The clinical study protocol and medical writing: A good fit?

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Abstract

The characteristics of the clinical study protocol (CSP) are discussed with regard to (i) its structure and (ii) its development process. The benefits of medical-writing involvement into both aspects are highlighted. In particular, medical writers are encouraged to participate in the development of the CSP template of their organisation.

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While the clinical study report (CSR) has been a part of the classical medical-writing repertoire since the inception of medical writing as a professional discipline several decades ago, the clinical study protocol (CSP) made it onto medical writing's radar only considerably later – and in many cases has still not done so. This is surprising given the eminent importance of this document; it is also rather unfortunate because – as I will try to demonstrate in this article – the CSP is a document type that can particularly benefit from medical-writing expertise. This holds true for two separate aspects: (i) the CSP document and its structure and (ii) the process of CSP development.

The CSP document: Structure and content

We must start with an observation that is remarkable in our highly regulated environment: there is no 'official' guidance available that addresses the content and structure of CSPs in as detailed a manner as, for example, ICH E3 does for CSRs. ICH E6 on Good Clinical Practice lists content items to be included in a CSP. However, this list is far from exhaustive; in particular, it is considerably less detailed than the guidance for the corresponding CSR section (ICH E3: Section 9 'Investigational plan'). Moreover, ICH E6 provides no advice on how the various pieces of information in a CSP are best organised and arranged. Recently, the SPIRIT (Standard protocol items: Recommendations for interventional trials) initiative has published a far more extensive list of content items – however, again without any guidance on how to best structure a CSP document.[1,2]

As a consequence of this lack of guidance, there is a huge variability across the pharmaceutical industry in how CSPs are organised and structured – which contrasts sharply with the industry-wide relative homogeneity of CSR appearance as shaped by ICH E3. In turn, the quality of CSP documents with regard to how they are organised and how they present their information can vary greatly. Hence, the proportion of poorly written documents is considerably higher for CSPs than for CSRs. The originators of ICH E3 must have had the same impression when they included in their guidance the explicit advice that 'in each [CSR] section describing the design and conduct of the study, it is particularly important to clarify features of the study that are not well-described in the protocol'. This is truly one of my favourite sentences in the whole of ICH E3. It spells out clearly and correctly that the job on methods description in the CSR is not done by blindly pasting the CSP text and adapting its tense.

Obviously, it is easier to prepare a well-organised, well-written, user-friendly CSR than it is to produce an equally high-standard CSP. Why is that? There is more behind this than just the availability or absence of formal guidance. An important reason for this difference is the necessity for built-in redundancies in the CSP. The CSP has to describe many separate, but interlinked aspects which address, for example, the way examinations are conducted, which variables are collected at these examinations, how the collected variables lead to derived variables, how these are statistically analysed, which conclusions may be drawn from the results, and how all this relates to the objectives of the trial. Presenting all these inter-related aspects clearly, separately, and logically, without confusing and tiring the reviewer

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with a mass of repetitive information, is a true challenge. Carefully managing redundancies in the CSP text is a key success factor for the preparation of a user-friendly CSP.

A further aspect which makes CSPs trickier than CSRs is the increased diversity of the CSP's target audience. While the CSR almost exclusively targets the reviewers in the regulatory agencies, the CSP targets a diverse set of readers which includes not only the investigators and their staff (obviously the most important audience), but also other external bodies such as ethics committees, independent data review committees, and regulatory agencies. Each sub-audience is primarily interested in selected CSP topics only; and none of them is likely to read a CSP from cover to cover. Consequently, user-friendliness of the CSP requires thoughtful structuring with meaningful headings to allow each sub-audience to quickly locate the pieces of information relevant to them.

Here, at the latest, is where a medical writer should enter the stage. The presentation of complex information in a well-structured manner, thereby addressing both of the above aspects, i.e. carefully managed redundancies and user-group-targeted organisation, is certainly a core competency of medical writing. Any CSP team is well advised to make use of this expertise. The most efficient utilisation of this competency goes even a step further: obviously, the principles of effective CSP organisation indicated above should already have been taken into account by the underlying CSP template and its associated guidance text. The absence of formal guidelines for CSP structure constitutes an enormous opportunity to develop a general CSP template that lays the foundations for future quality CSP documents. Wherever medical writers see a chance to contribute to a CSP template, they should not hesitate to do so as this can make a large difference to subsequent projects.

When it comes to populating the CSP template for a specific CSP, the CSP author should always be aware of the importance of the CSP's document quality: the way the CSP presents its information can have a huge impact on the smoothness of the trial conduct and thus on the quality of the data collected. Moreover, the CSP sets the stage for several other documents further down the road such as the statistical analysis plan, CSR, and clinical summaries. Therefore, the CSP should reflect very conscious and thoughtful decisions with regard to the choice of terminology, definition of terms, and the way information is worded.

Going into details of how exactly a CSP template could be structured and populated is beyond the scope of this article. Anyone interested in going further into the depth of this complex matter may consider the corresponding EMWA workshops.

The process of CSP development

Medical-writing participation in CSP development is not common practice; and if medical writers are involved, their experiences are mixed. For too many medical writers, active membership in a CSP team can be tantamount to weeks or even months in a torture chamber. Many medical writers will find themselves producing an endless series of consecutive draft versions of the full CSP document to accommodate continual input from the team members – only to be surprised by a team decision after the tenth draft to add to the study design a further treatment arm, a preceding wash-out period and three more visits during the treatment period, and also to change the statistical approach from superiority to non-inferiority – based on a re-defined primary variable.

In view of the aforementioned complexities and redundancies of the CSP document, implementing such modifications clearly represents a high burden. Obviously, something very wrong happened in this scenario. But how can such an inefficient mode of working be avoided?

First, although seemingly trivial, we have to acknowledge the importance of almost every trial for the sponsor. Typically, a clinical study is a substantial investment of resources, sometimes to the limit of the sponsor's capabilities or even beyond. Occasionally, even the sponsor's economic survival may depend on the positive outcome of one single study. Hence, the burden on the responsible people to make the right decisions in designing the study may be enormous. Moreover, even within the sponsor's organisation, multiple stakeholders, potentially representing conflicting positions, may want to have a say in the objective, design, and setup of the study. Getting everyone to agree on and commit to one final CSP can be a challenge under such circumstances. As a result, the necessary process of the sponsor's internal thought maturation is rarely a straightforward path; instead, the team may frequently change its mind and may even turn repeatedly in circles during this expedition.

In principle, there is nothing wrong with this, and we should not even think of picking the battle of changing it. What we can and should do, however, is to ensure that this process takes place on the basis of the right document type.

Here, a document referred to as study concept, protocol outline, or the like comes into play.

Regardless what we call it, this document is characterised by the following features. First, it is restricted to the main medical-scientific content items only (in particular, objectives; key in-/exclusion criteria; treatment arms; complete schedule of activities; definition of the main variables and their statistical analysis). Second, and more importantly, it is almost completely devoid of the built-in redundancies typical of a full CSP document. Hence, while it can be a real nightmare to incorporate multiple substantial content modifications into an existing complete CSP document, capturing these modifications in a study concept is easy and straightforward. All maturation steps of the main study features should take place using this study concept as the basis for discussion. Maintaining such a study concept document during the process of thought maturation within the CSP team is certainly a valuable service that medical writing can offer. Collecting and consolidating sometimes conflicting contributions in an efficient manner is an expertise we routinely provide.

Importantly, work on the complete CSP document should only start after agreement on the study concept, which should include input from external sources such as key opinion leaders as well as approval from the sponsor's internal governance bodies. Ideally, at the final review of the full CSP, no comments will be raised that could already have been raised upon review of the study outline.

Even if a new study is planned that will be very similar to a previously completed study, I strongly recommend following the study-concept approach for CSP development, rather than already starting on the full CSP by editing the approved CSP from the earlier study.

Experience tells us that many CSP teams want to see a complete draft CSP document sooner rather than later in the process. Obviously, an education process is needed to raise the comfort level of CSP teams with the study-concept approach. The main arguments to support our case are that: (i) the amount of information contained in the study concept actually suffices to support practically all discussions and decisions on the main study features, and (ii) expanding an approved study concept to a complete CSP document is very straightforward and can be done by a medical writer very quickly; thus, following the study-concept approach will not extend the overall CSP development timelines.

Conclusions

The CSP qualifies for inclusion into the standard medical-writing repertoire. It is a document type that can greatly benefit from medical-writing expertise with regard to both the organisation of the complete CSP document and the streamlining of the process of its development.

Take-home messages for medical writers

1. Get involved in the setup and maintenance of the CSP template used in your organisation.
2. Support the CSP team's ongoing discussions on the study design by maintaining a brief, concise study concept reflecting all decisions.
3. Make sure that work on the complete CSP document starts only once the study concept is finally approved.
4. Ensure that the final CSP is sound and consistent with regard to the choice of terminology, definition of terms, and the way information is worded.

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