FORMAT & PRESENTATION CLINICAL STUDY REPORTS

In this article, I would like to review some of the more practical aspects of the format and presentation of the Clinical Study Report (CSR); a key component of any registration application for a new pharmaceutical or biotechnology product. With the publication of EU Directive 2007/47/EC requiring"... clinical data even for Class I devices" the CSR will become an ever more important feature for medical devices too.

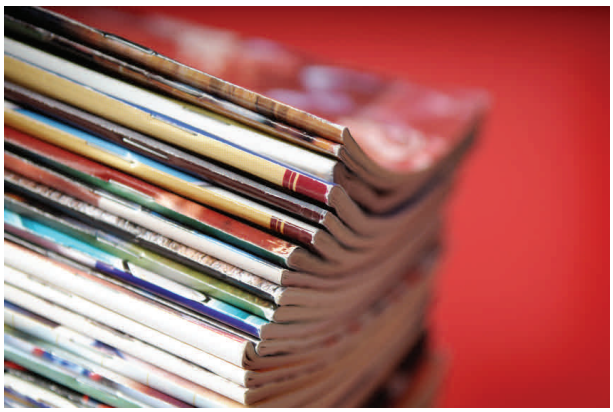
The CSR serves as the primary basis for communicating the sponsor's data from each individual clinical trial to a Competent Authority or Notified Body and is the foundation upon which subsequent 'Clinical Summaries', 'Clinical Overviews' or 'Clinical Evaluation Reports' will be built. In addition to its "regulatory role", the CSR will also likely serve as a basis for writing any subsequent manuscript, poster or oral presentation of the trial data. Irrespective of its use therefore, clarity of information and accuracy is key.

FORMAT

The first practical aspect any medical writer is faced with is what template or format should one follow. For pharmaceutical and biotechnology products intended for registration in any of the major territories (US, Europe, Japan) the answer should be simple...follow the ICH E3 guideline, published in November 1995. Details of this guidance can be found on the ICH website at:

http://www.ich.org/

As described in the introduction, this guidance is designed to, "...assist sponsors in the development of a report that is complete, free from ambiguity, well organised and easy to review". What is perhaps unclear is whether or not the intention of ICH was to use this as a true "guidance" document or as a mandatory template. Certainly with the introduction of e-CTD over the past few years and in particular its requirements towards granularity of data, my own experience suggests that a writer should seriously consider using this as a template.



Discussions at ICH level remain on-going however and in June 2011, the ICH published a final consultation paper with the aim of reaching consensus on this issue by June 2012.

On several occasions I have been asked how this format fits with an Abbreviated Study Report. Perhaps it's best to first answer the question "When is an abbreviated study report appropriate?" Again ICH E3 comes to our rescue, indicating that the omission of sections or summarising data may be acceptable (depending upon region) if the study being reported is an uncontrolled study, a study not designed to establish efficacy (or safety), a seriously flawed or aborted study or a study unrelated to the claims being made for the product. In such cases, my recommendation is to consider starting with the ICH E3 guideline and if possible (or practical) follow the main report headings as closely as possible, but omit or modify appendices as circumstances dictate. Importantly, sufficient detail on trial design and results needs to be available to at least allow a reviewer to determine whether or not a full CSR should be provided.

Regrettably, there is no such clear guidance when it comes to preparation of CSRs for medical device products, as most of the emphasis following the publication of 2007/47/EC relates to the Clinical Evaluation Report

(CER), which in essence is a summary of the findings from literature searches, previous clinical experience with the device (or similar devices) and the sponsor's own clinical investigations. Notwithstanding the CER, there is an obligation to provide Competent Authorities with a report of the investigation and so many companies have developed their own internal procedures and/or templates to help define the format. ProTherax Ltd can help with adoption of a template for the medical device CSR.

Whether you are dealing with a pharmaceutical or medical device CSR it is important to try and maintain a common font style within and between study reports, particularly where multiple reports are to be used within a regulatory submission. This common style makes it easier for the reviewer to read and review. If a company wishes to use different writers or agencies to prepare their CSRs, it is worthwhile investing in preparing a style guide, detailing which fonts are to be used for body text and headings and how figures and tables are to appear. For preparing body text, and in line with regulatory guidances, I favour true type fonts such as Times New Roman 12 or Arial 11

EASE OF REVIEW

The aim of any medical writer should be to prepare a study report that can be read and reviewed logically and easily; that includes use of clear language (bearing in mind that the CSR is likely to be reviewed by assessors whose first language is not English), ensuring that the report is written for its target audience (i.e. technically competent experts in the field but individuals who are unlikely to be familiar with your specific product). In particular, wherever possible avoid company specific acronyms, or at the very least ensure they are clearly defined in the report. Give consideration to the colours used in CSR Figures. Have you considered what the results may look like if the reviewer prints out the page on a black and white printer?

Importantly for a CSR, which may be several hundred pages, cross references, e.g. to tables, figures, sections or appendices must be clear; ideally these should be active links (hyperlinks) so that when reviewed electronically the reviewer can easily move around the report. Similarly, referencing to supportive information not derived from the clinical study will be important and should be in an appropriate (recognised) format such as the Vancouver style. With this in mind, it is worth considering the use of referencing tools such as Endnotes or Reference Manager.

ACCURACY OF INFORMATION

Perhaps most important of all, is ensuring the accuracy of the information presented, including not omitting "negative" data from the study report. After all, important benefit:risk decisions regarding the product's commercialisation will be made by an independent reviewer based on the assessment of the information in the study report. Remember that the CSR is not a manuscript, but a full and frank disclosure of the clinical data derived from the study.

Do not rely on the Quality Assurance process at the end of the study to audit your report; be pro-active and put in a place a robust QC process to check the accuracy of the data. In particular, the writer should ensure that all data in the CSR (e.g. text, tables, figures) have been cross checked against their respective source documents (e.g post-text table, subject listing, protocol, statistical analysis plan, etc.) and that any derived data such as expression of percentages adds up to 100% and any conclusions made on the basis of the data are indeed supported by the data.

Finally, recognise that the best CSRs utilise the efforts of several people, not just the medical writer; proactively involve your Statistics group, the Trial Manager, the Medical Monitor, the Principal Investigator, and if not written by a Regulatory person, get the Regulatory group to independently review the report for suitability for its inclusion in the registration application.