



ICH E3 “Structure and Content of Clinical Study Reports” – Template or Guideline?

by Stephen de Looze

And the Lord said unto Moses, Write thou these words: for after the tenor of these words I have made a covenant with thee and with Israel. And he was there with the Lord forty days and forty nights ... And he wrote upon the tables the words of the covenant, the ten commandments. Exodus 34:27

Whether the ten commandments represent the world’s first written standard operating procedure is certainly a debatable topic, but the biblical account of how they were written makes those of us who have been involved in writing global SOPs, standards, and templates for clinical documentation quite envious. Moses knew that he was subject to an authority on the matter (some would say, *the authority*), and there wasn’t a many-tiered international drafting committee to twist and turn every sentence according to a plethora of perspectives on a multitude of issues before the final document was issued.

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I first joined the ICH E3 expert working group under the auspices of the European Federation of Pharmaceutical Industries and Associations (EFPIA) in December 1992 and worked on the guideline until its release in 1995. Added together, the work was a lot less than forty days and forty nights, though at times it certainly felt much longer! I will give an overview of the labyrinthine ICH process for those not so familiar with it. An ICH guideline is initially drafted and redrafted by an expert working group, usually located in one of the ICH regions (Europe, Japan or the United States of America), until it is accepted by the ICH steering committee: step 1 of the ICH procedure. During step 1, there will be consultation between industry representatives across the regions. For step 2, the regulatory agencies in each region are additionally consulted, and drafts are circulated for comment: three regions with both industry and agency representatives in each region makes a total of six committees! During this stage, the document will probably be redrafted by the expert working group many times—I recall about a dozen drafts of ICH E3—before step 2 has been concluded. During step 3, the regulatory agencies and other official bodies exchange comments and resolve outstanding issues, possibly leading to yet more redrafting. Step 4 consists of endorsement of the final draft by the ICH steering committee, which recommends the guideline for adoption in the three regions. This is the stage at which, for our purposes, the guideline becomes “official”, though before this is formally the case, the guideline must be incorporated into domestic regulations: this is step 5, the final step.

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Lucky Moses, with everything straight from the horse's mouth (if that is an appropriate metaphor), and no redrafting. He would have had a much tougher time if he had had to deal with several committees and subcommittees of archangels and angels. I recall one particularly low point during a meeting of our expert working group when—rather late in the day and dead tired—as we were discussing laboratory safety variables (not a thrilling topic and one always discussed late in the day due to its location in the guideline), we received a fifty-page fax from the American regulatory agency spokesman with detailed comments on the last-but-one draft, which of course we had no option but to consider in full detail. Or another occasion, we arrived at a meeting thinking we were almost finished, only to discover that our redoubtable chairwoman had recently shared a railway carriage between New York and Washington with the aforementioned American agency spokesman, who promptly gave her a lengthy list of yet more suggestions for our next meeting.

During my regular EMWA workshop, “Preparing Clinical Study Reports”, I am often asked by participants why the ICH E3 guideline seems vague, incomplete and contradictory, especially on the subject of structure of clinical study reports, one of the very topics it purports to address. Surely, I am asked, a group of experts could have come up with something better than this. For those who have not been involved in international committee work, it is hard to imagine the complexity and political dimension to these discussions. The participants from the six committees do not enter the debate from a neutral standpoint: politics soon erupt around seemingly harmless scientific issues. This usually results in those middle-of-the-road, rather vague, carefully-worded compromise solutions.

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This complexity inherent in the ICH process was enormously increased for ICH E3, because of the nature of the topic itself: clinical study reports are a funnel for all the wealth of issues, data and information gathered during a clinical trial. These

reports draw on a range of disciplines—clinical, pharmacological, statistical and regulatory—which may not speak the same language even within a single pharmaceutical company. From my medical writer's perspective, another unfortunate aspect of ICH E3 was that the various committees were composed largely of individuals who, whilst having much experience of regulatory issues, reviewing reports, quality assurance, etc., were much less experienced in actually applying guidelines to real-life writing assignments.

Those of us on the expert working group representing writing functions began the project with the aim of producing a flexible, user-friendly template. After all, many of us had done the same for our own companies. We knew that writers regularly have to resolve conflicts and integrate contributions across disciplines, and are therefore ideally qualified to produce guidance and templates for writing documents. Moreover, specialist topics such as clinical trial design, choice of control groups, biostatistics, safety reporting, and so on, were already covered, or soon to be covered, by other ICH guidelines. Alas, the progress of the ICH E3 document through the ICH labyrinth was not to be so straightforward. As the drafts were discussed and rediscussed, various experts insisted that ICH E3 must go into these specialist topics in some detail, thereby

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increasing the scope of the guideline to cover topics such as clinical trial design, data collection, data analysis and statistical issues. Soon, it became apparent that the

guidance was becoming so complex that whole areas such as clinical pharmacology could not be adequately addressed within the timeframe set by the ICH steering committee. The structure of the guideline, initially designed to reflect the structure of a clinical study report, became increasingly modified to accommodate new aspects of the guidance itself.

As a result, many sections and subsections of ICH E3 can never be standard for all clinical study reports. For example, some sections describe several *possible* approaches to data analysis; there is even one section that only describes how to format an appendix. As a corollary, the section numbering also reflects the guideline, not a clinical study report based on the guideline. Several of us on the expert working group expressed our concerns that the structuring and numbering of the guidance would be taken directly and applied to the structuring and numbering of clinical study reports once the guideline was issued. Others thought that it would be *self-evident* that this could not be so. I well remember our chairwoman on several occasions declaring, “It is not a template!”. As a compromise, the following statement was formulated and now appears in the “Introduction” to the guideline: “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. [...] The numbering should then be adapted accordingly”. Unfortunately, this statement does imply that a run-of-the-mill study report might be able to preserve unchanged the exact structure and numbering of the guideline, though it can easily be shown that this cannot be so (for example, the title page is “chapter 1” in the guideline, but whenever is a title page “chapter 1” in a report?). This notwithstanding, the statement does provide quite unambiguously the possibility for optimising the structure and numbering of any and all clinical study reports.

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From the many dozens of comments that I have received as a result of my EMWA workshop, I know that all conscientious writers who try to apply the ICH guidance to the letter encounter major problems with superfluous, repetitious, and poorly organised sections. Can we, they ask me, simply write “not applicable” under superfluous headings, is a cross-reference acceptable instead of repeating information, can all the “non-applicable” sections just be deleted or at least grouped at the end of the report? What about studies that do not really match the guidance—vaccines, quality of life, phase I, phase IV, interim reports, and so on? Their healthy writing instincts are telling them that a document produced by following ICH to the letter may fall short of their own best writing practice. But they are unsure, despite the statement in the “Introduction” of the guideline that I quoted above, whether modification of the ICH E3 structure or numbering would constitute a contravention of the guidance. Even worse, they may have templates from clients who demand that ICH E3 be followed to the letter, as if it were indeed a template. (In a curious role reversal, a contract research organisation recently engaged by my company to write a clinical study report according to our internal guidelines, complained that these “did not comply with ICH E3”.)

The Write Stuff

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This rigid interpretation of ICH E3 generally appears to have been produced by individuals who think it is “playing safe” to adhere to the letter of the guideline. I therefore took up the latter issue with regulatory reviewers during various international conferences. Their unanimous opinion is that writers should strive to make clinical study reports as reviewer-friendly as possible, if necessary by adapting the ICH E3 guidance to the study in hand. One European agency reviewer even admitted that potential problems of ICH E3 had possibly been overlooked because during its finalisation, a huge amount of European reviewers’ resources were being diverted to establish the European Agency for the Evaluation of Medicinal Products. My advice, therefore, to all writers is: adhere to the spirit of the ICH E3 guidance, but do not treat it as a straitjacket in terms of report structure—follow your writer’s instinct!

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Well, I am sure that we have not heard the end of this story. I am often asked whether ICH E3 will be revised. Although the need to do so has been recognised by many of those involved in the ICH process, other initiatives, such as the Common Technical Document, now have a higher priority. I expect that for some time to come we will have to live with the ambiguities of ICH E3, and with “expert” interpretations of what the guidance was actually intended to mean. Come to think of it, even after three thousand years it is not so very different with the ten commandments either.

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