10-Step Commercial Clinical Protocol Authoring Guide

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A protocol is the most important document in a clinical study as it is the foundation for subsequent operational, regulatory, and marketing objectives for the development program. Developing a protocol is an extensive undertaking that requires a cross-functional team and consideration of the position and role of the study in the full product development program. Before the protocol authoring process even begins, a variety of activities and decisions are necessary to establish a strategy for success.

The following steps provide concepts and considerations that are essential in formulating the details that will become the protocol synopsis and ultimately the clinical study protocol.

1. **Begin With the End in Mind**
2. **Design the Study**
3. **Define Technical Details**
4. **Draft the Synopsis**
5. **Define Operational Details**
6. **Minimize the Potential for Amendments**
7. **Draft the Protocol**
8. **Draft the Informed Consent Form (ICF)**
9. **Design Case Report Forms (CRFS)**
10. **Design and Compile Operations Manuals**

Pre-Authoring

1 Begin With the End in Mind

Your program team should first prepare an Integrated Product Development Plan (IPDP). This plan, which is largely based upon the desired final Target Product Profile (TPP) and product labeling, maps out all activities through marketing application submission and clearly outlines the purpose, position, and necessity of each study in the product development program. Without these documents, you run the risk of completing a study that fails to advance your product's development or is markedly less valuable to development than it otherwise could be. In this regard, we are reminded of the immortal words of Yogi Berra: "If you don't know where you are going, you might wind up someplace else."

Among other things, the IPDP should contain the clinically meaningful endpoint(s) for your studies that will be acceptable to regulators and support the desired marketing claims for the product. Additionally, the IPDP should include an assessment of the actual and potential competitive products likely to be on the market at or near the time of product launch. This information will be essential for optimal study design and conduct, and will therefore improve the chances of ultimate product success. Cross-functional input and buy-in from all key internal and external stakeholders for each study, as well as on the full development plan, is a necessity.

2 Design the Study

Before you start thinking about the protocol study procedures and visit schedule, you need to understand your overall goals for the study, and how the data that are collected will not only support your product development strategy but ultimately move your program forward. For studies in the early phase of development, consider first outlining the study objectives, as well as the endpoints that specifically address those objectives in a measurable and meaningful way. The design of the study should then flow from those objectives and endpoints, making sure the technical and logistical aspects of the protocol maintain a focus on the end goals.

For all studies, consider developing the statistical analysis plan (SAP) before drafting the protocol. During SAP development, the study objectives and endpoints are comprehensively considered and designed, along with the specific analytical methods needed to optimally interpret the data. Choose a sample size that is based on realistic estimates of expected or required differentiation from placebo, that has sufficient statistical power to reliably detect outcomes and differences of interest, that meaningfully contributes to accumulation of an adequate safety database for your product, and that is sufficiently feasible to enable successful study completion. At that point, begin exploration of study design options with the protocol objective(s), SAP, and the TPP in mind.

In designing your study, take the following into account:

a. Map out how key study measures will be assessed, with what frequency, and in what kind of study population. Properly defining the study population is essential, particularly to ensure that the inclusion and exclusion criteria appropriately select for the eventual target population, as well as for optimal assessment of safety and efficacy in that population.

b. Be sure that existing animal toxicology data are adequate to support any proposed duration of dosing, dose levels, and subject eligibility criteria.

c. Be mindful of manufacturing capacity and schedules for study drug to ensure that your study is feasible given the cost of goods and timelines for manufacturing. You may have to adjust the dosing duration, dosage, number of dose levels, or your study timeline to accommodate manufacturing and cost-of-goods limitations.

   Even after your drug is manufactured, you may want or need to develop specialized packaging such as blister packaging or cold-chain logistics to help ensure study success.

d. Remember that the more complex the study design (e.g., number of arms, number of objectives and endpoints, number or complexity of assessments), the greater the chances for errors, omissions, data quality issues, and unexpected complications during study execution; and, therefore, the greater the chance for study failure. Study design should be laser focused on what is required to produce only the information necessary for product labeling and/or to progress the compound to the next stage of development. For this reason, it is also important to avoid the common temptation of adding "nice-to-have" but inessential study components during the course of protocol development.

3 Define Technical Details

Establish or obtain an International Conference on Harmonisation (ICH)-compliant protocol template and develop and maintain a style guide and/or list of writing conventions to ensure consistency and clarity within and between study documents. Establish the appropriate reviewing processes, and identify crossfunctional reviewers (editorial, regulatory, clinical, statistical, data management, medical, product safety, senior management, etc.). Record all key decisions and their rationale throughout the development and writing process. Failure to do so may result in frequently having to revisit issues, causing unnecessary delays and changes in the protocol or development plan.

4 Draft the Synopsis

Generate the study schedule of events, and draft the synopsis. The synopsis should be no more than about 10 pages total. Obtain feedback from cross functional subject matter experts, senior leadership from the sponsor/contract research organization (CRO), and potential clinical investigators and study site staff. Revise and finalize the synopsis: this is the foundation for the clinical study protocol.

Protocol

5 Define Operational Details

Consider essential operational logistics such as how best to obtain laboratory test results required to enroll and/or randomize subjects (e.g., local labs versus a central lab), total blood volume drawn, equipment and space necessary for subject evaluation, availability of specialist(s) for nonstandard assessments, storage and shipping requirements for clinical specimens and investigational product, and scheduling limitations/conflicts for study visits. Consult both sponsor and CRO operations staff and study sites as necessary to determine the feasibility of the proposed operational plan.

6 Minimize the Potential for Amendments

Consider what qualifies for inclusion in the protocol: while the protocol should include all key information required for study conduct and protection of subjects, detailed information that is not directly relevant to study conduct (such as how something is to be done rather than what is to be done) is often better suited for operations manuals, which can be more easily updated throughout the study. Avoid redundancy within the protocol; state everything once. Use the synopsis as a tool to establish the foundation of the protocol. At the completion of protocol development, the synopsis should be reviewed to ensure it accurately reflects the content of the final protocol, especially if it is intended to be appended to the protocol or used separately as an internal reference tool. Continuously revising the synopsis while the protocol is being written is unnecessary and discouraged as this often leads to errors in one document or the other, as well as in the resulting study.

7 Draft the Protocol

Prepare the protocol draft by expanding on the detail in the synopsis regarding the investigational plan, study schedule, analysis plan, safety monitoring, and the other outlined provisions. Much of the protocol should be derived from template language, which generally does not change from protocol to protocol, but rather, only changes periodically following revised regulatory requirements or other administrative preferences. The protocol should include information on the demographics of the disease being studied and should include provisions for recruiting a fully representative population. Too many studies fail in achieving this, which can affect product labeling and use, result in regulatory delays, and unfairly penalize minority populations. Before completing the protocol, obtain review from cross-functional subject matter experts (which often includes patient advocacy groups), the sponsor and/or CRO personnel, and select study investigators. Revise and finalize the protocol.

Concurrent and/or Post-Protocol

8 Draft the Informed Consent Form (ICF)

Using an established and compliant informed consent form (ICF) template, draft the ICF with finalized protocol information at the appropriate reading level for the intended study subjects, which is rarely greater than about an eighth-grade level. Obtain cross-functional subject matter expert and sponsor/CRO/site feedback. Revise and finalize the form, which may require site- and institutional review board (IRB)-specific information or even site/IRB specific template language. While the consent must include all required regulatory elements, strive to make the consent form as short as possible and without repetition. A consent form that is overly complicated or too long to be easily read and understood fails in its purpose.

9 Design Case Report Forms (CRFS)

Capture data efficiently (fewer queries) with appropriate and reasonable CRF pages. Be considerate of open-ended text boxes versus check boxes: while an open-ended text box is preferable for describing unexpected, non-categorical events, check boxes are better for categorical items (e.g., ethnicity) to reduce the need for queries and to facilitate downstream data analysis. The CRF should undergo interdisciplinary review by representatives from key functional areas (i.e., data management, biostatistics, programming, clinical operations, regulatory, safety, medical) prior to finalization.

10 Design and Compile Operations Manuals

The clinical sites will reference operations manuals for additional study information that is not specified in detail in the protocol (e.g., pharmacokinetic sampling procedures, shipping information, tissue collection procedures, investigational product preparation/dispensation, study contact information, etc.). Use the manuals as an easily accessible reference for site study staff and a repository for information that has the potential to change during the study (e.g., shipping addresses if personnel/vendors are likely to change).

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Over his 30+ year career, Dr. Shoemaker has extensive experience in all stages of investigational product development, has moderated dozens of regulatory authority meetings, and has managed and contributed to over one hundred INDs, over a dozen IMPDs, and dozens of successful marketing applications across the majority of reviewing divisions at FDA and several international regulatory authorities.

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With nearly 40 years of experience in clinical research, Dr. Jack Modell has spent considerable time within both the academia and pharmaceutical side of the industry. Along with serving on numerous advisory and editorial boards, Dr. Modell has published over 50 peer-reviewed articles in medical and scientific literature spanning several therapeutic areas.

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A proven leader in the industry for more than 20 years, Mr. Vaughn has supported over 50 pain trials, more than 30 marketing applications, and 5 FDA advisory committee meetings (both back room and bullpen) over the course of his career. In the past year alone, he has had speaking roles in 12 FDA Type A, B, and C meetings.

If you have any questions about the foundational steps and considerations necessary for building a successful clinical study protocol, please contact us to consult one of our Rho experts.

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