

clinical trials explained

acria

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The Purpose of Clinical Trials

In order for any medication to be approved by the Food and Drug Administration (FDA), it must be tested in clinical trials. Clinical trials show if a medication works and if it is safe.

At the beginning of the AIDS epidemic, people with HIV and AIDS flocked to clinical trials. At that time, no anti-HIV medications were available by prescription. The only way to get HIV treatment was through clinical trials. The medications were experimental—researchers did not know exactly what effects they would have in humans. But people were willing to take the risk; there were simply no other options.

Women, people of color and other affected populations have been historically under-represented in HIV-related clinical trials whose participants have been primarily white males. In order to better understand the way that HIV and anti-HIV medications work, all populations must be represented in clinical trials.

Even though there are approved medications for HIV, clinical trials are still extremely important. Researchers are working to develop medications with fewer side effects and easier dosing. These treatments must be tested in clinical trials. There are also trials that test different combinations of approved medications, and trials without medications (called observational trials) that look at behaviors or study disease progression. Without volunteers for these trials, progress in understanding and treating HIV is impossible.

Types of Clinical Trials

When a drug company develops a new medication, the process starts in test tube and animal studies. These studies give researchers an idea of how well a medication works and what kind of side effects it might have in humans. If the results of early studies look good, the drug company designs and pays for clinical trials to test the medication in humans. These trials are divided into three stages, which are known as Phase I, Phase II, and Phase III trials. Let's take a look at how they break down:

	Phase I	Phase II	Phase III
Question	Is the treatment safe?	Does the treatment work?	What are the long-term results in lots of people?
Risk	Riskiest —First trials in humans. Performed in HIV-positive and HIV-negative volunteers. Used to determine best doses.	Moderate risk —Some safety information about the drug is known.	Lowest risk —More information about safety and effectiveness is known.
Length	Shortest —A few weeks to a few months	Medium length —Usually about a year.	Longest —May last for two to three years.
Number of participants	Few participants	About one hundred participants	At least several hundred participants

Sometimes, Phase II and III trials are combined into a Phase II/III trial. This speeds up the process of gathering information. When all three phases are complete, the information from the trials is submitted to the FDA. The FDA reviews the information and then approves or rejects the new medication. Sometimes the FDA asks for more information or further trials before making the decision.

A drug company may run an **Expanded Access** program before the medication is approved by the FDA. In Expanded Access, individuals who won't benefit from medications already approved by the FDA may receive the medication. The company collects safety information from all Expanded Access participants.

If a medication is approved, the drug company may conduct Phase IV trials. Phase IV trials are used to gather long-term safety information. These trials involve thousands of people and can give information about very rare side effects. In addition to drug companies, the federal government and local agencies also

sponsor trials. Some examples are the **ACTG** (AIDS Clinical Trials Group) and the **CPCRA** (Community Programs for Clinical Research on AIDS). These trials answer important questions about HIV treatment and care, such as how soon after infection to start HIV treatment.

Thinking about Participating in a Clinical Trial

There are many reasons to think about joining a clinical trial. When you are deciding whether or not a trial is right for you, consider some of the risks and benefits.

Some Possible Benefits:

Access to medications that are not FDA-approved

You may have already tried every available anti-HIV medication. If your viral load is high and your T-cell count is low, a clinical trial can help you gain access to an experimental medication that may keep your HIV infection from getting worse. The experimental medication might lower your viral load, raise your T-cell count, and improve your health

Increased care

You may usually receive your care in a large clinic or see a doctor with many patients. As a result, you may not have as much one-on-one time with your doctor as you'd like. When you get involved in a clinical trial, you develop a relationship with the research team (the doctors and nurses running the trial). You may benefit from having more health professionals involved in your HIV care. The research team can be a great resource for questions about HIV.

"My first contact with any kind of medication was through a trial. I learned a lot about the virus itself and a lot about medications."

—K.M.

Your regular doctor will continue to supervise your care while you are in the trial. The trial staff will coordinate with your doctor and will send him or her your lab results so that you won't need to have tests repeated.

Helping others

Some people decide to join a clinical trial because they want to help others with HIV. Joining a clinical trial contributes to the development of new medications and strategies to treat HIV and HIV-related infections.

Some Possible Risks:

Safety concerns

The medication may cause unpleasant side effects. Phase I trials are riskiest because there is no safety information available. If you are resistant to all available anti-HIV treatments and have no treatment options, you might be willing to participate in a Phase I study. On the other hand, if you have never taken HIV medications before and have many treatment options, you might choose a lower-risk Phase II or Phase III study.

Health concerns

You may have to stop taking your current anti-HIV medications to participate in a trial. This could cause your HIV infection to progress more rapidly.

Protecting Your Rights

You might be hesitant to join a clinical trial because you are not sure if a research doctor can be trusted. In the past, there have been human rights abuses made in the name of scientific research. An example that you may be familiar with is the Tuskegee Syphilis Study. The study was conducted in Alabama by the United States Public Health Service to examine the effects of untreated syphilis. It began in the 1930s and continued until 1972. The African-American men who were recruited for the trial were not told about the purpose of the trial. They were also not told about penicillin when it became the standard treatment for syphilis in 1943.

The Tuskegee Syphilis Study was shut down in 1973. To prevent history from repeating itself, the National Research Act was passed in 1974. This Act led to the establishment of **Institutional Review Boards** (IRBs). *IRBs exist to protect the rights of trial participants.*

An IRB is a group that consists of people such as doctors, lawyers, community members, and members of the clergy. In order to run a clinical trial at a hospital, clinic, or private doctor's office, the research doctor must submit an application to the IRB at that site or to a central IRB. The application contains detailed information about the trial. The IRB reviews the application to make sure that the trial asks a worthwhile scientific question and that the trial design is ethical. The IRB also checks the safety monitoring of the trial.

The research doctor is required to submit regular reports about the progress of the trial and to inform the IRB about any severe side effects that trial participants experience. The IRB has the authority to shut down a trial that is not run properly.

Trials may also be reviewed by independent **Data and Safety Monitoring Boards** (DSMBs). When members of a DSMB review trial data, they look for patterns of side effects or treatment benefits. They may suggest changes to the trial design if they find clear benefits or disadvantages to one group in the trial. They might also recommend that a trial be shut down if there are serious safety issues.

Informed Consent

As part of the application to the IRB, the research doctor submits an **informed consent form** for review. This form includes complete information about the trial, written in easy to understand language. It also contains contact information for the IRB. If you have questions about your rights as a research participant or want to report a problem with the trial, you can call the IRB.

The first time that you go to a research site to learn about a trial, the research team will go over the informed consent form with you in detail. They will make sure that you understand everything about the trial, including any possible risks and the possible benefits. The form must include the following:

Basic Parts of Informed Consent

LOOK FOR THEM!

- 1. YES, this is research**
A statement that the study involves research.
An explanation of the purpose of the research.
The expected length of participation in the research.
A description of the research procedures [lab tests, physical exams, other procedures].
Identification of any procedures that are experimental.
- 2. There are risks**
A description of risks/discomforts to the participant.
- 3. And possibly benefits**
A description of possible benefits to you or to others.
- 4. There may be alternatives to participating in this trial**
A description of other procedures/treatments that are options for you if you decide not to participate in the trial.
- 5. Your research record is confidential**
A description of how your confidentiality will be protected.
- 6. You may get paid**
A description of any compensation.
An explanation of who covers expenses if you are injured in the trial.
- 7. If you have questions, ASK**
Contact information for questions about the trial and about your rights as a trial participant.
- 8. The decision to participate is yours**
Your participation is voluntary.
If you do not wish to participate, there is no penalty, and you will not lose benefits at the site.
You may withdraw from the study at any time.

—From the Code of Federal Regulations for Protection of Human Subjects

You are encouraged to take the informed consent form with you and talk it over with your doctor, your friends, and your family. If you decide to participate in the trial and are committed to following the trial procedures (which will include regular clinic visits and laboratory tests), you will sign the form when you return to the clinic. You will be given a copy of the form for your records.

If there are major changes to the trial while it is in progress, the consent form will be updated. The changes will be explained to you, and you will be asked to sign a new consent form.

Clinical Trial Terms

As you review the informed consent form, you may come across some of these terms:

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are the rules that say who is allowed to join a trial. The rules are different for every trial.

Inclusion criteria are characteristics you must have to participate in the trial. Some examples of inclusion criteria are:

- T-cell count greater than 200
- Willing and able to sign informed consent form
- Viral load greater than 10,000 copies

Exclusion criteria are characteristics that you must not have in order to participate in the trial. Some examples of exclusion criteria are:

- Active opportunistic infection
- Women who are pregnant or breastfeeding
- Any vaccination within the past month

Inclusion and exclusion criteria are used so that researchers can design trials to study the effects of medications at different stages of HIV infection. For example, a trial for people who are failing on their current treatment will only include people with high viral loads.

Inclusion and exclusion criteria are also used to protect people in trials. For example, if a medication is known to cause liver problems, people with damaged livers will not be allowed to participate in the trial.

"I was worried about the possible side effects, but I did my homework and knew what they were and what to do if I experienced them."
—P.D.

Placebos

A **placebo** is a substance that looks like a trial medication *but does not contain active drug*. The placebo is a pill if the trial medication is a pill, and it is a shot if the trial medication is a shot.

Placebos may seem unfair or unethical. Why would a doctor give something that doesn't work to someone with HIV? Placebos are used to help determine if an experimental medication works. Some people get the medication, other people get placebo, and the results are compared. That way, researchers can see if the medication being studied really works. Placebos are used if there is no approved drug to use for comparison.

Placebos are sometimes added to an approved regimen. When used this way, one group adds the experimental medicine to their treatment regimen and another group adds a placebo. The results are compared to see if there is any benefit to adding the experimental medication.

"I had a feeling of apprehension at first,
but the researcher helped a lot—his expertise, his personality
—he made me feel very comfortable."

—K.M.

As an example, let's look at how a placebo was used in a clinical trial of a drug called GM-CSF. The trial was designed for people taking anti-HIV medications who had a viral load higher than 1,500 copies. The main purpose of the study was to learn if GM-CSF lowers viral load in people with HIV. In this study, one group added GM-CSF to their treatment regimen and another group added placebo.

These people were assigned by chance to one of the two groups in a process called **randomization**. Randomization is like flipping a coin to see who gets what, the medication or the placebo. It is used to make sure that there is no bias in the trial.

Trials that use placebos are usually **double-blind**, which means that neither the research doctor nor the trial participant knows which medication the participant is taking. If both the research doctor and the trial participant know which medication is being used, the trial is **open-label**.

ACTG Study A5041

Trial medication:

GM-CSF, a medication approved by the FDA to increase and improve white blood cell function in people with leukemia. GM-CSF is not approved for the treatment of HIV infection.

Purpose of the trial:

The main purpose of the trial is to learn if GM-CSF reduces viral load in people with HIV.

Trial groups:

Part one (Weeks 1-16)—Randomized and double-blind:

Group 1—GM-CSF shot three times a week for 16 weeks.

Group 2—Placebo shot three times a week for 16 weeks.

Part two (Weeks 17-48)—Open-label:

All participants receive GM-CSF shot three times a week for 32 weeks.

At the end of the first 16 weeks of this trial, researchers will compare the viral loads of people who took GM-CSF with the viral loads of people who took placebo. If viral loads are lower in people who took GM-CSF, it shows that GM-CSF may be effective against HIV. If viral loads in the two groups are about the same, it shows that GM-CSF works about the same as a “dummy” shot and is not effective against HIV.

Not all trials use placebos. But if the informed consent form says that a trial uses a placebo, *ask lots of questions*. Find out if you will eventually have a chance to get the experimental medication as part of your participation in the trial if the drug is shown to work. Make sure that you are comfortable with the idea that you might get a placebo before you start the trial.

Financial Considerations

There should be no financial cost to you as a trial participant. Trial medication is always free, and the drug company or research site conducting the trial usually pays for all lab tests. However, some trials expect your private insurance or Medicaid to pay for some lab tests and other medications that might be used. Make sure that you understand how this works before agreeing to join.

Some trials pay participants. There are different reasons for getting paid to participate in a trial:

For your time

Some trials require visits that last much longer than a normal doctor’s visit. For example, you may stay overnight in the hospital to have doses of trial medications administered. In those circumstances, you may receive compensation for your time.

"After the results from the trial I was in were published, I thought to myself, 'I participated in a study that helped others.' That made me feel good."

—M.S.

For an *uncomfortable procedure*

Some studies require multiple blood draws, X-rays, pap smears, etc. You may receive compensation for your discomfort if you consent to such procedures.

For *assuming risk with little benefit to you*

You might receive compensation for taking on the risks of receiving an experimental medication, especially if it may not directly benefit you. This is common in Phase I trials.

The clinic may provide funds to cover transportation, food, and/or childcare. Ask your research nurse or doctor about such funds.

Some thoughts on payment:

Your health comes first. The highest paying trials are usually Phase I trials. These trials can be time-consuming and risky. They may require you to stop taking all of your other anti-HIV medications. Make the decision to join a clinical trial based on the possible benefits to your health, not for the money.

When a Clinical Trial Ends

As your participation in a trial draws to a close (several weeks or even several years after you started), you will start thinking about how to handle your HIV treatment after the trial ends. If you are receiving an experimental medication as part of the trial, you may continue to receive that medication, especially if it is about to become available by prescription. Members of the research team will work with you and your doctor to determine the best plan for your HIV treatment.

Many trial participants are interested in the results of their trial. The research team should inform you of the results as soon as they become available

Clinical Trial Information Resources

If you've decided that you would like to learn more about participating in clinical trials, start by talking to your doctor. He or she may know about trials in the area.

There are a number of resources you can use to find the right clinical trial for your needs. For information about trials in New York State and surrounding areas, visit ACRIA's online **Directory of HIV/AIDS Clinical Trials** at www.acria.org. Trials can be searched by treatment, condition, CD4 count, viral load, location and age. You can also call ACRIA at 212-924-3934, ext. 123 to speak with a treatment counselor or to receive a printed copy of the Directory.

Other trial resources include: **Study-Link**, a project of Clinical Directors Network, (212-382-0699 extension 33) for referrals to trials in the New York area, and **ACTIS** (AIDS Clinical Trials Information Service) for information about trials nationally (1-800-TRIALS-A). ACTIS offers information in English, Spanish and Portuguese, and their database of trials can be searched on the web at www.clinicaltrials.gov.

As a volunteer in a clinical trial, you can help yourself while helping others. We have come a long way in our understanding of HIV since the beginning of the epidemic thanks to people who joined clinical trials. As we continue to move forward, clinical trials will provide answers to many of the remaining questions about HIV infection. Without participants in clinical trials, we will never have more effective, safer drugs and treatment strategies.

Glossary of Terms

DOUBLE-BLIND: A procedure for assigning treatment regimens which keeps both trial participants and members of the research staff from knowing which participants are on which assigned treatments.

EXPANDED ACCESS: A method of distributing experimental drugs to patients who are unable to participate in clinical trials and have no other treatment options.

INSTITUTIONAL REVIEW BOARD (IRB) : A committee of physicians, statisticians, community advocates, and others which ensures that a clinical trial is ethical and that the rights of the study participants are protected. All clinical trials in the United States must be approved by an IRB before they begin.

INFORMED CONSENT: The voluntary consent given by a patient to participate in a trial. The patient must be informed of the trial's purpose, treatment, benefits and risks of participation, and the schedule of required procedures.

OPEN LABEL TRIAL: A trial in which the research staff and the trial participant know the treatment that is assigned.

PHASE I TRIAL: The first stage in testing a new drug in humans. The studies are usually done to gather preliminary information on the chemical action, dosage and safety of the drug using healthy volunteers. Usually done without a comparison group.

PHASE II TRIAL: The second stage in testing a new drug in humans. Performed in patients with the disease or condition being studied. The main purpose is to

evaluate the activity of a drug, and to possibly provide information on how well the drug works

PHASE II/III: A special classification for a trial that speeds up the process by combining two phases.

PHASE III TRIAL: The third and usually final stage in testing a new drug in humans. Used to collect information about the safety of a drug and how well it works. Once this phase is complete, the drug manufacturers may request permission from the Food and Drug Administration to market the drug.

PHASE IV TRIAL: A large trial designed to evaluate the long-term safety and effectiveness of a drug that has been approved by the Food and Drug Administration.

PLACEBO: An inactive agent given as a substitute for an active agent for the purpose of comparison.

RANDOMIZATION: The process of assigning patients to different treatments by chance.

SIDE EFFECTS: The action or effect of a drug beyond what it is supposed to do. The term usually refers to undesired or negative effects, such as headache, skin irritation, or liver damage. Side effects can be expected or unexpected, desired or undesired. Experimental drugs must be evaluated for both immediate and long-term side effects.

Adapted from Glossary of Medical, Statistical, and Clinical Research Terminology by Carlton Hogan, University of Minnesota, for the National AIDS Treatment Advocates Forum (NATAF)

Questions to Ask Before Joining a Clinical Trial

How often do I have to visit the study site and how long will each visit take?

What should I do if I miss an appointment?

What should I do if I miss a dose of my drug?

What are the immediate and long-term side effects of this drug?

What should I do if I get sick or get bad side effects while participating in the study?

Does the informed consent form list all of the risks and benefits?

Will the lab tests cost me anything?

Will I get the results of these tests?

Can I take nonprescription (over-the-counter) drugs or complementary therapies while I am in this trial?

Can I use prescription drugs while I am in this trial?

Can I take other experimental drugs?

Will I get any money for participating in the trial?

Will I get the study drug once the trial is over?

Will I need to return to the site once the trial is over?

How can I find out the results of the trial?



ACRIA is an independent, non-profit community-based AIDS research and education organization committed to improving the length and quality of life for people living with HIV/AIDS through medical research and treatment education.

ACRIA conducts a free Treatment Education Program to offer people living with HIV/AIDS the tools and information to make informed treatment decisions. Education program services include: workshops conducted on site at community-based groups throughout the New York City area in English and Spanish; technical assistance trainings for staff of AIDS service organizations; individual treatment counseling; community forums; and publications, including our quarterly treatment newsletter, *ACRIA Update*, and topic-specific brochures in English and Spanish. ACRIA's National Treatment Education Technical Assistance Program offers ongoing support to help non-medical service providers and community members in various parts of the country acquire the skills and information to provide HIV treatment education in their communities.

To learn more about ACRIA's studies or the Treatment Education Program, please call 212-924-3934. Information about ACRIA's programs and copies of *ACRIA Update* are also available on our web site: www.acria.org.

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