# Some considerations on the safety evaluation section of clinical study reports for studies with anticancer drugs

Vicente Alfaro

*Clinical R&D PharmaMar S.A.U., Spain*

**Correspondence to:**

Vicente Alfaro,
Clinical R&D PharmaMar S.A.U.,
Barcelona, Spain
valfaro@pharmamar.com;
www.pharmamar.com

## Abstract

The International Conference on Harmonisation (ICH) guideline E3 describes the structure and content of clinical study reports (CSRs). However, this standard structure should be interpreted according to the type of study and data, including modifications to the table of contents and adding, deleting, or rearranging some of the contents defined by the guideline to better display the results and improve the communication of information. One example is the Safety Evaluation section of CSRs for studies with anticancer drugs. A more logical, reader-friendly way of showing data is to reverse the order and numbering of the Safety and Evaluation sections, presenting Safety Evaluation as Section 11 (main endpoints are all of them safety variables) and Efficacy Evaluation as Section 12. In addition, phase I CSRs in oncology require new sections describing results regarding main endpoints: i.e., dose-limiting toxicities, the maximum tolerated dose, and recommended dose for phase II trials. Finally, adverse events that can be measured as laboratory abnormalities (e.g. neutropenia, thrombocytopenia, transaminase increases, etc.) may be underreported if they are only listed based on the adverse events rows of the case report form. Hence, laboratory abnormalities are better reported by objective laboratory results.

**Keywords:** Clinical study reports, Phase I, Safety, Dose-limiting toxicities, Recommended dose, Oncology

The International Conference on Harmonisation (ICH) guideline E3 describes the structure and content of clinical study reports (CSRs) of studies evaluating therapeutic, prophylactic, or diagnostic agents.[1,2] The guideline has not been revised since it was issued more than 15 years ago. However, in June 2011, the ICH Steering Committee endorsed a concept paper and the establishment of an implementation working group to prepare a question-and-answers (Q&A) document on the guideline.[3] The aims of the Q&A document are to align ICH E3 with requirements of the Common Technical Document (CTD), particularly those for electronic submission, and to clarify other issues encountered since the implementation of the guideline in 1996. One of the aspects being discussed is whether ICH E3 is a guideline or a template. Some companies or sponsors create CSRs that maintain the table of contents and all elements defined by the ICH E3, whereas other companies or sponsors interpret ICH E3 more broadly, including modifications to the table of contents and adding, deleting, or rearranging some of the contents defined by the guideline in order to better display the results and improve the communication of information. In fact, ICH E3 states in its introduction:

> Each report should consider all of the topics described (unless clearly not relevant) although the specific sequence and grouping of topics may be changed if alternatives are more logical for a particular study.

One example where ICH E3 needs to be followed in a more flexible way is the Safety Evaluation section of CSRs for studies with anticancer drugs. The main aim of phase I clinical trials with anticancer agents is to find the maximum tolerated dose (MTD) and recommended dose (RD) for phase II trials, based on a dose escalation design which involves the reporting of dose-limiting toxicities (DLTs).[4] Therefore, the reader of the CSR of a phase I trial in oncology would expect to find first the results about how DLTs, MTD, and RD were found. However, DLTs are part of the safety evaluation and, therefore, according to ICH E3, they


DOI: 10.1179/204748112X13303569555547

should be described in Section 12 of the CSR, after the efficacy results have been described. Furthermore, these are dose-escalating trials in which cohorts are based on the toxicity found with dose increments. If efficacy is described first, a lot of cross-references have to be made to the Safety Evaluation section in order to understand the rationale for cohort distribution. Although, the use of electronic PDF submissions with hyperlinked tables of contents may reduce the concern about whether efficacy appears before safety in this type of studies, a more logical and reader-friendly way of showing the data is to reverse the order and numbering of these sections, presenting the Safety Evaluation as Section 11 and the Efficacy Evaluation as Section 12. In these cases, it is useful to add a note at the beginning of the CSR stating the following:

> This report has been written according to the ICH Harmonised Tripartite Guideline E3: 'Structure and Content of Clinical Study Reports' (ICH step 5 version, July 1996). However, Sections 11 (Efficacy Evaluation) and 12 (Safety Evaluation) have been reversed and renumbered in accordance with the primary and secondary objectives of this phase I clinical trial.

This modified structure has been used in several CSRs submitted to the European Medicines Agency (EMA) in marketing authorization applications (MAAs) and has been accepted by the EMA in the validation process.

In addition to the change in the order of the safety and efficacy evaluation sections, phase I CSRs in oncology require a new section with a resumé of results regarding DLTs, MTD, and RD. The ICH E3 guideline does not in fact define this. Table 1 shows an example of a table of contents for a Safety Evaluation section in this type of CSR.

Another issue that affects the safety sections of CSRs in oncology concerns the Clinical Laboratory Evaluation section (Section 11.5 in the example table of contents shown in Table 1). Chemotherapy works by destroying very active cancer cells that grow rapidly. Unfortunately, chemotherapy also affects normal cells that grow rapidly such as blood cells forming in the bone marrow, cells in the hair follicles, or cells in the mouth and intestines. When a patient is undergoing chemotherapy to treat cancer, a lot hinges on the blood test results that precede each intravenous infusion. Low blood counts can indicate serious side-effects, including fatigue, bruising, and vulnerability to infection, and can also mean that treatment must be postponed while the patient's body recovers normal values or the dose has to be reduced in subsequent treatment cycles. Therefore, laboratory findings are of extreme relevance in oncology studies, and hematological and biochemical laboratory abnormalities have to be discussed in separate subsections in the Clinical Laboratory Evaluation section of the CSR.

Table 1: Structure for Safety Evaluation section in a clinical study report of a phase I clinical trial with an antitumor agent

| |
|---|
| 11 Safety Evaluation |
| 11.1 Extent of Exposure |
| 11.1.1 Cycles received |
| 11.1.2 Dose delays |
| 11.1.3. Dose reductions |
| 11.2 Maximum Tolerated Dose And Recommended Dose For Phase II Clinical Trials |
| 11.2.1 Dose level I |
| 11.2.2 Dose level II |
| … |
| 11.2.x Dose-limiting toxicities (DLTs), maximum tolerated dose (MTD) and recommended dose (RD) for phase II clinical trials |
| 11.3 Adverse Events |
| 11.3.1 Brief summary of adverse events |
| 11.3.2 Display of adverse events |
| 11.3.3 Analysis of adverse events |
| 11.3.3.1 Constitutional adverse events and pain |
| 11.3.3.2 Gastrointestinal adverse events |
| … |
| 11.3.3.x Other adverse events |
| 11.3.4 Listing of adverse events by patient |
| 11.4 Deaths, Other Serious Adverse Events, And Other Significant Adverse Events |
| 11.4.1 Listing of deaths, other serious adverse events and other significant adverse events |
| 11.4.1.1 Deaths |
| 11.4.1.2 Other serious adverse events |
| 11.4.1.3 Other significant adverse events |
| 11.4.2 Narratives of deaths, other serious adverse events and certain other significant adverse events |
| 11.4.3 Analysis and discussion of deaths, other serious adverse events and other significant adverse events |
| 11.5 Clinical Laboratory Evaluation |
| 11.5.1 Listing of individual laboratory measurements by patient and each abnormal laboratory value |
| 11.5.2 Evaluation of each laboratory parameter |
| 11.5.2.1 Hematological abnormalities |
| 11.5.2.2 Biochemical abnormalities |
| 11.5.2.3 Individual clinically significant laboratory abnormalities |
| 11.6 Vital Signs, Physical Findings And Other Observations Related To Safety |
| 11.7 Safety Conclusions |

Please note that we refer to laboratory findings as abnormalities and not as toxicities because patients often have asymptomatic increases or decreases in parameters like neutrophils or transaminases. Adverse events (AEs) are described in a different section (Section 11.3 in this model of CSR), usually in tabulated form as worst grade of toxicity per patient and per cycle of treatment. Toxicity is graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, currently version 4.0). However, AEs that can be measured as laboratory abnormalities (e.g. neutropenia, thrombocytopenia, transaminase increases, hyperbilirubinemia, etc.) may be underreported if they are only listed based on the AE rows of the case report form. This is because reporting depends entirely on the judgment of the investigator and the symptomatic characteristic of the laboratory event. Hence, laboratory abnormalities are better reported by objective laboratory results, also graded using the NCI-CTCAE. Therefore, these laboratory abnormalities should be excluded from AE tables and shown in detail and discussed only in the Clinical Laboratory Evaluation section. Nevertheless, symptomatic AEs due to laboratory abnormalities (e.g. febrile neutropenia) that result in treatment modification (dose reduction or cycle delay) or treatment discontinuation or represent a serious adverse event or lead to death should be described in detail in the respective section.

In conclusion, ICH E3 represents an interesting tool in medical writing, but does not have to be followed rigidly if modifications of the structure are logical and help to tell the history of results in a clear way. Variations of ICH E3 that maintain the goal of harmonized reporting of conduct and results of clinical trials are acceptable, as long as important deviations from the guideline are explained. This article focuses on safety sections, but variations of ICH E3 are also acceptable, for instance, for pharmacokinetic, pharmacodynamic, pharmacogenomic, or quality-of-life data.

## References

1. Alfaro V, Cullell-Young M, Tanovic A. Abbreviated clinical study reports with investigational medicinal products for human use: current guidelines and recommendations. Croat Med J 2007;48(6):871–7. Epub 2007/12/13.
2. ICH Topic E 3. Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95). 1996.
3. Final Concept Paper E3 Q&As. E3: Structure and Content of Clinical Study Reports. Available from: http://wwwichorg/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/Concept_papers/E3_Q_As_Final_Concept_Paper_15_June_2011pdf.
4. (CHMP) CfMPfHU. Guideline on the Evaluation of Anticancer Medicinal Products in Man. CPMP/EWP/205/95/Rev.3/Corr. 2005.

## Author information

**Vicente Alfaro** holds a Ph.D. in Biology, a PgC in Pharmacology/Pharmacoeconomics, and an MsC in Immunology (University of Barcelona, U.B.). He is an Associate Professor (U.B., 1991–2007), Head of Medical Writing since 1996 (Biomedical Systems Group, Prous Science and PharmaMar) and author of more than 80 peer-reviewed articles. He is also holds membership to AERTeM, EMWA, TIPPA and ISMPP.