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Clinical Trials 101

By Elizabeth Millard and Sarah Richards

What you need to know when considering participating in a medical study.

When Adrienne Skinner was diagnosed with cancer in 2013, she wasn't surprised. The 60-year-old New Yorker had a robust and busy life—raising four daughters as a single mom and working as an executive at a market research company—but concerns about cancer had been in the back of her mind for years.

A decade earlier, Skinner's sister and mother were diagnosed with Lynch syndrome, a genetic mutation that carries a high risk of digestive tract cancer. When Skinner found out that she, too, had the genetic mutation, she began getting yearly colonoscopies. During a routine annual exam, her bloodwork came back showing highly elevated liver enzymes. Skinner had stage IV ampullary cancer, a rare form that appears in a small area of the intestine where the pancreatic and bile ducts open.

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Skinner had surgery and started chemotherapy. It didn't work. She was put on a different chemo drug, and then another. She suffered through significant side effects. “I was looking at six more months of life, and that was a long shot,” she says.

Her oncologist found a trial at Johns Hopkins involving a drug that was already being used for certain types of cancers, like melanoma. Researchers were running the trial to determine whether the drug could be used for other cancers as well. Participation was limited to those who fit a certain set of criteria. Skinner was nearly rejected because her liver enzyme range was high, but researchers concluded she could participate in the two-year trial.

Every two weeks, Skinner took a train to Baltimore, received an injection of the drug, and returned home to New York the same day. After about four months, Skinner was cancer-free. "I realize that I'm incredibly lucky," she says. "But I know my experience with clinical trials is not the norm."

In many ways, she's right. Clinical trials, by definition, aren't initiated because researchers have the existing knowledge that the medication or treatment may cure a patient—though, as with Skinner, that might happen. "Clinical trials are essential for moving medicine forward," says Daniel Ford, an internist who directs the Johns Hopkins Institute for Clinical and Translational Research. "They are designed to find treatments that can benefit the largest number of people, with the least number of adverse effects. In some cases, they also benefit a participant on an individual level, but you have to keep in mind that that may not happen. However, by being part of a trial, you are helping doctors make good decisions for helping other patients in the long term."

Clinical trials are research studies done on people (as opposed to earlier trials on, say, mice), and they're designed to find out if a certain treatment works—for example, whether a new or existing drug is more effective at treating a certain disease than the current therapy. Trials may involve new drugs, or new ways of giving patients those drugs—such as in combination with other medication. They may test FDA-approved drugs on conditions other than the ones currently approved for treatment.

Trials aren't used only to evaluate medications. New surgical procedures, medical devices, vaccines, and diagnostic tests may also be evaluated with clinical trials. In order to be marketed in the United States, devices, drugs, and tests must pass strict regulatory conditions set by the Food and Drug Administration.

The National Institutes of Health estimates that there are nearly 250,000 clinical trials in progress across some 200 countries, running the gamut from the usefulness of a drug for mild Alzheimer's to the effectiveness of weight training in people with complex congenital heart disease. Yet, a clinical trial may not be the right fit for every person. If you are willing to consider receiving a promising but unproven type of health care, there are pros and cons to weigh before entering a trial.



So how do you know whether one is right for you or for someone in your care? Here are a few of the most frequently asked questions about clinical trials in the United States.

How do I decide if a trial is right for me?

Finding a clinical trial that suits your particular condition and your needs takes research. You can start by searching the NIH's [ClinicalTrials.gov](https://clinicaltrials.gov) site, one of the largest databases for both privately and publicly funded clinical trials. If that seems overwhelming, the independent nonprofit Center for Information and Study on Clinical Research Participation works with patients and families over the phone to find nearby clinical trials. Many patients also find out about clinical trials via their physician. Your doctor can help you decide whether a particular trial and study phase are right for you.

Will I get in?

Trials have rigorous inclusion and exclusion criteria to identify appropriate participants. That usually includes a screening visit and a set of patient protocols for the trial, such as not being on a particular medicine or being at a specific stage of a disease. The reason for strict eligibility is to make the trial as safe as possible for participants, and to ensure that the study yields consistent and scientifically valid results for the researchers.

Is my doctor still my doctor? Who is in charge of my care?

Every clinical study has a principal investigator, usually a physician. There will also be a research team made up of other health care professionals such as nurses and doctors. If you join a clinical trial it is important to clarify how the research team and your usual clinical team will work together.

Will it work?

Dina Lansey, a clinical research recruitment specialist at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, says cancer patients have a common question for her when considering a trial: Will the treatment being tested work? "'Work' tends to mean, Will they live longer and will it shrink their tumor?" says Lansey. "Although this is our hope, these are not questions we can answer about clinical trial drugs."

You may, if you have an advanced cancer like Skinner's, want to join a study to be cured. You're not alone. One British survey found that 89 percent of patients with advanced cancer who were participating in early-stage trials listed "possible health benefit" as being a very important factor in

deciding to join—despite studies reporting that the chance of a therapeutic response is less than 5 percent for participants in a Phase 1 trial. Still, participating in a clinical trial may allow you to access the most advanced treatment not yet widely available for an illness.

What are the risks?

Trials must follow a protocol that outlines exactly how a study will protect the health and well-being of participants, what procedures will be involved, how medications or devices will be used during the trial, what potential risks and benefits are expected, whether adverse events or side effects could occur, and how data will be collected and analyzed. Clinical trials are monitored carefully so that if adverse events occur, the protocol can be changed or the study stopped as quickly as possible.

While investigators strive to minimize risks, they do exist. Researchers are required by law to report to participants any adverse events in the clinical trial of an FDA-regulated treatment, such as side effects or a death. If new side effects or risks are identified while the trial is taking place, these new findings must be shared with all participants. “There’s never a risk-free study,” says Liz Martinez, a Johns Hopkins research participant advocate.

Are there other reasons to join a trial besides possible health benefits?

When patients consider signing up for a clinical trial, Lansey likes to remind them that many of the gains we’ve made in life expectancy are a result of new therapies that emerged from clinical trials, and many of the drugs we have available today were made possible through clinical trials and their volunteers. Participating may also provide a sense of meaning: Many patients volunteer with the hope that the study findings will one day help a family member or stranger facing a similar illness.

What do the “phases” mean?

Clinical trials can generally be divided into four phases. Phase 1 trials evaluate a treatment’s safety for the first time in a group of dozens of people. Phase 2 trials involve hundreds of individuals and determine the treatment’s effectiveness and further safety, while Phase 3 trials help confirm the treatment’s effectiveness and measure it against other treatments. Phase 4 trials—in which researchers further track the treatment’s risks and benefits—occur after the treatment has been approved by the FDA and is publicly available.

Gastrointestinal oncologist Daniel Laheru recently had a patient join an early-stage clinical trial, only to have the patient express concern after a friend cautioned him never to participate in early-stage trials. “It’s simplistic to say, ‘Just join the Phase 3,’” says Laheru. “We tell people that the treatments

they're getting now were at some point in a Phase 1 clinical trial. There are many aspects you should explore—including how the drug works, whether it'll be used alone or in combination with others, its expected side effects, and whether there will be biopsies or other special lab work involved."

Lansey also notes that Phase 1 trials do not necessarily involve new drugs that have never been tested on people. "If we do a clinical trial for the first time with a drug used in one particular disease but not another, this can be a Phase 1 trial," says Lansey. "If we do it in combination with drugs not previously in the combination before, it's a Phase 1."

Later-phase trials tend to involve more patients to allow comparisons between the new treatment and the existing standard treatment to determine whether the former is more effective.

What about placebos?

One of the most anxiety-causing aspects of choosing a trial can be whether you'll receive the treatment being tested or a placebo. Placebos—sugar pills or other harmless treatments given to patients knowing they'll have no effect—are used to determine whether the drug or procedure being studied is truly effective and that patients aren't simply benefiting from other aspects of the trial.

"The reality is that many patients show improvements in symptoms just by being involved in a clinical trial," says pulmonologist Nadia Hansel, an associate dean for research at Johns Hopkins Bayview Medical Center, adding that improvements might be owing to more frequent health care visits or better patient compliance.

Not every study is designed with placebos. Of those trials that do use them, the percentage of patients who receive the placebo varies widely, so it's important to ask the clinical team what your odds are prior to participating. In some trials, the researchers know which patients receive the treatment versus the placebo. This is a "single blind" study. The most rigorous clinical trials often involve placebos randomly assigned to certain patients, and neither you nor the doctor knows who is receiving what. This is what's known as a "double blind" study.

Will my existing treatment change?

Patients enrolled in clinical trials may not receive the clinical trial treatment along with another treatment. This is typically part of the inclusion/exclusion criteria of the study. You may have to decide to stop or complete a particular treatment before joining a trial—and you and your doctor will weigh the effectiveness of continuing that existing treatment versus the potential risks and benefits of the new one being offered in a study. If a treatment isn't working or there isn't one currently approved for your illness, the decision to participate in a clinical trial might be more obvious.

Who funds this research?

Trials can be funded by a variety of sources, including medical institutions, foundations, government agencies (like the National Institutes of Health), or pharmaceutical companies. Companies usually contract out later-stage trials to companies that specialize in clinical trials or to universities. Commercial companies now fund a large portion of clinical trials, and places like Johns Hopkins have policies in place so the results of these studies are as unbiased as possible.

Will I get paid?

Depending on the type of clinical trial, patients may or may not be paid to participate, so be sure to ask.

Will it cost me money?

There are often some costs to trial participants associated with a trial. Prior to joining, ask for a documented breakdown of expenses that will and won't be covered by the company or institution conducting the trial. Most will also help you navigate whether your private health insurance will cover the expense of participating (clinical trials are covered under Medicare, for instance). Don't forget to consider additional expenses, such as travel to the clinic site.

Can I drop out?

Researchers depend on patients sticking with a clinical trial so that they can get the medical answers they are looking for, but research participants are under no obligation to stay in a study if they want to leave. In Martinez's experience, the longer a study, the more likely a patient will quit. Some may also be too sick to continue. At each step, she encourages patients to voice their concerns to the study team. "You can say, 'Take out the needle' when it's in your arm," says Martinez. "You can quit at any time." If you drop out, the clinical trial staff may ask you to undergo some final tests as part of leaving the trial.

What happens when the study is over?

You may have to wait for the researchers to publish the results of this work in a peer-reviewed journal before learning the outcome of the study. Patients receiving lifesaving treatments may be able to continue taking a beneficial trial drug— depending on how the study was structured. (Check out our 10 Questions to Ask.) Drug companies sponsoring a clinical trial are under no obligation to continue providing treatment to participants afterward, cautions Martinez. If that's the case, she

suggests calling the company and asking, but there are no guarantees. You may also consider entering another trial, if the one you just finished doesn't disqualify you from participating.



Illustrations by Daniel Bejar

10 Questions to Ask the Researcher

1. What is the goal of this trial?
2. How much is known about how this drug works in humans?
3. How long will the trial last?
4. If this has been an ongoing trial, what has been the experience of patients up until this point?
5. What are the potential side effects I could experience, and how will those be addressed if they come up?
6. How will this trial affect the treatment I'm currently receiving?

7. Do I have to enroll now, or is the trial something I could pursue at a later date?
8. What are the out-of-pocket expenses I can expect? Is payment to participants involved, or will I have to seek approval from my insurance provider?
9. What are the factors that would cause me to be dropped from the trial? For example, is there a certain disease progression that would end my participation?
10. What happens when the trial is over? If the medication or treatment has been working for me, can I continue to take it?

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