Cancer Treatment

Clinical Trials

Clinical trials are tests done to determine whether new medications are safe and effective. Joining a trial can help advance medical science and may be a good way to obtain promising experimental therapies prior to approval, but it is important to weigh the potential risks and benefits.

The Drug Development Process

The process of developing new medications is complex, lengthy and expensive. Only a small fraction of compounds make it from the laboratory to clinical trials, and less than 10 percent of drugs that enter Phase I studies are ever approved, according to the Food and Drug Administration (FDA).

Preclinical studies: Drug candidates first undergo in vitro (Latin for “in glass”) testing in a laboratory. For example, researchers may test whether a compound kills cancer cells in a petri dish. If these tests are promising, the drug will often be tested in mice or other animals. But activity in a test tube or in animals does not mean that a drug will work in people.

Phase I: If a compound still looks promising, researchers submit an application to the FDA for designation as an Investigational New Drug. The first human trials usually include 10 to 100 participants, starting with healthy volunteers. These trials look for side effects and collect information about how a drug is processed in the body, known as its pharmacokinetics. Researchers also try to determine which dose will provide the best balance of activity and safety, a process known as dose ranging.

Phase II: Mid-level trials typically include a few dozen to a few hundred participants. They are designed to test whether a drug still appears safe in a larger group of people with cancer and to gather preliminary data on efficacy, or how well the therapy works under ideal conditions. Trials are sometimes divided into Phase IIa (pilot studies) and Phase IIb (small controlled studies).

Phase III: The largest and longest trials, usually enrolling several hundreds or thousands of participants, aim to determine how well a drug works in the population that will ultimately use it. This often involves comparing the new drug against existing therapies or a placebo. Data from major Phase III studies—known as pivotal trials—may be submitted to the FDA to support a New Drug Application for approval.

Phase IV: After a drug has been approved and is commercially available, post-marketing studies are done to see how well it works in the real world and to determine its long-term safety and effectiveness. This is important because uncommon adverse effects may show up only after a drug is used by many people over a long period.

Speeding Up the Process

It can take many years for an experimental drug to go from the laboratory to pharmacy shelves. However, there are mechanisms in place to speed up the approval of treatments for cancer and other life-threatening diseases and to help people gain access to promising therapies prior to approval.

The FDA's fast track process is designed to accelerate the development and review of treatments for serious conditions that fill an unmet medical need. The agency may give an experimental drug a breakthrough therapy designation after preliminary evidence shows that it may offer a substantial improvement over available treatments. Drugs that address an urgent need may receive priority review.

The FDA may grant accelerated approval to therapies that fill an unmet need. This approval is based on surrogate endpoints, which are clinical outcomes (for example, tumor shrinkage) that can be assessed sooner than overall survival. Drugs that receive accelerated approval must still complete Phase III testing to ensure that their early promise holds up with longer follow-up; if not, the agency may withdraw its approval.

Individuals with serious conditions who are unable to enroll in a clinical trial may seek expanded access to an experimental drug—also known as compassionate use—if there is no satisfactory therapy available and the probable risk from the therapy is not greater than the risk from the disease itself. The FDA grants most expanded access requests, but pharmaceutical companies are not required to provide their investigational drugs outside of trials, and insurers do not have to pay for them.

Trial Design

A good study design is critical to ensuring that a clinical trial can provide reliable information about a drug's safety and effectiveness. In particular, trials should include enough participants and last long enough to produce statistically significant results, meaning that the findings are unlikely to be attributable to chance alone.

All the relevant information about how a study will be conducted and which statistical methods will be used should be specified in the trial protocol. Institutional review boards at universities and hospitals make sure trials are ethical, and some studies have community advisory boards made of of people living with the disease.

A study's enrollment criteria describe who may participate. Required characteristics and

qualifications are known as inclusion criteria, while those that disqualify potential participants are called exclusion criteria.

Inclusion criteria for cancer trials specify the type of cancer, stage of disease and prior treatment history. Today, study criteria often include genetic characteristics that predict whether a drug will work. As inclusion criteria become more specific, it becomes more difficult to enroll enough people.

Researchers and pharmaceutical companies may be tempted to select trial participants who are most likely to do well on an experimental therapy. But it is important for trials to include a range of participants who reflect the population that will use the drug in the real world, such as people with advanced disease, those with coexisting health problems and people of all ages and from all racial and ethnic groups.

The gold standard for testing new drugs is the prospective randomized controlled trial. A prospective, or forward-looking, study selects a group of participants and follows them over time, while a retrospective study looks backward at events that happened in the past.

In these studies, people are randomly assigned to receive either the experimental therapy or a comparison intervention, known as a control. This could be a competing new drug, the currently available standard treatment or a placebo, an inactive mock treatment such as a sugar pill or saline injection. This is done to minimize the placebo effect, a phenomenon in which the treatment process alone can make a person feel better and even influence biological markers. It is generally considered unethical to leave people untreated in a placebo group if existing therapies are available.

Randomization—meaning any trial participant has an equal chance of ending up in any arm of the study—helps ensure that the groups receiving the different treatments are otherwise similar. But this also means that not everyone who joins a trial will receive the experimental drug under study.

Double-blind studies are another way to reduce bias, or unintentional favoritism. In these studies, neither the investigators nor the participants know who is assigned to which treatment arm. But blinding may not be possible in cancer trials where the administration method or side effects give away who is getting what. In open-label studies, everyone knows who is getting which treatment.

Study endpoints are milestones that must be met for the experimental therapy to be considered a success. The ultimate endpoint for cancer treatment is overall survival. But in some trials—especially those for early-stage or curable cancers—most participants will not die during the course of the study. Progression-free survival (meaning participants are still alive without worsening of disease) and overall response (meaning complete or partial tumor shrinkage) are endpoints that can be measured sooner. Cancer trials increasingly also include patient-reported outcomes, such as quality of life and ability to perform daily activities.

As a clinical trial progresses, researchers may report preliminary or interim results at scientific conferences or in medical journals. Preliminary results are reviewed by the study’s data safety

monitoring board; if the data indicate that a drug is either harmful or highly beneficial, the trial may be stopped ahead of schedule.

Joining a Trial

Joining a clinical trial can be a good way for people with advanced disease who have exhausted all available treatment options to gain access to promising new treatments. Those with less advanced disease may be motivated by altruism and a desire to help advance medical science for future patients.

When considering a trial, learn all you can about the study and the treatment being tested, as well as what other options are available. Before agreeing to join, participants should be given information about all aspects of the trial in language they can understand and must sign an informed consent document. But informed consent is not a contract—participants have the right to withdraw from a trial at any time for any reason.

It is important to weigh the potential benefits and drawbacks of participating in a trial. Benefits may include early access to promising new therapies, free drugs and medical monitoring, and care delivered by expert doctors and leading medical centers. Drawbacks may include inconvenient and time-consuming study visits, the need to stop or forgo other treatments and the risk of side effects.

Although they are governed by regulations to ensure that they are as ethical and safe as possible, trials of new therapie—especially novel types of drugs—can't offer guarantees. Researchers don't yet know how effective the treatment will be and can't rule out unforeseen adverse events. Although early studies offer important information about the safety and biological activity of a drug, they cannot predict how well it will work for a specific individual.

Find out about open clinical trials from doctors, nurses, social workers and other providers. Comprehensive cancer centers and university-affiliated hospitals often conduct trials, and community cancer centers increasingly do so as well. Patient advocates and support groups are also a good source of information.

For more information about clinical trials, see the following resources:

American Cancer Society

National Cancer Institute

National Institutes of Health database of trials for all diseases: www.clinicaltrials.gov

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