Most of us understand that drugs intended to treat people have to be tested in people. These tests, called clinical trials, determine if a drug is safe and effective, at what doses it works best, and what side effects it causes—information that guides health professionals and, for nonprescription drugs, consumers in the proper use of medicines. Clinical testing isn’t the only way to discover what effect drugs have on people. Unplanned but alert observation and careful scrutiny of experience can often suggest drug effects and lead to more formal study. But such observations are usually not reliable enough to serve as the basis for important, scientifically valid conclusions. Controlled clinical trials, in which results observed in patients getting the drug are compared to the results in similar patients receiving a different treatment, are the best way science has come up with to determine what a new drug really does.

That’s why controlled clinical trials are the only legal basis for the FDA to conclude that a new drug has shown “substantial evidence of effectiveness, as well as confirmation of relative safety in terms of the risk-to-benefit ratio for the disease that is to be treated.”

Does It Work?

It’s important to test drugs in the kind of people they’re meant to help. It’s also important to design clinical studies that ask, and answer, the right questions about investigational products.

The process starts with a drug sponsor, usually a pharmaceutical company, seeking to develop a new drug it hopes will find a useful and profitable place in the market. Before clinical testing begins, researchers analyze the drug’s main physical and chemical properties in the laboratory and study its pharmacologic and toxic effects in laboratory animals. If the laboratory and animal study results show promise, the sponsor can apply to FDA to begin testing in people.

Once FDA has seen the sponsor’s plans and a local institutional review board—a panel of scientists, ethicists, and nonscientists that oversees clinical research at medical centers—approves the protocol for clinical trials, clinical investigators give the drug to a small number of healthy volunteers or patients. These phase 1 studies assess the most common acute adverse effects and examine the size of doses that patients can take safely without a high incidence of side effects. Initial clinical studies also begin to clarify what happens to a drug in the human body—whether it’s changed, how much of it gets into the blood and various organs, how long it stays in the body, and how the body gets rid of the drug and its effects.

If phase 1 studies don’t reveal major problems, such as unacceptable toxicity, the next step is to conduct a clinical study in which the drug is given to patients who have the condition it’s intended to treat. Researchers then assess whether the drug has a favorable effect on the condition.

Usually, No Miracles

The process appears straightforward—simply recruit groups of patients to participate in a clinical trial, administer the drug to those who agree to take part, and see if it helps them. Sounds easy enough, and sometimes it is. In what may be medicine’s most celebrated clinical trial, Louis Pasteur treated patients exposed to rabies with an experimental antirabies vaccine. All the treated patients survived. Since scientists knew that untreated rabies was 100 percent fatal, it wasn’t hard to conclude that Pasteur’s treatment was effective.

But that was a highly unusual case. Drugs do not usually miraculously reverse fatal illnesses. More often they reduce the risk of death, but don’t entirely eliminate it. They usually accomplish this by relieving the symptoms of the illness, such as nasal stuffiness, pain, or anxiety. Or a drug may alter a clinical measurement—reduce blood pressure or lower cholesterol, for example—in a way that physicians hope will be valuable. Drug effects like these can be more difficult to detect and evaluate than a result as dramatic as Pasteur’s rabies cure.
This is mainly because diseases don’t follow a predictable path. Many acute illnesses or conditions—viral ailments like the flu, minor injuries, insomnia—can usually be counted on to go away spontaneously without treatment. Some chronic conditions like arthritis, multiple sclerosis, or asthma often follow a varying course—better for a time, then worse, then better again, usually for no apparent reason. And heart attacks and strokes, for example, have widely variable death rates depending on treatment, age, and other risk factors, so that the “expected” mortality for an individual patient can be hard to predict.

A further difficulty in gauging the effectiveness of an investigational drug is that in some cases, measurements of disease are subjective, relying on interpretation by the physician or patient. Such measurements can be influenced by a patient’s or physician’s expectations or hopes. In those circumstances, it’s difficult to tell whether treatment is having a favorable effect, no effect, or even an adverse effect. The way to answer critical questions about an investigational drug is to subject it to a controlled clinical trial.

Understanding Controls

In a controlled trial, patients in one group receive the investigational drug. Those in a comparable group—the controls—get either no treatment at all, a placebo (an inactive substance that looks like the investigational drug), a drug known to be effective, or a different dose of the drug under study.

Usually, the test and control groups are studied at the same time. In fact, usually, the same group of patients is divided into two subgroups with each subgroup getting a different treatment.

In some special cases, a study uses a “historical control,” in which patients given the investigational drug are compared with similar patients treated with the control drug at a different time and place. Sometimes, patients are followed for a time after treatment with an investigational drug, and investigators compare their status before and after treatment. Here, too, the comparison is historical. It is based on an estimate of what would have happened without treatment. The historical control design is particularly useful when the disease being treated has high and predictable death or illness rates. Then investigators can be reasonably sure what would have happened without treatment.

It’s important that treatment and control groups be as similar as possible in characteristics that can affect treatment outcomes. For instance, all patients in specific groups must have the disease the drug is meant to treat or the same stage of the disease. In a clinical trial of a drug to treat angina (chest pain associated with cardiovascular disease), for example, if one group of patients being studied actually had sore ribs rather than angina, their differing response to the drug could not be assumed to be due to its effectiveness or lack thereof.

Treatment and control groups should also be of similar age, weight, and general health status, and be similar in other characteristics that could affect the outcome of the study, such as other treatment being received at the same time.

A principal method used to achieve this is called “randomization.”
When It Helps to Be ‘Blind’

In clinical trials, the hope for a good outcome can influence patient selection so that the treatment group includes a disproportionate number of patients likely to do well whatever their treatment. The same kind of inadvertent bias can lead both patients and investigators to overrate positive results in the treatment group and negative findings among controls, and cause data analysts to make choices that favor treatment. Clinical trials that include such biases are likely to be incapable of assessing drug effect.

In conjunction with randomization, a design feature known as “blinding” helps ensure that bias doesn’t distort the conduct of a study or the interpretation of its results. Single-blindling consists of keeping patients from knowing whether they are receiving the investigational drug or a placebo. In a double-blind study, neither the patients, the investigators, nor the data analysts know which patients got the investigational drug. Only when the study is unblinded (the closely guarded assignment code is broken to identify treatment and control patients) do the people involved in the study know which is which.

Ethical Questions

Testing experimental drugs in people inevitably presents ethical questions. Is it ethical to give patients a placebo when effective treatment is available? Not all authorities agree on the answer. But the generally accepted practice in the United States—and one increasingly being adopted abroad—is that fully informed patients can consent to take part in a controlled-randomized-blinded clinical trial, even when effective therapy exists, so long as they are not denied therapy that could alter survival or prevent irreversible injury. They can voluntarily agree to accept temporary discomfort and other potential risks in order to help evaluate a new treatment.

In any trial in which a possible effect on survival is being assessed, it’s important to monitor results as they emerge. That way, if a major effect is seen—positive or negative—the trial can be stopped. This happened in the first clinical study of the AIDS drug zidovudine (AZT), when a clear survival advantage for patients receiving zidovudine was seen well before the trial was scheduled to end. The trial was then ended early, and within a week FDA authorized a protocol allowing more than 4,000 patients to receive zidovudine before it was approved for marketing. More recently, the results from the National Institute of Health’s Breast Cancer Prevention Trial were announced, which enrolled more than 13,000 women at high risk for breast cancer. The results showed a 45 percent reduction in new cases of breast cancer in women who took the drug tamoxifen (Nolvadex) versus women who took a placebo. It was this clear evidence of reduction in breast cancer in the tamoxifen group that led those monitoring the trial to recommend that the study be unblinded 14 months earlier than expected. These are examples of the ethical principle that if a lifesaving or life-extending treatment for a disease does exist, patients cannot be denied.

In some cases, a new treatment can be compared with established treatment, as long as the effectiveness of the latter can readily be distinguished from placebo and the study is large enough to detect any important difference.

It is also possible to evaluate new drugs in this situation in “add-on” studies. In this kind of trial, all participants receive standard therapy approved for treating the disease, but those in the treatment group also get the investigational drug. The control group gets either no added treatment or placebo. Any difference in results between the treatment and control groups can be attributed to the investigational drug. It is common to study new antiseizure drugs in this way, as well as new agents intended to reduce mortality after a heart attack.

Testing in Women, Children, and the Elderly

In recent years there has been growing interest at FDA in testing drugs in patient populations that have been relatively neglected in clinical trials, especially women and children. Children are generally not included in trials at all until the drug has been fully evaluated in adults, unless the drug is intended for a pediatric disease, such as acute lymphocytic leukemia. When children are not likely to use drugs frequently (for example, drugs to treat high blood pressure), they often have not
been included in clinical trials at all. To promote the inclusion of children, the FDA published a final rule in December 1994 revising the “Pediatric Use” subsection of the professional labeling requirements for prescription drugs to include more complete information about the use of a drug in the pediatric population (See “Pediatric Drug Studies,” p. 78).

Although both sexes now are generally represented in clinical trials in proportions that reflect gender patterns of disease, FDA and women’s health advocates agree that less care has been taken to develop information about significant differences in the ways men and women respond to drugs and other FDA regulated products. This convinced FDA in 1993 to recommend that women of all ages be included in clinical trials, and results analyzed by gender. The guidance did away with an FDA policy dating from 1977 that excluded women of childbearing potential from participation in early clinical studies because of a risk or potential risk of reproductive or developmental toxicity. The agency believes that institutional review boards, as well as clinical investigators and women themselves can gauge whether women’s participation in clinical trials is appropriate. In all cases, information should be made available informing all participants regarding the potential risk of fetal toxicity. The FDA’s Office of Women’s Health, which functions to include the sponsorship of many research projects, focused on gender-effects of marketed drugs, biologics, and medical devices.

In September 1997 the FDA issued a proposed rule to amend the provisions of its regulation governing investigational new drug applications (INDs). The proposal’s goal is to ensure that in future clinical trials, men and women with reproductive potential and life-threatening diseases are not automatically excluded based only on a risk or potential risk of reproductive and developmental toxicity.

As the population of those over 65 years of age continues to grow, the medical community has become aware that FDA-regulated products can produce effects in the elderly patients that are very different from those produced in younger patients. For example, elderly patients are more likely to have impaired mechanisms of drug excretion (e.g., decreased kidney function), to be taking other medications that can interact with a newly prescribed drug, or to have another medical condition that can affect drug therapy. The FDA believes that efforts should be made not to exclude older subjects, especially those over 75 years of age from clinical studies. The agency is encouraging sponsors to increase the number of older subjects, to analyze the data already collected, and to obtain modest additional drug activity information. In August 1997, the FDA published a final rule to promote safe and effective prescription drug use in the elderly by requiring such information to be included in the labeling.

The inclusion of women, children, and the elderly, as well as other populations in clinical trials convinced the agency in 1998 to require sponsors of all new regulated products to analyze safety and effectiveness data for important demographic subgroups, including gender and racial subgroups. Enrollment of subjects into clinical studies for drug and biological products must be tabulated by important demographic subgroups in IND annual reports, (e.g., age group, gender, and race), and must be included in all New Drug Applications (NDAs).

### Testing in Humans

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of Patients</th>
<th>Length</th>
<th>Purpose</th>
<th>Percent of Drugs Successfully Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>20–100</td>
<td>Several months</td>
<td>Mainly safety</td>
<td>70 percent</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Up to several hundred</td>
<td>Several months to 2 years</td>
<td>Some short-term safety, but mainly effectiveness</td>
<td>33 percent</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Several hundred to several thousand</td>
<td>1-4 years</td>
<td>Safety, effectiveness, dosage</td>
<td>25–30 percent</td>
</tr>
</tbody>
</table>

For example, of 100 drugs for which investigational new drug applications are submitted to FDA, about 70 percent will successfully complete phase 1 and go on to phase 2; about 33 percent of the original 100 will complete phase 2 and go to phase 3; and 25 to 30 of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).
This final rule allows the agency to refuse to review any NDA that does not analyze safety and efficacy information appropriately by gender.

Studying medical therapies in humans will probably never be an exact science. But steady progress in the methodology and, in a way, the philosophy of clinical trials is making the process more productive, more reliable, and more beneficial for us all.

A Skeptic’s Guide to Medical ‘Breakthroughs’

Everyone is gratified by news of a major drug breakthrough, especially if it promises help for people who are terminally ill or severely disabled. And if you or a loved one has been praying for such a drug, the news may seem like a miracle.

But can you accept the good news at face value? All too often you can’t, because many such reports are either exaggerated or seriously inaccurate interpretations of scientific findings. Really significant advances in drugs and drug therapy don’t happen nearly as often as magazines, television, or the Internet might lead you to believe. Sober skepticism is a good attitude to have when evaluating news about drug “breakthroughs.” Here are a few guidelines:

• Where did the news report appear? Is it in a newspaper, magazine, or broadcast that regularly covers health and medical affairs and assigns specialized reporters to the subject? Or is it part of a publication or broadcast that emphasizes sensational stories that seem too good to be true? Is the reporter someone whose coverage of health and medicine you believe to be accurate and cautious? If you are doubtful about the news medium in which the report appears, it’s probably best to take the story with a grain of salt.

• News stories about drugs producing complete cures and unscrupulous cyberspace marketers peddling “miracle” treatments especially in patients with cancer, AIDS, or other grave illnesses, are likely to be cruelly wrong.

• What is being reported? The results of one study in a small number of patients are seldom, if ever, conclusive. This kind of preliminary information is presented at scientific meetings or published in scientific journals whose editors and readers know how to interpret such findings. News stories may place undue importance on these reports and jump to conclusions that the researchers themselves know are unjustified.

• Ask your healthcare provider what he or she knows about the story. While healthcare practitioners can’t know everything, there’s a good possibility that they would know about a truly important medical advance.

Most medical science writers and reporters try diligently to provide accurate and authoritative information. They avoid unfounded speculation, and they strive to put exciting discoveries in perspective. Their stories don’t often grab front-page headlines or lead off the evening news, but they can be trusted to give you solid information. And that’s a great deal better than false hope.

Personal Participation

Anyone interested in participating in a clinical trial should discuss the idea with their physician. Doctors are generally aware of investigational drugs that might be of benefit to their patients and of clinical trials involving these drugs. Clinical trials are carried out at medical research centers such as teaching hospitals, at specialized clinics for people with AIDS, and even in doctors’ offices.

Although they often involve hospitalized patients, many clinical trials are conducted on an outpatient basis, with participants more or less going about their normal activities. The center or institution where a study is to be carried out often runs newspaper ads recruiting potential participants for clinical studies that tell readers where to call or write for further information.

Although investigational drug studies vary widely, some things should be expected by participants in virtually any clinical trial. For example, participants might have to give blood samples more often than during ordinary care. Tests to assess disease status might be more frequent. Participants are often required to keep detailed records of their symptoms and follow strict schedules.

It’s also important to understand that volunteering for a clinical trial does not guarantee that an individual patient will receive the drug under investigation. Control patients may get a placebo, a drug already approved for their condition, or perhaps no treatment at all. These and other aspects and implications of taking part in a clinical trial must be fully explained in advance by the people conducting the trial, and patients must agree to the conditions before they can participate. The hope of personally benefiting from a new drug—or the desire to take part in research that might one day benefit millions—is what makes people volunteer for clinical trials.