Regulatory Writing

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The discussion section of a clinical study report

The discussion section of a clinical study report (CSR) is often a source of doubt among medical writers. The advice is usually to keep the discussion section as short as possible and not go into any deep analysis or attempt to put the trial into context. The line of argument is that the best place to really discuss the findings is in the integrated summaries, where pooled data are presented and the focus is on the big picture. And as company positions may change over time, a discussion section that is too detailed and assertive may cause problems later. The 'shorter is better' approach is no doubt sound advice that is widely applicable, particularly to CSRs that will generally be read as part of a submission. But is it always true? This is what the International Conference on Harmonisation (ICH) has to say on the matter in the guideline for the structure and content of CSRs (topic E3)[1]:

> The discussion and conclusions should clearly identify any new or unexpected findings, comment on their significance and discuss any potential problems such as inconsistencies between related measures. The clinical relevance and importance of the results should also be discussed in the light of other existing data. Any specific benefits or special precautions required for individual subjects or at-risk groups and any implications for the conduct of future studies should be identified. Alternatively, such discussions may be reserved for summaries of safety and efficacy referring to the entire dossier (integrated summaries).

The first thing to note is that the guideline is not, *per se*, against actually including discussion in the discussion. There is the suggestion (in the last sentence of the above quote), in line with the 'shorter is better' advice, that summaries and overviews may be more appropriate places to compare the results of the trial with other trials. The 'such discussions' in the last sentence of this quote is, however, ambiguous in that might not refer to all the preceding points. My interpretation is that although we should avoid making detailed comparisons of the results of the trial with other results from the programme or other results in the literature (something best left to summaries), there are still questions about trial design and conduct that may be worthy of mention. Indeed, the first sentence of the above quote says that the discussion should 'clearly identify any new or unexpected findings…,' that is, are there any caveats in the interpretation of the data and are there findings that bring into question the proper conduct of the study? I think that it is legitimate to consider addressing such study-specific issues in the discussion section, and indeed, the guidelines would seem to encourage it.

It should also be noted that not all CSRs are submitted as part of an initial dossier. Some for example may form part of a follow-up measure, that is, the CSR corresponds to a study required by the health authorities as a condition for marketing approval. In this case, the CSR may well be read largely as a stand-alone document and not as part of overall dossier. In this case, the discussion should certainly address the peculiarities of the trial and, in the event that the outcomes are not as expected, justify why this might be. If the findings of the trial are not properly justified, the health authorities are likely to demand an explanation anyway.

In summary, while the discussion section should certainly not be a dissertation, there are some contexts where we should consider discussing certain study issues, perhaps even at length.

References

1. ICH harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports, E3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; Step 4, 30 November 1995 [cited 2012 Sept 1. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf.

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Updated interpretations of the ICH guideline on the structure and content of CSRs

The ICH recently published a set of questions and answers about the ICH E3 guideline on the structure and content of CSRs.[1] The original ICH guideline was published in November 1995.[2] Just to give an idea of how things have changed since then, in 1995 few people outside academia or large companies were using the Internet and, for those that were, the browser of choice was Mosaic; WordPerfect was holding its own against Microsoft Word; the PDF format was still a proprietary format that did not support hyperlinks and other features that we take for granted these days; and XML, the 'backbone' of all electronic submissions these days did not exist. So it is a bit of an understatement to say that the needs might have changed since the guideline first became available.

The questions and answers themselves therefore focus on alignment of E3 with the requirements of the common technical document (CTD), and its electronic version (eCTD) in particular. One of the main clarifications regards the length of the synopsis. This should be three pages or less according to the E3 guideline, but as explained in the questions and answers, the ICH M4E guideline on the eCTD allows up to 10 pages on the grounds that synopses are stand-alone documents that should be intelligible without reference to the rest of the report. For complex and large studies, three pages are often far too short, however concisely the synopsis may be written. The Q&A document, however, does not disavow the three-page suggestion. Thus, as in most documents, it still seems good advice to keep the synopsis as short as possible, but without losing sleep if three pages are just not enough.

Another point addressed by the Q&A document is whether the headings in the original E3 guideline should be interpreted as a template or not. The confusion is understandable to a certain extent in that the E3 guideline contains phrases such as 'efficacy and safety variables should be provided in section 14', which does sound like it is referring to Section 14 of a CSR, rather than a reference to Section 14 of the guideline. On the other hand, naming the title page Chapter 1 is rather absurd, and perhaps a reflection of just how keen companies are not to irritate health authorities by not giving them what (they, the companies, think) is expected. So this clarification comes as a victory for common sense.

We should also remember that the E3 guideline primarily refers to efficacy and safety studies, although it does suggest that a similar approach can be taken for clinical pharmacology studies. Both pharmacokinetics and pharmacodynamics will be a major feature of many CSRs, particularly in the earlier phases of development, so clearly sections need to be created to accommodate such results. Again, the Q&A document makes this explicit, and reiterates that the guideline should not be interpreted as a rigid template. Thus, for outcome measures such as quality of life, which were not as common when the guideline was drafted as they are now, some flexibility is needed for appropriate presentation.

References

1. E3 Implementation Working Group ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers (R1). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 6 July 2012 [cited 2012 Sep 1]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf
2. ICH harmonised Tripartite Guideline: Structure and Content of Clinical Study Reports, E3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; Step 4, 30 November 1995 [cited 2012 Sep 1]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf.

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