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A Guide to Programming Patient Narratives

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ABSTRACT

The ICH-E3 guidelines require patient narratives, which are targeted patient profiles of clinical importance. Patient narratives describe death, other serious adverse events, and certain other significant adverse events judged to be of special interest collected for a subject over the course of a clinical trial. The SAS programmer is expected to provide key data information to the medical writer. The Medical writer will review patient profiles to coincide with an event of interest and address the safety concerns of interest at the patient level. This paper will provide helpful insight on the traditional process of narrative generation; identify the requirements and gather information to program narratives.

INTRODUCTION

Patient narratives form an important part of clinical study reporting. It provides chronological account of all the events encountered by a subject during or immediately following a clinical trial. The regulatory submissions would require narratives not only for serious adverse events (SAEs), but also for events causing death or study discontinuation. Patient narratives are a part of safety data submitted to the regularity authorities for all phases of clinical trials. It involves review of patient profiles, data listings, and other information followed by manual writing of narratives as plain text.

According to ICH-E3 tripartite guideline on the Structure and Content of Clinical Study Reports (CSRs) (Section 12.3.2), a patient safety narrative should describe:

- The nature, intensity and outcome of the event.
- Clinical course leading to the event.
- Timing relevant to study drug administration.
- Relevant laboratory measures.
- Action taken with the study drug (and timing) in relation to the event.
- Treatment or intervention.
- Autopsy findings (if applicable).
- Investigator's and sponsor's opinion on causality.

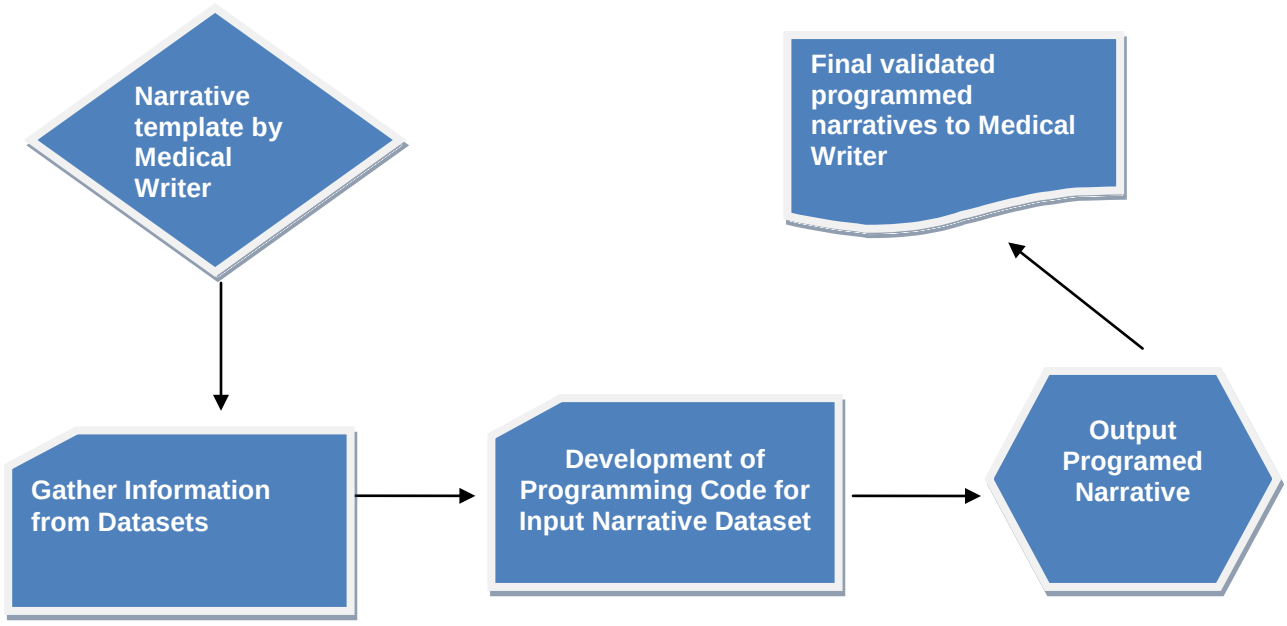
Patient narratives should also include following data to get a meaningful outcome:

- Patient Identifier.
- Age and sex of patient.
- General clinical condition of patient with duration of illness.
- Relevant medical history.
- Disease being treated.
- Relevant concomitant and prior medications with details of dosage.
- Investigational drug administered.
- Dose and duration of investigational drug administered.

NARRATIVE GENERATION

The SAS programmer plays a significant role in the creation of patient narratives. Medical writer requests a programmer to provide key information of all the significant events of a clinical trial, which can be in the form of listings or datasets based on their requirements. Narratives can be written for both unlocked and locked clinical database. Production of patient narratives as per reviewers' requirements can be quite challenging, considering variety of data that needs to be gathered from various datasets and shifting demands of the reviewer.

Display 1: Flow chart representing basic steps followed by a programmer to create a narrative report.



A narrative provides the complete story of an event chronologically and holds together relevant information from various sources liaising with medical experts. Since narrative writing involves expressing the messages clearly and effectively, the medical writer uses various data sources like CRF pages, analysis datasets, pharmacovigilance database, clinical database listings etc., to provide a template based on the project requirements. In most cases, a medical writer references listings or tables from the project while creating the template. Medical advisors review the final narrative template created by Medical writers. Narrative template and datasets may vary based on the therapeutic area and investigational drug. Identifying medical history and laboratory results 'relevant' to the event of interest can be challenging.

After receiving the template from medical writer, the programmer should ensure that the information in the template is available in the study database to avoid road blocks while programming. The programmer needs to incorporate different data from various domains such as Demographics, Adverse Events, Laboratory data, Medical History, Concomitant Medications, Exposure, etc. for each subject.

The patient narrative template is designed to deliver reports at the subject level. Generating individual reports could be time consuming and labor intensive. Most of the pharmaceutical companies and CROs have developed standard macros to ease the process and reduce the repetitive work across different projects.

Display 2: Sample of Narrative Template

Protocol:
Subject:
Assigned Treatment Group:
Race/Ethnicity/Gender:
Age at Screening: xx Years
Enrollment Date: DDMMYYYY
Randomization Date: DDMMYYYY
Date Study Drug First Administered: DDMMYYYY
Date Study Drug Last Administered: DDMMYYYY

Events Meeting Narrative Writing Criteria

Reason[a]	MedDRA PT (Verbatim)	Onset Date (Day)/Period[p]	End Date (Day)	CTCAE[b]; Related	Outcome[c]; Action[d]	SAE

a: Death; SAE=serious adverse event; PTAE=premature termination of treatment due to adverse event; PSAE=premature termination of study due to adverse event; EOI=Event of Interest
b: Standard Toxicity Grade 1, 2, 3, 4, 5
c: res=recovered/resolved; res seq=recovered/resolved with sequelae; not res=not recovered/not resolved; fatal; unk=unknown
d: dos wthdr=Drug withdrawn; dos del=dose delayed; dos no chg=Dose not changed; unk=unknown
p: CHE=Chemotherapy run-in period; NEO=Neoadjuvant period; ADJ=Adjuvant period

Relevant Past Medical History:
Relevant Prior Medications/Supplements/Therapies:
Relevant Concomitant Medications/Supplements/Therapies:
Ongoing Medications History: **(Listing xxxx Medical History)** **[MHDECOD]** **[MHDECOD]**
Study Drug Treatment: The patient entered the **XYZ** study **(protocol number)**, a multicenter, prospective, observational registry study and received the first **xxx** injection **xx** study days later into the **study**.
Description of Event(s), Including Follow-up: The patient experienced [AESEV=grade or severity] [**AEDECOD preferred** term bolded ()] on Study Day xx, [AESDY] xx days after the most recent previous Ozurdex injection. The event was classified as a/an [NREAS, NREAS, etc] eg, SAE, PTAE, PSAE, and OSE **(*list all categories met by event and modify sentence accordingly; note the use of serial commas*)**.
Laboratory Results:

Parameter	Date (day)	Visit	Result	CTC Toxicity	Indicator	Range Lower Limit	Range Upper Limit

The header section of the narrative (Display 2) provides the demographic details of a subject. From a programmers' perspective, we obtain this information from the demographics dataset (DM or ADSL). Events of interest are provided in a chronological order along with past medical history, concomitant medications, study drug treatment, and other relevant information. The adverse event dataset plays a vital role in the narrative generation since it provides all the events occurring during the conduct of the trial. Relevant laboratory results during the event are also provided in the narrative.

PROGRAMMING CHALLENGES:

A key issue to consider while transforming analysis datasets to narrative datasets is how to handle one or many contributing data points contained in the analysis datasets, such as adverse events and concomitant medications. If the dataset is not clean and patient safety narratives are written prior to database lock, updates are required based on the final database lock data. This approach can be time consuming than preparing all narratives after database lock. This process is feasible for projects with a large number of narratives required to be drafted in a short span.

Due to the descriptive nature of the report, programming the narrative dataset is driven based on high content. Hence, working through formats, indention, embedded data, text that needs to be included in the narrative dataset can be challenging and intensive. As analysis datasets contain information at an event level parsing over multiple rows for medical history and concomitant medications, a programmer has to reformat and concatenate multiple rows into a single string. This information is embedded into the text of a narrative sentence stored in a narrative dataset.

Display 3: Sample Narrative Output for Concomitant Medications:

SUBJECT	CMDECOD	CMTRT	CMSTDTC	CMENDTC
001	SERETIDE	ADOAIR250DISKUS	10/15/2015	1/13/2016
001	SALBUTAMOL	SALBUTAMOL	12/16/2015	12/16/2015
001	SALBUTAMOL	SALBUTAMOL	1/14/2016	1/28/2016
001	FLUTICASONE PROPIONATE	FLUTIDE 200 DISKUS	8/3/2015	1/20/2016
001	FLUTICASONE PROPIONATE	FLUTIDE 200 DISKUS	4/1/2016	
001	SALBUTAMOL SULFATE	SULTANOL INHALER 100MCG	10/24/2015	10/24/2015
001	SALBUTAMOL SULFATE	SULTANOL INHALER 100UG	1/21/2016	4/1/2016

The subject's relevant concomitant medications at the time of the event included Adoair250Diskus, Salbutamol, Flutide 200 Diskus, Sultanol Inhaler 100mcg, and Sultanol Inhaler 100UG.

Multiple rows of medical history concatenated with start dates are combined into a single string with delimiters. The ODS line break instructions are used to list the terms in a single cell of the narrative document.

Display 4: Sample Narrative Output for Medical History:

Prior Medical History:

C/w undifferentiated pleomorphic sarcoma, unk
Cholecystectomy, unk
Glaucoma surgery, unk
Vocal cord benign nodule removed, unk
Tooth root fracture, unk-01Sep2015
Shortness of breath upon exertion, unk-02Sep2015
Spindle cell sarcoma, 19Jan2015-unk
Anemia, 03Sep2015-04Sep2015

Generating a sample narrative output and having it checked by the Medical Writer to get a final approval for any updates or changes is much more viable than generating it for all the subjects meeting the criteria.

CONSISTENCY

Creating a narrative report from a draft narrative that is included in the clinical study report usually involves several review processes such as medical writing, medical reviewers, and Quality Assurance to make sure all the information fit together and the narrative accurately represents data from the sources. As a programmer, while preparing a large number of patient safety narratives, it is essential that consistency is maintained throughout the project. Hence, excel spreadsheets can be used as an excellent tracking tool for managing high volumes of safety narratives, which can be shared with the Medical Writer on a regular basis.

CONCLUSION

Patient narratives have become an integral part of the data cleansing and review for the clinical trials data. Developing an automated narrative process with robust and reusable SAS-based macro application would result in saving a lot of hours, which can be repeated on multiple studies. The discussion of the macro that we used is beyond the scope of this paper.

REFERENCES

1. ICH Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports E3. Current Step 4 version dated 30 November 1995. Page 24.
2. United States Food and Drug Administration, "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application", July 1988.

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