Clinical Trials: The Fundamentals

Dear Reader,

Clinical trials are the heart of medical research. It is critical to follow the procedures and be aware of the challenges involved in designing a clinical trial. This e-book is intended for early stage clinical researchers who are interested in designing a clinical trial and wish to learn more about it. We have tried to compile some of the essential information in this free downloadable e-book and hope that you find it informative.

We have also added some popular links at the end as additional resources that you can refer to. These pieces will also lead you to the original sources, which will definitely provide you detailed information.

Happy Reading!

Regards,

Enago Academy Team

Overview:

Conducting Clinical Trials

Clinical trials are carried out with stringent research standards that help ensure patients' interests are protected whilst also establishing reliable study results. Authors and researchers can learn the importance of conducting such trials in adherence to these guidelines. Researchers will get an insight into the various phases of clinical trial studies. In the opening part of this ebook, we look at:

- The basics of clinical trials
- Learn about trial protocol
- Learn about the various types of clinical studies: Interventional and Observational and the various phases involved

Clinical Trials Process

Registration is usually also mandatory for journal publication. In this section of the e-book, you can learn more about:

- How to go about preparing a clinical trial
- Various checklists required for journal publication
- Informed consent
- Institutional review board
- Learn how to register and publish a clinical trial

Ethical Requirements

Monitoring clinical trials is essential to ensure that the clinical studies maintain scientific integrity and do not violate ethical standards. This is done both at the institutional level as well as regulated by the governments. In order to ensure that the clinical research meets both a scientific standard and an ethical standard, the World Health Organization (WHO) suggests a "recommended format for a research protocol." In this section, we learn about:

- Declaration of Helsinki
- ICH Good Clinical Practice
- Codes of Ethics

OpenTrials: Open Database for Clinical Trials

OpenTrials is an open database for clinical trial research that has an aim to increase access to trials data and also improve transparency in the various clinical trial processes. This database is developed by Open Knowledge International and it is an open access, online database of materials from clinical trials worldwide. In this section, we learn about how OpenTrials works and also gain insights into:

- Funding and data sources
- Challenges involved in OpenTrials

This free e-book is full of comprehensive insights that will help researchers learn about the clinical trial development process and the ethical requirements involved in order to conduct and publish clinical research.

Contents

Clinical Trials

Clinical trials are the core of medical research. Investigations are performed to determine how new treatments will work in human patients and valuable data concerning the benefits and risks of new drugs, medical approaches, and procedures are collected. Clinical trials are conducted to find effective ways to understand, prevent, diagnose, and treat diseases. However, clinical studies are also conducted to improve the quality of life of patients with chronic illnesses.

What Are Clinical Trials?

Clinical trials are studies that test the safety and efficacy of a treatment or device. The trial results show which medical treatments work efficiently for certain diseases or groups of patients.

Clinical trials are carried out with strict scientific standards. These standards help ensure that patients' interests are protected whilst ensuring reliable study results.

Clinical studies are one of the final stages of the drug development process. Scientists develop and test new drugs in a laboratory. Once the drug discovery process is complete, the next step is animal testing. However, it has been found that some treatments that work well on animals, doesn't always work on humans. This paves way for clinical trials in humans.

The results from these studies are critical because they help advance medical treatment and improve patient care significantly.

Trial Protocol

Each clinical trial is designed very carefully to provide the greatest amount of information at the lowest possible risk, and to achieve this, a protocol, or an action plan, is prepared. This plan describes what is to be done in the study, how it will be done, which information would be gathered, and why the different parts of the investigation are necessary.

The eligibility criteria for participating in a clinical trial are also listed in the protocol. Some studies require participants with a particular illness. Whereas some studies seek healthy volunteers or people with specific characteristics regarding gender, age, weight, lifestyle/habits, or others.

Interventional and Observational Studies

Clinical trials are of two types: Interventional and Observational studies. In case of interventional studies, the participants are treated in accordance with a research plan created by study investigators and the results are usually compared with the data obtained for subjects who receive either no treatment or a treatment that is already available. The “intervention” may include new drugs or devices, novel medical procedures, or changes in the participants’ behavior (diet, sport activities, etc.)

In an observational study, the participants are monitored to assess health outcomes under particular conditions. However, in this case the investigator has no direct control over the experiment and makes no attempt to affect the outcome of the study. Observational studies are advantageous as they involve patient populations that are closer to clinical practice, they are cheaper than interventional studies, and are used to investigate rare outcomes, detecting unusual side-effects. Another advantage is that some studies are performed quickly and easily.

Before a new drug or an innovative medical approach can be tested on humans, extensive laboratory research is required, sometimes spanning over several years. In most cases, this research involves conducting experiments on animals and/or human tissues. In case the studies prove to be successful, the investigators may send the data to an independent committee (usually comprises physicians and scientists) who would then approve and monitor any further tests involving human participants.

Phases of Clinical Trials

Clinical trials are conducted in several phases, and each one of them has a different purpose and is designed to answer a particular set of questions.

Phase I studies usually involve a small number of healthy volunteers (20–100) and are designed to assess the safety of a drug, device, or procedure; determine the appropriate dosage range; and identify any potential side-effects. If a treatment is found to be safe enough, it can be tested in phase II.

Phase II studies are conducted to determine whether a treatment is effective or not and to further evaluate its safety. These trials normally involve a few hundred participants (100–300).

Phase III studies are carried out on large groups (i.e. several hundreds to several thousands) of participants to confirm the effectiveness of a new medical approach and to monitor its benefits along with any adverse effects. Most Phase III studies are randomized trials, which means that one group of patients receives the new treatment while a “control” group is treated by following the standard procedure or by using a placebo. Phase III trials may also study different populations and dosages or assess the effect of combining a new procedure with other treatments. Once Phase III is complete, a new medical approach or drug may be approved by a regulatory agency such as the US Food and Drug Administration.

Phase IV studies are performed after a new drug, device, or procedure has been marketed. These studies are designed to collect additional data regarding the effect of the approved drug (device or procedure) in various populations and determine any long-term side-effects it may have.

Clinical Trials Process

Let us look at the process of registering and conducting clinical trials as well as the ethical considerations.

Carrying out a clinical trial requires careful planning, diligent work, and the consideration of several legal and ethical aspects. During the process, valuable information is collected and analyzed to address specific research questions. The results of the study are then presented to different audiences in peer-reviewed journals or as clinical study reports.

Preparing a Clinical Trial

Each clinical trial starts with a clear idea that usually results from extensive laboratory studies. In such a trial, the most promising treatments from the lab are tested on a selected number of human subjects to confirm the safety, applicability, and effectiveness before being marketed and/or applied to the public.

At the beginning of the study, the researchers develop a study protocol, which is a plan in which all the questions and procedures are clearly defined. The study protocol must be designed very carefully in order to safeguard the participants' health and provide significant data for the study. It should clearly describe the reasons for conducting the research and explain its relevance in the context of current knowledge. The goals and objectives of the study must also be defined, and this should be done as simply and specifically as possible.

The credibility and scientific value of a clinical study strongly depend on the study design and methodology, so detailed information on the expected duration of the trial; the type of measurements, tests, data analysis, and interventions that will be made; the procedures that will be used; and the characteristics of the participants (e.g. inclusion and/or exclusion criteria) should also be included in the protocol.

Informed Consent

To protect the interests of participants in a clinical trial, researchers must also provide them with enough information on the risks and potential benefits of the study so that they can decide whether they want to take part in the trial or not. Anyone planning to participate in the trial must then sign an informed consent document to declare that all the required information was provided and that he or she understands the implications. However, an informed consent document is not a contract and participants may withdraw from a study at any time, even after signing it.

Institutional Review Board

Most clinical trials in the United States are reviewed, approved, and monitored by an Institutional Review Board (IRB) to ensure that "the rights and welfare of human subjects are protected during their participation". An IRB is an independent committee that normally include both individuals with scientific or medical expertise, who can review the procedures and scientific validity of the study design, as well as non-scientists, who may identify any risks related to social, legal, or cultural considerations.

Registering and Publishing a Clinical Trial

Registering a clinical trial when it begins and making all the information related to the study publicly available has many benefits. Registration is usually also mandatory for journal publication.

To register a clinical trial, researchers must:

- Determine who is responsible for registering the study and which Protocol Registration and Results System (PRS) account should be used.

- Understand the submission requirements.
- Login to the registration system and enter the required information.
- Preview, revise, and submit the record.

The results obtained in clinical trials are often published in peer-reviewed journals, and when doing so, it is important to maintain the statistical and reporting integrity of the published manuscripts (especially if they deal with research on human subjects). This can be achieved by checking the articles against common reporting guidelines, such as the Consolidated Standards of Reporting Trials (CONSORT) Statement, the Standards for the Reporting of Diagnostic Accuracy Studies (STARD), or the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

If the results of a clinical trial are particularly important, they may also be presented at meetings or featured in news media. Once a new approach has proven to be successful, it may become the standard of medical practice.

Ethical Requirements

Medical advancements save lives. However, new procedures, tools, and products require thorough testing to ensure they are at least as safe and effective as the current standard of care. Advancements in human medicine typically occur through two different phases of biomedical research: pre-clinical and clinical. Pre-clinical research is vital to gaining an understanding of biological mechanisms, to determining whether a new treatment might prove beneficial, and to predicting potential negative side-effects of a drug or procedure. However, without clinical research, the safety and efficacy of a new medical treatment cannot be known with certainty. In fact, due to low treatment efficacy and excessive negative sid nly about 7% of new drugs pass through clinical research and into general medical practice.

While clinical trials are necessary for the advancement of medicine, they also require close monitoring to ensure that they maintain scientific integrity and do not violate ethical standards. Many governments regulate these studies at both the clinical and pre-clinical levels. To ensure that clinical research meets both a scientific standard and an ethical standard, the World Health Organization (WHO) makes available a “recommended format for a research protocol.” Typically, a single drug goes through 25–30 separate trials on its way to the clinic, with each trial adjusting the research protocol based on knowledge acquired during previous stages of research.

Declaration of Helsinki

In 1964, the World Medical Association produced the Declaration of Helsinki, which has since been amended several times, most recently in 2013. This declaration established the first official set of guidelines for maintaining ethical standards in clinical research. However, while this document guides the structuring of local legislation and regulation, it is not law itself. Further, despite covering many vital components of ethical principles relevant to biomedical research in human subjects, the Declaration of Helsinki does not specifically instruct ethics committees, such as IRBs, in how they should function.

ICH Good Clinical Practice

In 1996, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) produced Guidelines for Good Clinical Practice, called ICH GCP E6. This group is composed of members from the European Union, the United States, and Japan and aims to speed the development of new therapies from the laboratory to the clinic, while upholding the highest ethical standards and measures of quality control regarding both safety and effectiveness. While the Declaration of Helsinki covers guidelines for good ethical practices in clinical research, the ICH GCP provides information on specifics pertaining to operational practices of running a clinical trial that will ensure the safety and rights of subjects in a trial, while also maintaining rigorous standards to guarantee that data collected are of sound scientific value. The ICH GCP has gained such wide-ranging acceptance as an international guide for clinical trials that results from studies conducted in one region can be used to apply for a new drug application in another region if the study has followed ICH GCP guidelines. Offering further guidelines on different legal rules and ethical standards across 96 different countries, the Office for Human Research Protections in the US department of Health and Human Services has compiled a list of more than one thousand laws and regulations pertaining to research involving human subjects in a document called the “International Complication of Human Research Protections.”

Both the Declaration of Helsinki and the ICH GCP mention the importance of receiving supervisory support and approval from an ethics committee prior to the initiation and throughout the duration of a clinical trial. These ethics committees, sometimes called IRBs, typically reside over ethical considerations for clinical studies for only one institution, but ensure compliance with all local regulations and legislation.

Codes of Ethics

The Clinical Center at the US National Institutes of Health has established seven principles based on several codes of ethics meant to guide clinical research:

- Independent review: In the United States, several types of groups (granting agencies, IRBs, and data and safety monitoring boards) ensure that a trial follows sound ethical practices.

- Informed consent: Participants must only be included in a trial if they give their voluntary consent after receiving all pertinent information on a trial. In the cases of children or individuals who are medically unable to give their consent, the individual should have the benefit of a proxy decision maker who is aware of the likely wishes of the subject.

- Fair subject selection: Subjects should be chosen to sufficiently address the intended query of the study, while "minimizing risks and enhancing benefits to individuals and society." Study subjects should include members of all groups (gender, race, age), unless members of a particular group must be excluded for a strong reason (scientific or health of the subject).

- Scientific validity: The study should be scientifically sound to ensure that resources are not squandered and subjects do not take unnecessary risks with no likely beneficial outcome.

- Favorable risk-benefit ratio: While clinical trials inherently include some risk, the potential benefits must be sufficient to balance these risks. Researchers must work to minimize the risks and maximize the benefits to the best of their abilities.

- Respect for potential enrolled subjects: Rights of study participants must be respected throughout the trial, including during the selection process:

    - Right to privacy ○
    Right to withdraw
    - Right to new information gained during the study

    - Right to maintenance of their welfare, including monitoring and treating and removal from the study if required

    - Right to know the study results

- Social and clinical value: A clinical trial should seek to address a question whose answer has the potential to improve the current standard of care to a degree sufficient to justify the resources used and the risk taken by study participants.

Clinical research offers great value. However, subjects involved in clinical trials incur risk. Researchers must use extreme care in the design of their study to ensure that it provides the most value possible and that is strictly adheres to both local and international ethical guidelines.

This calls for better accessibility to data to facilitate research, and to increase discoverability. Read on to learn more about OpenTrials, a publically accessible online database containing information regarding all the clinical trials conducted.

OpenTrials: An Open Database for Clinical Trials

Data gathered in clinical trials is critical to effective medical treatment, as they allow doctors to make informed decisions in patient care. Researchers and policymakers also rely on clinical trials when designing research proposals and crafting regulations, respectively. However, approximately only half of the results from clinical trials are published. Further, positive results are published more frequently than negative results, representing a publication bias in the availability of clinical trial data.

With an aim of increasing access to data and improving transparency in clinical trial processes, Open Knowledge International is developing OpenTrials, an open access, online database of materials from clinical trials worldwide. The Laura and John Arnold Foundation (LJAF) is funding phase one of development for OpenTrials and is working through the Center for Open Science (COS). LJAF seeks to make lives better by determining areas of society that underperform and by then increasing accountability, transparency, and availability of relevant information within these systems; COS shares a similar mission, but with a focus on research, while Open Knowledge International seeks specifically to ensure that knowledge is widely available and accessible across the globe. The OpenTrials project, under the direction of Dr. Benjamin Goldacre, combines the aims of these organizations in the arena of clinical trial research.

How OpenTrials Works

OpenTrials will be built as structured open data and will provide an indexed online location for all documentation associated with clinical trials, hosting these documents using an easily searchable format that will tie all relevant documentation to each individual trial. Numerous documentation and data will be available for each trial:

- Registry entries
    - Industry registers
    - National registers
- Relevant academic journal articles
- Regulatory documents containing descriptions of a given trial
- Structured data on methods and results (systematic reviewers or other researchers will extract this data as presented on OpenTrials)
- Clinical study reports
- Additional documents
    - Blank consent forms
    - Case report forms
    - Ethical approval paperwork
    - Patient information documents
- Protocols