Guidelines for Writing Protocols

The protocol is the operating manual for a clinical trial, and every detail must be considered.

BY ARON SHAPIRO

A well-written protocol is the single-most important quality control tool in a clinical trial. The protocol details research plans for a clinical trial and serves as the study's operating manual. It describes the study's background, rationale, objectives, design, subject population, methodology, statistical evaluation methods, and organization. Essential for all studies, protocols are particularly important in multicenter trials because investigators and their staffs must enroll a uniform subject population and closely follow clinical procedures in order to minimize variability and provide a robust dataset from all sites. A well-written protocol ensures that the study is designed to precisely test the hypotheses proposed and that the study will use a uniform methodology to strengthen the quality of the study's outcome.

This article provides guidelines for writing a sound protocol. Although retina clinical trials vary depending on the disease and population being studied, following the International Conference on Harmonization guidelines for Good Clinical Practices (GCPs) will help to assure the US Food and Drug Administration, the study's sponsor, and the investigating team of the study's ethical and scientific integrity.

TITLE PAGE

A protocol's title page must include the full title of the study, its purpose and objectives, the sponsor's name, the date of issue, the protocol version (if amended or not), the phase of drug development (ie, phase 1, 2, or 3), and the Investigational New Drug application number under which the study will be conducted. The full title should be concise, but it should also provide readers with an accurate summary of the study, including the study design, drug product to be tested, active comparators and/or negative control, indication, patient population, and setting. It is important to number and date every version of the protocol during its development. The protocol will likely undergo a large number of changes as reviewers examine each edition of the draft, and marking clearly on the title page the version of each protocol will reduce the likelihood of confusion and clerical error.

INTERNAL COMPONENTS

Contact Information

Contact information should be provided so that investigators and staff have a point of reference for questions regarding study conduct and subject safety. Key contact points include the responsible sponsor parties, the study managers who are responsible for running the study across sites and who are often from a clinical research organization, and the clinical monitor who can be contacted in the case of adverse events or questions of subjects safety. Signatures of all individuals should accompany their contact information to indicate their approval of the protocol.

Synopsis

A concise synopsis provides an overview of all study aspects and mirrors the outline of the protocol itself. Each section of the synopsis is divided into formatted headings and subheadings, which will then be used in the table of contents after completion of the first draft. A list of abbreviations typically follows the table of contents.

Introduction and Background

The introduction provides the rationale for why the trial is being conducted. The first half of the introduction provides a broad review of the disease in question, detailing the population affected and the epidemiology, pathophysiology, signs, symptoms, and outcomes of the disease. This portion of the introduction also lists current treatment modalities.

The second half of the introduction focuses on the drug product being tested, elaborating on its mecha-

nism of action, its preclinical pharmacodynamic and toxicologic profile, including a review of any previous clinical experience. If the study proposes off-label use of a drug already approved by the US Food and Drug Administration, it is important to provide justification for its use and to address potential safety concerns in the proposed study population.

Study Objectives

Every clinical trial has a primary objective, and often multiple secondary objectives, that state the research questions to be tested. Objectives should be simple and specific, and they should be listed early in the study description. The objectives must be achievable within the scope of the trial proposed. Every effort should be made to resist the temptation to add too many objectives, or to add objectives that may be too ambitious for the study's design.

Endpoints

Objectives provide the overall aim of the study, but efficacy and safety endpoints are the variables or parameters that comprise the actual dataset that will be collected from study measures and procedures. For example, in a study on the effects of a particular drug on diabetic macular edema, the primary and secondary endpoints might be, respectively, mean change from baseline in ETDRS BCVA at month X, and percentage of subjects who gained at least 15 letters from baseline at month X. In this example, the measure (ie, procedure) is BCVA, and the endpoint (ie, data point) is mean change in BCVA from baseline to month X. All studies should include primary safety endpoints to be measured, such as incidence and severity of systemic and ocular adverse events, or change from baseline in physical examination parameters.

Study Design and Methodology

This section must be planned carefully because it provides highly detailed guidance on the actual conduct and procedures involved at each study visit. The study's design, methods, and procedures must support the specific study objectives. The type of study to be conducted must be stated explicitly (ie, whether it is pilot, observational, retrospective or prospective, placebo- or active-controlled, single- or double-blind) and whether the drug is in phase 1, 2, or 3 of development. The arms (or treatment groups) and the number of subjects per arm to be enrolled in and/or complete the study are also described in this section. Note that in written documents pertaining to clinical trials, study participants should be referred to as "subjects," not "patients." In most cases, a diagram or flow chart will accompany the list of procedures to be performed at each visit. Also, a table of the study's procedures, which readers may easily reference, should be included. The expected length of time for each study visit and for the entire study should be noted in this section.

It is extremely important that the protocol describe the population to be tested. The inclusion and exclusion criteria for selection of subjects should be listed. (An initial statement on recruitment strategies [eg, patient database, advertisements, notices, etc.] is sometimes included.) First, demographic restrictions are noted; these describe whether the subject should be of a certain age, sex, or race. A positive medical history of the disease in question is usually the initial inclusion criterion, followed by the presence of definable and modifiable signs and symptoms of the disease, graded ideally in a standardized and reproducible fashion. The optimal study population will have disease of moderate severity, because too mild or too severe disease might not allow the demonstration of change or drug treatment effect. Researching protocols of similar studies often yields useful insights for selection criteria for subject inclusion. Exclusion criteria are an exhaustive list of prohibited concomitant medications and diseases. Instruction on how subjects will be withdrawn and plans for data collection and follow-up with withdrawn participants are outlined in this section.

The study methods and procedures—including interventions, tests, visits, and the sequence of all study activities—are listed next. Thorough details of what occurs at each study visit, the time periods allowed between visits, and the frequency with which procedures or tests should be performed are included here. If a drug treatment is to be administered, then the dose, frequency, route, and duration of treatment should all be specified. Investigators and designated study personnel are also accountable for the study medication and supplies, so it is important to note how and where materials and supplies are to be stored.

Information on the observations to be made, how they will be made, and how frequently they will be made are listed next in this portion of the protocol. These observations, results of the various tests or measures adopted in the protocol, will comprise the final dataset (ie, the primary and secondary efficacy and safety endpoints) to be statistically evaluated by researchers. If symptom or quality-of-life data are to be collected via questionnaire, a sample of the questionnaire should be appended to the protocol. When using established procedures, a reference to the appropriate published work is typically sufficient; however, for new or modified

procedures, a thorough description should be included. Procedures for data collection and recording should also be described. It is important to note the methods that will be implemented to ensure the validity and quality of data. A statement on confidentiality is also a necessary component of this section. Who will collect the data? Who will have access to the data? Statements describing how long and where data will be kept and who will be responsible for ensuring confidentiality are included in this section of the protocol.

During the study, periodic monitoring will occur to ensure that the protocol, GCPs, and applicable local regulations are being followed. A study monitoring plan that allocates adequate time for monitoring activities is often included in an appendix. A section outlining the assurance of adequate procedures for the monitoring of adverse events may either be found here or under a separate heading. Detailed definitions of adverse events and serious adverse events, and the information surrounding the recording and reporting of such instances, must be provided.

Statistical Methods

This section should provide all statistical considerations for data analysis. First, the hypotheses and/or null hypotheses being tested are fully described with statistical nomenclature. Then, the populations to be used for statistical analyses or different datasets are defined. These usually include the full analysis set, which is composed of all enrolled subjects; the per protocol set, which includes all subjects in the full analysis set who did not have any major protocol violations; and the safety analysis set, which is made up of all subjects who received any study medication. A detailed plan for the statistical analyses of primary and secondary endpoints, the variables to be used to assess baseline comparability of the groups, how the data will be reported (ie, means, standard deviations, medians, etc.), and statistical tests and analyses and data conventions to be used are also found in this section. The statistical calculations and justification about the proposed sample size are necessary components of the statistical methods. All of this information should be provided in a complementary document, the Statistical Analysis Plan, or SAP, in which statistics and data tables to be generated are reported in greater detail.

Ethical Considerations

A statement should be made that the clinical study is being conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization guidelines on GCPs, and applicable local regulatory requirements and laws. This section will also outline subject confidentiality and rights and state that it is the responsibility of the principal investigator, or person designated by the investigator, to obtain a freely signed informed consent from each subject, or from the subject's legally acceptable representative, prior to inclusion in the trial.

Publication Plan

The protocol may include the sponsor's publication plans following the study. For example, the protocol must indicate if there will be access to raw data and the right to publication by all investigators, and in which publications or conference presentations researchers plan to present data.

References

A sequentially numbered list of references matching those cited in the text and for all points that can be attributed to a specific source is needed to ensure validity of facts.

Appendices

The appendices include all documents that are being provided with the protocol for review. These may include questionnaires, consent forms, recruitment materials, screening tools, participant instructions, the investigator's brochure, diagrams, study flow chart, and any other appropriate materials. Detailed procedures for conducting certain tests and for grading signs and symptoms that are described in the study design and methodology section should also be included. In this way, the protocol is a critical tool for assuring consistency and reproducibility across sites when conducting a multicenter clinical trial.

CONCLUSION

To ensure an effective, timely institutional review board review, it is in the best interest of the sponsor to pay close attention to the organization and clarity of the information presented in the protocol. It is imperative that the information in the protocol be consistent with the information provided in the consent form and other study documents.

This column certainly does not address all issues that may be required to adequately describe a clinical study to an institutional review board; however, it is a strong framework for groups preparing such documents. ■

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