AbbVie
Clinical Trials

Clinical Trial Protocol

Long before patients are recruited and enrolled in a clinical trial, there is extensive planning on how the trial will be conducted by those who fund and run the trial. Their planning is focused on specific details, including the objectives, trial design, methods used for data collection and analysis, and organization.[1] Ironing out all of these details among all of the clinical trial personnel, before enrolling or even speaking to potential participants, helps ensure that there is a plan of action for every step of a clinical trial, that the safety of all trial participants is protected, and that the data collected and analyzed are reliable. This "action plan" for a clinical trial is defined in a written document called a clinical trial protocol.[2]

How does a clinical trial protocol ensure that the various steps outlined in the action plan are adhered to by the different personnel involved in the trial? Having a document that describes every step of a clinical trial ensures that everyone facilitating or organizing the trial agrees on these details and will follow them.

Some trials may involve participants in different locations around the world. The clinical trial protocol also helps ensure that clinical trial personnel in every location are doing the same things in the same way.

It is useful to think about the clinical trial protocol as a detailed cooking recipe.[1] If you have never made a dish before, how do you know where to start? A recipe provides you with a list of ingredients and step-by-step instructions on how to use those ingredients. A clinical trial protocol is the recipe for properly running a specific trial: it guides clinical trial personnel during the trial and tells them how to conduct a clinical trial.

What Are the Steps Involved in Clinical Protocol Development?

How a clinical trial protocol is developed and the information included greatly depend on the type of clinical trial. For example, a protocol for a phase 1 clinical trial, which may use a small number of healthy volunteers to determine side effects of study treatment and how the body absorbs, distributes, and eliminates a drug, will be different from a phase 3 clinical trial, which may include hundreds to thousands of participants with a specific disease. For more information on what happens during the different phases of a clinical trial, see "Clinical Trial Phases".

Typically, clinical protocol development and the writing of a clinical trial protocol involve healthcare professionals, scientists, and the individuals who fund the trial. While there is no required format for writing a clinical trial protocol, a lot of information is essential to ensure that the trial is being conducted in a way that is safe for participants and has a solid scientific rationale. Generally accepted guidelines, called Good Clinical Practice (GCP), define what mustbe included in a protocol, so that anyone writing a protocol does so in a clear and uniform way. GCP guidelines are accepted internationally and are published

by the International Council for Harmonisation (ICH).[3] You can think of these guidelines as a set of clinical trial protocol best practices.

To better understand clinical protocol development and how it may differ depending on the type of trial, let's take a look at the topics that are covered in a clinical trial protocol.

What Information Is Included in a Clinical Trial Protocol?

A lot of information is packed into a clinical trial protocol. As a participant, you may not see the protocol at all, but knowing what kind of information is included may give you some comfort that plans are in place should you experience an adverse event, if the risks of participation start to outweigh the benefits, or if you just feel like you do not want to participate in the trial anymore. Let's take a look at what is included in the clinical trial protocol.

Clinical Trial Protocol Sponsors and Principal Investigators

What is this trial all about and who is organizing and funding it?

This first section of the protocol includes key information about the "sponsor" and the "principal investigator." You may be wondering, "Who are these people and what is their role in the clinical trial?"

Depending on the trial, the sponsor can be a pharmaceutical company, academic medical center, voluntary group, or other organization. Federal agencies may also act as sponsors through specialized departments such as the National Institutes of Health, the U.S. Department of Defense, and the U.S. Department of Veterans Affairs. Doctors or other healthcare professionals, as well as individuals, may also act as sponsors.[4]

You may also find information within this section of the protocol on the clinical trial principal investigator (PI). The PI is often a medical doctor and is responsible for actually running the clinical trial and directing research teams that may include doctors, nurses, social workers, and other healthcare professionals.[4]

A brief summary of the protocol will also be included here, which gives a general overview of the trial, including the objectives, study design, endpoints, sample size, data analysis, and others. Each of these will be discussed in more detail below.

Background, Scientific Rationale, and Clinical Trial Protocol Development

What do scientists and doctors already know about this exploratory treatment?

The "Background and Scientific Rationale" section of the protocol includes a description of the population being studied (i.e., people with a certain disease, of a certain age or gender, etc.), a review of the literature and studies that justify the use of a study treatment for this population, how the study treatment should be given, how much should be given, and how often and how long the study treatment should be given.

Background information may include a summary of non-clinical studies that were conducted in a laboratory and/or pre-clinical studies conducted using animals. Depending on what type of trial you are in involved in, there may be a summary of the prior clinical research or research that has involved the study treatment and its use in other human volunteers. Reviewing all of this information to make informed decisions about how the trial should be run is a critical piece of the clinical protocol development puzzle.

Taken together, the potential benefits of the exploratory treatment should outweigh the potential risks, and this should be clearly justified in this section of the protocol.

See more information on the potential risks and benefits and your rights as a patient.

Research Trial Objectives and Purpose

Why is a particular clinical trial being performed?

And what are the primary and secondary goals? How will investigators and sponsors know if they've reached these goals?

The research trial objectives and purpose of a clinical trial protocol have the answers to these questions.

The primary and secondary objectives, or goals, of the study are based on informed experience in clinical trial protocol best practices. The primary and secondary endpoints are also described in detail in this section as well. Endpoints are events or outcomes that can be objectively measured and used to determine if an experimental treatment or procedure is more beneficial than another treatment or placebo.

For example, a clinical trial that is testing an experimental treatment and its effect on a type of cancer may look at a 5-year survival rate or the disappearance of a tumor. Other examples of endpoints include improvements in quality of life or relief of symptoms. It is important that these endpoints can be objectively measured using validated imaging or laboratory techniques or clinical rating scales. A clear explanation of how these endpoints relate to the trial objectives is crucial for investigators and sponsors to justify using a specific endpoint.

The Clinical Research Trial Design

The trial design is largely a step-by-step guide that tells investigators how to conduct a clinical trial. Just as we've outlined the questions that each section of a clinical trial protocol is designed to answer, common questions that participants may have are highlighted below, as well as some of the answers regarding a clinical trial protocol.

These abbreviated descriptions of information pertaining to protocols are by no means an all-inclusive list.

- **What do investigators think will happen during the trial?** Based on the scientific rationale for organizing the clinical trial, the investigators can make an educated guess as to what the effects of a study treatment will be. This is called a research hypothesis and will be clearly stated.
- **What type of trial are you participating in?** One critical detail included in the trial design is the type (i.e., phase 1, phase 2, etc.) and the design of the trial. We've discussed some of the differences between these types of trials already.
- **How will investigators know if the experimental treatment is better than another treatment or placebo?** Answering this question refers to how a trial is designed and the different treatments (i.e., experimental, placebo, standard-of-care, etc.) that will be administered to people, as well as the process for deciding which participant gets which study treatment (i.e., randomization, meaning random assignment to a study treatment group).
- **How do clinical trial personnel avoid bias when they are treating and evaluating participants?** Depending on the type of trial you are involved in, you and/or trial personnel may be "blinded" or not told what study treatment is being administered.
- **How will you know when you are receiving study treatment, when you have a medical visit, when tests are being done, etc.?** Another large part of the trial design is the study plan, which is illustrated as a flow chart and includes answers to questions about your involvement. Rules on when a participant would be advised to stop participation in the clinical trial are also outlined and a definition is included that explains when your participation in a trial is officially over.
- **Who is qualified to participate in a clinical trial?** Criteria on who specifically should be included in the trial and who should be excluded from the trial are

clearly defined before a trial starts. These are called inclusion and exclusion criteria, respectively. All together, these criteria are referred to as eligibility criteria. Participants in the trial, for example, may be all women, all men, all within a certain age range, or all have a specific stage of their disease. One inclusion criterion that is true of all clinical trials is a signed informed consent form. By signing this form, you are agreeing that you understand the risks and benefits of participating in a trial. In short, the consent form will contain an abridged version of the clinical trial protocol and will be much less technical so that a broad audience can understand it. You can find more information on informed consent here.

Assessment of Efficacy and Safety in Clinical Protocols

How will safety be protected and monitored throughout a clinical trial?

Detailed descriptions of what is entailed during study visits to the clinic at every step of the clinical trial process are included in the clinical trial protocol. All study procedures and evaluations are related to measuring the treatment efficacy and monitoring safety issues.

The "Safety Assessment" section of the protocol also describes the adverse events that could occur and how they will be reported.

Clinical Trial Data and Statistical Analysis

What happens after investigators perform tests and collect the data?

Once all of the data from a clinical trial are collected, they have to be analyzed. There are many complex ways to determine if primary and/or secondary endpoints have been reached, and this section of the protocol outlines in detail how this will be done.

The same is true for safety data and the analysis of any adverse events reported during the trial.

Sometimes, certain protocols may have a "planned interim analysis," where a sponsor can analyze data and determine whether the experimental treatment is efficacious and safe before the trial is completed. Depending on the analysis, the trial may be continued or stopped due to futility.[5]

Protocol Ethics, Regulatory, and Legal Issues

How do you know if the clinical trial is ethical?

The uniform ethical principles that are used to guide a clinical trial are outlined in the protocol. In general, there are seven guiding principles for conducting an ethical clinical trial. They include:[6]

- Social and clinical value
- Scientific validity
- Fair subject selection
- Favorable risk-to-benefit ratio
- Independent review
- Informed consent
- Respect for potential and enrolled subjects

For more information on these topics, read patients' rights and ethics. This section of the protocol also describes how the protocol will be reviewed by external review committees and how your data and those of other participants will be kept confidential.

Who Reviews and Approves a Clinical Trial Protocol?

All protocols for privately sponsored or federally funded trials must be reviewed by a third-party review board, called an institutional review board (IRB) or an independent

ethics committee (IEC). These are groups of people who are responsible for protecting participants who take part in the study. They also ensure that studies are compliant with all federal laws. The members of the review board can include healthcare professionals, scientists, and non-healthcare professionals.[7]

IRBs/IECs are responsible for evaluating the clinical trial protocol and determining whether it is medically, legally, and ethically acceptable. In essence, they determine if the question the trial is designed to answer is worthwhile and if the proposed protocol can do this while still keeping participants safe.[7] Review and approval by IRBs/IECs are critical steps in clinical protocol development.

As we've mentioned already, informed consent is a critical first step in enrolling participants in a trial, and the IRB monitors this process very closely to ensure it is happening in an ethical way. As a participant, you can contact the IRB directly, should you have any concerns about the trial or about your safety.[7] The IRB will follow the progress of a clinical trial and monitor for safety concerns.

While the Food and Drug Administration (FDA) is not required to approve a clinical trial protocol, the protocol must be submitted to them before the trial can begin. They are also able to audit any of the study sites if there is any reason to think that unethical practices are occurring or there are other serious problems.

Data safety monitoring boards (DSMBs) also monitor many clinical trials as they occur. The DSMB is a group of doctors and scientists that analyze trial data during interim analyses that are planned to occur at certain times during the clinical trial. The DSMB may also detect safety concerns that are serious enough to halt the trial in order to minimize harm to participants.[7]

Potential Problems that Can Arise Within Clinical Trial Protocols

Having a well-written and detailed clinical trial protocol is important to avoid confusion while a clinical trial is being run. However, protocol deviations can occur due to the intentional or unintentional actions of participants or personnel.

A protocol deviation is generally considered to be a departure from a clinical trial protocol, that was not previously approved by the IRB/IEC.[8] A deviation can fall into two categories:[8]

- Those that have the potential to be significant, meaning they could potentially affect subjects' safety and/or data integrity
- Those that are insignificant, meaning they could not affect these things

Deviations should be rare during a clinical trial, but when they do occur, they are taken very seriously. The clinical trial protocol best practices, outlined by the ICH GCP, specify that deviations must be reported to the IRB/IEC as soon as possible. The IRB/IEC will determine into which category listed above that the deviation falls.

One of the most common and avoidable deviations that participants can help to avoid are called "out-of-window" visits. These deviations occur when participants miss their scheduled visits to the clinic. Specific guidelines may be written into a clinical trial protocol on how these missed visits are handled. As a participant, you can help avoid these missed visits by letting clinical trial personnel know when you will be unavailable due to vacation, travel, or lack of transportation. Illness and forgetfulness can also lead to missed clinic visits, so be sure to communicate your visit dates to caregivers. In doing so, caregivers can help to communicate with clinical trial staff if you need to reschedule a visit.

Clinical trial staff may also use scheduling software to keep clinical trial visits organized, which may provide reminders about clinical trial visit dates.[8]

What Does a Clinical Trial Protocol Mean for You?

Clinical trial protocols help protect participants by ensuring that all steps of a clinical trial are specified and maximize the potential benefits, while minimizing the potential risks. They also tell all investigators in the trial how to conduct a clinical trial. While a protocol is not written with the intention of having participants understand every technical detail of a trial, it is useful for them to know that investigators are following a specific set of clinical trial protocol best practices, determined during clinical protocol development, to keep you as safe as possible. There are additional measures, such as IRB review and monitoring, that ensure participants remain safe throughout the course of a trial.

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