Volunteering for Clinical Research

Most of us want a cure for our disease or a disease that may be affecting someone we love. Many of us would be happy just to settle for a safe and effective treatment, such as insulin for diabetes. However, neither cures nor treatments will become available without medical research.

When scientists are developing a new treatment for a common disease, it is relatively easy to find enough volunteers for a clinical trial. In that case, people have the luxury of saying, “Let somebody else be the guinea pig,” while we await a new allergy medicine or arthritis drug that has been proven to be safe and effective. However, people with rare diseases do not have that luxury because there may be very few patients on whom to test a new treatment, or few who meet certain eligibility requirements. Thus, the burden falls on us to volunteer for clinical trials if we are ever to have improved treatments or cures.

Stages of Research

“Basic research” is performed in a laboratory, usually in test tubes and animals. Basic research usually takes many years because scientists have to extensively test potential new treatments extensively before the FDA will allow them to be tested in humans. Examples of basic research include testing whether an agent may affect a certain cell, or determining if it is stable enough to use in humans.

“Clinical research” is research that is performed on humans, usually in a hospital clinic or a doctor’s office. There are four stages of clinical research: Phase I, Phase II, Phase III, and Phase IV.

Phase 1

After years of basic research indicates that a new compound is probably safe, and possibly effective, Phase I trials of clinical research can begin. If the drug to be tested is a possible treatment for a prevalent disease, Phase I studies usually involve a small number of healthy volunteers who do not have the target disease. However, if the drug is for a rare disease, Phase I studies may involve a small number of people with the disease.

The goal of Phase I testing is solely for safety. Volunteers are told they should not have any expectation that the drug will be therapeutic. Since this will be the first time the drug is used on humans, scientists do not know the proper dosage so they may start very low and escalate the dosage with each successive group of several patients until side effects appear.

Phase II

If Phase I studies show that the drug is relatively safe, Phase II studies can begin. In Phase II, a larger number of volunteers with the target disease participate so doctors can learn more about the safety of the drug, and look for initial signs that the drug may also be effective. Each group of volunteers may be given different dosages in order to identify the most effective dosage with the least side effects. Only about 25 to 30 percent of experimental treatments survive Phase I and Phase II clinical trials by showing evidence of being relatively safe and effective.

Phase III
Phase III clinical trials involve the largest number of patients, and use the experimental treatment on more volunteers than Phase I and II combined. Phase III trials are the most important in terms of proving that a drug is safe and effective for a given health condition at an appropriate dosage. The FDA relies mostly on the data from Phase III clinical trials to determine whether a new drug should be approved for commercial availability, and what information should be provided to doctors on the product’s labeling (e.g., precautions, side effects, etc.).

Throughout Phase I, II, and III, volunteers are put through extensive tests to determine how the medication is impacting them, both in terms of effectiveness and side effects. These tests are specific to the proposed use of the medication, and may include blood and urine tests, x-rays, MRI or CAT scans, spinal taps, EKGs, and EEGs.

**Phase IV**

Phase IV trials are sometimes called “post marketing trials” and are often requested by the FDA when there are certain unanswered questions at the time the drug is approved for commercial availability in the United States. For example, the FDA may sense that a new drug for asthma will be used in combination with other asthma drugs, so they may ask the manufacturer to conduct Phase IV combination drug trials to answer these remaining questions after the drug is approved for sale. Often, the issues addressed in Phase IV trials would be impossible to look at in smaller groups of patients, and so it is important that these things are monitored once the medication goes into widespread use.

**Placebo-Controlled Clinical Trials**

The FDA often requires Phase II and Phase III trials to be “placebo controlled” in order to prove that an experimental drug is effective and that any positive result is not merely based on a patient knowing that he/she is taking an experimental treatment. In a placebo-controlled trial, some patients are on an inactive substance (placebo), and other patients are on the real treatment. In this way, the results of each group can be measured to ensure that the effect seen is real and not imagined. Placebo-controlled trials are important because science has proven that placebos can be as powerful as real medicine. Some people will be convinced that they feel better even though there was no active ingredient in the placebo, while others will claim to get side effects from a placebo that are very similar to real side effects. Therefore, most patients have to show more (statistically significant) symptom improvement with the real drug than they do with the placebo in order to prove that a drug is truly effective.

**Double-Blind**

In a double-blind, placebo-controlled trial, neither the patient nor the doctor knows whether the patient has taken the real treatment or the placebo. This “blinding” eliminates a chance that the doctor will be biased when he/she evaluates the patient to determine if the treatment helped. Double-blind studies are done not only with drugs, but also with devices and even surgery. For example, in a clinical trial of brain tissue transplants in people with Parkinson’s disease, the surgeon and the patient did not know whether the patient was receiving real brain tissue injections into the brain, or an inactive placebo. In “single-blind” clinical studies, only one of the parties (either the doctor or the patient) will be unaware of the active treatment. A trial in which both the doctor and the patient know if the patient is on active treatment or placebo is called an “open label trial”. For purposes of FDA approval, open label, non-placebo controlled trials are rarely considered by the FDA in their decisions regarding marketing approval.
Placebo Controversy

Some people with serious and life-threatening diseases do not want to participate in placebo-controlled clinical trials because they do not feel it is fair to ask them to take a placebo. Because of the controversy about placebos, FDA has allowed a wide variety of accommodations that do not sacrifice the critically important information that scientists gain from use of placebos in double-blind trials. For example, in the Parkinson’s studies mentioned above, during the first year many of those who received placebo brain injections felt their symptoms improved just as much as the people who received the real brain tissue cells. Some scientists therefore theorized that the surgery itself might have had an effect on the brain’s ability to compensate for deficient dopamine.

The FDA also allows “crossover” studies so that no one will be denied the active compound. In crossover studies, volunteers may take a placebo for several weeks or months, and then cross over to the real drug for an equal amount of time. Conversely, a patient might begin with the active treatment, and several weeks later cross over to placebo. In this way, not only can groups of patients be compared, but individual patient results can be measured when on each “treatment arm”.

FDA does not require that half of the people in a clinical study take placebos. In some studies, only one-third or one-fourth of the volunteers will take a placebo and the rest may take the real treatment. Thus, your chance of getting a placebo may be relatively small. In other studies involving a disease that already has an accepted treatment, no placebos may be warranted because patients on the new drug can be compared to a “control group” of patients taking the standard treatment. In this case, the new drug has to be proven as safe and effective as the old drug, or safer, or more effective.

What Protections Do Research Volunteers Have?

Protection of human subjects in research can be confusing. A lot depends on where the clinical trial takes place because local bioethics committees may interpret the rules in different ways. Thus, a clinical trial in Europe or Asia falls under different rules than one in the United States. In the USA, the rules governing clinical trials at a hospital that receives federal funds are more comprehensive than the rules governing research at a local doctor’s office where no federal funds are involved.

The basic tenet of research involving humans is “informed consent.” This means no person is permitted to participate in research without his or her knowledge about the risks and possible benefits of the experiment, and his or her consent must be obtained. If a person is incapacitated and cannot give voluntary consent, or is a minor, there are specific rules applying to family members and legal guardians who can, under certain circumstances, provide consent.

Informed consent for a person who volunteers for clinical research must be provided in writing and orally. There must be no coercion or undue influence, and the experiment must be explained in language that is understandable to the volunteer. All possible risks and discomforts must be explained, as well as possible benefits. The researcher must also tell the volunteer about other possible treatments or procedures that might help them, as an alternative to the treatment being offered in the experiment.

The informed consent must also explain how the research team will keep the patient’s records confidential, and whether hospital staff, the FDA, or a company may have access to those records. If a
volunteer is injured by an experiment, the informed consent must explain that the institution will provide treatment, and whether there may be costs to the patient for such treatment.

An informed consent document must provide contact information, both for someone who can answer questions about the clinical trial and for the person to be contacted if the volunteer should be injured. It must clearly explain that a person can refuse to participate in the trial without any objections from his or her doctor or hospital. If a person decides to participate, but later wants to withdraw from the trial, he is free to do so without any loss of benefits and no penalty. The document must also explain that the doctor can terminate a person’s participation, even if the patient objects, under certain circumstances (e.g., if you don’t comply with your doctor’s instructions, if there is evidence that the drug is not safe, or if harmful side effects may be experienced).

Costs

If you are considering participating in a clinical trial, be sure to note any costs that you may incur, or whether you will be paid for your participation. Most clinical research is free because either the government or a corporate sponsor covers the costs, and in some circumstances volunteers may be given small sums to cover their costs of travel, daycare, meals, etc. There should be no cost to you for any treatment of injuries arising out of your participation in the experiment.

The FDA does not permit manufacturers to charge a fee for experimental drugs or medical devices (except under certain very unusual circumstances which FDA must individually approve), so you should not have to pay anything to participate in a clinical trial. In the case of medications for rare disorders, some small drug companies are forced to charge and have obtained approval from the FDA to do so, but they often have services to assist with insurance reimbursement or other financial assistance should you require it. Some hospitals, however, may try to recoup costs by charging your insurance company. It is therefore important to clarify all financial matters in advance, and in writing, before you decide whether to volunteer.

Benefit Vs. No Benefit

The most important thing to be aware of, if you are considering participation in medical research, is that you should have no expectation to benefit from an experimental therapy. The reason that a treatment is experimental is that it has not yet been proven to be safe or effective. If by chance you happen to benefit from an experimental treatment, you will undoubtedly be very grateful, but you should not expect it. You must also be very sensitive to risks because there will be risks, both known and unknown, in any experiment. At a minimum, however, other patients with your disease will undoubtedly benefit in the future from the knowledge gained by scientists from your clinical trial, even if the experimental treatment doesn’t help you. In fact, your primary motivation for volunteering in a clinical trial should be to help others.

Original source of information: National Organization for Rare Disorders. For more information on rare diseases, visit their website at www.rarediseases.org.