

CDISC Data Standards Can Facilitate Composition of Adverse Event Narratives

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Adverse Event (AE):

- Any unfavorable and unintended sign, symptom or disease temporally associated with the drug product whether or not it is considered related.
- Includes concurrent illness or injury, worsening of pre-existing signs, symptoms or conditions and post-treatment events that occur as a consequence of participation in the clinical trial.
- Time frame: from informed consent until 30 days after last dose of study drug

Serious Adverse Event (SAE):

- Any AE at any dose, regardless of drug relationship that results in any of these outcomes:
 - Death
 - Life-threatening event
 - In-patient hospitalization or prolongation existing hospitalization
 - Persistent or significant disability/incapacity
 - A congenital anomaly/birth defect
 - An important medical event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed.

AE Narrative:

- Summarizes details surrounding the AE to enable understanding of circumstances that may have led to its occurrence, management and outcome.
- Details include:
 - Dose of study drug at time of event onset
 - Duration of exposure at time of event
 - AE severity
 - Action taken & outcome
 - Causality assessment
 - Concomitant medications taken at event onset or those used to treat the event
 - Demography
 - Medical history, labs, ECGs, vital signs
 - Other AEs in close proximity

Composition of Narratives:

- Requires medical writer to review a host of data sources (e.g. original SAE report faxed from clinical site, hospital admission/discharge reports, data listings).
- A time-consuming process.
- Requires additional review and QC.
- Often written once full data becomes available, thus a rate-limiting factor in study report completion.

- Clinical Data Interchange Standards Consortium (CDISC) is a global, non-profit organization started in 1997.
- Develops standards for data models (SDTM, ADaM), study design and support of clinical trial documents.
- FDA encourages their use and implementation for the submission of new drug applications (NDAs).
- Useful for statistics, programming and data management.
- How can they benefit the medical writer?

JMP Clinical Software System



- Provides easy-to-use, interactive displays for safety analysis
- Tools that can be used by:
 - Medical Monitors, Reviewers, Writers
 - Clinicians
 - Biostatisticians
- Relies on Standards
 - CDISC data Standard (SDTM and ADaM)
 - Standard Reporting (FDA Reviewer Guidance, ICHE3)
 - Standard Industry Visualizations
 - Standard Tools: JMP, SAS

JMP Clinical Narrative Method:

- A SAS program generates AE narratives written to an RTF file.
- Viewable and editable in Microsoft Word or other word processing software.
- Summarizes content of CDISC subject level data set (ADSL) and SDTM domain data sets (i.e. DM, AE, MH, DS, CM, EX, EG, LB, VS).
- Once generated, may be further modified with additional details from SAE report or other study domains.
- Extensive logic in place to modify written text based on presence/absence of certain information.

JMP Clinical Narrative Method:

- Various options to tailor content:
 - Generate reports by event or subject
 - Refer to trial participants as subject or patient
 - Choose investigator reported or standardized names for medications and medical history
 - Include concomitant medications and their indications
 - Select number of days surrounding event onset for reporting other potentially-related events
 - Summarize findings
 - » baseline results and/or abnormalities
 - » Present closest results before/after the event onset
 - Subset subjects, events or findings tests of particular interest
 - » events meet SAE criteria or are treatment emergent

JMP Clinical Narrative Example:

- For illustration, use data from a clinical trial of aneurysmal subarachnoid hemorrhage (SAH)
 - Haley, EC, Kassell, NF and Torner JC (1993) *J Neurosurg.* 78:537-547
- 902 subjects treated with Nicardipine or placebo.
- 310 subjects had a total of 683 SAEs.
- Our program generated the 683 narratives < 1 min.

JMP Clinical Sample Narrative:

Subject: 281004

Randomized Arm: Placebo

Investigator: 281A]

Drug and Dose at Event Onset: 41 mg/h of Placebo

Serious Adverse Event (coded term [reported term]): HEPATIC FUNCTION ABNORMAL [HEPATIC FUNCTION ABNORMAL]

Subject 281004 was a 57-year-old white female. Her medical history included convulsions 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 malignancy (start date unknown). She began dosing with 41 mg/h of placebo on 05MAY1988 (Day 1). The subject discontinued the trial on 29JUN1988 (Day 56) due to death.

On 12MAY1988 (Day 8) the subject experienced a hepatic function abnormal (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 41 mg/h of placebo and had been at this dose for 8 days. The SAE occurred 7 days after the first dose of 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 alveolitis (moderate), atelectasis (moderate), gastrointestinal necrosis (severe), hyperglycaemia (moderate), ileus paralytic (severe), isosthenuria (moderate), pneumothorax (moderate) and pyrexia (moderate). Concomitant medications taken at the onset of the SAE included dexamethasone, phenobarbital, acetaminophen, codeine compound 1/2 and dopamine.

On the closest lab test day on or prior to the start of the event, the subject had the following abnormal on-study lab tests: high alp [126 U/L, range = (40 - 120)], high bili [0.0106656 mmol/L, range = (0.0009999 - 0.003333)], high bun [12.495 mmol/L, range = (2.499 - 7.497)], low co2 [73.916 mg/dL, range = (100.004 - 130.44)], high ldh [600 U/L, range = (105 - 333)], low pco2 [3325 Pa, range = (4655 - 5985)] and high pt [12.6 sec, range = (11 - 12.5)].

On the closest ECG test day on or prior to the start of the event, the subject had the following on-study ECG tests: desadd1 (still within normal limits but compatibl), desadd2 (longer present tracing attached), desgen (tachycardia), prmean (121 msec), qrsdur (41 msec), qtmean (160 msec) and rtmean (400 msec).

On the closest vital signs test day on or prior to the start of the event, the subject had the following on-study vital signs performed: diabp (70 mmHg), hr (144 BEATS/MIN) and sysbp (158 mmHg).

The investigator considered the AE to be unlikely related to study medication. The final outcome of the event was reported as fatal on 12MAY1988 (Day 8).

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Narrative contents:

Key info

Subject: 281004
Randomized Arm: Placebo
Investigator: 281A
Drug and Dose at Event Onset: 41 mg/h of Placebo

Event

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DM, MH, EX, DS

On 12MAY1988 (Day 8) the subject experienced a hepatic function abnormal (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 41 mg/h of placebo and had been at this dose for 8 days. The SAE occurred 7 days after the first dose of 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.

Other AEs, Con meds

Adverse events that occurred within a ± 3 -day window of the onset of the SAE included alveolitis (moderate), atelectasis (moderate), gastrointestinal necrosis (severe), hyperglycaemia (moderate), ileus paralytic (severe), isosthenuria (moderate), pneumothorax (moderate) and pyrexia (moderate). Concomitant medications taken at the onset of the SAE included dexamethasone, phenobarbital, acetaminophen, codeine compound 1/2 and dopamine.

Narrative contents:

Labs

On the closest lab test day on or prior to the start of the event, the subject had the following abnormal on-study lab tests: high alp [126 U/L, range = (40 - 120)], high bili [0.0106656 mmol/L, range = (0.0009999 - 0.003333)], high bun [12.495 mmol/L, range = (2.499 - 7.497)], low co2 [73.916 mg/dL, range = (100.004 - 130.44)], high ldh [600 U/L, range = (105 - 333)], low pco2 [3325 Pa, range = (4655 - 5985)] and high pt [12.6 sec, range = (11 - 12.5)].

ECGs

On the closest ECG test day on or prior to the start of the event, the subject had the following on-study ECG tests: desa dd1 (still within normal limits but compatibl), desa dd2 (longer present tracing attached), desgen (tachycardia), prmean (121 msec), qrsdur (41 msec), qtmean (160 msec) and rtmean (400 msec).

Vitals

On the closest vital signs test day on or prior to the start of the event, the subject had the following on-study vital signs performed: diabp (70 mmHg), hr (144 BEATS/MIN) and sysbp (158 mmHg).

Causality, Outcome

The investigator considered the AE to be unlikely related to study medication. The final outcome of the event was reported as fatal on 12MAY1988 (Day 8).

Benefits:

- Allow medical writers and clinicians to focus on science rather than spend time sifting through source data to generate narratives de novo.
- Compose narratives in stages as subject completes study prior to database lock.
- Edit/add detail from additional sources as it becomes available.
- Compare edited narratives to those generated with final locked database to highlight any data changes that should be incorporated into the final narrative.
- Use software to generate initial draft to reduce errors and time spent for QC.

Conclusions:

- CDISC standards make it possible to develop a flexible tool available to everyone. Understanding data formats, requirements and relationships within and between domains is critical for development of easy to use and powerful software.
- Automatic generation of AE narratives illustrates the power and benefits of adopting CDISC standards.

Thank you.

Questions?



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