Advanced Clinical

INSIGHT BRIEF

Optimizing Patient Narratives: Best Practices for Ensuring Patient Safety and Minimizing Risk

Advanced Clinical

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Introduction

Clinical narratives, which provide brief summaries of specific events experienced by patients during a clinical trial, detail safety information for inclusion in the clinical study report. This is then submitted to regulators as part of the dossier for the investigational drug under study. Yet safety departments may use a "one-size-fits-all" approach to writing these narratives, potentially introducing unnecessary risks into the interpretation of individual cases and studies.

It may seem prudent to include every detail of a patient's medical history in a case narrative, but this can obscure the most relevant points. An overabundance of information can make it hard for regulators to assess the cause of a safety issue. In contrast, a thoughtful approach that combines a patient's relevant medical history with safety event details and a focus on potential causes of the event, helps regulators clearly understand what took place, along with the likely cause. This insight brief, authored by experts from Advanced Clinical, describes the elements needed in a custom patient narrative to add value for sponsors, site staff, patients and regulators.

Regulatory Requirements for Narrative Writing

Requirements for serious adverse event (SAE) narratives vary between regulators. The U.S. Food and Drug Administration (FDA) requires a brief narrative including:

- All relevant information
- A description of similar events
- An analysis of the significance of the suspected adverse reaction

Health Canada asks for:

- A summary of relevant clinical and related information
- They specify that the narrative should serve as a comprehensive, standalone medical story
- All information must be captured accurately

The European Medicines Agency (EMA) mandates that narrative information should:

- Present in a logical, chronological order
- Include information on:
  - Unblinding and expectedness
  - Outcomes and therapeutic measures
  - Relevant medical history
  - Concomitant medications
  - An assessment of causality
  - Potential alternative explanations for the SAE

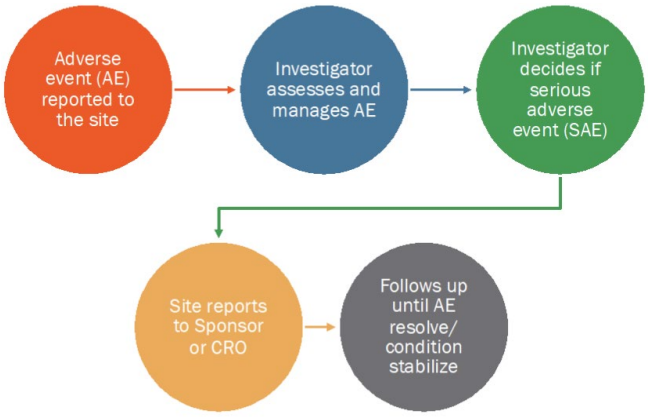
The flow of information about adverse reactions during a clinical study starts at the Investigator site where all initial information is gathered for the narrative (Figure 1). This is then put into a standardized format in the safety database. From here, it can be reported to the regulatory authority, ethics committee, institutional review board and other sites involved with the study. The safety team is responsible for selecting appropriate information to send to regulators to inform decisions later in the study life cycle. It is important to recognize that there is no direct link between the site and the regulator; all safety data must come through the safety team.

Figure 1: Flow of information within a clinical study

Roles and Responsibilities of Investigators as Related to Adverse Events

Roles and responsibilities are clearly defined by regulators (Figure 2). The adverse event (AE) must be reported to the site, where this is assessed and managed by the Investigator, who makes the determination of whether an SAE has occurred. The site then reports the event to the sponsor or clinical research organization (CRO), based on the requirements of the protocol, following up until the AE resolves or the condition stabilizes.

Figure 2: Roles and responsibilities of Investigators



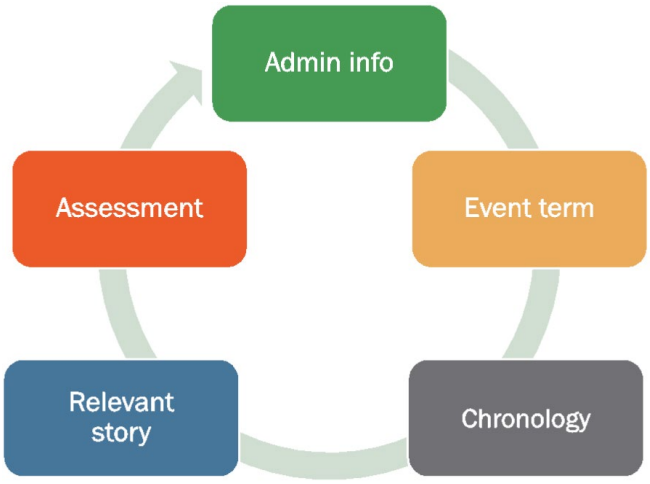
There are important differences between the severity and seriousness of AEs. Severity is assessed based on the intensity of the event, which can be determined using Common Terminology Criteria of Adverse Event (CTCAE) or other grading systems. Seriousness is based on patient/event outcome and can be determined using SAE criteria, and it serves as a guide for defining regulatory reporting obligations. To ensure correct classification, case processors should be thoroughly trained on the protocol specifics, investigator brochure, regulatory definitions and requirements and the particular, therapeutic area.

Key Steps in Case Narrative Creation

It is important to pay special attention to multiple pillars when creating patient narratives (Figure 3):

- Administrative information
- Event term (name of event)
- Chronology
- Relevant story
- Assessment of the event

Figure 3: Key pillars for creating a patient narrative



The Structure of Clinical SAE Narratives

When writing a patient narrative, the subject and the event are considered separately.

From the subject perspective, key factors in assessing events include:	
Age	For example, particular events may be more common in old age or very rare in children.
Life events	These may be relevant; for example, pregnancy, immunosuppression or recent trauma (could be relevant for psychiatric events).
Medical history	A holistic view is needed, followed by a focus on conditions that are relevant to the patient at that particular time. Factors to consider include whether the subject has experienced a particular event before; whether the event may be related to drug administration; and whether there have been any recent medical changes.
Supporting labs and tests	Supporting labs and tests: Medical input can help determine which are relevant.

From the event perspective, important elements include:	
Chronology	The relationship between the administration of the study drug or study procedures. The timeline should be clearly laid out.
Dechallenge/ rechallenge information	If available, this information—which refers to withdrawing the test drug following an AE, and then readministering it while continuing to monitor for reactions—should be included.
Events clearly associated with drug administration	These may include known reactions to administered drugs, such as the skin reaction Stevens-Johnson syndrome or drug-induced, liver injury.
Concomitant medications	These should be considered—along with known side effects and whether any concomitant medications were started or stopped, or the dose amended—within around two weeks of the event.

Once decisions have been made on what to include, the next step is to develop the narrative as a stand-alone document. As shown in Figure 4, the major elements in the structure of clinical SAE narratives are:

- Study title
- Subject demographics
- Relevant concomitant medications
- Study drug administration (route, frequency, chronology of event)
- Details of event including potential alternative causes, providing a story of the event in chronological order
- Outcome of event and action taken with study drug (the site may have to be queried on this for updates to complete the narrative)
- Investigator and sponsor causality assessment

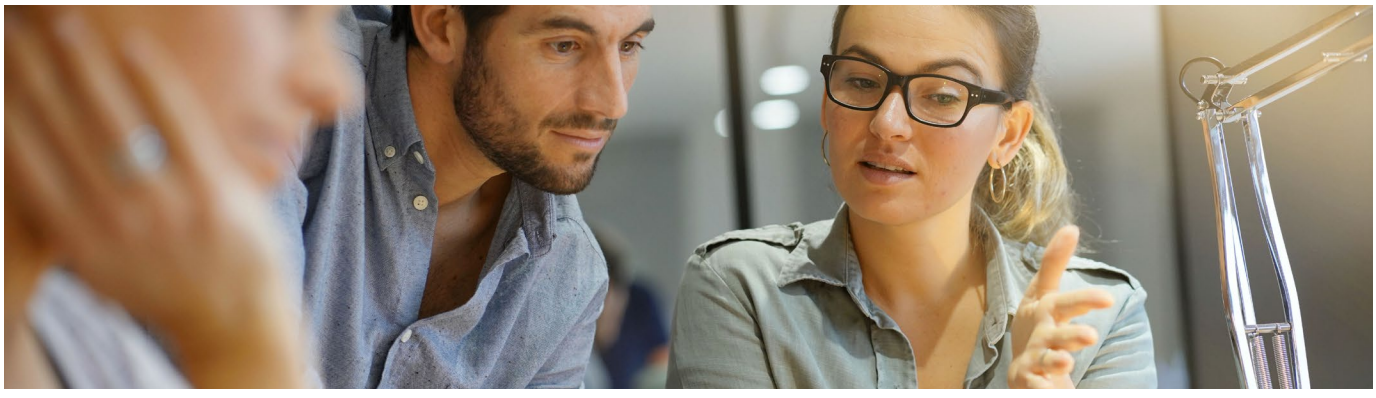


Figure 4: Structure of clinical SAE narratives

Several aspects of a narrative should be clarified to ensure consistency. These include sentence structures (for example, some sponsors prefer to start a sentence with a date to help clarify chronology), date formats (these differ between countries), medical history and concomitant medications that are considered relevant based on the safety review, inclusion or exclusion of normal ranges for laboratory results, trade names or generic only for drugs, and whether to add follow-up information as a paragraph at the end of the consolidated narrative rather than updating the full narrative.

As a final step, a self-check for the quality of the narrative should be performed using a checklist of important elements, reviewing every line to ensure that no errors are missed and correcting all discrepancies.

Conclusion

To provide optimum value for patients, site staff, sponsors and regulators, a high-quality patient narrative should summarize all relevant clinical and related information. The document should cover patient characteristics, therapy details, medical history, clinical course of the event, diagnosis, AEs (including outcomes), laboratory evidence (including normal ranges) and any other information that supports or suggests an AE. This document provides a comprehensive, stand-alone "medical story" written in a logical, time sequence with key information from supplementary records and, if appropriate, relevant autopsy or post-mortem findings. The patient narrative should support the causality assessment, including investigator and sponsor comments, providing high-quality information to inform stakeholder assessments of drug safety and to protect patient safety throughout the drug development life cycle.