TYPES AND PHASES OF CLINICAL TRIALS

Clinical trials are studies to test new drugs, already approved drugs, devices, or other forms of treatments. Many clinical trials look at new ways to detect, diagnose, or measure the extent of disease. Some even look at ways to prevent diseases from happening.

Clinical trials are used to learn whether a new drug, treatment, or combination works and is safe to use for people. Clinical trials are important in developing new treatments for serious diseases like cancer. All new treatments must go through clinical trials before being approved by the Food and Drug Administration (FDA). Cancer clinical trials can take years to complete. It can take months, if not years, to see if a cancer treatment does what it is meant to do.

Why do we need clinical trials?

Clinical trials show us what works (and what doesn't) in medicine and health care. They are the best way to learn what works in treating diseases like cancer. Clinical trials are designed to answer some important questions:

- Does the new treatment work in people? If it does, doctors will also look at how well it works. Is it better than treatment now being used? If it's not better, is it as good and cause fewer side effects? Or does it work in some people who aren't helped by current treatments?
- Is the new treatment safe? No treatment or procedure – even one already in common use – is without risk. But do the benefits of the new treatment outweigh the risks?
- Is this treatment better than the standard treatment given for this disease? Clinical trials help show if a new drug or treatment, or a new treatment combination, works better than what is now used.

Answering these questions, while giving as few people as possible an unknown treatment, often requires several clinical trials in different "phases." Each phase is designed to answer certain questions while keeping the people taking part as safe as possible. Results from these phases show if the new drug or treatment is reasonably safe and effective.

Pre-clinical (or laboratory) studies

Pre-clinical studies, also called laboratory studies, include:

- Cell studies: These are often the first tests done on a new treatment. To see if it might work, researchers look for effects of the new treatment on cancer cells that are grown in a lab dish or a test tube. These studies may be done on human cancer cells or animal cancer cells.
- Animal studies: Treatments that look promising in cell studies are tested next on cancers in live animals. This gives researchers an idea of how safe the new treatment is in a living creature.

Pre-clinical studies give a lot of useful information, but not all that is needed. Humans and mice can be very different in the way they absorb, process, and get rid of drugs or treatments. A

treatment that works against cancer in a mouse might or might not work in people. There could also be side effects and other problems that didn't show up when the treatment was used in mice but could show up in people.

If the pre-clinical studies are completed and the treatment still seems promising, the US Food and Drug Administration (FDA) must give permission before the treatment can be tested people.

The investigational new drug (IND) application

Before a clinical trial can be started, the research must be approved. An investigational new drug or IND application or request must be filed with the FDA when researchers want to study a drug in humans. The IND application must contain certain information, such as:

- Results from studies so that the FDA can decide whether the treatment is safe for testing in people.
- How the drug is made, who makes it, what's in it, how stable it is, and more.
- Detailed outlines for the planned clinical studies, called study protocols, are reviewed to see if people might be exposed to needless risks.
- Details about the clinical trial team to see if they have the knowledge and skill to run clinical trials.

The research sponsor must commit to getting informed consent from everyone on the clinical trial. They must also commit to having the study reviewed by an institutional review board (IRB) and following all the rules required for studying investigational new drugs

Phases of clinical trials

Clinical trials are usually conducted in phases that build on one another. Each phase is designed to answer certain questions. Knowing the phase of the clinical trial is important because it can give you some idea about how much is known about the treatment being studied. There are benefits and risks to taking part in each phase of a clinical trial.

Although there are clinical trials for devices as well as other diseases and treatments, drugs for cancer patients are used in the examples of clinical trial phases described here.

Phase 0 clinical trials: Exploring if and how a new drug may work

Even though phase 0 studies are done in humans, this type of study isn't like the other phases of clinical trials. The purpose of this phase is to help speed up and streamline the drug approval process. Phase 0 studies may help researchers find out if the drugs do what they're expected to do. This may help save time and money that would have been spent on later phase trials.

Phase 0 studies use only a few small doses of a new drug in a few people. They might test whether the drug reaches the tumor, how the drug acts in the human body, and how cancer cells

in the human body respond to the drug. People in these studies might need extra tests such as biopsies, scans, and blood samples as part of the process.

Unlike other phases of clinical trials, there's almost no chance the people in phase 0 trials will benefit. The benefit will be for other people in the future. And because drug doses are low, there's also less risk to those in the trial.

Phase 0 studies aren't widely used, and there are some drugs for which they wouldn't be helpful. Phase 0 studies are very small, often with fewer than 15 people, and the drug is given only for a short time. They're not a required part of testing a new drug.

PHASE I CLINICAL TRIALS: IS THE TREATMENT SAFE?

Phase I studies of a new drug are usually the first that involve people. Phase I studies are done to find the highest dose of the new treatment that can be given safely without causing severe side effects. Although the treatment has been tested in lab and animal studies, the side effects in people can't be known for sure. These studies also help to decide on the best way to give the new treatment.

Key points of phase I clinical trials

- The first few people in the study get a very low dose of the treatment and are watched very closely. If there are only minor side effects, the next few participants get a higher dose. This process continues until doctors find a dose that's most likely to work while having an acceptable level of side effects.
- Phase I trials are also looking at what the drug does to the body and what the body does with the drug.
- Safety is the main concern. The research team keeps a close eye on the people and watches for any severe side effects. Because of the small numbers of people in phase I studies, rare side effects may not be seen until later phases of trials when more people receive the treatment.
- While some people may benefit from being on one, disease response is not the main purpose of a phase I trial,
- Placebos (inactive treatments) are not used in phase I trials.
- Phase I trials usually include a small number of people (up to a few dozen).
- Phase I trials most often include people with different types of cancer.
- These studies are usually done in major cancer centers.

Phase I trials carry the most potential risk. But phase I studies do help some patients. For those with life-threatening illnesses, weighing the potential risks and benefits carefully is key. Sometimes people choose to join phase I trials when all other treatment options have already been tried.

PHASE II CLINICAL TRIALS: DOES THE TREATMENT WORK?

If a new treatment is found to be safe in phase I clinical trials, a phase II clinical trial is done to see if it works in certain types of cancer. The benefit the doctors look for depends on the goal of the treatment. It may mean the cancer shrinks or disappears. Or it might mean there's a long period of time where the cancer doesn't get any bigger, or there's a longer time before the cancer comes back. In some studies, the benefit may be an improved quality of life. Many clinical trials look to see if people getting the new treatment live longer than most people do without the treatment.

Key points of phase II clinical trials

- A group of 25 to 100 patients with the same type of cancer get the new treatment in a phase II study. They're treated using the dose and method found to be the safest and most effective in phase I studies.
- Usually in a phase II clinical trials, everyone gets the same dose. But some phase II studies randomly assign people to different treatment groups. These groups may get different doses or get the treatment in different ways to see which provides the best balance of safety and response.
- Placebos (inactive treatments) are not used in phase II trials.
- Phase II studies may be done at major cancer centers, community hospitals or even doctors' offices.

Larger numbers of patients get the treatment in phase II trials, so less common side effects may be seen. If enough patients benefit from the treatment, and the side effects aren't too bad, phase III clinical trials are begun.

PHASE III CLINICAL TRIALS: IS IT BETTER THAN WHAT'S ALREADY AVAILABLE?

Treatments that have been shown to work in phase II clinical trials must succeed in one more phase before they're approved for general use. Phase III clinical trials compare the safety and effectiveness of the new treatment against the current standard treatment.

Because doctors do not yet know which treatment is better, study participants are often picked at random (called **randomized**) to get either the standard treatment or the new treatment. When possible, neither the doctor nor the patient knows which of the treatments the patient is getting. This type of study is called a **double-blind study**. Randomization and blinding are discussed in more detail later.

Key points of phase III clinical trials

- Most phase III clinical trials include a large number of patients, at least several hundred.
- These studies are often done in many places across the country (or even around the world) at the same time.
- Phase III clinical trials are more likely to be offered in local community hospitals and doctor's offices.

- These studies tend to last longer than phase I and II studies.
- Placebos may be used in some phase III studies, but they're never used alone if there's a treatment available that works. Sometimes, a patient who is randomly assigned to the placebo for part of the study will at some point be offered the standard treatment as well.

  As with other trials, patients in phase III clinical trials are watched closely for side effects, and treatment is stopped if they're too hard to manage.

SUBMISSION FOR FDA APPROVAL: NEW DRUG APPLICATION (NDA)

In the United States, when phase III clinical trials (or sometimes phase II trials) show a new drug is more effective or safer than the current treatment, a new drug application (NDA) is submitted to the Food and Drug Administration (FDA) for approval. The FDA reviews the results from the clinical trials and other relevant information.

Based on the review, the FDA decides whether to approve the treatment for use in patients with the illness the drug was tested on. If approved, the new treatment often becomes a standard of care, and newer drugs may be tested against it before they can be approved.

If the FDA feels that more evidence is needed to show that the new treatment's benefits outweigh its risks, it may ask for more information or even require that more studies be done.

PHASE IV CLINICAL TRIALS: WHAT ELSE DO WE NEED TO KNOW?

Drugs approved by the FDA are often watched over a long period of time in phase IV studies. Even after testing a new medicine on thousands of people, all the effects of the treatment may not be known. Some questions may still need to be answered. For example, a drug may get FDA approval because it was shown to reduce the risk of cancer coming back after treatment. But does this mean that those who get it are more likely to live longer? Are there rare side effects that haven't been seen yet, or side effects that only show up after a person has taken the drug for a long time? These types of questions may take many more years to answer, and are often addressed in phase IV clinical trials.

Key points of phase IV clinical trials

- Phase IV studies look at drugs that have already been approved by the FDA. The drugs are available for doctors to prescribe for patients, but phase IV studies might still be needed to answer important questions.
- These studies may involve thousands of people.
- This is often the safest type of clinical trial because the treatment has already been studied a lot and has likely been given to many people. Phase IV studies look at safety over time.
- These studies may also look at other aspects of the treatment, such as quality of life or cost effectiveness.

You can get the drugs used in a phase IV trial without being in a study. And the care you would get in a phase IV study is very much like the care you could expect if you were to get the treatment outside of a trial. But in phase IV studies you're helping researchers learn more about the treatment and doing a service to future patients.