

[Home](#) > [Act](#) > Types of Clinical Trials

Resources

Types of Clinical Trials

By [Tom Hollon, PhD](#)

Reviewed by [Miriam Komaromy, MD](#)

Last updated October 24, 2000

Before a new drug, surgical procedure, or therapy becomes available to the public, it must go through a rigorous testing process and be evaluated by the US Food and Drug Administration (FDA). This testing process consists of a series of clinical trials that are designed to test the safety and usefulness of the new drug compared to the current standard treatment.

The clinical trials that make headlines are usually what are called phase III trials. These are large-scale tests with hundreds or thousands of patients. They are the culmination of earlier phase I and phase II trials that include many fewer people and still earlier preclinical experiments with animals. They are also the final tests in humans before the FDA is asked to authorize sale of new medicines.

- [Why Are Large-Scale Trials Needed?](#)
- [What Goes on Prior to a Large-Scale Phase III Trial?](#)
- [What Are the Different Types of Phase III Trials?](#)
- [What Happens After the Trials Are Over?](#)
- [What Questions Can't Be Answered by Phase III Trials?](#)

Why Are Large-Scale Trials Needed?

Clinical trials are designed to test whether a drug is safe for humans, and whether the drug is effective in treating human diseases or conditions. Although

Many volunteers are required because people are highly

Conditions

Alzheimer's
Breast Cancer
Colon Cancer
Diabetes
Heart Disease
Hemochromatosis
Ovarian Cancer

Tools

Cancer QuickScreen
TreeBuilder
Medical Glossary
Opinion Poll
Disease Quizzes

Become a Member

Register

Genetics 101

Overview of Genetics
Inheritance Patterns
DNA Mutations
Changing Your Risk
Genetics and the Future
Personalized Medicine
Ashk. Jewish Genetics
Inherited/Sporadic Cancer

Genetic Testing

The Testing Process
Where Is Testing Done?
Who Orders Genetic Tests?
Costs of Genetic Testing

Ethical Issues

Genetic Information
Genetic Discrimination
Health Insurance

Research Participation

Types of Clinical Trials
What Should I Know?
From Gene To Cure
List of Clinical Trials

Resources

Genetic Counseling
Find a Genetic Counselor
Find a Support Group
Getting Medical Records
Talking With Your Family
Help for Adoptees
Help for Birth Parents

Managing Your Risk



Awards

"Genetic Health

does more than hit just a home run — it's a grand slam in the bottom of the ninth to win the game ... one of the very best health-related sites we have ever had the pleasure to view." — Wally Gross, Surfers Choice Review Team



"This coveted award

is only given to sites which excel not only in user-friendly design but also in depth of content. Your site has exceeded all of our expectations in these areas. We were particularly impressed by the amount of detailed and useful information that you make available to your

the drug has generally gone through extensive animal testing before the trial begins, animal trials cannot always predict how new medicines will affect humans. Even the most painstaking tests with animals give only approximate indications of how people will respond to drugs. At some point, after thorough study in animals (and when the FDA is convinced human experimentation will probably be safe), tests with humans become necessary.

variable in how they respond to drugs

Not only is it necessary to test new drugs in humans, but they need to be tested in a large number of humans in order for the results of the trial to be clear. The reason so many volunteers are required is that people are highly variable in how they respond to drugs. It is not unusual, for example, for a drug to be somewhat effective in only 30 percent of those who take it. For medical researchers to prove such a slight benefit requires testing the drug in as many as several thousand patients.

This extensive testing is part of what drives up the cost of new drugs – the average development time is over 10 years and costs from 500 to 700 million dollars.

[▲top](#)

What Goes on Prior to a Large-Scale Phase III Trial?

An enormous amount of testing has gone on by the time a drug is ready for phase III. In general, a new drug or treatment goes through preclinical testing in animals, then small phase I and phase II trials in humans before being ready for large-scale testing.

Many volunteers are required because people are highly variable in how they respond to drugs

Preclinical testing

visitors." — Eye-
Dentity Web Team



When a drug is discovered that seems to have medical potential, a drug company will test it exhaustively in animals, looking for signs it may be poisonous, cause cancer, or cause birth defects. Animal studies will also be used to estimate the initial drug doses to be tested in humans.

When animal experiments are finished, the company asks the FDA for permission to begin clinical trials. The FDA only grants approval once they are satisfied that the animal experiments are sound and that clinical trials are likely to be safe.

Phase I

The first test of the drug in humans is known as phase I. It is designed to find out if the drug is safe rather than whether the drug is effective. Phase I is also used to learn what drug doses to use in later trials, how the drug is broken down in the body and excreted, and study short-term side effects.

Phase I trials are designed to find out if a drug is safe for humans

A phase I trial rarely has more than 100 participants. Often healthy people are enrolled in phase I trials rather than patients on the assumption that if the drug has unexpected side effects, healthy people have the best chance of escaping permanent harm. But on other occasions, as with a drug treating a serious disease like cancer, phase I subjects may be patients who have failed standard treatments.

Phase II

If a drug passes the safety tests of phase I, it advances to a phase II trial with up to 200 participants. The goal of a phase II trial is to learn more about safety and side effects, sharpen estimates of

Phase II trials are often the first time a drug is tested in actual patients

proper doses, and get an early appraisal of whether the drug is going to work. This trial is often the first time a drug is tested in actual patients.

[▲top](#)

What Are the Different Types of Phase III Trials?

The phase III trial consists of hundreds or thousands of people.

Commonly, phase III will be conducted at several medical centers to see if people treated in different locales have similar

experiences. The central question of a phase III trial is whether the drug works. Phase III will also give doctors an extensive look at the drug's side effects. There are many different ways of conducting a phase III trial.

The central question of a phase III trial is whether the drug works

Blinded, randomized trials

Many Phase III trials are randomized, double-blind trials. Randomized means people are assigned at random either to receive the new drug, the standard treatment for that disease, or a nonfunctional substitute (such as a sugar pill). This last group is often called the control group, or the placebo group. Because phase III must answer definitively whether the drug works, it's important to compare people who receive it with others who do not.

Randomization is a way to help ensure that different groups in the trial have similar characteristics. This makes it easier to compare outcomes between groups

A good example of how people are randomly assigned to study groups is the phase III trial for Herceptin, which treats a form of breast cancer. In this trial women either received the standard breast cancer treatment with Herceptin or the standard treatment without Herceptin. In this case, there was

no control group who received just a sugar pill because to do so would be to not treat women with a potentially fatal illness. In this trial, the women who received Herceptin with the standard treatment became the test group; the others, the controls.

Women were assigned at random to the two groups. This means that the average age of the two groups was roughly similar as was the severity of their cancer so the results can be compared. If the two groups had differed considerably in age or health, researchers would not be able to tell if the drug itself was effective, or if the women in that group were just younger or healthier.

Herceptin's trial was also considered double-blind, which means that neither the women nor their doctors knew who was receiving Herceptin. Of course, it is natural for doctors to want to know what treatments their patients are getting, and in single-blind trials they do. There, only the trial participants are unaware of which group they are in. But double-blind trials are considered better because they prevent doctors from acting on preconceived notions they may have about whether or not the drug works.

Double-blind means that neither the doctor nor the trial participant knows whether the participant is receiving the experimental treatment

For example, a doctor in the Herceptin trial might have been tempted to offer extra treatment to participants that weren't getting Herceptin. But the physician's attempt to compensate for the fact that the participant wasn't receiving the study drug would have collided with the requirement to keep groups comparable in everything except who received the new drug. Unintentionally, the doctor might have interfered with the trial, casting doubt on its conclusions. This is why it is considered good practice for phase III trials to be double-blind.

Open trials

Not every trial is blind. In unblinded trials, often described as open trials, both doctors and participants know what treatments are being given. Trials of surgical procedures and comparisons of medical devices are often by nature open. One of the problems with an open drug trial is that many participants may not want to take placebos, because they presume the drug will be better. Open trials, like single-blind trials, are considered to be more prone to error than double-blind procedures.

Factorial trials

When patients are being treated with a combination of drugs, as is current practice for HIV infection, a new drug may be evaluated by testing it in combination with other drugs rather than by itself. A factorial design trial may be used for this purpose. A simple factorial design would have one group testing therapy A, another testing therapy B, a third group testing A and B combined, and a control group testing neither A nor B. Factorial designs are considered an efficient way to test medicines in combination, but their results are not always easy to interpret.

Crossover trials

In a crossover trial, each participant gets both treatments being tested. Some participants are assigned at random to receive drug A, and later, drug B. Others receive B, then A. To produce valid results, the effect of the first drug must end before the second drug is taken, and vice-versa. This requirement can be hard to satisfy, and is one reason crossover trials are not often used.

Orphan Drug Trials

Orphan drug trials test drugs designed to treat

diseases affecting fewer than 200,000 Americans. Some are rare genetic diseases that occur when missing or defective enzymes prevent essential biochemical reactions from happening. Because affected individuals are so few, an orphan drug may be tested only on a small number of participants, who generally are so sick that if the drug works, their improved health is readily apparent.

[▲top](#)

What Happens When the Trials Are Over?

When the trials end, the drug company submits its data to the FDA and asks for permission to market the drug. The FDA approves the drug if it agrees that the drug is safe and effective. If it isn't convinced, the agency will reject the application or may request additional data before making a final decision. Approval moves the drug into everyday medical practice. The FDA then begins surveillance of side effects experienced by patients within the general population.

After a successful phase III trial, FDA approval moves the drug into everyday medical practice

Finally, there is the question of what happens to you if you benefit from a drug in a clinical trial and need to continue using it between the time the trial ends and the FDA grants approval. Especially for serious diseases, the FDA sometimes allows companies to distribute drugs prior to approval on grounds of compassion.

[▲top](#)

What Questions Can't Be Answered by Phase III Trials?

Even after phase III trials, certain side effects may remain unknown. For example the trials may not have included enough people to detect rare side effects, or the drug may show harmful interactions with a common medication. After the drug enters

the market and many thousands of people start taking it, these rare side effects and drug interactions can surface. If the side effects are severe the FDA has to take action. It may require stronger side effect warnings, narrow conditions for the drug's use, or even force it to be withdrawn from the market.

[▲top](#)

References

Lee, Chi-Jen (1993) Development and Evaluation of Drugs—from Laboratory through Licensure to Market. Boca Raton: CRC Press.

Friedman, L. M., et al. (1996) Fundamentals Of Clinical Trials. St. Louis: Mosby.

Haffner, M.E. (1998) The Impact of the Orpan Drug Act. Modern Drug Discovery, Sept/Oct:45-52.

Kessler, D and Feiden, K. L. (1995, March). Faster Evaluation of Vital Drugs. Scientific American. p. 48-54.

Bazell, R. (1998) Her-2—The Making of Herceptin, a Revolutionary Treatment for Breast Cancer. New York: Random House.

| | | |
|-------------------------------------|--------------------------|--|
| <<Previous Article | Main Topic Page | Next Article>> |
| no previous article | Act Home | What You Need to Know About Participating in Clinical Trials |



©Copyright 2000, 2001 Genetic Health. All Rights Reserved.
Your Privacy Is Our Highest Priority - [Full Privacy and Security Statement](#)
[Contact Us](#)