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Patient Safety Narratives in Clinical Studies

Patient safety narratives form an important part of clinical study reporting. This paper describes current regulatory requirements with regards to safety narratives, a proposed process for their development and review and examines ways to simplify the reporting process; thereby reducing the burden of time and cost.

Safety narratives should be prepared for all phases of clinical studies, whether conducted in healthy volunteers or in patients with the disease/condition under study. For ease of reporting, they shall be referred to as patient safety narratives throughout this paper (although narratives for healthy volunteers/subjects in Phase I studies should be considered included).

Guidance

According to the International Conference on Harmonisation (ICH) tripartite guideline on the Structure and Content of Clinical Study Reports (CSRs) E3 (Section 12.3.2), a CSR should contain brief narratives describing each death, each other serious adverse event, and other significant adverse events that are judged to be of special interest because of clinical importance.[1]

The guidance document indicates that events clearly unrelated to the test drug/ investigational product may be omitted or described very briefly. In the interests of transparent reporting, it is suggested herein that patient safety narratives be prepared for all criteria detailed above.

A patient safety narrative provides a full and clinically relevant, chronological account of the progression of an event experienced during or immediately following a clinical study.

As Per ICH E3 guidelines, a patient safety narrative should describe:

- the nature, intensity and outcome of the event,
- the clinical course leading to the event,
- an indication of 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,
- post mortem findings (if applicable), and
- Investigator's and Sponsor's (if appropriate) opinion on causality.

Specifically, narratives should include:

- patient identifier
- age and sex of patient; general clinical condition of patient, if appropriate
- disease being treated (if this is the same for all patients, this information is not required) with duration (of current episode) of illness
- relevant concomitant/previous illnesses with details of occurrence/duration
- relevant concomitant/previous medication with details of dosage
- test drug administered, including dose, if this varied among patients, and length of time administered.

Format and Location

The guidance is less specific with regards to the format and location of patient safety narratives, stating [they] can be placed either in the text of the CSR or in Section 14.3.3 (Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events), depending on their number. Although no cut-off is specified, this author suggests that five or fewer narratives may logically and clearly be reported in text, although this is dependent on several factors including therapeutic area, complexity of reporting, relevant course of events, and flow of information in the CSR. If in doubt, it is recommended that narratives should be prepared as separate documents and compiled in Section 14.3.3 during CSR publishing.

Additional Considerations

It is important to identify the approximate number of patient safety narratives to be prepared early in the planning process. This determines the narrative format and impacts the timing of production (that is, whether prior to or following database lock).

If patient safety narratives are written from draft (unclean) data prior to database lock, updates are required based on the final (clean) data. This approach can consume more time than preparing all narratives after database lock, but is more feasible for projects where a large number of narratives are required to be drafted in a short span (e.g., for a regulatory submission).

Good communication is essential for the success of any project, but is particularly important for projects including the preparation of a large number of patient safety narratives. There should be a good understanding of requirements by all parties, and agreement of the scope and main principles prior to project start.

Information Sources

A Medical Writer will use various sources of information when preparing patient safety narratives. These include Council for International Organisations of Medical Sciences (CIOMS) forms, Case Report Forms (CRFs), MedWatch forms, Data Clarification Forms (DCFs) and clinical database listings.

Since source data are captured during study conduct and narratives are often prepared prior to database reconciliation and lock, a Medical Writer is often able to identify data discrepancies between the clinical study database and other sources. The situation is complicated further as CIOMS forms are updated on an ongoing basis during a clinical study. A Medical Writer is well placed to assess the impact of any discrepancies and provide feedback to a Sponsor, thereby assisting with the data cleaning process.

Process

The narrative production process differs across companies and is dependent to a small degree on whether reporting is performed internally or by a Clinical Research Organisation (CRO). The emphasis of this paper will be reporting by the CRO, and specifically Quanticate.

When significant numbers of narratives are required, it is useful to develop a template to define overall structure and content, and obtain approval from all stakeholders prior to initiation of work. In the template, consideration should be given to a number of factors, including order of information, sentence structure, date format, relevance of specific medical history and concomitant medications, use of trade or generic names for medications, and whether normal ranges should be included for some/all laboratory test results.

A comprehensive template that is flexible enough to suit Sponsor requirements whilst maintaining internal consistency is a very effective tool. However, care should be taken to ensure all writers involved in the preparation of the narratives understand the limitations of the template, and feel empowered to deviate from it as data required for transparent reporting.

It is recommended that patient safety narratives be produced as follows:

- Preparation of first draft narrative from patient/subject data by the Medical Writer.
- Scientific and editorial peer review by the CRO project lead to check the document is accurate, complete, and consistent with requirements and across documents.
- Clinical review of draft narrative: It is recommended that this be performed by the Sponsor or designate, although Quanticate can provide this service as necessary.
- Medical Writer revision based on clinical review: If the writer does not agree with clinical review comments, for example where requested amendments conflict with the evidence or where changes would introduce inconsistencies between narratives, or where review comments are unclear, these should be discussed with the Sponsor or designate, as appropriate, and responses retained on file.
- Quality control (QC) review based on final patient/subject data. Given the often large number of narratives required for individual studies and small size of each document relative to the CSR, it is recommended that a single QC review be performed towards the end of the process, rather than QC review of the first draft and final deliverable.
- Medical Writer revision based on QC review findings. Note: where significant findings are identified during QC review, these should be discussed with the Sponsor and clinical reviewer, as appropriate, and further updates should be checked for consistency and accuracy.
- Approval by the Sponsor after a final review.

The process can be scaled according to number of narratives required. In scenarios where there are few subjects/patients with events that require safety narratives, a Sponsor may prefer to review the narratives as part of the draft CSR, which would normally undergo QC review prior to release, and a final QC review prior to finalisation.

Consistency

When preparing a large number of documents for a single purpose, including patient safety narratives, it is essential that consistency is maintained. A large project will require the involvement of several Medical Writers. A CRO project lead should be assigned to act as a single point of contact to work closely with the Sponsor and other stakeholders. In addition to managing communication and delivery, he/she should act as a peer reviewer, ensuring consistency of reporting across all narratives, reviewing as if he/she was part of the Sponsor study team.

During a large project, it is not unusual for the scope of work and content of narratives to evolve over time, particularly where narratives are prepared on an ongoing basis. For example, it may become apparent from events reported during an ongoing study that specific endpoints (e.g., liver function test results) are more important than considered originally.

An effective single point of contact will be able to work with the Sponsor to ensure the process specifications are adapted quickly, and will disseminate the relevant information to the writing team in a timely manner, through meetings and the use of study specific documents. Where it is necessary to update narratives already prepared and possibly reviewed, this person will again work with the Sponsor to identify a solution that integrates updates into the overall narrative development process in the most effective and expeditious way.

Tracking

The majority of Phase II-V studies have a large number of patients meeting pre-agreed patient safety narrative criteria. Excellent project management skills are essential for tracking such projects where a large number of narratives are written by several writers, particularly later in a project where the delivery of newly drafted narratives overlaps with the return of clinical review comments and QC checking, and finalisation of narratives at the end of the process. The importance of careful management should not be underestimated; ensuring accuracy and consistency across a large number of narratives is a challenging and time consuming task.

Tracking is critical in projects involving a large number of patient safety narratives. Microsoft Excel spreadsheets can be used as an excellent tracking tool for managing high volumes of narratives, and it is particularly useful if all stakeholders are able to adapt their processes, if necessary, to share the same documents. In practise, this may not be possible, particularly where a CRO, for example, records confidential information, such as time spent per narrative for budgetary purposes.

Delivery

Whatever the size of the project, it is beneficial to deliver patient safety narratives in batches with pre-agreed units/numbers for Sponsor review. The batch size will be dependent on total number of narratives to be prepared, data availability, completion timelines, number of writers working on the project and reviewer availability, and should take into account any ramp up time required.

Experience shows that it is preferable to deliver a small number of patient safety narratives (e.g., five to 10 depending on complexity) prepared by one writer (usually the project lead) for Sponsor review in the first instance. This allows for fine tuning of the content, presentation and process prior to implementing preparation on a larger scale. Restricting the number of people involved early in the process allows for faster resolution of any issues such that a streamlined process can be agreed quickly and minimises confusion when rolled out to the larger team. By working in this way, duplication of efforts can be kept to a minimum, which is beneficial to all parties. The in house team can subsequently be trained on the agreed Sponsor requirements.

When sending the narratives for review, it is advisable for the CRO project lead to clearly state the timeframe within which all review comments should be returned, thereby minimising unnecessary delays, and to request that comments from all reviewers be provided in a consolidated manner.

Future Directions

CIOMS Forms

It is becoming more common for Sponsors to consider including direct links to CIOMS forms from CSR appendices instead of including individual patient safety narratives. This approach should be used with caution. CIOMS forms are completed by an Investigator in the country in which the study is being conducted; sometimes, with English not his or her first language. These forms are updated frequently as key information becomes available, which makes data repetitive and unwieldy. One patient may have several CIOMS forms for separate events, which cross reference one another. A Medical Writer can spend several hours distilling the most relevant and up-to-date information from such forms in order to prepare a narrative that is succinct, accurate and readable for a single patient. Since the purpose of a patient safety narrative is to present a full and clinically relevant, chronological account of the progression of an event or events, a regulatory reviewer may not take kindly to having to derive a clear account from one or more lengthy CIOMS report(s).

Furthermore, the Note for Guidance on the Inclusion of Appendices to Clinical Study Reports in Marketing Authorisation Applications, specifies that in Appendix 16.3 of the CSR, CIOMS reports (or equivalent) and CRFs should be available on request.[2] Since CIOMS forms should be made available as required and are not mandated, it may be considered less acceptable for them to be linked routinely to the CSR in place of patient safety narratives.

Automation of Patient Safety Narrative Preparation

Another development in clinical study reporting is the automation of patient safety narrative preparation using programming and statistical support to prepare output directly from SAS datasets. Several case studies and papers are publicly available which document the benefits of such an approach (which include increased standardisation, reduced preparation time and reduced cost).

With time invested at the start of an individual project or program of work to define the fields to be presented, the benefits are real, particularly for patient safety narratives for significant non serious adverse events that are judged to be of special interest. There are some limitations to this approach which should be considered at the outset:

- Serious adverse events - Since data relating to serious adverse events are obtained directly from other sources such as CIOMS forms, routine automation of reporting is generally not practicable. However, such narratives can be partially automated with information such as demographics, study treatments, event details (onset and resolution dates, severity, relationship to study drug, etc.), prior medications, ongoing medications at event onset, and medications started during an event, output as routine. Such information is useful to the Medical Writer and can save a significant amount of time when drafting a narrative.
- Timing - As detailed above, the timing of narrative preparation is a key decision at the start of the reporting process. When following an automated process, there is little benefit to starting prior to database lock as any changes made during Medical Writer review will be lost when the narratives are re-run from clean data. If timings are such that increased efficiencies are required, this approach may be followed as long as the programmed outputs based on clean and draft data are compared, preferably via an automated process, with changes flagged to the Medical Writer for inclusion late in the narrative writing process, but ideally prior to Sponsor review.

Working with Sponsors, Quanticate is able to offer a low-cost solution providing defined output where SAS datasets are provided in a specific format. If SAS datasets are not available, but other data formats such as Microsoft Excel spreadsheets are used, the same information may be extracted through additional programming techniques. It is recommended that Medical Writer review be included to ensure complete, coherent and consistent reporting.

Individual Case Safety Reports

It is important to avoid confusion between patient safety narratives and Individual Case Safety Reports (ICSRs). ICSRs are a core component of pharmacovigilance (PV) services and drug safety, and differ from patient safety narratives in a number of respects.

A patient safety narrative in, or appended to, a CSR describes all relevant events for a single patient, with relevant background information as detailed above. An ICSR concerns one patient, one or more identifiable reporter(s), one or more suspected adverse reaction(s) that are clinically and temporally associated, and one or more suspected medicinal product(s).[3]

In the context of a clinical trial, an individual case is the information provided by a primary source to describe a serious adverse event related or unrelated to the administration of one or more investigational medicinal products to an individual patient at a particular point of time.[4] The event reported should be the diagnosis. If a diagnosis has not been made at that time, the case may contain several signs and symptoms instead and, therefore, more than one reported event. ICSRs prepared post-marketing can differ from this in that several event terms may be reported in a single case; these events should be temporally or clinically associated and they will be ordered according to clinical relevance for the product, i.e., a serious unexpected event would be designated the 'primary event' for reporting purposes, whereas non-serious or expected events would be ranked lower within the case. Furthermore, in post-marketing ICSRs, all spontaneous reported events are considered related to the medicinal product unless specified otherwise by the reporter, whereas in a clinical setting the Investigator makes his or her interpretation as to causality.

The regulations pertaining to ICSRs are both complex and precise and dictate that reports be presented in a standardised format. This can prove to be challenging, particularly for smaller companies involved in drug development and they often outsource this work to CROs such as Quanticate who can provide an end-to-end PV service on their behalf.

References

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This whitepaper was written by a principle member of Quanticate's Medical Writing team. Quanticate is an established leading global provider of programming, statistics, data management, pharmacovigilance and medical writing services. For further information please contact enquiries@quanticate.com or visit our website: www.quanticate.com