Guidance for Industry

E3 Structure and Content of Clinical Study Reports

Questions and Answers (R1)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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ICH

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Contains Nonbinding Recommendations

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I. INTRODUCTION[2]

Since the ICH E3 guidance was made final, experiences implementing the guidance in the ICH regions have given rise to requests for clarification. This question and answer (Q&A) document is intended to facilitate implementing the ICH E3 guidance by clarifying key issues.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. QUESTIONS AND ANSWERS

A. Content and Structure (1)

Q1: ***Some in the pharmaceutical industry have expressed concern that the ICH E3 guidance,* Structure and Content of Clinical Study Reports *(ICH E3), is intended as a requirement (i.e., a template that must be followed). The fact that the ICH M4 guidance for the Common Technical Document (CTD) refers to specific structural elements described in ICH E3 (e.g., Clinical Study Report (CSR) section headings) may have contributed to this interpretation. Interpretation of ICH E3 as a rigid template***

[1] This guidance was developed within the Efficacy Implementation Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. The Q&As in this document have been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, June 2012. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Arabic numbers reflect the organizational breakdown of the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, June 2012.

can result in presentation of redundant and suboptimal information in CSRs. This is a particular problem when ICH E3 is used for studies for which it was not designed (e.g., pharmacokinetic studies or studies with health economic or quality of life outcomes). Can ICH reaffirm that ICH E3 is a guidance and not a required template and that ICH E3 can be adapted to report studies that fall outside the original scope of ICH E3?

A1: Yes. ICH E3 is a guidance, not a set of rigid requirements or a template, and flexibility is inherent in its use. "The [guidance] is intended to assist sponsors in the development of a report that is complete, free from ambiguity, well organized, and easy to review." Modifications and adaptations to the structure presented in the guidance that lead to better display and communication of information are encouraged.

The introduction to ICH E3 (page 3) clearly indicates that ICH E3 is to be interpreted as a guidance, not a set of requirements: "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. Some data in the appendices are specific requirements of individual regulatory authorities and should be submitted as appropriate. The numbering should then be adapted accordingly."

To illustrate this flexibility, consider demographic baseline information. ICH E3 suggests presentation of this information in the efficacy evaluation, but many variations of this presentation are possible. For example, if the efficacy and safety populations differ substantially, it would be appropriate to present demographic and baseline characteristics for the safety and efficacy populations in the safety and efficacy sections or in a new section preceding the efficacy and safety results sections.

If particular types of information or topics are not addressed in ICH E3 or if their location is not specified, this information or topic should be placed in the section that is most relevant. For example, pharmacokinetic or quality of life results could be placed in appropriately identified subsections of the efficacy and safety results sections, or they could be placed in new, appropriately identified results sections.

If a report does not address all the aspects of ICH E3 that are relevant for a given study, this should be clearly indicated and the rationale for doing so should be provided — for example, if there is no presentation of efficacy for an efficacy study. A rationale is not necessary if sections presented in ICH E3 are reordered, renamed, or deleted (if warranted by the study design) or if new sections are added.

It should be noted that ICH E3 was developed for submission of adequate and well-controlled clinical effectiveness studies. Nevertheless, the basic principles described can be applied to other kinds of trials, such as clinical pharmacology studies and open-label safety studies, recognizing that not all sections or data presentations may be appropriate or important for these other types of trials. Sponsors are encouraged to adapt the recommendations in the guidance as appropriate (e.g., by deleting sections that are not relevant or adding important sections that are not mentioned in the guidance).

Q2: The ICH E3 guidance provides limited guidance on the synopsis. In the ICH M4E guidance, additional guidance on the synopsis of a CSR is given, including its use as a stand-alone document and its length. Although ICH E3 asks for a usual maximum length of 3 pages, ICH M4E extends this page limit for more complex and important studies (e.g., to 10 pages). How should both guidances be read together?

A2: The recommendations made in the ICH E3 guidance, which was developed before ICH M4E, should be combined with the suggestions made in the M4E guidance. Because the synopsis will be used as a stand-alone document within a Common Technical Document, it should be written so that it can be understood and interpreted on its own (i.e., without the other sections of a CSR). In addition to a brief description of the study design and critical methodological information, the synopsis should provide efficacy and safety results, as well as other critical information, including data on the study population, disposition of subjects, important protocol deviations, and treatment compliance. Cross-references to other sections of the CSR should be avoided. As explained in ICH M4E, complex or large and important studies may call for a synopsis longer than three pages. The 10-page example given in M4E is not an absolute requirement or limit but should not need to be exceeded greatly. The use of a tabular format for the synopsis is not mandatory.

B. Appendices (2)

Q3: The CSR appendices described in the ICH E3 guidance include material now available in the Trial Master File (TMF) in accordance with ICH E6. Should documents available in the TMF be included in the CSR appendices?

A3: Documentation needed to review the CSR should be included in the CSR appendices. It is not sufficient for such documents to be included only in the TMF, which is not submitted in the marketing application.

Documents that provide critical information on a study, such as the protocol (16.1.1), statistical methods (16.1.9), list of investigators and study sites, and sample case report forms, would always be needed by reviewers assessing a study and should be included in the trial report even if they are in a TMF. Certain documents may be required for the CSR by individual countries or regions, in which case they should be included. For example, according to the ICH guidance *E6 Good Clinical Practice: Consolidated Guidance*,[3] an audit certificate (16.1.8) should be provided when required by applicable law or regulation. If there is any uncertainty about whether documents should be included or not, the appropriate regulatory agency can be consulted.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or the FDA Biologics guidance page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Supportive documents, such as investigator curricula vitae, ethics committee approvals, informed consent forms, and batch numbers per subject are in the TMF or clinical supply database and should generally not be included in the CSR appendices.

Any documents not submitted and subsequently requested by the regulatory authority should be provided promptly.

Q4: ***How can I include data not mentioned in the ICH E3 text or appendices since the guidance predates the ICH M4 guidance associated with the CTD and Electronic Common Technical Document (eCTD)? Specifically, what are the options for submission of data for topics such as pharmacokinetics, pharmacodynamics, pharmacogenomics (genomic markers), gene therapy, stem cells, biomarkers, devices, quality of life, assay validation, data monitoring/review committees, electrocardiogram, other safety reports, images, pictures/scans, diagnostic tests for individualized therapy, and patient-reported outcomes?***

A4: It is appropriate to create new headings in the CSR and new appendices for these topics. The guidance provides for and focuses on efficacy and safety variables known at the time. Other topics should be well referenced in the CSR body and clearly identified in the table of contents.

Current submission options include:

1. Stand alone reports. These can be placed in "parallel" with the main clinical study report in the eCTD. For example, a clinical pharmacology study might have the clinical study report, a pharmacokinetic report, and an assay validation report. For an efficacy study with patient reported outcome (PRO) measures, there might be a PRO report. Each of these reports can be referenced under the same heading in the eCTD and placed alongside one another in the eCTD folder for that study. The nature of the information should be clearly described in the title of the document that is provided through the eCTD.

2. Study tagging files. In a region where study tagging files are used, it is recommended that a file-tag option from the "valid values list" be used — for example, safety report, antibacterial, special-pathogen (see Specifications for Study Tagging Files, http://www.ich.org/products/electronic-standards.html).

Alternatively, if a file-tag that adequately describes the material you are planning to submit is not available, you can request that a new file-tag be made available. This request should be submitted to your regional authority. In the event that this change cannot be accommodated within your time frame, you can place the document with the main body of the report (i.e., the document would be tagged with the "study-report-body" file-tag). The nature of the information should be contained in the title of the document that is provided through the eCTD.

Please refer to the most recent version of the "valid values list," as it is periodically updated as changes are requested.

C. Terminology (3)

Q5: ***A subject's death could potentially be captured in two separate data listings:***

- ***a. The listing referenced in section 12.3.1.1, Deaths. This section calls for sponsors to include a listing of "all deaths during the study, including the post-treatment follow-up period, and deaths that resulted from a process that began during the study."***
- ***b. The listing referenced in section 12.3.1.2, Other Serious Adverse Events. This section defines other serious adverse events as events "other than death but including the serious adverse events temporally associated with or preceding the deaths."***

There is concern that including events with fatal outcomes in section 12.3.1.2 may lead to double counting or miscounting of deaths. Can this issue be clarified?

A5: It is true that the structure and definitions provided in the ICH E3 guidance could result in deaths appearing in section 12.3.1.2 (as per E3 numbering), Other Serious Adverse Events, if an event terminated with, or was associated with, a subject's death. However, this should not result in double counting or miscounting of deaths. Although deaths may or may not be included in the listing for section 12.3.1.2, all deaths should be captured in the listing for section 12.3.1.1. That is, any subject death reported under section 12.3.1.2 as an "other serious adverse event" with a fatal outcome would also have been captured under deaths in section 12.3.1.1.

Q6: ***Section 12.2.2 of the ICH E3 guidance states that all adverse events occurring after initiation of study treatments should be displayed in summary tables. The example table in section 12.2.2 of ICH E3 (Adverse Events: Number Observed and Rate, with Subject Identification) is really a listing that will rarely be brief enough to place in the body of the study report. Moreover, in addition to severity, relatedness, and subject identifiers (shown in the example table), each adverse event should include the original investigator's verbatim term. How is it possible to include all of this information in a summary table? Can this table be modified?***

A6: The body of the clinical study report (ICH E3 section 12.2.2) should include a summary table of relatively common adverse events – those occurring in at least a particular percentage of subjects who received the investigational drug. This summary tabulation compares treatment and control groups and does not include subject identifying numbers or verbatim adverse event terms.

Of note, the example table provided in section 12.2.2 of the guidance is not meant to be presented in section 12.2.2 of the report, but in section 14.3.1, which is not part of the text of the clinical study report.

The ICH E3 guidance did not attempt to display all possible presentations of adverse event information, but rather outlined the summary table intended for section 12.2.2 and provided an illustration of the far more detailed display that would be placed in section 14.3.1. The example provided for section 14.3.1, however, does not try to illustrate all possibilities, but shows individuals with adverse events by body system, severity, and perceived drug-relatedness for treatment group "X." Listings should also display investigator's verbatim terms for each event and could be used to show demographic or disease-specific information, dosage, duration of treatment, or treatment cycle (for cancer chemotherapy).

Because it can be impractical to display all of this information in a single listing, such analyses can be presented in individual listings (e.g., by dose or other subgroup of interest). When adverse event data are presented by subgroup, however, a display of overall adverse events should also be included. For example, for a drug for subjects with chronic kidney disease, adverse events could be tabulated separately for subjects receiving or not receiving dialysis, but a table that includes adverse events in all subjects should also be included.

The listings that provide more comprehensive adverse event information, specifically subject identifiers and verbatim terms for each adverse event, should be provided in the study report, in sections 14.3.1 and 16.2.7. If each adverse event is to be characterized extensively (i.e., many items in the listing), electronic approaches may be appropriate.

Q7: Section 10.2 of the ICH E3 guidance requests an accounting of important protocol deviations. However, the flowchart in Annex IVa of ICH E3 (Disposition of Patients) recommends that data be provided on the number of subjects withdrawn from the study because of "protocol violations." Neither the term "protocol deviations" nor "protocol violations" has been previously defined by ICH. What is the distinction between a protocol deviation, important protocol deviation, and a protocol violation? Can these terms be clarified? In addition, does the guidance provide for sponsors' flexibility in defining what constitutes an important protocol deviation for a trial?

A7: A *protocol deviation* is any change, divergence, or departure from the study design or procedures defined in the protocol.

Important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. For example, *important protocol deviations* might include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

Protocol violation and *important protocol deviation* are sometimes used interchangeably to refer to a significant departure from protocol requirements. The word *violation* can also have other meanings in a regulatory context. However, in Annex IVa of the ICH E3

guidance (Disposition of Patients), the term *protocol violation* was intended to mean only a change, divergence, or departure from the study requirements, whether by the subject or investigator, that resulted in a subject's withdrawal from study participation. (Whether such subjects should be included in the study analysis is a separate question.)

To avoid confusion over terminology, sponsors are encouraged to replace the phrase "protocol violation" in Annex IVa with "protocol deviation," as shown in the example flowchart below. Sponsors can also choose to use another descriptor, provided that the information presented is generally consistent with the definition of *protocol violation* provided above.

The ICH E3 guidance provides examples of the types of deviations that are generally considered *important protocol deviations* and that should be described in section 10.2 and included in the listing in Appendix 16.2.2. The definition of *important protocol deviations* for a particular trial is determined in part by study design, the critical procedures, study data, subject protections described in the protocol, and the planned analyses of study data. In keeping with the flexibility of the guidance, sponsors can amend or add to the examples of important deviations provided in ICH E3 in consideration of a trial's requirements. Substantial additions or changes should be clearly described for the reviewer.

EXAMPLE FLOWCHART

DISPOSITION OF PATIENTS