Clinical Study Protocols: How to Write to Solve Problems Now and Avoid Big Ones in the Future

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Leading the transformation of R&D
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Too many protocols are poorly written – wrought with inconsistencies in endpoint descriptions, timing of assessments, approaches to gathering data – and lacking consistency across the programme. The identification of different responsibilities, under the clear leadership of the medical writer, is necessary to improve the quality of clinical study protocols – to prevent problems and mistakes that can result later, during conduct of the clinical trial, or afterwards, when reporting on trial results.

Historically, protocol generation has been the responsibility of clinical and operations teams, who are understandably focused on ensuring that the appropriate data are identified for collection to support the study objectives and that the study is initiated as quickly as possible, often with the mindset that any inconsistencies will be corrected in future amendments. These poorly written protocols present challenges both during the study, when site personnel try to understand the requirements of an inconsistent document, and after the study, when clinical study report and submission document writers try to understand, and are often forced to re-write inconsistent study design and assessment descriptions.

In addition to these existing challenges, the growing requirements for disclosure and transparency are driving the need for additional thought and care in protocol development to ensure that the value of the information obtained in a study is balanced with the patient experience. Protocols, historically unlike any other regulatory document, have various audiences such as the Private Investigator, study coordinator, regulator and the patient at heart. Writing protocols consistently and clearly, from the first version, requires ownership of the process that understands the various goals of a protocol document and can provide the consideration, quality, and leadership that will ensure that these downstream challenges

<table>
<thead>
<tr>
<th>Strategy and design</th>
<th>The protocol accurately reflects the objectives of the study. It is clear and consistent and has the correct assessments to determine the success of the study</th>
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</thead>
<tbody>
<tr>
<td>Ethics</td>
<td>The protocol has been drafted with ethical considerations in mind. The study takes into consideration the patient experience and the concerns or reservations of individual patients both for ethical reasons and to ensure feasibility of recruitment</td>
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<tr>
<td>Re-usability</td>
<td>The protocol is optimised for re-usability in downstream documentation. From registration of the protocol to the extension of the protocol into the statistical analysis plan and clinical study report, relevant considerations have been explored to address how the protocol is being written for the ease of the next steps in documentation (eg description and selection of endpoints) (see Figure 1)</td>
</tr>
<tr>
<td>Process/controls</td>
<td>Process and controls have been agreed upon and implemented. Decisions regarding where the protocol will “live,” who owns the core protocol and amendment, strategies and technology solutions for maintaining version control, and the process for obtaining approval have been made and are being followed</td>
</tr>
<tr>
<td>Alignment</td>
<td>The protocol is aligned with all relevant company standards and associated documentation. It is consistent with applicable style guidance, similar approaches and descriptions within the same programme, the informed consent form (ICF), and the CRF. The protocol should be able to function as the starting point for the lexicon for the entire programme, which should carry all the way through to marketing application</td>
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<tr>
<td>Innovation</td>
<td>The protocol includes thoughtful input from multiple functions regarding both the design and assessments as well as relevance of that design and those assessments across the clinical programme (eg leveraging ideas across therapeutic areas and programmes, reducing the tunnel vision of the clinical teams, exploring new tolerances by the regulatory health authority (eg modelling and simulation to support some objective and end points), collecting certain data that will be valuable to contribute to a future bridging analysis etc)</td>
</tr>
<tr>
<td>Time</td>
<td>Everyone on the protocol team has had the opportunity to spend the necessary time and focus on performing the tasks that bring their highest value</td>
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Table 1: Fundamental goals of protocol writing
are minimal, re-usability of the content is high, and rework, including additional clinical interpretation, is low.

“The first step in any clinical study is the protocol; if that first step is organised, well-placed, and developed with the downstream activities in mind, the rest of the journey will go that much more smoothly”

Jen Moyers, Protocol Workstream Lead

Protocol creation, including document standards and drafting processes, is part of an ongoing and lively debate that generally exists between two camps: the clinical and operations functions and centralised medical writing. The clinical and operations functions own the content of protocols and tend to prioritise study design elements and consistency with other downstream documents (e.g., the case report forms (CRFs) and risk monitoring plans), with a goal of initiating the study as quickly as possible. In contrast, the centralised medical writing functions tend to focus on internal document consistency, clarity of thought, downstream re-usability in other areas of the dossier, and adherence to company standards. As always in these kinds of debates, the two sides tend to focus on either/or solutions, where one side is right and the other wrong, when a better solution can usually be found somewhere in the middle. Ensuring that the fundamental goals of the protocol remain the focus throughout protocol development will help ensure that a quality protocol is generated, from the first version. These fundamental goals include those listed in Table 1.

With all of these fundamental goals to consider, it is clear that there needs to be an understanding of the ownership and value of each. The owners of process and content knowledge are usually the medical writing or regulatory functions. The clinical and operations functions are focused on selecting the optimal design and getting the study started, as they should be. However, the coordination of efforts necessary for protocol creation, in addition to the time commitment required, is often more than the clinical and operations functions can handle in addition to their existing priorities. Therefore, when these functions are also the owners of a process, that process is frequently cut short in an effort to progress the document, often leading to unnecessary amendments and issues downstream in the reporting phase. This can result in a study that generates inconclusive data, extension of study timelines to collect additional measurements, inconsistencies that require explanation to health authorities, and more involved quality assurance activities, all requiring additional costs and potentially putting the programme at risk.

With the rise of patient centricity, there is also a need to engage the patient community and advocates to enhance feasibility and to get perspective on the key objectives and the measures to which we are willing to go (or not to go) to collect them. The role of clinical operations is critical to drive this process, engaging with the patient community and focusing on getting the clinical sites up and running. Clinical trials are increasingly more complex, often weaving collection of data for biomarkers, imaging biopsies,
A long-tenured executive with Synchrogenix and a strategic regulatory solutions provider, Kelley Kendle possesses a keen understanding of the regulatory landscape, coupled with a strong focus on client relationships. She has been instrumental in developing solutions to address the industry’s needs. With over 15 years of experience in drug development, Kelley is both an internal and external subject matter expert. As President, she is responsible for driving Synchrogenix’s strategic growth, including mergers and acquisitions, business process, and organisational dynamics.

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