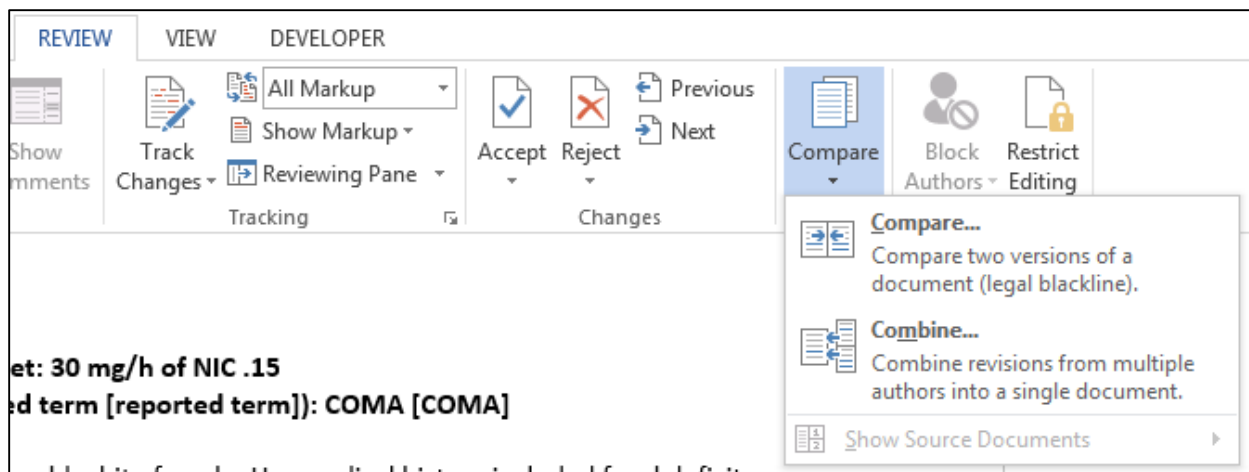


Figure 9. Compare Documents Feature of Microsoft Word

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RECOMMENDED READING

- Implementing CDISC Using SAS: An End-to-End Guide

CONTACT INFORMATION

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