Chapter 16

Writing a Protocol

Elizabeth A. Bartrum, and Barbara I. Karp National Institutes of Health, Bethesda, MD, United States

Abstract

Writing a research protocol is a key step in the conversion of a set of ideas for a research project into a coherent infrastructure that will result in obtaining data to support or refute a stated hypothesis. The written protocol document serves as a guide for investigators and staff conducting the study and also contains the information needed for regulatory bodies, such as the Institutional Review Board, Food and Drug Administration, and others, to conduct their reviews. The protocol addresses rationale, scientific aims, targeted population, and procedures and risks within the regulatory framework where the study will be conducted. It should account for the protection of its subjects through monitoring and analysis of risks, with an emphasis on maximizing the protections of its participants while ensuring the integrity of the data. This chapter will outline the process, structure, and examples of the important elements and considerations when writing a protocol.

Keywords

Clinical research; Clinical research protocol; Informed consent; Template

Outline

Introduction

Clinical research is the goal of many entering medicine and science careers. The ability to obtain observations at the bedside and study how and why a disease process happens is a hallmark of scientific discovery. The process of converting an idea into an infrastructure that results in clinically valid information is, in essence, creating a clinical protocol. In the modern era, the means of developing an idea into study with scientific rigor that also fulfills regulatory requirements for research with human participants is best met through writing the protocol document. The written protocol is the roadmap for the conduct of every phase of the study, including the rationale, scientific aims, targeted population, and analysis plan. The protocol lays out the procedures, risks, and protections. It further provides the plans for monitoring the study for the safety of participants, for the integrity of the study, and for compliance with regulations. This chapter reviews the general guidelines for writing a protocol in the United States.

Regulatory Oversight

In the early stages of conceptualizing a research idea, it is important to identify the regulatory bodies that will have oversight of the study. It would be unfortunate to spend a great deal of time writing a protocol and gaining departmental or institutional approvals, only to learn that additional regulatory requirements pertain, so that the investigator faces further administrative burden rather than being able to proceed directly to conducting the research.

Regulatory bodies may include those enforcing federal, state, and local area laws as well as those with oversight of policies specific to the institution. In the United States, federal regulations for human subjects research center around the US Code of Federal Regulations (CFR), 45 CFR 46, otherwise known as the "Common Rule."[1] As described in Chapters 4 and 5, the Common Rule includes minimum standards for the research protocol, consent form, and requirements for the Institutional Review Boards (IRBs) that must review the research (see Chapter 4). If a research study in the United States involves an investigational drug or device, it will also need to comply with regulations from US Food and Drug Administration (FDA), specifically 21 CFR 50 and 21 CFR 56.[2,3] Studies conducted by or in conjunction with the Department of Defense (DoD) are also subject to DoD regulations.[4] Institutions may require additional internal reviews. For example, a radiation safety committee may be required to review studies with ionizing radiation; the institution may require a review to identify the burden on the utilization of its resources or a pediatric safety committee review may be required if a study enrolls children. Principal Investigators must assure compliance with review requirements at federal, state, local, and institutional levels.

In addition to laws, there are often requirements from funding agencies and institutions with which one is affiliated. Some institutions mandate the use of standardized templates or forms for the protocol, consent form, and other documents that help investigators fulfill all the requirements. It is prudent to contact the institution's office affiliated with Human Subjects Protection Program or the IRB to check for availability of templates and guidance. Furthermore, new investigators navigating the process of protocol writing, obtaining approval, and running a study for the first time will find it helpful to seek guidance from a seasoned mentor

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Writing a Protocol

Once the idea for the study is conceptualized, the first major issue to address is the development of the study design, which informs the study's basic infrastructure. Once the study design has been determined and the general regulatory boundaries of the research are identified, then the research protocol can be written. It is important to think of each section as being intertwined with the others. One section builds on another, so that during writing one can rely on or cite already written concepts. If the section does not further clarify the progress of writing the study, then the writer should pause and reevaluate the need for that section.

There are two major categories of clinical protocols: observational studies and clinical trials. Other kinds of clinical research protocol design include case studies, screening protocols, training protocols, and others that may not fit easily into one of these categories. Further descriptions of study designs can be found elsewhere in this book.

Clinical Trials

Clinical trials are studies in which an intervention is given to a well-defined group of individuals. The US National Library of Medicine categorizes clinical trials into "phases" depending on the intended goal related to safety and/or efficacy and size of the population to be enrolled (Table 16.1).

Elements of a Protocol

The written protocol serves as a guideline for the conduct of the study, delineating the rationale, procedures, and analysis plans for the investigators and includes plans and protections for participants. The written

protocol also must incorporate elements needed for all required and optional reviews, such as that by scientific review committees, study sections, IRBs, the FDA, auditors, funding sources, and regulatory bodies. An organized approach and following a standardized template or format helps to assure that all elements needed for each aspect of protocol use and review are present.

Table 16.1

Phases of Clinical Trials

Phase I	Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
Phase II	The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
Phase III	The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.
Phase IV	Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.

Modified from the National Library of Medicine. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0022682/.

Elements of a protocol include those that reflect the scientific and human subjects' protections aspects of the study, such as the hypotheses, aims, selection of study population, design and procedures, analysis plan, and steps to minimize risk. Other elements are those that address administrative and regulatory oversight issues, such as monitoring, reporting to sponsors and regulatory bodies, and identification of conflicts of interest. Finally, there are those elements that contribute to understanding the protocol document such as a table of contents, references, and list of abbreviations.

There is no set order to the sections of a protocol. However, the organization should be assembled to be logical, avoid redundancy, and enhance understanding by the investigators who will use it as a working guide to the study and by reviewers who will evaluate it. Table 16.2 provides some sample approaches to protocol section organization.

Key Protocol Components

In the sections that follow, information is provided on key components for a written protocol, what information is pertinent to that component, and an approach to protocol organization.

Precis

Most protocols start with the précis or abstract, a concise summary of key protocol elements including the objectives, study population, design, and outcome measures. Although first in the protocol, the précis is often written last, once all study elements are known and can be summarized.

Introduction or Background

In the introductory section of the protocol, the study hypotheses and objectives are placed in the context of the scientific field of inquiry. This section sets up the rationale for the study, describing the disease or condition being studied, citing and synthesizing earlier preclinical and clinical research on the topic of the study, and explaining why the current research question is pertinent, important, interesting, or novel. In this section, the planned study intervention (if any) can be introduced. The introductory section should contain information, for example, on why a new or repurposed drug is being applied to the particular disease under study. The section

may explain the gap in existing knowledge about a condition that the study will attempt to close. If a research drug is being evaluated, information should be provided on what is known about the drug, including its mechanism of action, pharmacology, pharmacokinetics, pharmacodynamics, toxicology, and known drug interactions. Similarly, research with devices should provide adequate background information for reviewers to assess the utility and safety of the device in the context of the study.

Table 16.2

Sample Approaches to Protocol Organization

Example I[a]	Example II[b]
Précis: Table of Contents List of Abbreviations 1. Introduction and Background 2. Study Hypotheses/Objectives 3. Subjects: Inclusion/Exclusion Criteria 4. Study Design and Methods a. Recruitment b. Screening c. Procedures d. End of study procedures 5. Management of Data and Samples 6. Additional Considerations a. Use of ionizing radiation b. Use of gene therapy 7. Risks and Discomforts 8. Subject Safety Monitoring 9. Outcome Measures 10. Statistical Analysis 11. Statement on Equitability, Information on Inclusion/Exclusion of Vulnerable Populations 12. Anticipated Benefit 13. Classification of Risk (for the Study as a Whole) 14. Consent Documents and Process 15. Data and Safety Monitoring 16. Quality Assurance 17. Reporting of Unanticipated Problems, Adverse Events, and Protocol Deviations 18. Alternatives to Participation 19. Privacy 20. Confidentiality 21. Conflict of Interest 22. Legal agreements 23. Research and Travel Compensation 24. References 25. Appendices	Statement of Compliance Signature Page Table of Contents List of Abbreviations Protocol Summary 1. Key roles and Contact Information 2. Introduction: Background and Rationale 3. Objectives 4. Study Design 5. Study Enrollment and Withdrawal 6. Study Intervention 7. Study Schedule 8. Study Procedures/Evaluations 9. Assessment of Safety 10. Study Oversight 11. Clinical Site Monitoring 12. Statistical Considerations 13. Source Documents and Access 14. Quality Control and Assurance 15. Ethics/Protection of Human Subjects 16. Data Handling/Record-Keeping 17. Publication/Data Sharing Policy 18. References 19. Supplemental Materials 20. Appendices

[a] Combined NeuroScience IRB. *CNS IRB protocol and consent templates 2016*. Bethesda (MD): Intramural Research Program, National Institutes of Health. (Available on request).

[b] National Institute of Dental and Craniofacial Research. NIDCR clinical trial (interventional) protocol working shell [online]. Available at: http://www.nidcr.nih.gov/Research/Toolkit/-startup2.

In short, the Introductory/Background section should allow someone reading or reviewing the study to understand what the study is about and how it fits into the broader realm of research on that disease or condition.

Hypotheses and Objectives

The Introduction/Background section then provides the context for understanding the specific study

hypotheses and objects. The study hypotheses are what the study is intended to demonstrate. The hypotheses drive the study design that, in turn, allows data to be collected, which supports or negates the hypotheses. The hypotheses further determine the study objectives. Study objectives define the specific aims of the research. The objectives may include a summary of the outcome measures.

Studies usually have primary outcome measures that tie back directly to the objective of the study and secondary outcomes, which may be more exploratory measures reflecting secondary goals of the research. The primary outcome measures should be clearly defined and measurable. The time point at which they will be assessed also should be explicitly identified.

The hypotheses, objectives, specific aims, and outcome measures should be clearly articulated and succinct.

Study Design and Methods

Once the objectives, outcome measures, and specific aims are determined, the focus turns to assembling the processes and key procedures into a coherent whole. The timing as well as type of research procedures should be chosen to be the most efficient and safest way to obtain the data needed to achieve study goals.

The specifics of study procedures are delineated in the Study Design and Methods section. Practicality as well as scientific needs must be considered. The duration of the study should reflect the disease or condition and intervention being studied. The frequency of study measurements needed to capture the primary outcome measure must be defined. Pragmatic concerns such as the availability of funding or other resources, access to necessary equipment, and the term of appointment of the investigators must be considered. If the study goals cannot realistically be achieved with the available time and resources, then the primary outcomes should be reconsidered to assure they are achievable within the available parameters. It is more prudent to develop a study that can be completed and provide results, than to design a study which is ideal in theory, yet practically cannot be completed.

It is helpful to depict the study procedures from the participant's viewpoint and in chronological order. Such an organization will help investigators and reviewers understand the flow of visits, observations, and interventions throughout the course of participation. A study timeline or flow chart (Table 16.3) may help provide a study overview.

Table 16.3

Example of a Study Timeline Flow Chart

Scheduled Visit Week	B	0	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			X			X				X			X
AE assessment and current meds	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	X							X							X
Visual acuity	X	X	X	X	X	X	X	X		X		X		X	X
Slit lamp exam and tonometry	X	X	X	X	X	X	X	X		X		X		X	X
Dilated fundus exam	X	X	X	X	X	X	X	X		X		X		X	X
Inflammation grades	X	X	X	X	X	X	X	X		X		X		X	X
Substudy evaluations (site-specific)		(X)						(X)							(X)
Study Therapy															
Open-label therapy		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory															
CBC with differential	X	X	X	X	X	X		X		X		X			X
Hematology, LFTs, and urinalysis	X			X		X		X		X		X			X
Pregnancy test for females	X							X				X			X

Recruitment

From a participant perspective, study procedures start with recruitment. The protocol should describe the recruitment process, including the source of participants. Recruitment materials that inform potential subjects about the availability and nature of the study require IRB review and may be provided in protocol appendices. Recruitment materials should be prepared to be consistent with the protocol document. The practicability of recruitment should be considered. If a rare population is being studied or if eligibility criteria are stringent, it may be difficult to accrue enough subjects to complete the study in a timely manner.

Screening

A key element of the research process is ensuring eligibility. Screening subjects to determine if they qualify may require taking a formal medical history, reviewing existing medical records, a physical examination, blood tests, imaging, or other procedures. If the screening procedures are done as part of the study, they must be incorporated into the written protocol with a description of the methods and their risks or discomforts. If subjects are screened separately from the protocol, the method should be briefly acknowledged.

Procedures

All participant research procedures and clinical care procedures related to the research should be described, preferably in chronological order. The duration of individual procedures and cumulative time commitment, including number and timing of visits and total duration of participation in the study, should be stated. It should be clear where procedures will be done and if inpatient admission is required. Required and optional

study procedures should be identified. Plans for the participants' end of participation, including transfer of care back to their own physicians, completes the section on study procedures.

While it is important to establish a study schedule based on the research need, it is equally important to consider the practicality of the schedule. A rigid schedule may be difficult to adhere to for either investigators or participants. If exact timing is not critical to the study, time windows should be built in for each study visit or procedure. For example, rather than specifying that a procedure will occur every 7 days, it might be preferable to allow the procedure to be performed every 4–10 days. Incorporating flexibility whenever it will not interfere with achieving study goals will help avoid protocol deviations.

Some protocols include procedures that are required for clinical care of the participant rather than to provide research data. It is important to differentiate these to the extent possible. Procedures for clinical care are generally done on an individual basis, based on the participant's medical needs. These may include evaluating a clinical status, confirming a diagnosis, or treating a complication or intercurrent illness.

In studies with more than one cohort, the participant groups may undergo different procedures or combinations or schedules of the same procedures. In this case, it may be preferable to provide separate descriptions of procedures by cohorts within the protocol.

Risks, Discomforts, and Inconveniences

Research studies should be designed from inception to be as safe as possible for participants. Making a study safe requires identifying the risks, discomforts, and inconveniences of each study procedure and intervention and the cumulative burden of participation. Thus, each subject procedure in the protocol should have a corresponding delineation of its associated risks, even if only to acknowledge that the risks are minimal.

The risks of experimental research drugs and devices deserve emphasis, especially for early phase studies. Information on the risks of novel drugs or devices may be found in published preclinical or clinical studies, the package insert, or Investigator Brochure. This information should be synthesized and summarized in the protocol. The possibility of unforeseen risks for drugs or devices being used for the first time in people is especially important to note. If risk information specific to the research drug or device is unavailable, then the investigator should identify potential risks based on devices or drugs with a known similar mechanism of action. For later phase studies, where data on safety are available, the protocol should focus on describing adverse effects that are common even if they are nonserious as well as serious adverse effects even if they are rare. The incidence of adverse effects should be stated if known.

Once the risks are delineated, the steps needed to minimize risks can be more easily identified and incorporated into the protocol. Protections may include, for instance, pregnancy testing before exposure to radiation or imaging, monitoring the electrocardiogram during procedures with cardiac effects, performing phlebotomy to obtain blood for blood count or blood chemistry monitoring. Some participants may need to be excluded from specific procedures for safety reasons. For example, people with metal implants may need to be excluded from magnetic resonance imaging. It is important to identify the timing as well as the type of monitoring. A case in point is if a study drug has been shown to cause an elevation in liver function tests beginning at 3 days after administration and peaking 2 weeks after drug administration, then a “safety visit” at 1 month will miss the critical window between 3 days and 2 weeks to detect this adverse effect.

Individual subject monitoring during participation is an important component of risk minimization to consider. Information on subject monitoring could be incorporated into this section or placed in a separate section on monitoring (see below).

Protocol Risk Category Determination

Taking into account the cumulative risks and burdens of participation, the level of risk for the protocol as a whole should be defined as "minimal risk" or "more than minimal risk."

For studies enrolling minors, it should also be determined if a "more than minimal risk" study is no more than a minor increment over minimal risk. For minors, the risk level of the study as a whole, along with consideration of whether there is direct individual benefit, determines whether the study fits into a category of approvable research under 45 CFR 46 subpart D.

If there are multiple study populations, then the overall risk and benefit may be different for individual study populations. In that case, the risk determination for each population should be separately recorded.

Protocol Benefit Category Determination

Assessment of the overall benefit of study participation also is required. The classification of benefit should be weighed based on reasonable expectation of benefit for the individual subject. Direct benefit to an individual subject is not a requirement for protocol approval. The possibility of indirect benefit, such as gaining generalizable knowledge may be sufficient depending on the nature and risks of the study. Compensation for research participation and ancillary care received during participation are generally not considered direct benefits but are, rather, incidental to the research.

Overall Benefit-to-Risk Ratio Determination

Each study must have a favorable benefit-to-risk ratio as assessed by the investigators and IRB record. This determination is especially crucial in studies including minors, as the benefit and risk analyses both contribute to determination of whether the study is approvable under 45 CFR 46 subpart D. Some institutions apply a similar consideration of benefit and risk to clinical research with other vulnerable populations, such as adults without consent capacity due to cognitive impairment.

Data and Safety Monitoring

Individual subject monitoring (discussed above) is the first type of monitoring described in this chapter. A second type of monitoring addresses cumulative and emerging study data. "Data and safety monitoring" is the process by which the data from all participants are evaluated as a whole to determine if there are trends that affect the integrity of the study or subject safety. The Data and Safety Monitoring section of the protocol should identify who will monitor the study, what they will review, and how often by frequency or trial benchmark. The protocol should identify suspension or stop rules for the entire study in the event that a problem is identified.

The selection of the monitor and method of data and safety monitoring should reflect the risks of the protocol. For minimal risk studies, data and safety monitoring by a study investigator or other individual may suffice. Masked clinical trials and studies where any of the investigators have a financial conflict of interest are best monitored by an individual or group independent of the study. An independent monitor ensures objective review of the data and also provides for review of unmasked data if needed to identify a safety concern, without corrupting the integrity of the study. As described in Chapter 10, clinical trials may require a Data and Safety Monitoring Board (DSMB), sometimes called a Data and Safety Monitoring Committee (DSMC), which is a formal monitoring committee of experts. For studies with DSMB oversight, the DSMB should be identified and their monitoring plan for the particular protocol described in the protocol document.

Quality Assurance Monitoring

Quality assurance (QA) monitoring is a third type of monitoring all studies require. QA monitoring ensures

that all the specifics of a trial and applicable regulatory requirements are followed. For example, QA monitors may look at the following:

- the temperature of freezers where samples are stored to assure they remain within study-specified ranges and sample integrity,
- signatures and dates on consent forms to assure validity,
- dates of procedures to confirm they are within study windows, and
- completeness of individual participant files.

The monitors, process, and timing of QA assessments vary with study and institution. The plan for QA monitoring for the specific protocol should be recorded in this section.

Unanticipated Problem, Adverse Event, and Deviation/Violation Reporting

In research, as in life, nothing proceeds perfectly as planned. Many problems can arise during a research study. Common problems fall into two main categories: adverse events and deviations. Adverse events are untoward medical occurrences. Deviations are unplanned changes from the written protocol. Examples of adverse events include a known or previously unknown side effect of a drug, a prolonged hospitalization, or surgery. Examples of deviations might include a missed study visit, a procedure occurring outside of the prescribed study window, or any other situation where the study does not adhere exactly to the written protocol. Some adverse events and deviations are also "Unanticipated Problems," i.e., those that are unexpected, at least possibly related to the research agent, and suggest an increased risk of harm than was previously known. IRBs, the FDA, sponsors, and other regulatory bodies all require reporting of adverse events and deviations but may have different or additional rules governing the types of events that require reporting, how they are reported, and the time frame of reporting. The investigators must, therefore, know the requirements for their study and incorporate an appropriate reporting plan into the protocol.

Study Population: Eligibility Criteria

Choosing an appropriate study population is another key to conducting a safe and scientifically valid study. Defining the study population is an intricate balance. Being too inclusive may create a heterogeneous population with too many factors to control during analysis. Conversely, being too restrictive could eliminate some who could validly participate and may hinder recruitment efforts, making it difficult to enroll a sufficient number of participants to complete the study. The protocol should delineate both inclusion criteria (who can be in the study) and exclusion criteria (who cannot be in the study) based on scientific need and safety concerns.

In each study, the inclusion criteria should, at a minimum, (1) identify the disease or condition people must have to participate, (2) define the acceptable age range, and (3) delineate all other factors required to be in the study. Exclusion criteria should focus primarily on the protection of participants, with careful consideration of criteria needed to exclude those for whom participation would be unsafe. For example, the study of a research drug that is metabolized by the liver may be unsafe for those with known liver disease. There also should be exclusion of those with factors that may interfere with assessment of study outcomes. For example, a study on pain may require exclusion of anyone taking pain medication, which would obscure study results. Similarly, individuals with other lung diseases may need to be excluded from a study of asthma.

Studies may have more than one population or cohort of participants. A study may enroll those with a condition and healthy volunteers as a comparison group. In this case, it may be helpful to provide separate listings of eligibility (inclusion/exclusion) criteria for each cohort, rather than to try to combine them into a single list.

Writing eligibility criteria as a bulleted or numbered list may make the criteria easier to review and implement than describing them in a free text paragraph.

One of the 45 CFR 46 criteria for IRB approval of research is that subject selection be equitable on the basis of gender, race, ethnicity, religion, nationality, and similar factors. All eligible persons should be considered for study unless there is a compelling safety or scientific rationale for exclusion of a population. If it is anticipated that the enrolled subjects will not reflect the racial and ethnic composition of the population in the recruitment area, an explanation should be provided. If, for example, the disease being studied is more common in a minority subpopulation, the rationale for the anticipated unbalanced distribution should be stated.

Similarly, if an entire group or population, such as women or those of a particular race or ethnicity, will be excluded, a strong scientific or safety justification is needed to assure fair and equitable representation in research whenever possible (see Chapter 13). However, there may be safety concerns for some populations that validly limit their ability to participate. For example, studies with known maternal/fetal risk may exclude women who are pregnant. Non-English speakers may not be able to validly participate in a study of language or may have their safety compromised if they are in a study that requires close and careful monitoring and communication of mood or psychiatric symptoms. However, care should be taken not to exclude subpopulations, for example, non-English speakers, women, or others unfairly.

Vulnerable Populations

The Common Rule recognizes the "...special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons." It further provides regulatory protections for pregnant women/fetuses, prisoners, and children in subparts B, C, and D, respectively. Protocol-specific safety measures may be needed for these and other "vulnerable populations." For example, a protocol enrolling children should include provisions for having pediatric expertise among the clinical staff as well as age-appropriate instructions and equipment. Studies enrolling illiterate or uneducated participants should include a means for obtaining consent and providing critical study information that is not dependent on written materials.

Alternatives to Participation

Participants must be told, via the informed consent process, of any therapeutic alternatives to participation in a clinical trial. It is helpful, therefore, to incorporate information on alternatives in the protocol document as well. The alternatives may include standard care (rather than a research intervention) for patients with the disease under study or participation in another clinical trial (if available). It should be acknowledged if the drug, device, or intervention under study can be obtained outside of the study, such as through a prescription for off label use.

Privacy

"Privacy" refers to protecting the integrity of the person. Considerations for privacy should be outlined, such as assuring that study procedures are conducted in an individual room with the door closed rather than in an open area, and limiting persons present to those needed for the procedure.

Confidentiality

Confidentiality protects the subjects' personally identifying data and records. Each protocol should contain a written plan for protecting confidentiality. Confidentiality can be maintained by assigning records, data, and samples a code that does not embed personal identifiers and keeping the key to the code separately and

securely. Further protections may include limiting access to identifiable data and the key to the code and keeping records secured in double-locked storage and on secure, protected servers and computers.

Confidentiality is especially important in studies that collect sensitive information, such as that on illegal drug use, alcohol abuse, or sexually transmitted diseases. For these studies, a Certificate of Confidentiality[5] (CoC) should be considered. The CoC, obtained from the National Institutes of Health (NIH), protects participants from having their research information released under court order. The use of a CoC should be noted in the protocol.

Statistical Analysis

The statistical analysis section provides crucial information on how the collected data and samples will be analyzed to achieve the primary and secondary study aims. The statistical analysis section should have sufficient information for reviewing committees to be able to determine that the methodology is sound and valid for the planned analyses.

The statistical analysis section also needs to provide information, such as a power analysis (see Chapter 25) to support the accrual number request. The number of planned subjects to enroll should be adequate to provide sufficient data for valid results, while also being the minimum number needed as well to avoid unnecessary exposure of participants to research risks. The expertise of a statistician should be obtained when designing the study and again when writing the statistics section of the protocol.

Management of Data and Samples

This section should delineate the storage and management plan of research samples and data to assure their integrity and availability for analyses to fulfill the objectives of the study. There is growing recognition, however, that the utility of collected research data and samples is not limited to the study under which they were collected. Secondary use of research data and samples is increasingly common and yielding important results. The protocol should, therefore, anticipate and plan for management of data and samples after the study analyses are completed. The protocol should clearly articulate if samples and data will be retained after the study is complete, whether data and/or samples may be shared with others, the purposes for which they may be used, and any restrictions on use. The protocol management plan must reflect information in the consent form on the additional use of data and samples. If participants are offered options, the participants' choices as to further use should be outlined.

Qualifications of Investigators

Study safety relies on the use of qualified research staff as much as on minimizing risks of procedures. The "qualifications of investigators" section of the protocol may identify those who perform certain research procedures solely by training or credentials. Individuals who play key roles may be identified individually by name, degree, specific role in the study, and relevant experience and training to fulfill that role. Steps should be taken to assure an adequate number of staff and that the staff, as a whole, encompasses the full range of expertise needed to conduct the study, both from a procedural/analytical perspective and with regard to participant safety. For example, if advanced imaging techniques will be used, the study should include investigators with expertise in the conduct of the imaging procedures and analysis of the data. If children are enrolled, there should be investigators with pediatric expertise. If there are anticipated adverse effects or complications from a study intervention (such as cardiac toxicity), appropriate specialists (such as a cardiologist) should be included.

Legal Agreements

Various legal agreements may be needed for collaborations with researchers outside of one's own institution, when working with a commercial entity, a sponsor, or a granting organization. These legal agreements may come in many forms such as Clinical Trial Agreements (CTA), Cooperative Research and Development Agreements (CRADA), Memoranda of Understanding (MOU), Material Transfer Agreements (MTA), or Data Transfer Agreements (DTA) as described in Chapter 29. The protocol should identify collaborators, sponsors, commercial entities, and others associated with the study.

Conflict of Interest

A financial conflict of interest arises in research when an investigator has a potential monetary stake in a specific study outcome. For example, an investigator who owns stock in a company producing the drug under study may benefit financially if the study succeeds or may lose money if the study fails. The written protocol document should identify all potential and actual conflicts of interest for study investigators and staff, in accordance with the requirements of the investigators' institution.

Compensation

Many studies compensate participants for the time and inconvenience of participating in a research study. The amount, method, and timing of compensation should be stated in the protocol. This section also should describe if study cohorts will be compensated differently. Conditions on compensation should be specified, for example, if compensation will be prorated if a participant fails to complete all study procedures, or if a fee for those requiring a companion also will be provided.

Consent Process and Documents

Obtaining informed consent from each research participant is one of the most important precepts of conducting ethical research. There are four important elements to consider with regard to obtaining valid and fully informed consent: (1) the participant and/or his/her legal representative (as applicable), (2) the person obtaining consent, (3) the consent process, and (4) the written form that conveys the study information.

Persons Providing Consent

Consent must be obtained from the participant directly whenever possible. There are, however, some study populations, individuals, or conditions that make direct participant consent impossible. Common groups without consent capacity include minors, who always lack legal capacity to consent and may lack cognitive capacity to understand participation, and adults whose cognitive impairment is extensive enough to limit their understanding of the implications of participation. Additional situations may include persons who are comatose, sedated, or under the influence of specific classes of drugs.

The protocol should identify whether subjects must be able to provide their own consent or if a legally authorized representative may provide consent on their behalf. Legally authorized representatives may take many forms. Parents and legal guardians generally represent their minor children. The Common Rule requires consent of both parents for participation of their minor child in research that is more than minimal risk without direct benefit. Two-parent consent also may be required for minimal risk research or research with potential benefit if, for example, the parents are divorced and have joint custody, depending on the rules at the research site. Some institutions make use of a medical or research durable power of attorney (DPA). A DPA designates an individual authorized by the participant to make medical decisions on his/her behalf if the participant is not able to. Some studies permit a participant's next of kin to provide consent. It is important to

have provisions to invoke surrogate consent for ongoing participation in studies where consent capacity is likely to be lost during the course of participation, as in studies of patients with neurodegenerative disorders. In writing the protocol, consider whether surrogate consent may be needed and under what conditions. Institutions also may have particular requirements about the use of surrogate consent for adults and regarding acceptable consent surrogates.

Regardless of parent or surrogate consent, children and adults without consent capacity should agree to be in a study. Their agreement should be based on written assent whenever possible. Dissent from the participant should always be respected.

Individuals Obtaining Consent

Those who obtain consent must be fully knowledgeable about the study and its risks and able to answer questions from the participant. They also must understand the consent process, which is as important as a well-written consent form. The higher the risk of the protocol, the more critical it is that the person obtaining consent be able to independently answer questions and assess the risk of the individual considering participation. For example, the person obtaining consent for a questionnaire study with study procedures including only a single blood draw would not likely need the same level of education and training to consent subjects as the person obtaining consent for a Phase I investigational drug study or a gene therapy study. The protocol should identify those authorized to obtain consent either by individual qualification or by group credentials.

Consent Process

The planned consent process should be delineated in the protocol. The standard approach to obtaining consent includes the consenting investigator meeting in person with the potential participant. The investigator explains the study. Together, they review the written consent document. The participant is given the opportunity to have any questions answered. If the participant agrees to enter the study, he/she signs the form. The signature of a witness also may be required.

Alternate forms of the consent process may be acceptable, provided the potential participant is fully informed, has the opportunity to ask questions, and has a way to indicate agreement to participate. For example, an alternate consent process may be needed if someone is not able to read the consent form. For those who are blind, a Braille or audio consent process may be needed. Those who are illiterate may also need a verbal consent process. A common variation in the consent process is the use of the "short form process" described in 45 CFR 46.117. The protocol should identify if the short form process will be used and the script of the study that will be presented through the use of a translator. Alternate forms of the consent form process need to be written in the protocol document and approved by the IRB prior to their use.

The Common Rule permits waiver of informed consent or waiver of written consent if certain criteria are met (see 45 CFR 46.117). If waiver of informed consent or waiver of written consent will be utilized, the protocol should specify how those criteria are satisfied.

Consent Form

Preparing the consent form should possibly be the last step of writing a protocol once the design, processes, and protections of the protocol are all in place. The consent form can then be written as a lay description of the protocol (Table 16.4). For studies with multiple populations that undergo differing procedures with different risks, separate population-specific consent forms may be needed. It is best, however, to consolidate consent forms to the extent possible to avoid using the wrong form for a study population and to simplify administrative review. The consent form should be written in lay terminology; consents are often aimed at an

eighth grade reading level. 45 CFR 46.116.a designates required elements for consent forms and additional elements to be added when appropriate. As can be seen from the summary of elements in the following section, many elements parallel information in the protocol.

The Common Rule: The eight basic elements of informed consent include the following:

1. A statement that the study involves research. An explanation of the purpose and procedures, including identification of any procedures which are experimental. The expected duration of the subject's participation;
2. A description of any reasonably foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6. Information on compensation and medical treatments for research-related injury or where further information may be obtained;
7. An explanation of whom to contact for answers to questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury; and

Table 16.4

Sample Approaches to Consent Form Organization

Example I*	Example II*
1. Purpose of the Study 2. Background/Facts Leading to the Study 3. Study Population 4. Inclusion Criteria/Who Can Be in the Study 5. Exclusion Criteria/Who Cannot Be in the Study 6. Procedures a. Study Overview (Number of Visits/Time Commitment) b. Procedure Details c. End of Study Procedures/Transfer of Care 7. Risks, Discomforts, and Inconveniences 8. Use of Stored Data and Samples 9. Potential Benefit 10. Right of Withdrawal 11. Conditions for Early Withdrawal 12. Return of Results From the Study 13. Study Termination 14. Alternatives to Participation or Treatment 15. Disclosure of Any Conflicts of Interest 16. Confidentiality Protections 17. Compensation for Participation 18. Notification of Posting on CCtrials.gov 19. Care and Compensation for Research-Related Injury 20. Who to Contact With Questions About the Study or Rights as a Research Participant	1. Why is this study being done? 2. Why are you being invited to participate? a. Who can participate? b. Who cannot participate? 3. How many people will take part in this research study? 4. How long will you take part in this research study? 5. What do we do to decide if you are eligible for this research study? 6. What procedures, drugs, or other treatments are involved in this research study? 7. What are the risks and discomforts of this research study? 8. Are there any benefits to you if you take part in this research study? 9. What other choices do you have? 10. Are there reasons that your research participation may end early? 11. What will happen when the research study is over? 12. Will your clinical and other test results be shared with you? 13. Will the results of this research study be shared with you? 14. Will any of your blood, tissue, or other samples be stored and used for research in the future? 15. Will you receive any compensation (money or other) for taking part in this research study? 16. Do any of the researchers have a financial interest related to this research study? 17. What privacy and confidentiality procedures apply to the information gathered about you in this study? 18. What is the policy regarding research-related injuries? 19. Who can answer your questions about the research and your rights as a research subject?

[3] Combined NeuroScience IRB. *CNS IRB Protocol and Consent Templates 2016*. Bethesda (MD): Intramural Research Program, National Institutes of Health. (Available on request).

8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

There are six additional elements for informed consent to be considered if appropriate to the study. They are as follows:

9. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
10. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
11. Any additional costs to the subject that may result from participation in the research;
12. The consequences of a subject's decision to withdraw from the research and procedures for orderly

termination of participation by the subject;
13. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
14. The approximate number of subjects involved in the study.

Many consent forms also include the protocol eligibility criteria and information on compensation for time and effort. To facilitate the broadest possible use of research data and samples congruent with the participant's wishes, consent forms also should include information on circumstances under which data/samples may be shared, what will be shared, any restrictions on sharing, and if the participant will receive compensation for discoveries based on their data or samples. When appropriate, participants should be given the opportunity to agree to or deny use of their samples and data outside of the protocol.

When applicable, the consent form should include information on the need for surrogate consent for adults, on the involvement of commercial sponsors, and on financial conflicts of interest. There may be additional consent requirements specific to the investigators' institution.

References

This section contains the reference citations for publications or communications cited in the protocol.

Appendices

Appendices are a useful way to provide ancillary information related to the research. The appendices may contain, for example, the rating scales used in the study, eligibility checklists, investigator flowsheets, and recruitment materials.

Summary

The process of writing the protocol document aids in shaping the study and consolidating thinking about the study design, methodology, and analytic plan. An organized approach using a structured template further promotes incorporation of information on risks, safety protective measures, and different levels of monitoring, and assures regulatory requirements are satisfied. A cohesive, well-written protocol also enhances the ease of the various regulatory reviews needed, making the review process more efficient. A well-written protocol document stands as a comprehensive guide to the conduct of the study.

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References

1. U.S. Department of Health and Human Services. *Code of federal regulations – title 45 public welfare part 46. Protection of human subjects [online]*. Available at: