

## What is a Clinical Trial?

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There are different types of clinical trials. Some studies are conducted in order to evaluate a new drug, some to test a medical device, and some are epidemiological studies (studies that examine the relationship of a human population and health related issues). All of these trials have certain similarities and differences.

Every trial (or study) should have a well designed study plan. This study plan is called a protocol. A protocol is like an instruction guide. It describes what is being tested, how it is being tested, what is being measured and how it is being measured.

For medical studies that involve human participants, an ethics committee usually reviews the protocol. The ethics committee is called the Institutional Review Board or IRB for short. Only after the IRB reviews and approves the protocol can the researcher start the trial and begin recruiting subjects for the study.

Together with the protocol the IRB usually approves an informed consent document. An informed consent document provides you with important information about the study such as the procedures that will be done during the study and the risks involved from participating in the study, who will pay for the study procedures, and what happens to you should you become injured or ill while participating in the study. The informed consent will also tell you how your personal information, both your current health information and any other information that will be collected during the study, will be used and who will have access to it. In order to participate in the study, you must first read and sign the informed consent document.

It is important that you take your time reading the informed consent and write down any questions you may have. Be sure all of your questions are answered by the study doctor or the study staff before signing the informed consent. Signing an informed consent form is a process of questions, answers and explanations. It is not just your signature on a piece of paper!

### **Studies conducted in order to bring a new drug on the market (Pharmaceutical Studies)**

It takes on average 10 to 12 years to develop a drug from the laboratory until it sells on the market. Some big companies try to reduce this time to 5 or 6 years. In the year 2000, worldwide, 58 billion US dollars was spent by the pharmaceutical industry to research and develop drugs. Approximately one in five drugs that are tested in humans will get FDA market approval.

## **Preclinical Studies**

In the first stage the new drug is tested in tissue cultures. The mechanism of action is studied in the test tube or in living cells; these are called in vitro studies. Researchers try to find out how the drug is absorbed and metabolized by the cells, how it reacts with other drugs, and how much drug can kill the cell. Most in vitro studies are carried out in a concentration that is similar to a proposed concentration of study drug in the human body.

The next step is to test the new compound in animals. The acute toxicity of the drug has to be tested in at least two species of animals. Usually one rodent (i.e. mice, rats) and one non-rodent are used. This is done because a drug that affects one species might not affect the other species. In these studies one usually tests how much drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of the drug and its breakdown products. One also examines how fast the drug and its metabolites are eliminated from the body.

When all these tests look promising the company that develops the drug might apply with the FDA for the permission to try the drug in humans. From five thousand (5000) compounds tested approximately five will appear promising enough to test it in humans.

## **Clinical Studies**

The clinical studies are divided into four (4) phases.

### **Phase 1**

Phase one studies are conducted in small groups, 20 to 80 mostly healthy volunteers. Sometimes patients with the disease in which the drug is supposed to be effective are studied. The tests study how the drug will be metabolized in the human body, the mechanism of action in humans and how safe it is. Other items that are studied in these trials are absorption, distribution, metabolization (breakdown) and excretion of the drug in the human body. One also studies the safe dosage range of the drug. After the trial is completed and the data is analyzed the participant has the right to request to know what s/he received.

### **Phase 2**

In phase two studies approximately 100 to 300 volunteers with the disease take the study drug. These studies are done to evaluate the effectiveness and the safety of the drug for a particular disease in patients with the disease. These studies determine the common short term side effects and risks associated with the study drug. Depending upon the type of investigational drug and the condition it treats, studies in this phase can last from six (6) months to three (3) years. Most phase 2 studies contain a group of patients that are treated with the original study drug and one group that are treated with a placebo (an inactive compound). Most studies randomize the participants to one of the treatment groups. That means participants will be assigned by chance to either the group that

receives study drug or to the group that receives placebo. Neither the patient nor the treating physician knows what the participant receives. This is called double-blinded. After the trial is completed and the data is analyzed the participant has the right to request to know what s/he received.

### **Phase 3**

Phase 3 studies are conducted if the previous results (results from phase II studies) suggested that the drug is effective. They are intended to gather more information about effectiveness and safety of the study drug. The overall benefit –risk ratio will be evaluated. The results from this study will provide the basic information for labeling the drug with side effects and for the indication of use. Phase 3 studies can contain several hundreds to several thousands of patients with the studied disease. The duration of a phase 3 trial is from one to four years. Studies are usually randomized and double-blind (see phase 2 for definition of these terms). After the trial is completed and the data is analyzed the participant has the right to request to know what s/he received.

### **Phase 4**

Phase 4 trials are performed after a medicine has received approval to be sold. In these studies the drug is prescribed in a clinic. Patients will usually sign a consent form. The studies are used to develop a new treatment for the medicine. Other indications are to compare the drug with other treatments for the condition and determine the clinical effectiveness of the medicine in a much wider variety of patient types in conditions of real life.

Phase 4 trials usually involve several thousands of patients. Phase 4 studies evaluate safety and try to find more side effects of the drug.

### **Medical Device studies (Investigational Device studies):**

There are different medical devices. Medical devices are implants (i.e pacemaker), devices to monitor a patient (i.e. blood pressure cuff), devices to sustain human life (i.e. ventilator) or devices important in diagnosing, curing or treating a disease (i.e Vest in ALS Study). Other medical devices are for example disposable contact lenses or wound dressings. An investigational device is a medical device which is the subject of a clinical trial in order to evaluate effectiveness and/or safety of the device. Like the pharmaceutical studies these studies require a research protocol, approval through the IRB ethics committee and signing a consent form. Patients will usually have to come in more than once for a follow up visit, just like in a pharmaceutical studies.

### **Epidemiological studies**

Epidemiological studies examine the relationship of a human population and health related issues. For example it might examine ALS in a population and the exposure of this population to toxins in the environment as a cause. Some of the knowledge gained

from epidemiological studies has been applied to the control of environmental and biological threats to health. One example is smoking which appears to increase risk of ALS.

Studies are either observational or experimental. There are three types of observational studies: cross-sectional studies, case-control studies and cohort studies. Observational studies use questionnaires or surveys. There is no other intervention except for asking questions and maybe medical examinations, laboratory tests or x-ray examinations. The studies require review by an ethics committee and the signing of a consent form.

### **Observational studies**

A cross-sectional study (survey) is done on a random sample of the population. Subjects answer questions, receive medical exams or give blood for laboratory tests. This type of study is used to test a hypothesis about a possible cause of disease or a risk factor.

A case control study compares the past history of exposure to a risk in patients who have a known disease. It also examines individuals (controls) who are similar in age, sex and their exposure to the risk factor, but they do not have the disease. This type of study is usually used to test rare diseases, because it requires a small number of patients. A difference in the exposure frequency among cases and controls can be statistically analyzed to test the hypotheses.

A cohort study is a longitudinal (long-term) and prospective (to look into the future) study. Individuals with exposure to a risk factor are identified and followed over a period of time (usually years). It is measured how many people who have the exposure to the risk factors are getting the disease. These studies usually use questionnaires, routine medical examinations and laboratory tests. Informed consent is required.

An exception is a retrospective cohort study. In this study one looks into the medical records of patients and links them to exposure to a drug, x-ray or other risks in the past.

### **Experimental studies:**

In an experiment the investigator alters intentionally circumstances under a defined and controlled condition. It studies what happens by changing the circumstances. This is only ethical if one does not know enough about the procedure or the circumstance one changes and its result on the patient. One example for this is a randomized controlled trial. This study design is used in most pharmaceutical or medical device studies. One does not know enough about the drug or the medical device and its effects on humans. Therefore, it is ethical to compare patients who received the study drug or medical device to patients who receive inactive substance (placebo) or patients who don't get the medical device.

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