Best Practices in Clinical Research Protocol Writing: Eight tips from an IRB member

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DESCRIPTION
The clinical research protocol is the single most important document to ensure critical elements of the research study are communicated to investigators conducting the study, the IRB, and federal regulatory agencies.

TOPICS
- PROTOCOL CONTENT GUIDELINES
- PRECLINICAL AND CLINICAL DATA
- RESEARCH ACTIVITIES
- SUBJECT DESCRIPTIONS
- REVIEW OF PROTOCOL
- OBSERVATIONAL VS. INTERVENTIONAL RESEARCH
- FDA AND IRB PERSPECTIVES
- PEDIATRIC PROTOCOL
The clinical research protocol is the single most important document to ensure critical elements of the research study are communicated to investigators conducting the study, the IRB, and federal regulatory agencies.

The tips below address some of the most frequently observed errors and omissions in protocol content encountered by IRB members during review of research studies. They are arranged in order of complexity, from the most basic to the more nuanced.

Adherence to these protocol writing tips will help sponsors and investigators conducting research studies meet critical milestones and avoid postponements by the IRB, study delays, and wasted resources.

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**Tip 1: Always use protocol content guidelines.**

IRBs frequently receive protocols missing entire sections or critical details that are necessary for understanding the research and how it will be conducted.

There are many helpful protocol content guidelines available on the internet, and links to some examples are included at the end of this tip sheet. Review the ones that reflect the anticipated study design, and utilize them as a writing template. Most protocol content guidelines contain a detailed list of items to be included under each section of the protocol. Address each item in the draft of the protocol to ensure necessary content is not inadvertently omitted as the protocol is finalized.
Remember, a well-written, detailed protocol increases the likelihood a research study will yield high-fidelity data and minimizes the number of protocol amendments. It is also a valuable reference document from which to generate future manuscripts, presentations, grant renewals, and related research protocols.

**Tip 2: Include all relevant preclinical and clinical data in the background of the protocol**

The background of the protocol should include all published and unpublished data supporting the rationale for a research study.

It is common for IRBs to receive investigator-initiated protocols in which there is little supporting evidence for conduct of the study. In many of these cases, a quick internet search by an IRB member reviewing the study or a conversation between the IRB chairperson and investigator reveals that relevant data exists, but were omitted from the protocol. This omission is particularly common in investigations involving blood products or stem cells, studies of clinical efficacy of a laboratory developed test, and studies of approved medical devices or drugs.

The investigator may presume that because the test article(s) is approved and/or used routinely in medical care, little rationale for conduct of the study is necessary. Granted, the practice of medicine is not subject to regulations for the protection of human subjects—but if interventions are used as part of a clinical investigation, the IRB (frequently the first, if not the sole entity, reviewing such protocols) is required to consider them in determining whether the research design is sound and safe. Because the IRB bases this determination largely on the preclinical and clinical evidence provided in the background of the protocol, omission of this information can lead to delays in IRB approval of the study.

**Tip 3: Both the protocol and consent form should include all research-related activities and be consistent with each other. All research activities should be tied to a research aim.**

All activities in the protocol performed solely for research purposes should support a primary, secondary, or exploratory aim of the study. In addition, all research-related activities listed in the consent form should be well-described in the protocol.

It is common for IRBs to review protocols in which research activities in the protocol are not tied to study aims, and consent forms often contain research activities that are not included in the protocol. For example, the consent form may seek permission for bio-banking activities that are not mentioned in the protocol. Such inconsistencies often lead to delays in IRB review and approval due to required revisions in the protocol and consent form.
These common mistakes can be avoided by using protocol content guidelines appropriate for the study (see examples at the end of this tip sheet) and by comparing the protocol and consent form to confirm consistency between the two.

**Tip 4: Take care to describe, in detail, all study activities subjects will undergo.**

Protocols developed by biotechnology and device start-up companies often lack sufficient details regarding exactly what, where, and how study activities will be conducted. This lack of detail makes it difficult for an IRB to understand and approve a research plan.

To facilitate IRB review, a protocol should include a description of study activities that occur during each subject visit and a table of study activities by visit. These activities should be described in enough detail in the protocol that investigators conducting the study could carry out the study activities without additional information. For more complex studies, the appendices may contain detailed information regarding how study interventions are performed.

For first-in-human device studies, the only information available about the investigational device may be a simple device manual (user’s guide). In addition to the device manual and a review of preclinical and clinical evidence of safety and efficacy in the protocol background, include information and diagrams depicting how the investigational device will be applied to the subject, and describe how long the subject will be exposed to the device. In the study visits section, include the data collection procedures for the investigational device and any comparator devices.

If the device is exempt from an Investigational Device Exemption (IDE) application, include the rationale for exemption in the background of the protocol.\(^1\) If a nonsignificant risk (NSR) determination is requested from the IRB, the background of the protocol should also include the rationale for why the device is not significant risk (SR).\(^2\)

**Tip 5: Obtain an independent scientific and/or medical review of the protocol from colleagues not directly involved in the research plan.**

One invaluable, yet frequently overlooked, best practice is to ask colleagues outside the primary research team for a peer review of the protocol. The protocol should contain enough details and rationale that scientific and/or medical colleagues not directly involved in the research plan will understand and “buy into” the study, including study design, endpoints, and data analysis plan. If these colleagues are unclear on aspects of the protocol, then regulatory agencies and the IRB may have similar difficulty.
In addition to improving the clarity of a protocol, a peer review can identify whether additional rationale in support of the research design is needed and whether the protocol should include a justification for why alternative designs were not selected.

**Tip 6: When writing a protocol evaluating standards of care, consider the difference between observational and interventional research designs.**

It is common for investigators evaluating approved drugs, devices, and standards of care used in routine clinical practice to mistake interventional studies for observational studies that involve only minimal risk, data collection procedures. Care must be taken to appropriately characterize whether the study is observational or interventional as there are important distinctions that influence the IRB’s review and ability to approve the study.

**In determining whether a study evaluating standards of care is observational or interventional, consider the following distinctions:**

**Observational** research evaluating standards of care involves the collection of data generated in the course of routine clinical treatment of a patient. The study design does not influence the physician’s decision-making process or the treatment the patient receives.

**Characteristics of Observational Research Evaluating Standards of Care:**

- The treatment the patient receives is based on what is best for the individual patient.
- The study protocol does not influence or modify the physician’s decision-making, the physician’s recommended course of action, or clinical treatment the patient receives.
- The patient can choose the treatment he/she believes is the best option.

**Examples Include:**

- Prospective collection of data from subjects’ medical records as part of a registry study of the safety and effectiveness of FDA-approved coronary artery stents. (Additional research procedures such as lab tests or questionnaires may be added as part of the study, but the primary intervention was determined by doctor and patient, and would have occurred regardless of whether the study is conducted.)

- As part of subject eligibility for a research study of the clinical utility of a laboratory developed test, the pathologist conducting the study searches the pathology lab database for patients whose physicians have previously ordered the test as part of the patients’ medical care.
“The treatment the patient receives is based on what is best for the individual patient.”
In contrast, **interventional** research evaluating standards of care has the features of a clinical trial of an unapproved test article in which the protocol, not the patient’s physician, determines the prescribed or assigned treatment the individual receives.

**CHARACTERISTICS OF INTERVENTIONAL RESEARCH EVALUATING STANDARDS OF CARE:**

- The treatment the subject receives is not primarily based on what is best for the individual subject, but rather intended to enhance knowledge related to treatment of the disease condition.
- The treatment the subject receives is determined by the study protocol, not based on a physician’s recommendations.
- The subject cannot choose the treatment he/she believes is the best option but rather is prescribed, assigned, or randomized to a treatment based on the study protocol.

**EXAMPLES INCLUDE:**

- Subjects are randomized 1:1:1 to three FDA-approved brain aneurysm embolization devices used in routine clinical practice, to compare safety and effectiveness of the devices.
- A laboratory test ordered routinely in clinical practice is ordered by the physician investigator after potential subjects are enrolled in a research study that aims to determine whether the test results influence the physician’s treatment recommendations.

**Key differences in protocols and consent forms for observational and interventional studies**

When writing protocols evaluating standards of care, first ask whether the treatment is prescribed by the patient’s physician to benefit the individual patient (**observational**) or prescribed/assigned to a research subject to enhance knowledge related to treatment of the disease condition (**interventional**).

**IF THE STUDY MEETS THE CRITERIA AS OBSERVATIONAL:**

- Only the risks associated with the additional research activities, not the risks associated with routine clinical care, need be described in the protocol and consent form.\(^3\)
- The protocol and the consent form must clearly separate those activities that are part of routine clinical care the subject receives outside the study from those activities conducted for study purposes only.
- The risk/benefit analysis should only include the risks and benefits associated with the additional study-related activities, not the risks and benefits of clinical care the subject receives outside the study.
IN CONTRAST IN CONTRAST, FOR AN INTERVENTIONAL STUDY EVALUATING STANDARDS OF CARE:

- The protocol and consent form must clearly describe the reasonably foreseeable risks associated with each standard-of-care treatment subjects receive on study. The rationale for inclusion of these risks is that some proportion of research subjects will be prescribed, assigned, or randomized per protocol to a different standard-of-care treatment (associated with a different set of risks) than they would have ordinarily received as a patient outside of the study.4 5

- Because assignment to a standard-of-care treatment is made within the protocol and not based on a physician’s assessment of individual risk and benefit, the protocol’s inclusion and exclusion criteria must be well-described, and as specific as possible, to avoid enrolling subjects who may be at increased risk if exposed to any particular treatment arm. The inclusion and exclusion criteria must also attempt to include only those individuals likely to benefit from the research. Importantly, because of its subjective nature, investigator discretion is insufficient as an eligibility criterion.

Using the correct protocol writing template at the start of the study design will help avoid the pitfall of blurring the lines between observational and interventional studies evaluating standards of care. As examples, see the observational and interventional templates at the end of this tip sheet.

Tip 7: For protocols involving medical devices and drugs, write the protocol from both the FDA and IRB perspectives, which are complementary but distinct.

- The FDA focuses on the safety and efficacy of a drug or device in the population at large. This requires a robust study design with validated safety and efficacy endpoints. The results of the study must provide rigorous evidence that FDA approval of the drug or device is consistent with the public good.6

- The IRB is concerned with the rights and welfare of the individual subjects in the trials that are conducted to support FDA approval. To this end, the IRB reviews the integrity of the study design to determine whether the potential for individual benefit (if any) is maximized while the risks associated with the study are minimized.7

Early in its inception, look critically at the study design, not only from the FDA perspective but also the IRB’s. Most drug and device companies are very familiar with the FDA’s requirements but are less aware of how the IRB makes decisions regarding study approval. The IRB is concerned with whether risks to subjects are minimized; whether the risks are reasonable in relation to the anticipated benefit to participants (if any); and the importance of the knowledge that may be expected to result.
Because of these constraints, the design should attempt, as much as possible, to use data from procedures the subject would already be undergoing. In other words, invasive procedures/treatments performed solely for research purposes should be minimized. This minimization of risk becomes especially important in children and those with diminished decision-making capacity because the regulations decrease the tolerance for risk without corresponding benefit for these individuals.

FDA approval of a research design is not the same as, and does not guarantee, IRB approval. If consideration is not given to both perspectives, it is possible for the FDA to approve conduct of the study and the IRB to disapprove it. The possibility of this occurring is higher when known effective therapy is withheld from subjects in a placebo arm, especially if protocol-mandated rescue therapy or individual stopping rules are poorly articulated or absent. Likewise, a sham arm that includes invasive procedures posing serious risks without potential for individual benefit will be an issue for the IRB, particularly if the protocol does not adequately articulate the rationale for the study design.

Include a compelling rationale in the background section of the protocol for a study design that involves procedures presenting more than minimal risk to participants without benefit (such as inclusion of a placebo arm, a sham arm, or a medication washout period). The protocol should also include a risk/benefit analysis and provide details describing additional safety measures to mitigate any risks, such as use of rescue therapy, and individual and study stopping rules.

Ideally, an explanation will also be included as to why the study integrity cannot be maintained without these procedures or alternatively, an explanation of why these procedures are low risk or potentially beneficial to subjects. If the FDA has commented on the design or other designs were rejected, this information should also be included. It may be necessary to consider an independent data monitoring committee (DMC) and interim analyses for higher-risk studies. If so, the protocol should also describe these data and safety monitoring procedures.

Tip 8: Ask for assistance from an IRB chairperson or IRB regulatory consultant in the early stages of development of a pediatric protocol.

In pediatric trials, it can be challenging to balance the scientific imperative for robust research design with the ethical and regulatory requirements for risk and benefit for the individual children in the study. Many problems associated with pediatric study design could be avoided by consideration of the FDA regulations and guidance, and by seeking advice from an IRB chairperson or IRB regulatory consultant before the trial design is finalized.

For trials involving minors, the IRB is required to consider additional safeguards (“Subpart D”) for children, which include a risk/benefit analysis of each arm of the study. This means the IRB is required to determine the approvability of the
overall protocol only after considering the active investigational arm and the comparator arm, separately. The Subpart D findings available to IRBs are as follows:

- **21 CFR 50.51 – Clinical investigation not involving greater than minimal risk**

As defined under HHS 46 CFR 102 (i) and FDA 21 CFR 50.102 (i), minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. This standard is based on the experience of healthy children regardless of whether the study population is a group of children routinely exposed to higher-risk interventions as part of the care for their specific condition (such as children with cancer who are treated with chemotherapy).

- **21 CFR 50.52 – Clinical investigation involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects**

“The IRB will analyze each study arm to determine whether the potential for benefit to the child outweighs the risks and whether the risks are justified.”

The IRB will analyze each study arm to determine whether the potential for benefit to the child outweighs the risks and whether the risks are justified. The risk/benefit ratio must be at least as good as the available alternatives to the child outside the study.

Standard of care a child receives in the study is not considered to be a benefit of the research. However, there are conditions under which the IRB may consider a standard-of-care arm to be of benefit to the child. For example, the protocol may include additional monitoring procedures that could potentially detect a life-threatening event earlier than routine clinical monitoring. If this is the case, the protocol should provide a rationale for why additional monitoring is beneficial and describe the interventions that will be taken in response to the findings.

The standard-of-care arm may also be considered of benefit to the child if the protocol design allows a child who is failing the standard-of-care arm to cross over into the potentially beneficial investigational arm.

- **21 CFR 50.53 – Clinical investigation involving a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects’ disorder or condition**
When the individual child will derive no benefit from an assigned research arm, careful consideration should be given to what constitutes a minor increase over minimal risk. Generally, the procedures should be consistent with those expected in the course of medical care for the child’s condition and pose no significant risk or irreversible harm to the child.

For each study arm in which the child will derive no benefit from the research (typically a standard-of-care or placebo arm), the protocol should provide a detailed rationale with data supporting why each research procedure does not exceed a minor increase over minimal risk. In addition, include why the particular study design was chosen and others rejected.

Importantly, research that offers no direct benefit, but poses a minor increase over minimal risk must yield information that is of importance for the understanding or amelioration of a disorder or condition in children. If the inclusion of healthy children is absolutely necessary to answer the scientific question, the protocol should provide an extensive discussion of (i) why inclusion of this group is necessary to answer the research question (and why other designs are not appropriate); (ii) the importance of the research question to the health of children in general; (iii) why there is no way to provide benefit to this group; (iv) how risks have been minimized for this group.12

- 21 CFR 50.54 – Clinical investigation not otherwise approvable that presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children

This type of research is rare, as it requires a referral by the IRB to the FDA for additional review. Review by the FDA under 21 CFR 50.54 is not the same as the routine review conducted by the FDA for scientific merit.13

It is possible for the FDA to approve a pediatric study design from a scientific perspective, and for the IRB to subsequently determine the research falls under 21 CFR 50.54 and refer the study to the Commissioner of Food and Drugs for review and a Subpart D determination. Investigators and sponsors should therefore shape a pediatric protocol to minimize risk as much as possible and ask for an IRB chairperson assessment or IRB regulatory consultation prior to internally finalizing the study design.

Protocol content guidelines and templates

Recommended protocol content guidelines and generic writing templates for observational and interventional studies:

- Basic protocol writing template: Seattle Children’s Hospital IRB. https://www.seattlechildrens.org/doc/basic-protocol-template.doc
Best Practices in Clinical Research Protocol Writing: Eight tips from an IRB member


- Observational protocol writing template: Seattle Children’s Hospital IRB. https://www.seattlechildrens.org/doc/observational-protocol-template.doc


REFERENCES
6. U.S. Food and Drug Administration, Promoting Safe and Effective Research for 100 Years, http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/ (February 2006)
7. 21 CFR 56.111(a)
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