

# Teacher 411: Clinical Research Trials

*Teacher 411s are written for teachers to provide insight into the latest research developments and more confidence in teaching the highlighted subject. The information is not necessarily intended for distribution to students but certainly may be at the teacher's discretion. Glossary terms indicated in **bold**.*

## General Overview

A **clinical research trial** is a research study in which human volunteers are used to answer specific health questions. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people and ways to improve health. There are five types of clinical trials:

- **Treatment trials** test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
- **Prevention trials** look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.
- **Diagnostic trials** are conducted to find better tests or procedures for diagnosing a particular disease or condition.
- **Screening trials** test the best way to detect certain diseases or health conditions.
- **Quality of Life trials** (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.

## Clinical Trial Process

The clinical trial process depends on the kind of trial being conducted. The clinical trial team (doctors, nurses, social workers, and others):

1. checks the health of the participant at the beginning of the trial
2. gives specific instructions for participating in the trial
3. monitors the participant carefully during the trial
4. stays in touch after the trial is completed

Clinical trials are conducted in phases. The trials at each phase have a different purpose and help scientists answer different questions:

- In **Phase I trials**, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
- In **Phase II trials**, the experimental study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.
- In **Phase III trials**, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.
- In **Phase IV trials**, additional information is collected about drug risks, benefits, and optimal use.

## History

Most medical treatment throughout history was “experimental” and not organized “research.” In 1747, James Lind performed the first study of different therapeutic agents to find a treatment for scurvy, a condition caused by vitamin C deficiency. In the 19<sup>th</sup> century, elementary clinical trials began, including the use of **placebo** or a known inert substance that is usually used in parallel with an active substance in a clinical trial (mint water for rheumatic fever). It wasn't until 1900 that a patient entering a physician's office in America had more than a 50% change of being helped. Many milestones were made in 20<sup>th</sup> century research including the practice of **blinding** and **randomization**. Later, the **Food and Drug Administration (FDA)** began to regulate drugs by requiring proof of safety, potency, and purity.

The need for standardized clinical trial procedures was spurred by the **Nuremberg trials** which revealed the inhumane clinical trials conducted by the Nazis. Although the primary medical issue was inhumane experimentation on victims of the Reich, defense attorneys were able to argue that some things Nazi physicians had done were acceptable according to current Western standards of human experimentation—which were poorly articulated. As a result, Article 1 of the Nuremberg Code was created: “The voluntary consent of the human subject is absolutely essential.”

Another infamous study was conducted in the United States from 1932 to 1972. The **Tuskegee Studies** was conducted in Alabama and involved research of the natural history of untreated syphilis, a sexually transmitted disease, in Black men. Available prescriptions were withheld from participants (although the men were told they were being treated). These studies involved major research ethics violations including: lack of written research protocols, total absence of informed consent, immorality of withholding known therapy from illiterate minorities, racial overtones, and questionable validity of the research data. This led to the establishment of **Institutional Review Boards (IRB)** and the **Belmont Report**.

### Ethical and Legal Considerations

The ethical and legal codes that govern medical practice also apply to clinical trials. In addition, most clinical research is federally regulated with built in safeguards to protect the participants.

The **Belmont Report** identifies three fundamental ethical principles for all research that involves human subjects:

- **respect for persons**—individuals should be treated as autonomous agents and persons with diminished autonomy are entitled to protection
- **beneficence**—persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being
- **justice**—fairness of distribution and what is deserved

In addition, applications of these general principles to the conduct of research led to consideration of the following requirements:

- Informed consent
- Risk / benefit assessment
- Selection of subjects of research

**Informed consent** is the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is also a continuing process throughout the study to provide information for participants. To obtain consent, researchers must: provide ample opportunity for consideration, minimize coercion / undue influence, and be done in simple and clear language so the subject understands.

The requirement that research be justified on the basis of a favorable **risk/benefit assessment** bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Therefore, risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account.

The principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects. Potential vulnerable populations must always be taken into consideration when selecting subjects and seeking informed consent. This includes: infants, children, elderly, prisoners, mentally compromised, minorities, and emergency patients. All clinical trials have guidelines about who can participate or **inclusion/exclusion criteria**, which help to identify appropriate participants, keep participants safe, and produce reliable results. The factors that allow someone to participate in a clinical trial are called **inclusion criteria** and those that disallow someone from participating are called **exclusion criteria**. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions.

Every clinical trial in the United States must be approved and monitored by an **Institutional Review Board (IRB)** to make sure the risks are as low as possible and are worth any potential benefits. An IRB is an independent committee of physicians, statisticians, community advocates, and others that ensures that a clinical trial is ethical and the rights of study participants are protected. All institutions that conduct or support biomedical research involving people must, by federal regulation, have an IRB that initially approves and periodically reviews the research.

Sources:

National Institutes of Health: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

The Belmont Report: [www.hhs.gov](http://www.hhs.gov)

The University Clinical Research Center, University of Texas Health Science Center at Houston

# Clinical Research Trials

## Glossary of Terms

**ADVERSE REACTION:** (Adverse Event.) An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time

**ADVOCACY AND SUPPORT GROUPS:** Organizations and groups that actively support participants and their families with valuable resources, including self-empowerment and survival tools.

**APPROVED DRUGS:** In the U.S., the Food and Drug Administration (FDA) must approve a substance as a drug before it can be marketed. The approval process involves several steps including pre-clinical laboratory and animal studies, clinical trials for safety and efficacy, filing of a New Drug Application by the manufacturer of the drug, FDA review of the application, and FDA approval/rejection of application.

**ARM:** Any of the treatment groups in a randomized trial. Most randomized trials have two "arms," but some have three "arms," or even more.

**BASELINE:** 1. Information gathered at the beginning of a study from which variations found in the study are measured. 2. A known value or quantity with which an unknown is compared when measured or assessed. 3. The initial time point in a clinical trial, just before a participant starts to receive the experimental treatment which is being tested. At this reference point, measurable values such as CD4 count are recorded. Safety and efficacy of a drug are often determined by monitoring changes from the baseline values.

**BIAS:** When a point of view prevents impartial judgment on issues relating to the subject of that point of view. In clinical studies, bias is controlled by blinding and randomization.

**BLIND:** A randomized trial is "Blind" if the participant is not told which arm of the trial he is on. A clinical trial is "Blind" if participants are unaware on whether they are in the experimental or control arm of the study; also called masked.

**CLINICAL:** Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science.

**CLINICAL INVESTIGATOR:** A medical researcher in charge of carrying out a clinical trial's protocol.

**CLINICAL TRIAL:** 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 in people. Trials are in four phases: Phase I tests a new drug or treatment in a small group; Phase II expands the study to a larger group of people; Phase III

expands the study to an even larger group of people; and Phase IV takes place after the drug or treatment has been licensed and marketed.

**COHORT:** In epidemiology, a group of individuals with some characteristics in common.

**COMMUNITY-BASED CLINICAL TRIAL (CBCT):** A clinical trial conducted primarily through primary-care physicians rather than academic research facilities.

**COMPASSIONATE USE:** A method of providing experimental therapeutics prior to final FDA approval for use in humans. This procedure is used with very sick individuals who have no other treatment options. Often, case-by-case approval must be obtained from the FDA for "compassionate use" of a drug or therapy.

**COMPLEMENTARY AND ALTERNATIVE THERAPY:** Broad range of healing philosophies, approaches, and therapies that Western (conventional) medicine does not commonly use to promote well-being or treat health conditions. Examples include acupuncture, herbs, etc.

**CONFIDENTIALITY REGARDING TRIAL PARTICIPANTS:** Refers to maintaining the confidentiality of trial participants including their personal identity and all personal medical information. The trial participants' consent to the use of records for data verification purposes should be obtained prior to the trial and assurance must be given that confidentiality will be maintained.

**CONTRAINDICATION:** A specific circumstance when the use of certain treatments could be harmful.

**CONTROL:** A control is the nature of the intervention control.

**CONTROL GROUP:** The standard by which experimental observations are evaluated. In many clinical trials, one group of patients will be given an experimental drug or treatment, while the control group is given either a standard treatment for the illness or a placebo.

**CONTROLLED TRIALS:** Control is a standard against which experimental observations may be evaluated. In clinical trials, one group of participants is given an experimental drug, while another group (i.e., the control group) is given either a standard treatment for the disease or a placebo.

**DATA SAFETY AND MONITORING BOARD (DSMB):** An independent committee composed of community representatives and clinical research experts that reviews data while a clinical trial is in progress to ensure that participants are not exposed to undue risk. A DSMB may recommend that a trial be stopped if there are safety concerns or if the trial objectives have been achieved.

**DIAGNOSTIC TRIALS:** Refers to trials that are conducted to find better tests or procedures for diagnosing a particular disease or condition. Diagnostic trials usually include people who have signs or symptoms of the disease or condition being studied.

**DOSE-RANGING STUDY:** A clinical trial in which two or more doses of an agent (such as a drug) are tested against each other to determine which dose works best and is least harmful.

**DOUBLE-BLIND STUDY:** A clinical trial design in which neither the participating individuals nor the study staff knows which participants are receiving the experimental drug and which are receiving a placebo (or another therapy). Double-blind trials are thought to produce objective results, since the expectations of the doctor and the participant about the experimental drug do not affect the outcome; also called double-masked study.

**DOUBLE-MASKED STUDY:** See Double-Blind Study.

**DRUG-DRUG INTERACTION:** A modification of the effect of a drug when administered with another drug. The effect may be an increase or a decrease in the action of either substance, or it may be an adverse effect that is not normally associated with either drug.

**EFFICACY:** (Of a drug or treatment). The maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. In the procedure mandated by the FDA, Phase II clinical trials gauge efficacy and Phase III trials confirm it.

**ELIGIBILITY CRITERIA:** Summary criteria for participant selection; includes Inclusion and Exclusion criteria.

**EMPIRICAL:** Based on experimental data, not on a theory.

**ENDPOINT:** Overall outcome that the protocol is designed to evaluate. Common endpoints are severe toxicity, disease progression, or death.

**EPIDEMIOLOGY:** The branch of medical science that deals with the study of incidence and distribution and control of a disease in a population.

**EXCLUSION/INCLUSION CRITERIA:** See Inclusion/Exclusion Criteria.

**EXPANDED ACCESS:** Refers to any of the FDA procedures, such as compassionate use, parallel track, and treatment IND that distribute experimental drugs to participants who are failing on currently available treatments for their condition and also are unable to participate in ongoing clinical trials.

**EXPERIMENTAL DRUG:** A drug that is not FDA licensed for use in humans, or as a treatment for a particular condition

**FDA:** See Food and Drug Administration.

**FOOD AND DRUG ADMINISTRATION (FDA):** The U.S. Department of Health and Human Services agency responsible for ensuring the safety and effectiveness of all drugs, biologics, vaccines, and medical devices, including those used in the diagnosis, treatment, and prevention of HIV infection, AIDS, and AIDS-related opportunistic infections. The FDA also works with the blood banking industry to safeguard the nation's blood supply.

**HYPOTHESIS:** A supposition or assumption advanced as a basis for reasoning or argument, or as a guide to experimental investigation.

**INCLUSION/EXCLUSION CRITERIA:** The medical or social standards determining whether a person may or may not be allowed to enter a clinical trial. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. It is important to note that inclusion and exclusion criteria are not used to reject people personally, but rather to identify appropriate participants and keep them safe.

**INFORMED CONSENT:** The process of learning the key facts about a clinical trial before deciding whether or not to participate. It is also a continuing process throughout the study to provide information for participants. To help someone decide whether or not to participate, the doctors and nurses involved in the trial explain the details of the study.

**INFORMED CONSENT DOCUMENT:** A document that describes the rights of the study participants, and includes details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the informed consent document. The participant then decides whether or not to sign the document. Informed consent is not a contract, and the participant may withdraw from the trial at any time.

**INSTITUTIONAL REVIEW BOARD (IRB):** 1. A committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. All clinical trials in the U.S. must be approved by an IRB before they begin. 2. Every institution that conducts or supports biomedical or behavioral research involving human participants must, by federal regulation, have an IRB that initially approves and periodically reviews the research in order to protect the rights of human participants.

**INTENT TO TREAT:** Analysis of clinical trial results that includes all data from participants in the groups to which they were randomized even if they never received the treatment.

**INTERVENTION NAME:** The generic name of the precise intervention being studied.

**INTERVENTIONS:** Primary interventions being studied: types of interventions are Drug, Gene Transfer, Vaccine, Behavior, Device, or Procedure.

**INVESTIGATIONAL NEW DRUG:** A new drug, antibiotic drug, or biological drug that is used in a clinical investigation. It also includes a biological product used *in vitro* for diagnostic purposes.

**IRB:** See Institutional Review Board.

**MASKED:** The knowledge of intervention assignment. See Blind

**NATURAL HISTORY STUDY:** Study of the natural development of something (such as an organism or a disease) over a period of time.

**NEW DRUG APPLICATION (NDA):** An application submitted by the manufacturer of a drug to the FDA - after clinical trials have been completed - for a license to market the drug for a specified indication.

**OFF-LABEL USE:** A drug prescribed for conditions other than those approved by the FDA.

**OPEN-LABEL TRIAL:** A clinical trial in which doctors and participants know which drug or vaccine is being administered.

**ORPHAN DRUGS:** An FDA category that refers to medications used to treat diseases and conditions that occur rarely. There is little financial incentive for the pharmaceutical industry to develop medications for these diseases or conditions. Orphan drug status, however, gives a manufacturer specific financial incentives to develop and provide such medications.

**PEER REVIEW:** Review of a clinical trial by experts chosen by the study sponsor. These experts review the trials for scientific merit, participant safety, and ethical considerations.

**PHARMACOKINETICS:** The processes (in a living organism) of absorption, distribution, metabolism, and excretion of a drug or vaccine.

**PHASE I TRIALS:** Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients.

**PHASE II TRIALS:** Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.

**PHASE III TRIALS:** Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling.

**PHASE IV TRIALS:** Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use.

**PLACEBO:** A placebo is an inactive pill, liquid, or powder that has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the treatment's effectiveness.

**PLACEBO CONTROLLED STUDY:** A method of investigation of drugs in which an inactive substance (the placebo) is given to one group of participants, while the drug being tested is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is more effective in treating the condition.

**PLACEBO EFFECT:** A physical or emotional change, occurring after a substance is taken or administered, that is not the result of any special property of the substance. The change may be beneficial, reflecting the expectations of the participant and, often, the expectations of the person giving the substance.

**PRECLINICAL:** Refers to the testing of experimental drugs in the test tube or in animals - the testing that occurs before trials in humans may be carried out.

**PREVENTION TRIALS:** Refers to trials to find better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.

**PROTOCOL:** A study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes 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, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment

**QUALITY OF LIFE TRIALS (or Supportive Care trials):** Refers to trials that explore ways to improve comfort and quality of life for individuals with a chronic illness.

**RANDOMIZATION:** A method based on chance by which study participants are assigned to a treatment group. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms. The researchers do not know which treatment is better. From what is known at the time, any one of the treatments chosen could be of benefit to the participant.

**RANDOMIZED TRIAL:** A study in which participants are randomly (i.e., by chance) assigned to one of two or more treatment arms of a clinical trial. Occasionally placebos are utilized.

**RISK-BENEFIT RATIO:** The risk to individual participants versus the potential benefits. The risk/benefit ratio may differ depending on the condition being treated.

**SCREENING TRIALS:** Refers to trials which test the best way to detect certain diseases or health conditions.

**SIDE EFFECTS:** Any undesired actions or effects of a drug or treatment. Negative or adverse effects may include headache, nausea, hair loss, skin irritation, or other physical problems. Experimental drugs must be evaluated for both immediate and long-term side effects.

**SINGLE-BLIND STUDY:** A study in which one party, either the investigator or participant, is unaware of what medication the participant is taking; also called single-masked study.

**SINGLE-MASKED STUDY:** See Single-Blind Study.

**STANDARD TREATMENT:** A treatment currently in wide use and approved by the FDA, considered to be effective in the treatment of a specific disease or condition.

**STANDARDS OF CARE:** Treatment regimen or medical management based on state of the art participant care.

**STATISTICAL SIGNIFICANCE:** The probability that an event or difference occurred by chance alone. In clinical trials, the level of statistical significance depends on the number of participants studied and the observations made, as well as the magnitude of differences observed.

**STUDY ENDPOINT:** A primary or secondary outcome used to judge the effectiveness of a treatment.

**STUDY TYPE:** The primary investigative techniques used in an observational protocol; types are Purpose, Duration, Selection, and Timing.

**TOXICITY:** An adverse effect produced by a drug that is detrimental to the participant's health. The level of toxicity associated with a drug will vary depending on the condition which the drug is used to treat.

**TREATMENT IND:** IND stands for Investigational New Drug application, which is part of the process to get approval from the FDA for marketing a new prescription drug in the U.S. It makes promising new drugs available to desperately ill participants as early in the drug development process as possible. Treatment INDs are made available to participants before general marketing begins, typically during Phase III studies. To be considered for a treatment IND a participant cannot be eligible to be in the definitive clinical trial.

**TREATMENT TRIALS:** Refers to trials which test new treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

Source:

National Institutes of Health: [www.clinicaltrials.gov](http://www.clinicaltrials.gov)