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CLINICAL TRIALS

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ABSTRACT

A clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical Trials also called medical research and research studies] are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work. Leads for clinical trials usually come from researchers. Once researchers test new therapies or procedures in the laboratory [animal studies] and get promising results, they begin planning Phase I clinical trials [in humans].New therapies are tested on people only after laboratory and animal studies show promising results. Clinical Trials make it possible to apply the latest scientific and technological advances to patient care. When a new medical treatment is studied for the first time in humans, it is not known exactly how it will work. With any new treatment, there are possible risks as well as benefits.

Keywords: Medical Research, Vaccines, Therapies, Phase I, Scientific.

1. INTRODUCTION

Clinical trials often involve patients with specific health conditions who then benefit from receiving otherwise unavailable treatments. In early phases, participants are healthy volunteers who receive financial incentives for their inconvenience. Usually, one or more pilot experiments are conducted to gain insights for design of the clinical trial to follow. In medical jargon, effectiveness is how well a treatment works in practice and efficacy is how well it works in a clinical trial. In the U.S., the elderly comprise only 14% of the population but they consume over one-third of drugs.[1] Despite this, they are often excluded from trials because their more frequent health issues and drug use produce unreliable data. Women, children, and people with unrelated medical conditions are also frequently excluded.[2] These data include measurements like vital signs, concentration of the study drug in the blood, and whether the patient's health improves or not. The researchers send the data to the trial sponsor who then analyzes the pooled data using statistical tests. Except for very small trials limited to a single location, the clinical trial design and objectives are written into a document called a clinical trial protocol. Because the clinical trial is designed to test hypotheses and rigorously monitor and assess what happens, clinical trials can be seen as the application of the scientific method, and specifically the experimental step, to understanding human or animal biology.

Definition

A clinical trial is a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (vaccines, drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Types

1. Interventional Trials
2. Prevention Trials
3. Observation Trials
4. Diagnostic and Screening Trials

- Interventional trials (also called treatment trials) are clinical trials which set out to test treatments or combinations of treatments which have not yet been officially approved. For example, a pharmaceutical company may have developed a new drug which it believes would be effective in the treatment of Alzheimer's disease but must first test it on human volunteers in accordance with strict and rigorous guidelines in order to ensure that it is safe and effective.[3]
- Prevention trials involve tests to find ways to prevent particular medical conditions or if people have them already, to prevent them from reoccurring. The emphasis of these studies might be on medicines, vitamins and minerals or lifestyle changes.[4]
- Observational trials investigate health issues in large groups of people. The participants in such trials do not receive any treatment but may be asked to provide information, blood samples.[5]
- Diagnostic and screening trials are aimed at finding new ways to detect and diagnose medical conditions (e.g. a better test, a more effective procedure or a more sophisticated tool).[6]

Design

Clinical study design is the formulation of trials and experiments in medical and epidemiological research, sometimes known as clinical trials. Many of the considerations here are shared under the more general topic of design of experiments but there can be others, in particular related to patient confidentiality and ethics.

An essential component of initiating a clinical trial is to recruit study subjects following procedures using a signed document called "informed consent". Generally, children participating in clinical trial cannot automonously provide informed consent, but depending on their age and other factors may be required to provide informed assent

1. Treatment studies

1.1 *Randomized controlled trial*: A randomized controlled trial is the study design that can provide the most compelling evidence that the study treatment causes the expected effect on human health.[7]

1.2 *Blind*: The subjects involved in the study do not know which study treatment they receive. If the study is double-blind, the researchers also do not know which treatment is being given to any given subject. This 'blinding' is to prevent biases, since if a physician knew which patient was getting the study treatment and which patient was getting the placebo, he/she might be tempted to give the (presumably helpful) study drug to a patient who could more easily benefit from it. In addition, a physician might give extra care to only the patients who receive the placebos to compensate for their ineffectiveness.[8]

1.3 *Non- Randomized Studies*: The design of a quasi-experiment relates to a particular type of experiment or other study in which one has little or no control over the allocation of the treatments or other factors being studied. The key difference in this empirical approach is the lack of random assignment.[9]

2. Observational studies

2.1 *Cohort Study*: A cohort study or panel study is a form of longitudinal study (a type of observational study) used in medicine, social science, actuarial science, and ecology. It is an analysis of risk factors and follows a group of people who do not have the disease, and uses correlations to determine the absolute risk of subject contraction.

2.2 *Case Control Study*: A case-control study is a type of study design in epidemiology. Case-control studies are used to identify factors that may contribute to a medical condition by comparing subjects who have that condition (the 'cases') with patients who do not have the condition but are otherwise similar (the 'controls').

2.3 *Cross Sectional Study*: A Cross-sectional studies (also known as Cross-sectional analysis) form a class of research methods that involve observation of all of a population, or a representative subset, at one specific point in time.

2.4 *Ecological Study*: An ecological study is an epidemiological study in which the unit of analysis is a population rather than an individual. For instance, an ecological study may look at the association between smoking and lung cancer deaths in different countries.

Phases

Scientists and researchers are constantly in the process of developing new treatments or tests for various diseases and conditions. Clinical trials serve as a vital component for improving the treatment of medical conditions as they lead to higher standards of patient care.

These tests are then tried out on animal models first and then on humans to closely monitor the potential benefits and drawbacks of new or existing tests and treatments. Clinical trials consist of 3 Clinical phases before it is eligible for approval by the Food and Drug Administration (FDA). Each phase of a clinical trial is

designed in such a way to obtain specific information about the new treatment or drug.

1. Pre Clinical Testing
2. Phases 0
3. Phase I
4. Phase II
5. Phase III
6. Phase IV

Pre Clinical Testing: Before a drug may be tested on humans, pre-clinical studies must be conducted either in vitro but usually in vivo on animals to mainly determine if the drug is safe. Animal studies are also done to provide data regarding absorption, distribution, metabolism ,toxicity and excretion of a new drug / molecule. Different strengths of the experimental drug are administered to test the drug's ability to improve performance and behavior in animals, and to reveal harmful side-effects that may occur. Based on the results obtained from these initial studies , the drug compound may be slightly modified to make it more effective. The duration of the study can range from 1-6 years depending on the proposed action of the new drug and also to make sure that the drug can be safely tried out on humans.

Phase 0: This phase is aimed at determining whether a drug will behave in humans in the way that pre-clinical testing indicated. A small dosage, below the amount expected to be used therapeutically, is given to a small number of subjects to determine if the drug will act on the part of the body on which it was designed to act. For example, a drug designed to lower cholesterol would be tested to see if it acts on particular parts of the body (blood vessels, the heart, etc.) and to see if that interaction is in line with expectations. This can prevent further, unnecessary testing in the event of a drug's not acting as predicted

A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development. They enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data.

Phase I: In Phase I trials the new / experimental drug or treatment is tried out on a small group (20-80) of healthy human subjects for the first time, after it has been well tested in lab and animal studies. This initial phase of testing typically takes several months.

This phase is designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in a clinical trial clinic, where the subject can be observed by full-time staff. These clinical trial clinics are often run by contract research organisations (CRO) who conduct these studies on behalf of pharmaceutical companies or other research investigators. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase I trials also normally include dose-ranging, also called dose escalation studies, so that the best and safest dose can be found and to discover the point at which a compound is too poisonous to administer.[10] The tested range of doses will usually be a fraction of the dose that caused harm in animal testing. Phase I trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have terminal cancer or HIV and lack other treatment options. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre. Pay depends on length of participation.

There are different kinds of Phase I trial:

SAD

Single Ascending Dose studies are those in which small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. This is continued until pre-calculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up (at which point the drug is said to have reached the Maximum tolerated dose (MTD).

MAD

Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug. In these studies, a group of patients receives multiple low doses of the drug, while samples (of blood, and other fluids) are collected at various time points and analyzed to acquire information on how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level.

Food effect

A short trial designed to investigate any differences in absorption of the drug by the body, caused by eating before the drug is given. These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug while fasted, and after being fed.

Phase II: After a drug's initial safety has been established, Phase II trials are commenced. In this stage, the drug is administered to a larger group of people, allowing further study of a candidate's effectiveness. Phase II trials also continue the safety assessments started in Phase I. The main purpose, however, is to determine a drug's efficacy, or whether its effect on the body is significant enough to warrant further testing

When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

Phase II studies are sometimes divided into Phase IIA and Phase IIB.

- Phase IIA is specifically designed to assess dosing requirements (how much drug should be given).
- Phase IIB is specifically designed to study efficacy (how

well the drug works at the prescribed dose(s)).

Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

Phase III: Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions.

It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency. This allows patients to continue to receive possibly lifesaving drugs until the drug can be obtained by purchase. Other reasons for performing trials at this stage include attempts by the sponsor at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug. Studies in this phase are by some companies categorised as "Phase IIIB studies."

While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory agencies such as FDA (USA), or the EMA (European Union), for example.

Once a drug has proved satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authorities[3] in different countries. They will review the submission, and, it is hoped, give the sponsor approval to market the drug.

Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines, but in case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market.

Phase IV: Phase IV trial is also known as Postmarketing surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials.

Clinical Trials Protocol

A clinical trial protocol is a document that describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial. The protocol usually also gives the background and reason the trial is being conducted, but these could be provided in other documents referenced in the protocol (such as an Investigator's Brochure).

The protocol contains a study plan on which the clinical trial is based. The plan is designed to safeguard the health of the participants (while limiting their financial liability) as well as answer specific research questions. The protocol describes, among other things, what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, study participants are seen regularly by the research staff (usually medical doctors and/or nurses) to monitor their health and to determine the safety and effectiveness of the treatment(s) they are receiving.

Informed Consent

Informed consent is a phrase often used in law to indicate that the consent a person gives meets certain minimum standards. As a literal matter, in the absence of fraud, it is redundant. An informed consent can be said to have been given based upon a clear appreciation and understanding of the facts, implications, and future consequences of an action. In order to give informed consent, the individual concerned must have adequate reasoning faculties and be in possession of all relevant facts at the time consent is given. Impairments to reasoning and judgment which may make it impossible for someone to give informed consent[11] include such factors as basic intellectual or emotional immaturity, high levels of stress such as PTSD or as severe mental retardation, severe mental illness, intoxication, severe sleep deprivation, Alzheimer's disease, or being in a coma.[12]

Ethical Conduct

Ethics is defined as the science of the morality of human acts. And because actions reflect the motives of the doer, ethics is said to be the study of human motivation, and ultimately, of human rational behavior.[13]

Ethics, also known as moral philosophy, is a branch of philosophy that addresses questions about morality — that is, concepts such as good and evil, right and wrong, virtue and vice, justice and crime, etc.

Major branches of ethics include:

- Meta-ethics, about the theoretical meaning and reference of moral propositions and how their truth values (if any) may be determined;

- Normative ethics, about the practical means of determining a moral course of action;
- Applied ethics, about how moral outcomes can be achieved in specific situations;
- Moral psychology, about how moral capacity or moral agency develops and what its nature is;
- Descriptive ethics, about what moral values people actually abide by.

Clinical trials are closely supervised by appropriate regulatory authorities. All studies that involve a medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial. The local ethics committee has discretion on how it will supervise noninterventional studies (observational studies or those using already collected data). In the U.S., this body is called the Institutional Review Board (IRB). Most IRBs are located at the local investigator's hospital or institution, but some sponsors allow the use of a central (independent/for profit) IRB for investigators who work at smaller institutions.

Controversy

In 2001, the editors of 12 major journals issued a joint editorial, published in each journal, on the control over clinical trials exerted by sponsors, particularly targeting the use of contracts which allow sponsors to review the studies prior to publication and withhold publication. They strengthened editorial restrictions to counter the effect. The editorial noted that contract research organizations had, by 2000; received 60% of the grants from pharmaceutical companies in the U.S Researchers may be restricted from contributing to the trial design, accessing the raw data, and interpreting the results.[14] Seeding trials are particularly controversial.

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