CHAPTER

24

Writing a Protocol

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Doing clinical research is the goal of so many interested in clinical medicine. We are constantly urged to bring observations from the laboratory into the clinic as quickly as possible. We are anxious to know if there is any human consequence to these findings. If the phrase "the devil is in the details" has relevance, it certainly does when it comes to clinical research. Although an idea for a clinical study may be very good, the challenge is putting it into a format and structure that has a good chance of yielding clinically valid information. The process of converting an idea into an infrastructure that results in clinically valid information is in essence creating a clinical protocol. There is a more formal definition for a protocol: "a complete written description of, and scientific rationale for, a research activity involving human subjects."[1] This chapter reviews the general guidelines of protocol writing in the United States.

1. TYPES OF PROTOCOLS

There are two major categories of clinical protocols. The first category is natural history protocols, which can be retrospective reviews of cases/histories. Case reviews are usually not initially performed with patients but with their data. Follow-up with questionnaires or further testing can certainly come from the initial review. Natural history studies can also follow what happens to patients with a specific disorder. The second major protocol category is an interventional study or clinical trial designed to change the course of a disease through a therapy or the use of instrumentation. Interventional protocols exist in four phases. Phase I studies initially are performed in the evaluation of new drugs and are designed to determine safe doses of a drug. Phase II studies search for evidence of efficacy and provide further safety testing; they usually are conducted using 20–100 people and may or not involve a placebo. A phase III study is carried out when previous experience has identified the degree of activity of a drug, its approximate dose, and possible side effects. In a phase III study, one writes a protocol to compare a new intervention with a currently standard practice or placebo. Phase III studies are performed when a drug is being considered for Food and Drug Administration (FDA) approval for a license of a new indication and usually involves hundreds or thousands of participants. Finally, phase IV, or postapproval, studies may be performed and are designed to monitor safety in thousands or millions of subjects. For those interested in multicenter studies as well as their ethical aspects, several texts can be consulted.[2–5]

2. WRITING A PROTOCOL

Often, an idea for a protocol comes about after your research group or clinical colleagues have seen and discussed a particularly interesting case that might stimulate you to think about a specific question. Usually, there is a real enthusiasm about the prospect of doing a study, and that is good. However, once the enthusiasm begins to ebb, the difficult work begins (Table 24-1). Generally, the principal investigator of the study will assume the responsibility of coordinating

TABLE 24-1 Basic Elements of Body of Protocol

Précis of 400 words
Table of contents/outline
Introduction
Study background
Animal/human research
Describe new techniques
Will an Investigational New Drug request be sought?
Objectives
Study design and methods
Inclusion and exclusion criteria
Women and children
Monitoring subjects and criteria for withdrawal of subjects from study
Define end points and criteria for withdrawal
Human subjects protection
Subject selection
Benefits and risk/discomforts
Compensation?
Adverse events
Protocol consent and assent
Appendices
References

these considerations. Someone must write the initial protocol, and it is the principal investigator who will begin with the help from the coinvestigators of the study. What is the question you wish to ask? Is this something that can be asked in the context of a clinical study? Are patients available to be evaluated? Often, there is a very good idea, but the types of patients needed may not be available. Would the study being considered put the patients at any risk? Every study carries some degree of risk, but whatever the risk, the risk must be justified by the possible benefit. If there are adverse events, how will these be handled? There are important practical considerations as well. Once studies begin, there is a need for coordination of visits, collection of data, and the handling of phone calls or other inquiries to the study. All these need to be considered before beginning a study.

It usually makes sense to include all persons who are involved in the protocol as associate investigators on the protocol. This has become more important as concerns about conflict of interest in clinical research are being concretized in a more formalized evaluation (see Chapter 11). The principal investigator should use the associate investigators' expertise in the development of the protocol. Each associate investigator should review the protocol, with special attention to the part related to his or her expertise. The principal investigator must collect the comments of her or his associate investigators and create the final protocol, which is then submitted for review.

3. WHAT HAPPENS TO YOUR PROTOCOL?

Before going to the institutional review board (IRB), many institutions will have a pre-IRB committee that will review protocols for scientific quality and potential cost. Other regulatory agencies, such as the FDA, may need to be informed as well. For some protocols, such as randomized, masked studies, a data and safety monitoring board may be constituted to review the data and safety of a study as it progresses. The protocol is sent to this group for its concordance and suggestions.

4. ESSENTIAL ELEMENTS TO THE PROTOCOL

The elements to a clinical protocol may vary to some degree between academic institutions, and what differs are the added features required by an institution. An interventional trial usually requires more information and will be scrutinized very carefully.

4.1. Précis

The body of the protocol begins with the précis, a short (400 words or less) description of the study. The précis should describe the objectives, study population, design, and what outcomes will permit you to evaluate the study.

4.2. Introduction

The introduction describes the background of the study that is being proposed, often with a description of the disorder under study and the general study design. If the protocol is a clinical trial using a new drug or technique, these should be described. An outline of the research, both human and animal, that has been done to date should be provided as well as a justification of the dosing in this study that is different from that of other studies already performed. The mechanism of action of a new drug or how a new device works should be included.

4.3. Objectives

The objectives section can be short and succinct. It describes what will be accomplished with the study and often is divided into primary and secondary objectives.

4.4. Study Design and Methods

The study design and methods describe how the objectives will be achieved. The following questions should be addressed: Is the study a clinical trial or a natural history study? What type of patients will be recruited? What type of disease will the patients have? Will the patients be followed as clinic patients, inpatients, or both? Will this be a follow-up to a study that was recently completed? What is the patient recruitment plan? The IRB will seriously review the number of patients and proposed period of time for the study. A power analysis to determine the number of patients required should be presented. Many studies are stopped because patient recruitment is far below what the investigators claimed they would be able to obtain. Special consideration needs to be given to "vulnerable" patient populations, such as children and those with mental infirmities. A detailed description of what will be done should be provided. Will patients receive a new medication and, if so, will it be compared to a standard therapy? Will patients be randomized and, if so, how? What is the role of the pharmacy? An outline of the number of visits and the tests planned is essential. This is called a protocol timeline. (Table 24-2). A description of the methods and procedures and how potential complications will be managed is required. Projection of the need for special resources, such as research bloods (or other fluids), should be provided. The impact of the protocol on standard of care requirements for the hospital should also be outlined.

TABLE 24-2 Example of a Protocol Timeline

Scheduled Visit Week (See protocol for handling of delayed or missed treatments.)	B[1]	0[1]	2	4	6	8	10	12	14	16	18	20	22	24	26
General Assessments															
Medical history	X														
Brief body systems review and examination	X	X[1]			X			X				X			X
AE assessment[2] and current meds[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of life determinations	X							X							X
Vital signs (BP, respiration, temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual System Exams															
Manifest refraction[3]	X							X							X
Visual acuity	X[3]	X[1]	X	X	X	X	X	X[3]		X		X		X	X[3]
Slit lamp exam and tonometry	X	X[1]	X	X	X	X	X	X		X		X		X	X
Dilated fundus exam	X	X[1]	X	X	X	X	X	X		X		X		X	X
Inflammation grades	X	X[1]	X	X	X	X	X	X		X		X		X	X
Substudy evaluations (site-specific)		(X)						(X)							(X)
Study Therapy															
Open-label therapy[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory															
CBC with differential	X	X[1]	X	X	X	X		X		X		X			X
Hematology,[5] LFTs,[5] and urinalysis	X			X		X		X		X		X			X
Pregnancy test for females	X							X				X			X
Serum test drug and anti-antibodies		X[6]	X[6]	X[6]	X[6]										X[6]

[1]The baseline (week B) visit may immediately precede the initial (week 0) treatment if all requirements for enrollment have been met and are documented. Listed evaluations (marked with [1]) under week 0 should be repeated only if > 5days had elapsed since the initial baseline visit, or if medically indicated.

[2]Adverse events should be reported at any time between scheduled visits as necessary. At each visit, a review with directed questions is performed with the patient regarding adverse events in the interval since the last visit, including an assessment of the injection site(s). Current medications are recorded at each visit.

[3]Manifest refractions must be performed when scheduled and repeated as indicated, including whenever a drop in BCVA ≥ 10 ETDRS letters (≥ 0.20 logMAR) occurs within a 12-week period.

[4]Continuation of study therapy will occur unless a safety or withdrawal study end point is reached. If an end point has been reached, the participant will exit the trial.

[5]Hematology and liver function tests include sodium, potassium, chloride, CO_2 (total), creatinine, glucose, urea nitrogen, alkaline phosphatase, ALT/GPT, and AST/GOT.

[6]Serum test drug and anti-idiotypic antibody levels will be performed at all phase II sites. The default intervals will be at days 0*, 14*, 24, 35*, and 182*. Up to three additional intervals may be specified to obtain pharmacokinetic (PK) samples from participants during the early induction phase. (The * means trough value.) Participating sites will be shipping out coded specimens to a sponsor-designated central laboratory.

4.5. Inclusion and Exclusion Criteria

A careful description of inclusion and exclusion criteria is necessary for successful subject recruitment to a protocol. A clear and succinct list of particulars needed for a patient is necessary. For example, for a study involving patients with diabetes, what type of diabetes will be studied? Will it be necessary for patients to be on a specific insulin regimen? Will patients likely have certain medical complications requiring prolonged hospitalization? Similar information is required for the exclusion criteria. Are there age limitations? Not only are there inclusion and exclusion criteria related to the disease under study but also there are exclusion criteria because patients are unable to undergo certain tests. For example, one possible exclusion could be hypersensitivity to an imaging dye required for testing. Another might be prior drug use or stage of a disease. If a particular category of patients are to be excluded from the study, a thoughtful justification for the exclusion is necessary.

4.6. Women, Children, and Minorities

Phase III clinical studies and natural history studies should be designed so that the results can be stratified to establish whether or not benefits occur in men, women, children, and minority populations. This may not be possible for phase I clinical trials, in which a limited number of patients will be studied.

4.7. Monitoring Subjects and Criteria for Withdrawal of Subjects from Study

The risk/benefit ratio is carefully considered by IRBs. The protocol should describe criteria to minimize harm. Expected minor and serious adverse events criteria for detecting and reporting adverse events need to be described in detail. The protocol needs to define event end points and when a patient will be withdrawn because of adverse events. Examples might be worsening of an underlying medical condition or a patient's poor compliance with the protocol. Of course, a patient has the right to withdraw from the protocol at any time. If a patient is terminated or withdraws from a protocol, details of what type of follow-up is necessary should be provided. If the study is using a new intervention, which most often is performed under an Investigational New Drug request, then a separate section is needed.

4.8. Compensation

Payment of clinical research subjects has been an established policy for quite some time.[6] The amount of remuneration varies depending on the type of research protocol. For some studies, details of travel and subsistence provisions are required in the protocol.

4.9. Protocol Consent and Assent

Informed consent is one of the most important elements of a protocol. Required elements of the consent document include the following:

1. A statement that the study involves research.
2. An explanation of the purpose of the research, an invitation to participate, an explanation of why the subject was selected, and the expected duration of the subject's participation.
3. A description of procedures to be followed and identification of which procedures are investigational and which might be provided as standard care. Use of research methods such as randomization and placebo controls also needs to be described.
4. A description of any foreseeable risks or discomforts to the subject, an estimate of their probability and magnitude, and a description of what steps will be taken to prevent or minimize them, as well as acknowledgment of potentially unforeseeable risk.
5. A description of any benefits to the subject or to others that may reasonably be expected from the research and an estimate of their likelihood.
6. A disclosure of any appropriate alternative procedures or courses of treatment that might be advantageous to the subject.
7. A statement describing to what extent records will be kept confidential, including examples of who may have access to research records, such as hospital personnel, the FDA, and drug sponsors.
8. For research involving more than minimal risk, an explanation and description of any compensation and any medical treatments that are available if subjects are injured through participation, where further information can be obtained, and whom to contact in the event of a research-related injury.
9. An explanation of whom to contact for answers to questions about the research (include the name and telephone number of the principal investigator) and the research subject's rights.
10. A statement that research is voluntary and that refusal to participate or a decision to withdraw at any time will involve no penalty or loss of benefits to which the subject is otherwise entitled.

11. A concluding statement indicating that the subject is making a decision whether or not to participate, and that his or her signature indicates that he or she has decided to participate, having read and discussed the information presented.

12. If the subject is or may become pregnant, a statement that the particular treatment or procedure may involve risks, foreseeable or currently unforeseeable, to the subject or to the embryo or fetus.

13. A description of circumstances in which the subject's participation may be terminated by the investigator without the subject's consent.

14. Any costs to the subject that may result from participation in the research.

15. The possible consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation.

16. A statement that the principal investigator will notify subjects of any significant new findings developed during the course of the study that may affect the subjects and influence their willingness to continue participation.

17. The approximate number of subjects involved in the study.

18. If the investigator is not planning to return results to the subjects, a statement should be included that explains the reasons for planned nondisclosure and recognizes the subject's right to that information under the Privacy Act. The following language has been recommended for use in protocols at the National Institutes of Health Clinical Center:

> The investigators conducting this study do not plan to provide you with the results of any medical tests or evaluations or other information pertaining to you, or other research data or results because (the results will be preliminary) (the results will require further analysis) (the results may reveal unwanted information about family relationships) (further research may be necessary before the results are meaningful). (If meaningful information is developed from this study that may be important for your health, you will be informed when it becomes available.)
>
> By agreeing to participate in this study, you do not waive any rights that you may have regarding access to and disclosure of your records. For further information on those rights, please contact Dr. _____ (principal investigator).

Consent forms should be written in simple language, at a sixth- to eighth-grade level, always trying to use short terms. The consent document should outline what the patient is to expect during the study. What are the tests to be done? What should the patient expect, and are there any adverse effects the patient might suffer? Are you giving a new medication or new surgical technique? The investigator needs to outline why he or she is considering this approach, the possible problems, the possible advantages, and also what alternative therapies are available. Will blood be taken? Define how much blood will be obtained and put the amount in terms that can be easily understood, such as teaspoons or tablespoons. If a new medication is provided by a drug company, this should be stated in the informed consent. Conflicts of interest of investigators need to be addressed (see Chapter 11). The informed consent should describe whether researchers participating in the protocol have a relationship with the drug company. The consent document also should outline whether or not the investigators will receive royalty income if the study is successful.

Remember that the consent process is an evolving process and institutions may have specific requirements. For example, one possible addition is HIV testing. Specific wording is available to cover many of the required and suggested concepts that were mentioned previously. A translated consent document is required when English is not the primary language of the population you are planning to recruit.

4.10. Child Assent

The assent is how you obtain a child's agreement to participate in a clinical research study. The form is usually shorter and simpler than the consent document, but you still need to outline what you plan to do and what the child should expect. This, of course, is a complicated subject since the child's age, maturity, and psychological state will effect whether the child is even capable of understanding what will happen. You need to consider this and the IRB will determine whether it agrees with the approach outlined.

The written consent document does not substitute for a detailed oral explanation of the protocol to the patient. Patients should have an opportunity to ask and receive good answers to all questions in order to be sure they are fully informed.

References

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