

# Clinical Trials

## **Clinical Trials—Helping Patients Fight Cancer**

Clinical trials are research studies conducted on human volunteers, to answer specific scientific questions. In cancer research in particular, clinical trials strive to answer questions about ways to prevent, diagnose and develop novel therapies to treat different types of cancer. At the same time, these trials often help scientists gain valuable insights into the biological mechanisms of the disease.

Clinical trials are one of the last steps in the long process of cancer drug development, which begins in the laboratory, progresses to pre-clinical testing in animals, and then, once the drug has been shown to be safe and effective in animals, moves to the clinical trials phase. An essential step in the development of new therapies, clinical trials enable researchers to determine appropriate dosing and administration of a new drug, and provide a means to confirm the efficacy of a new drug in humans, while identifying any potential side effects. In addition, health authorities use data from clinical trials to look for evidence that new therapies are at least as safe and effective as, or safer and more effective than, existing therapies.

The approach to conducting clinical trials is similar in countries around the world, particularly when those studies are international, multi-center trials, as are many of today's studies. Patients with potentially life-threatening diseases for which there are limited treatment options, such as many types of cancer, often search for the most effective treatment available. Participating in clinical trials gives patients the potential to gain access to new, promising therapies before they are commercially available.

People decide to participate in clinical trials for many reasons: some are patients who desire more intense medical and scientific attention to their case; others seek the opportunity to receive the most current treatment options, or want to take a more active role in the treatment decisions that will affect their lives. While there is no guarantee that participating in a clinical trial will lead to a positive outcome or that a patient will receive the new therapy that is being tested during the clinical trial, patients who participate are playing a critical role in improving treatment for future patients.

For clinical trials to be successful, they require the dedication and commitment of physicians, research staff and patients alike. That is why it is important to have an understanding of the clinical trials process, the benefits and risks of participating in these studies, and the resources through which patients or physicians can locate clinical trials for which they wish to volunteer.

## **The Phases of Clinical Research for Cancer Treatments**

In the investigation of cancer treatments, there are four phases of clinical research. Each is designed to answer specific questions about a drug's safety and effectiveness. In all of these phases, researchers closely monitor patients' reactions to the drug, to ensure safety. Cancer trials differ somewhat from most other types of clinical trials. Because of the nature of the disease, to ensure that patients do not go untreated, most cancer treatment trials are designed to compare new treatments to existing standard treatments (the best available current treatment), as determined by the results of past research. Comparisons to placebo (sugar pill) are generally only used in cancer treatment trials when there are no other appropriate treatment alternatives available.

Each phase of the clinical trial depends and builds upon research results from an earlier phase, so the treatment being tested in Phase I will progress on to the next phase only when it has proven to be at least as safe as the current standard of care. These data are reviewed and approved by review boards before the more advanced phases of research begin.

In **Phase I trials**, researchers determine the most appropriate dosing and administration of a drug (pill, capsule, liquid, injection, etc.), usually in a small number of patients (sometimes as few as twelve). In this phase, researchers determine the tolerability of the drug and monitor carefully for any harmful side

effects. While some efficacy data may also be collected during this phase, evaluating efficacy is not a primary goal until Phase II.<sup>1</sup>

**Phase II trials** continue to study the safety of the drug while also evaluating its efficacy. During this phase, researchers evaluate how the drug works and how it affects the body. Patients are given the highest tolerable dose (the highest dose with the fewest side effects, as determined in Phase I trials), and researchers look for evidence that the tumor is shrinking or that the cancer cells are decreasing or have disappeared. Phase II studies can include groups of 25 to 100 patients. Generally, the groups are matched with regard to such criteria as age, sex, and the stage of the disease.<sup>2</sup>

**Phase III trials** are initiated to provide more in-depth information about a drug's safety and efficacy compared with existing standard treatment and/or a placebo. In Phase III cancer trials, however, placebos rarely used, except in cases where no standard treatment option exists, or if the drug is being tested in patients in whom the standard treatment has either been completed or has been unsuccessful (refractory patients) and there are no further existing options.<sup>3</sup> Patients in these trials usually are randomly divided into at least two groups:

**Intervention Group**—This group takes the new, investigational drug

**Control Group**—This group takes either the standard treatment or, if there is no other treatment, a placebo

Phase III trials can have hundreds or even thousands of participants, depending upon the disease being studied and the design of the study. Phase III studies need to provide statistically significant clinical data for the drug to progress to the next stage or for the data to be submitted to global health authorities for marketing approval. They are generally conducted at more than one site simultaneously, often internationally, at physicians' offices, clinics and hospitals.

**Phase IV** trials are conducted when a manufacturer or independent researcher wants to test a drug's effectiveness in a different medical condition or type of cancer than that for which health authorities initially approved the drug, in a different formulation or for a different use than was originally studied or approved. These trials can also help researchers gain a better understanding of a drug's use in existing applications.<sup>4</sup>

### Types of Clinical Trials

Before any study is conducted, a principal investigator, often a physician, prepares a study action plan, called a protocol. The purpose of the protocol is to describe the objectives, or goals of the study, how it will be conducted and monitored, how many patients will be entered in the study, and why it is necessary to conduct research on all of the points set in the protocol. Any physician who takes part in the clinical study must follow the protocol.<sup>5</sup>

#### Eligibility Criteria for Clinical Trials

Participants must meet certain conditions of the clinical trial before they can enter the study. Generally, participants in a study are alike in key ways:

**Type and stage of cancer**

**Age**

**Gender**

**Previous treatments**

**Results of certain laboratory tests**

Enrolling participants with similar characteristics ensures that the results will be due to the treatment under study rather than other factors.<sup>6</sup>

#### There are different types of clinical trials for cancer:

**Treatment trials** study promising new therapies in patients who have cancer.

**Quality of life studies** study ways to improve comfort and quality of life for patients who have cancer.

**Prevention trials** study ways to reduce the risk, or chance, of developing cancer, and are usually conducted with healthy people who have not had cancer.

**Screening trials** study ways to detect cancer, and are often conducted to determine whether finding cancer before it causes symptoms decreases the chance of developing symptoms or dying from the disease.

**Diagnostic trials** study tests or procedures that could be used to identify cancer more accurately, and also at an earlier stage.<sup>7</sup>

### Common Terminology to Describe Clinical Trials

**Double-blind**—A method used to prevent bias in a clinical trial. Neither the patients nor the investigators know which participants are taking the study treatment versus the standard treatment.

**Multi-center**—These are trials in which identical research protocols are used at multiple trial sites or centers.

**Multi-national**—Trials are conducted in multiple countries.

**Open-label**—A study in which both the physician and patient know which of the treatments the patient is getting.

**Randomized**—A method through which study participants are assigned to a treatment group based on chance.

**Single-blind**—Trials in which participants do not know which treatment group they are in until the conclusion of the study, but their physicians do know.

### Participating in Clinical Trials

Clinical trials are generally sponsored by government organizations, not-for-profit charities or pharmaceutical companies. The decision whether or not to participate in clinical trials is very important. Perhaps the most important benefit to enrolling is the potential for gaining advance access to treatment that might not be commercially available for years to come, and which may prove to be safer and more effective than existing treatment options.

Of course, there is no guarantee that the patient will receive the new therapy, even by enrolling in a study. Rather, depending upon the trial, there is always a chance that the patient will receive placebo or the current standard of care (the same drug that is most likely to be prescribed to patients not participating in a trial). But, it is important to remember two points. First, in cancer trials, drugs are rarely compared to placebo. Second, the research in which the patient is participating is critical to the process of making new and better drugs available for all cancer patients. Without patient volunteers, there can be no new therapies.

Other potential benefits of participating in clinical trials include increased access to medical professionals who are supervising your care, and closer monitoring of results and possible side effects of treatment.

Patients who do enroll in clinical trials are encouraged to ask questions or raise any concerns they might have at any stage. Patients should keep a journal and a list of questions that they can bring in to ask their physician at each visit. They can also bring a friend or family member when talking to their physician about their case to help them remember to ask questions and remember the answers. Participants in clinical trials have the right to leave the study at any time and can also be taken off the study if investigators learn that an agent may cause harm.<sup>8</sup>

Of course, all investigational drugs do have some risks, and patients should discuss them with their physicians prior to joining a clinical trial. Generally, possible risks include unknown or more severe side effects than have been detected in earlier trials; poorer efficacy than may have been anticipated; and in a randomized clinical trial, lack of choice regarding which treatment is administered to which patient.<sup>9</sup>

### For the Safety of Participants

There are several levels of safeguards in place to ensure the welfare of each clinical trial participant:

**Informed Consent:** This is a document that provides patients with key facts about the clinical trial. As a standard practice, physicians should review the content of this document, with all patients enrolling in any clinical trial. The document explains the purpose of the trial, expected benefits, known risks, and the

responsibilities of the patient. Patients are required to sign an informed consent form if they agree to enroll in the clinical trial.<sup>10</sup>

Any institution that conducts studies has committees that thoroughly review all potential clinical trials. The review boards include:

**Institutional Review Board (IRB)** The IRB is a group, usually made up of physicians, other scientists, and non-medical personnel (including clergy and lay persons), that is responsible for protecting the welfare of study participants and making sure that the study complies with the ethical and legal codes that govern medical practices in the United States, Asia, and Europe. The IRB is responsible for reviewing the study protocol and ensuring that the trial follows pre-defined ethical criteria/standards, and that the potential benefits of the new treatment outweigh any risks.

In Europe, all clinical trials must be approved by an IRB that is called the Ethical Review Committee. This committee reviews the study protocol, and monitors the study to ensure patient protection and safety. Clinical research in Europe is conducted in accordance with standards of ethics called the Declaration of Helsinki, the Guidelines for Good Clinical Practice that was approved by the International Conference on Harmonisation.

Clinical trials in Asia are monitored by trial site-specific IRBs. If a clinical trial is conducted at a hospital, then the IRB within the hospital reviews the protocol and actively monitors the trial.

**Data Safety Monitoring Board (DSMB)** The DSMB is an independent group of physicians and scientists—not otherwise involved in the trial—who look at the study statistics, monitor clinical trials at various pre-determined checkpoints and can recommend that the investigators stop or modify a study early. The DSMB can make this recommendation when the research shows that the new treatment is significantly more effective than the placebo or the comparative therapy.

Similarly, if safety concerns arise (risks of the new treatment outweigh the benefits) the DSMB can stop or modify the study to ensure patient safety. The DSMB can recommend whether the study should go forward as originally planned based on the data they review.<sup>11</sup>

### **Clinical Trials and Children**

For children under 18 years old who want to participate in a clinical trial, special considerations are necessary. Physicians, parents and the child or young adult will engage in an ongoing, interactive dialogue, called the assent process. This is a process where the child or young adult has the opportunity to ask questions about the study and can feel more in control and more involved in the trial as a result. The child's parents or legal guardians play a key role in deciding if their child should participate in the clinical trial. They review all information about a clinical trial for their child, interact with the research team and learn how the study will work, its objectives, the possible benefits and risks of participating, and the child's rights and responsibilities.

Before the assent process can begin, parents or guardians must give their permission for their children to participate, and then the child or young adult is given a form explaining the purpose of the research, expectations of study participants, and procedures they will undergo. Strict guidelines exist for patients under 18 and the physician should discuss the full scope of the study and the patient's rights and role with the patient and the parents during this informed consent process.

The parent or legal guardian is involved in every step of the assent process, and if the child is too young to understand the specifics of the trial, the parent or legal guardian will make the decision whether or not to have the child participate in the trial.<sup>12</sup>

### **How Can Patients Find Clinical Trials?**

Information about clinical trials around the world can come from a variety of sources. Physicians can suggest a particular study, or patients can search the Internet for clinical trials being conducted. To find trials on the Internet, patients can type in key words or phrases such as "cancer clinical trials" or "clinical trials." They also can research trials at the *metaRegister* Web site, an international searchable database containing a list of randomized and controlled clinical trials.<sup>13</sup>

Patients should also contact national and international cancer associations and cancer-patient groups to request information on ongoing or planned clinical trials and to request information or educational materials such as books or videos on their disease.

### Finding Clinical Trials

Patients who would like to participate in clinical trials can research a variety of sources.

- Physicians or cancer specialists.
- Cancer Associations or Cancer Societies such as the **metaRegister**, or the **European Organisation for Research and Treatment of Cancer**.
- The Internet—Cancer associations or cancer societies will provide links to organizations that sponsor or conduct clinical trials.
- Patient Groups
- Pharmaceutical companies—Large pharmaceutical companies conduct or sponsor clinical trials. Information can be found on their

Some pharmaceutical companies support clinical trial databases that can be accessed on their Web sites, and often sponsor clinical trials.<sup>14</sup>

### Sponsoring Clinical Trials

Clinical trial sponsors are usually institutions or individuals who are seeking better treatment for cancer or better ways to prevent or detect cancer.

### Conclusion

Clinical trials are an essential method for finding innovative, safer and more effective treatment options to fight cancer. Patient health and safety are the most important considerations during the trials. As science provides new insights into potential ways to fight the many cancers that exist today, clinical trials will continue to provide the best means for helping people find treatment

options that will help them lead a fuller, longer, and better life.

### *It's important to note...*

- Clinical trials are carefully designed with patient safety as a top priority
- Participants in clinical trials are often so closely monitored that they receive more frequent care than patients who are not involved with clinical research—side effects are carefully tracked and monitored, and treated if warranted
- Clinical trial participants who take the study drug have the advantage of being the first to gain access to important new therapies.
- Clinical trial participants have the satisfaction of knowing that they have made an important altruistic contribution to medical knowledge, and to the patient community by contributing research for future treatments for other patients.<sup>15</sup>

## Questions to Ask Your Physician Prior to Enrolling in Cancer Clinical Trials

### Understanding clinical trials

What clinical trials exist that might be appropriate for me to enroll?  
Which of these studies would fit my needs/disease/situation the best?  
What is the purpose of the study?  
What Phase is the trial in?  
Why do researchers think this approach may be effective?  
Will I live longer/better if I participate in this study?  
Who has reviewed and approved the study protocol?  
How long will the study last?  
How are study results and safety of participants being checked?  
Who decides if I take the new drug or the old drug?  
Who will sponsor the study?  
What were the results of the earlier trials?

### Patient Responsibility

What will my responsibilities be if I participate?  
Will I have to pay for the study medication? Office visits?  
Will my health insurance cover the cost?

### Quality of care

What are the potential side effects?  
Who will be in charge of my care?  
Will I still be seeing my regular physician?  
What happens when the study is completed—will I still be able to get the drug?  
Where will I receive my medical care? Will I have to relocate to another city?

### Quality of Life during the study

What kinds of therapies, procedures and /or tests will I undergo during the trial?  
Will they hurt, and if so how much, for how long?  
How do the tests in the study compare with those I would have outside of the trial?  
Will I be able to take my regular medications while in the clinical trial?  
How could being in this study affect my daily quality of life?  
Why should I join the study if there are other drugs out there that I can take?  
What if I want to leave the study?  
Can I talk to other people in the study?<sup>16</sup>

## **Glossary**

**Action Studies**—Studies that focus on finding out whether actions people take (i.e. quitting smoking) can prevent cancer.

**Agent Studies**—Studies that focus on examining whether taking certain medicines, vitamins, minerals, or food supplements can prevent cancer.

**Consent Form**—(also called Informed Consent) A document that provides key facts about a clinical trial study (study agent, any tests patients may have to take, and possible risks and benefits.) All participants in the studies must sign this.

**Control Group**—This group takes either the standard treatment being compared to the new treatment, or a placebo (a pill that contains no active ingredients).

**Data Safety and Monitoring Board**—A group that provides oversight of a clinical trial and reviews the results to see if they are acceptable. This group determines if a trial should continue or be closed at various checkpoints throughout the study.

**Double-blind**—A method used to prevent bias in a clinical trial. Neither the patients nor the investigators know which participants are taking the study drug and which are not.

**Informed Consent**— This is a document that provides patients with key facts about the clinical trial (study drug, any tests patients may have to take, and possible risks and benefits.) All participants in the studies must sign this.

**Institutional Review Board**—A group usually made up of physicians, other scientists, and non-medical personnel, responsible for protecting the welfare of study participants and making sure that the studies comply with federal law and ethics.

**Intervention Group**—This group is taking the new treatment agent that's being tested in a clinical trial study.

**Open-label trial**—A clinical trial in which researchers and participants know which drug or vaccine is being administered.

**Protocol**—The action plan for the clinical trial study, which explains key points of the study including: purpose of the study, how many people will participate, and eligibility criteria.

**Randomization**—People are assigned by chance (often by a computer) to receive either the standard or new treatment agent.

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- <sup>1</sup> European Organisation for Research and Treatment of Cancer; [Http://www.eortc.be](http://www.eortc.be)
- <sup>2</sup> [http://www.cancer.org/docroot/ETO/content/ETO\\_6\\_3\\_Clinical\\_Trials\\_-\\_Patient\\_Participation.asp](http://www.cancer.org/docroot/ETO/content/ETO_6_3_Clinical_Trials_-_Patient_Participation.asp)
- <sup>3</sup> [http://www.cancer.org/docroot/ETO/content/ETO\\_6\\_3\\_Clinical\\_Trials\\_-\\_Patient\\_Participation.asp](http://www.cancer.org/docroot/ETO/content/ETO_6_3_Clinical_Trials_-_Patient_Participation.asp)
- <sup>4</sup> <http://www.cancerbacup.org.uk/Trials/Understandingtrials/Typesoftrials>; American Cancer Society: [http://www.cancer.org/docroot/ETO/content/ETO\\_6\\_3\\_Clinical\\_Trials\\_-\\_Patient\\_Participation.asp](http://www.cancer.org/docroot/ETO/content/ETO_6_3_Clinical_Trials_-_Patient_Participation.asp); and The National Cancer Institute: <http://www.cancer.gov/clinicaltrials>
- <sup>5</sup> The National Cancer Institute: <http://www.cancer.gov/clinicaltrials/understanding/how-trials-are-done>
- <sup>6</sup> <http://www.cancer.gov/clinicaltrials/understanding/how-to-take-part>; European Organisation for Research and Treatment of Cancer; <Http://www.eortc.be>
- <sup>7</sup> Emerging Med: [http://www.emergingmed.com/pub\\_AboutClinicalTrials.asp](http://www.emergingmed.com/pub_AboutClinicalTrials.asp)
- <sup>8</sup> <http://www.cancerbacup.org.uk/Trials/Understandingtrials/Givingconsent>
- <sup>9</sup> American Cancer Society: [http://www.cancer.org/docroot/ETO/content/ETO\\_6\\_3\\_Clinical\\_Trials\\_-\\_Patient\\_Participation.asp](http://www.cancer.org/docroot/ETO/content/ETO_6_3_Clinical_Trials_-_Patient_Participation.asp); and The National Cancer Institute: <http://www.cancer.gov/clinicaltrials>
- <sup>10</sup> The National Cancer Institute: <http://www.cancer.gov/clinicaltrials/conducting/informed-consent-guide/page2>
- <sup>11</sup> American Cancer Society: [http://www.cancer.org/docroot/ETO/content/ETO\\_6\\_3\\_Clinical\\_Trials\\_-\\_Patient\\_Participation.asp](http://www.cancer.org/docroot/ETO/content/ETO_6_3_Clinical_Trials_-_Patient_Participation.asp);
- <sup>12</sup> The National Cancer Institute; <http://www.cancer.gov/clinicaltrials/understanding/childrensassen0101>
- <sup>13</sup> <http://www.ncrn.org.uk/Portfolio/dbase.asp>; and [www.ncrn.org.uk/portfolio/dbase.asp](http://www.ncrn.org.uk/portfolio/dbase.asp)
- <sup>14</sup> American Cancer Society: [http://www.cancer.org/docroot/ETO/content/ETO\\_6\\_3\\_Clinical\\_Trials\\_-\\_Patient\\_Participation.asp](http://www.cancer.org/docroot/ETO/content/ETO_6_3_Clinical_Trials_-_Patient_Participation.asp); and The National Cancer Institute: <http://www.cancer.gov/clinicaltrials>
- <sup>15</sup> <http://www.cancerbacup.org.uk/Trials/Understandingtrials/Risksandbenefitsofbeingtreatedinatrial>
- <sup>16</sup> The National Cancer Institute; <http://www.cancer.gov/clinicaltrials/understanding/questions-to-ask-about-participating>