CHAPTER 8: CLINICAL TRIALS

INTRODUCTION

The mainstream health care system in the United States is predominantly an evidence-based system. This means that new drugs and treatments go through a series of research studies in people to determine if they are safe and effective before they become accepted medical practice. The studies used to determine the effectiveness and safety of new drugs and treatments are called clinical trials.

This chapter explains different types of clinical trials and the processes involved in each type of trial. Potential advantages and disadvantages are discussed. If you are interested in participating in a clinical trial, discuss your interest with your health care providers.

WHAT IS A CLINICAL TRIAL?

Clinical trials are medical research studies in which people enrolled as participants help doctors find out if a new treatment or procedure is safe and effective. Clinical trials are used to test all types of medical interventions. New tests and procedures are tested to find out if they are safe and effective for diagnosing disease. New drugs, treatment schedules, and surgical procedures are tested to determine if they are safe and effective treatments for specific diseases. Dietary regimens, nutritional supplements, exercise programs, and other interventions are tested to discover if they are able to prevent disease safely and effectively. Most new medical interventions are tested in clinical trials before being made available to the general public.

Each clinical trial is carefully designed to answer a specific medical question. Clinical trials are controlled to ensure that at the end of the trial, researchers are able to answer the

question being considered. With the help of people who enroll, clinical trials enable doctors to find better ways to prevent, diagnose, and treat cancer.

This book is written primarily for people who have recently been diagnosed with lung cancer and their families. Therefore, this chapter will focus on treatment clinical trials. Many types of cancer treatments are tested in clinical trials. New chemotherapy drugs, surgical procedures, radiation techniques, vaccines, and biological therapies are a few examples. The importance of clinical trials in bringing new therapies to people facing cancer cannot be overstated. Every new cancer therapy made available to people afflicted with cancer has been tested in clinical trials. The treatment options available to people facing cancer today were made possible by people with cancer who have participated in clinical trials in the past.

Quality of life studies are another type of clinical trial of interest to people currently facing cancer. Quality of life trials are also called supportive care trials. These trials study drugs, procedures, and other measures that are intended to improve the comfort and quality of life of people with cancer. These trials are conducted in much the same way as treatment trials. For the sake of simplicity, treatment trials will be used to discuss the clinical trial process. Keep in mind that most of what is said about treatment trials also applies to supportive care trials.

CLINICAL TRIAL OVERVIEW

Before any new cancer treatment is tested in people, it is first studied in the laboratory. Various techniques are used to test different types of treatments. Drugs and biological treatments are often tested using cancer cells that are grown in a laboratory. Some treatments are tested in animals. Regardless of the techniques used, all new treatments have undergone extensive testing before they are considered for clinical trials. The testing performed in the laboratory before clinical trials begin is called *preclinical testing*.

In the United States, the Food and Drug Administration (FDA) oversees clinical trials in which new drugs or treatments are studied. In cancer research, these clinical trials are

conducted to find cancer treatments that are more effective and/or safer than treatments that are already in use. Individual doctors, groups of doctors, medical schools, cancer centers, or other medical institutions can sponsor cancer treatment trials. Drug companies and diagnostic equipment companies also sponsor clinical trials.

Clinical Trial Funding

Most cancer trials conducted in the United States are fully or partially supported with federal money. The National Cancer Institute (NCI) sponsors many cancer clinical trials through four nationwide programs.

- The Cancer Centers Program

  The Cancer Centers Program of the NCI supports cancer research at major academic and research institutions throughout the United States. This program supports both laboratory-based research and clinical trials.

- The Clinical Trials Cooperative Group Program

  The Clinical Trials Cooperative Group Program supports organizations that conduct clinical trials consistent with national priorities for cancer treatment research. The groups in the program are able to rapidly enroll patients from multiple centers into a clinical trial. This helps ensure that large trials can be completed as quickly as possible. As of 2005, 12 Cooperative Groups were funded by this program. Cooperative Groups participating in lung cancer research in 2005 are listed below.

  American College of Radiology Imaging Network
  American College of Surgeons Oncology Group (ACOSOG)
  Cancer and Acute Leukemia Group B (CALGB)
  Eastern Cooperative Oncology Group (ECOG)
  National Cancer Institute of Canada, Clinical Trials Group
  North Central Cancer Treatment Group (NCCTG)
  Radiation Therapy Oncology Group (RTOG)
  Southwest Oncology Group (SWOG)

- Community Clinical Oncology Program

  The Community Clinical Oncology Program (CCOP) encourages community-based doctors to work with scientists conducting NCI-supported clinical trials. The CCOP increases the number of patients and doctors who can participate in clinical trials

operated at major research centers. It also helps researchers conduct large-scale cancer studies quickly.

- Specialized Programs of Research Excellence

  In 1992, the NCI established the Specialized Programs of Research Excellence (SPOREs) to promote clinical and laboratory research. The goal of the SPORE program is to bring new ideas and discoveries from the laboratory to the clinical care setting quickly. The SPORE programs sponsor many unique, innovative clinical trials. As of 2005, there are six lung cancer SPORE programs. An exploratory program (*) is also underway.

Johns Hopkins University
Baltimore, Maryland

Univ. of California, Los Angeles
Los Angeles, California

University of Colorado
Denver, Colorado

University of Pittsburgh
Pittsburgh, Pennsylvania

University of Texas
Dallas, Texas

Vanderbilt University
Nashville, Tennessee

***Dana-Farber Cancer Institute/Harvard Cancer Center**
Boston, Massachusetts

The Clinical Trial Protocol

The action plan for a clinical trial is called the trial *protocol*. The protocol outlines the purpose of the trial and the research questions being investigated. The protocol also describes the trial design and study procedures. This includes specific medical criteria for determining who will be enrolled in the trial, what drugs will be administered and their dosing schedule, testing and follow-up procedures, and other study details.

The protocol ensures that all people enrolled in a trial are treated the same way, even if they are treated at different locations. Strict compliance with the clinical trial protocol is necessary to insure reliable study results. The clinical trial protocol is developed by the trial's lead researcher who is called the principal investigator. The protocol must be reviewed and approved by the organization sponsoring the clinical trial. Each location participating in the

trial must also submit the protocol to their Institutional Review Board for the Protection of Human Subjects in Research (IRB). As the name implies, the function of the IRB is to protect the rights and welfare of people who participate in clinical research. All protocols are reviewed to insure that:

- participants are selected fairly
- stringent informed consent procedures are in place
- all risks for participants have been minimized
- participants' privacy and confidentiality will be protected

No participants can be enrolled in a clinical trial until IRB approval has been obtained.

Informed Consent

All people enrolled in clinical trials are required to sign an informed consent form. When you sign an informed consent form, you are confirming that you:

- have discussed the clinical trial protocol with your doctor and/or nurse,
- have been told about the possible risks and benefits of participating and not participating in the trial, and
- are participating in the trial because you choose to do so of your own free will

If you have any questions about the clinical trial protocol, discuss them with your health care provider. Be certain you understand all the possible risks and benefits of the trial and your responsibilities. If you are unclear about anything having to do with the trial, ask for clarification before signing the informed consent form. You can always talk with your doctor, nurse, or someone else on the clinical trial team if additional questions come up during the trial.

You can withdraw from a clinical trial at <u>any</u> time if you choose to do so. Signing an informed consent form does not prevent you from withdrawing from a clinical trial.

TYPES OF CLINICAL TRIALS

Three types of clinical trials must be successfully completed before the FDA will approve a new drug for a specific condition or disease. The three types of trials are called phase I,

phase II, and phase III trials. Each phase trial has a different purpose, which will be explained later in this section. The process of evaluating a new drug in people begins with a phase I trial. If the results of the phase I trial demonstrate acceptable safety, testing progresses to a phase II trial. If acceptable safety and benefit are demonstrated in the phase II trial, a phase III trial is conducted. A phase IV clinical trial is sometimes conducted after a drug becomes available to the public.

Phase I Trials

Phase I trials involve the first testing of a new drug in humans. The focuses of a phase I trial are the safety of the drug and how best to administer it. The purposes of a phase I treatment trial are:

- to find out the best way to administer the drug, for example, by mouth, injected into the blood, or injected into the muscle
- to study how often should the drug be given
- to determine the highest, safe dose that can be administered
- to discover if there are any negative side effects from the drug

A phase I trial enrolls a small number of people, usually 10-20. People enrolled in phase I cancer treatment trials have often exhausted all other treatment options. They are enrolled with the hope that the new drug may benefit them, although determining clinical benefit from the drug is not the primary purpose of a phase I treatment trial.

Phase II Trials

A phase II trial is conducted on new drug or drug combination that appeared safe in a phase I trial. The purposes of a phase II treatment trial are:

- to continue to evaluate the safety of the drug
- to study how the body *metabolizes* and eliminates the drug (this is known as pharmacokinetic data)
- to collect preliminary data about the effectiveness of the drug for a specific condition

A phase II trial enrolls between 20-100 people. The goals of a phase II treatment trial are to confirm drug safety and determine if there appears to be sufficient benefit to patients to warrant further study. The FDA requires phase II clinical trial information to prove the safety of a new drug before allowing it to be sold.

Phase III Trials

Phase III treatment trials are conducted for new drugs or drug combinations that show promising results in phase II trials. The purpose of a phase III trial is to compare a new drug or drug combination to other available treatments. The study design used for most phase III treatment trials is called a *randomized controlled trial*. These trials have at least two treatment protocols or treatment arms. People in the *experimental treatment arm* receive the new drug. People in the *control arm* receive the current standard of care, in other words, the best currently approved treatment. Some phase III trials have additional treatment arms to allow multiple comparisons between different treatment protocols. Phase III trials require large numbers of people to enable researchers to reliably answer the study questions. Phase III trials typically enroll 200-1,000 people or more. These trials usually enroll people from many different sites located throughout the country. A phase III treatment trial must conclusively show effectiveness through objective measures of patient benefit before the FDA will approve a new drug to treat a specific condition or illness. After the completion of the phase III trial, the sponsor of a new drug can file a New Drug Application (NDA) with the FDA. The NDA is the final step required to make a new drug available to people outside a research setting.

People enrolled in phase III treatment trials usually must agree to a process called *randomization*. In the randomization process, you are assigned by chance to one of the treatment groups. In other words, you do not have a choice about what treatment you receive. Further, many phase III treatment trials are *blinded trials*. In a blinded trial, you will not know whether you are receiving experimental or standard treatment. Blinding is important to ensure that the results of the trial are valid. In a double-blind trial, neither you nor your health care providers will be aware of what drugs you are receiving.

Phase IV Trials

Phase IV clinical trials examine the long-term effects of drugs or treatments after they have received FDA approval. Since this type of trial is not required to market a drug, it is not as common as the other types of clinical trials. Phase IV trials are most often sponsored by pharmaceutical companies. Another term used for phase IV clinical trials is *post-marketing surveillance studies*.

FDA REVIEW AND APPROVAL PROCESSES

Clinical trials that propose to evaluate a new drug must first submit an Investigational New Drug (IND) application to the FDA. The application contains all the information that has been gathered in preclinical testing of a new drug. If the FDA determines the drug is reasonably safe and may have clinical benefit, the IND is approved. This approval is required before clinical trials can begin.

When the results of phase I and II treatment trials for a new drug indicate the drug is safe and shows promise in terms of effectiveness, the sponsor has a pre-NDA meeting with the FDA. At this meeting, the sponsor, principal investigators, and the FDA decide what needs to be done in the phase III treatment trial to determine conclusively whether the new drug is safe and effective for a specific condition or disease. The phase III trial is conducted according to what has been agreed upon at the pre-NDA meeting.

Upon completion of a phase III cancer treatment trial, the drug sponsor submits a New Drug Application to the FDA. Once the NDA is filed, an FDA review team evaluates whether the information from the clinical trials show that the new drug is safe and effective for its proposed use. Review teams for cancer therapies include *oncologists*, chemists, statisticians, pharmacologists, and other experts. The review team also includes a cancer survivor who brings the patient perspective to the discussions. If the FDA decides the benefits of a new drug outweigh the risks, the drug receives approval for marketing in the United States.

An FDA approved drug is generally paid for by health insurance if it used for the purpose for which it was approved. However, a doctor can prescribe an FDA-approved drug for any purpose he or she determines is appropriate. If a drug is used for a purpose other than the one for which it was approved, this is called *off-label use* or *unapproved indications use*. This situation may come up in cancer treatment. For example, there are times when a drug approved for one cancer is still in trials for another form of cancer. Your doctor may such a drug is your best treatment option. Your doctor has every right to prescribe the drug for you, but its use in this case would be for an unapproved indication. Some health insurance companies will not pay for drugs that are used for unapproved indications. Cancer advocates are working to change this situation.

PARTICIPATING IN A CLINICAL TRIAL

Clinical trials offer people with cancer an alternative to standard treatment. Many who participate in clinical trials see it as an opportunity to receive quality health care while making a valuable contribution to medical science and humanity.

> **I am such a believer in clinical trials, particularly because I am a part of what seems to be a pretty large percentage of people for whom chemotherapy was not effective. My first trial was a pretty easy choice because I was getting the trial drug in addition to what would have been the chosen protocol for my type and stage of lung cancer…. I also know that my oncologist, who is involved in a large number of clinical trials, does so at great expense in both time and money. He wouldn't do it if he wasn't really convinced that these trials are critical to finding help for his patients…. I am convinced that we must have a variety of weapons in our arsenal against cancer … no one treatment can possibly work for all of us. The more choices we have in treatment, the more likely we will find one that works. That can only happen if we have lots of research to find new and better ways to fight the disease.**
>
> **—Ann, diagnosed with stage IIIB NSCLC in 2002 at age 54**

The decision whether to participate in a clinical trial is a highly personal choice, especially when you are facing a potentially life-threatening illness. There are several factors to take into consideration when making such an important decision. This section provides information that will help you think through your options. If you are interested in clinical trials, discuss the option with your health care providers and those closest to you. The choice to participate, however, is yours and yours alone. You know best what is right for you.

Possible Advantages of Participating in a Clinical Trial

There are a number of possible advantages to participating in a clinical trial.

- Clinical trial participants are often treated by leading doctors in the field of cancer research.
- Participation may provide you with access to new drugs or treatments that are not yet available outside of a clinical trial.
- You may feel a greater sense of control over your health care situation by actively choosing to participate in a clinical trial.
- There is a possibility you may receive more effective treatment than the current standard of care.
- People who participate in clinical trials often derive a sense of satisfaction from making a valuable contribution to lung cancer research.
- The knowledge that you are helping other people with lung cancer may give you a sense of personal accomplishment.
- Part of your treatment may be provided free of charge.

> **I went on the Internet and checked out various types of clinical trials. There are many interesting studies going on. My oncologist thought that going into an Iressa™ study would be my best hope, and fortunately, it was. It shrunk my cancer, whereas before [going on Iressa™], chemo was not working [for me]. I am very happy participating in this trial. If for some reason I need to try something else, I will definitely be looking for another [clinical] trial.**
> **– Judy, diagnosed with stage IV NSCLC in 2002 at age 59**

Possible Disadvantages of Participating in a Clinical Trial

Participation in a clinical trial has possible disadvantages that should be considered. Although great efforts are made to protect the safety of people participating in clinical trials, there is no such thing as risk-free medical care. Generally, potential risks are greatest in phase I trials. Risks are usually diminished in phase II trials, and are lowest in phase III and IV trials. Some potential risks or disadvantages of clinical participation are:

- You may experience unexpected side effects. New drugs and procedures may have adverse effects or risks that are unknown to the trial sponsors and your health care providers.

- There is always the possibility that the new drug will prove to be ineffective or less effective than the current standard of care.
- If you are in a randomized trial, you may not receive the experimental drug you were hoping to receive.
- Even if the new treatment is effective for most people, it may not work for you.
- You may not like the idea of participating in a medical experiment.
- If you are participating in a blinded trial, you may find it hard to handle not knowing what treatment you are receiving.
- You may be uncomfortable with not having a choice about what treatment you receive if you participate in a randomized trial.

Health Insurance Coverage and Clinical Trials

As of January 2001, Medicare covers the costs associated with clinical trials involving cancer diagnosis or treatment. However, private health insurance coverage varies for clinical trials. Each plan has its own rules about what costs are covered when you are participating in a clinical trial. Some plans offer only partial coverage in a clinical trial setting if the plan considers the study treatment experimental or investigational. Health insurance companies decide what services they will pay for by developing coverage policies. Health plans usually designate a service as 'established' if there is sufficient evidence to show that it is safe and effective. If the plan judges the available data insufficient, a service may be deemed 'investigational' and not covered under the plan. Since each health insurance plan differs in terms of coverage of services rendered in a clinical trial, you need to check with a representative from your plan to determine their coverage for clinical trials.

Some health insurance plans have specific criteria a clinical trial must meet for the plan to cover associated costs. Other plans have specific limitations for clinical trial coverage. Examples of such criteria and limitations are listed below.

- The clinical trial must be sponsored by an organization whose review and oversight of the trial is scientifically rigorous.
- The clinical trial must be judged by plan administrators to be medically necessary. Often this judgment is made on a case-by-case basis.

- Coverage may be limited to phase III trials.
- Documentation may be required before the plan will approve participation in a clinical trial.
- Coverage may be limited to clinical trials the plan deems cost-neutral, meaning the cost to the insurance company is not more than would be required for standard treatment.
- A plan may cover only clinical trials involving conditions for which there are no standard therapies.
- An insurance company may require proof of the qualifications of the medical staff and the care facility before covering the costs of unique services.

There are two types of costs associated with clinical trials, patient care costs and research costs. Patient care costs are divided into two categories, usual care costs and extra care costs. Usual care costs include doctor visits, hospital stays, x-rays, and laboratory tests that would be necessary regardless of whether you are receiving standard treatment or are participating in a clinical trial. These costs are usually covered by health insurance plans and Medicare. Extra care costs are for visits, tests, or procedures that are required by a clinical trial, but would not be necessary if you were receiving standard treatment. Extra care costs are sometimes paid by the sponsoring organization or the research institution. If there are extra care costs that are not paid by the trial sponsor or research institution, you may be able to get your health insurance to pay these costs. You will have to work this out with your insurance provider in advance.

Research costs are the costs associated with conducting a clinical trial. These costs include data collection, investigators' time, nurses' time, data analysis, and other administrative costs. Study participants are not required to pay anything toward these costs. These costs are usually paid by the study sponsor.

Talking With Your Health Care Providers

If you are interested in participating in a clinical trial, talking with your current doctor is a good way to begin collecting information. He or she can answer your questions, or may put

you in contact with others who will be better able to assist you. If your health care provider seems hesitant about clinical trials, he or she may have concerns that have little to do with you such as:

- Health care providers who do not regularly participate in clinical research may feel unprepared to discuss the topic of clinical trials.
- Your doctor may be concerned about the demands on his or her time if you are participating in a clinical trial. He or she may be worried about having enough time to take care of you and the other patients in the practice.
- If you are not feeling well, your doctor may be worried that the demands of a clinical trial may be too much for you.
- Your doctor may be convinced that standard treatment is the best option for you, and reluctant to recommend another treatment option.
- Your doctor may be concerned about losing you as his or her patient if you participate in a clinical trial.

You may need to look for other sources of information if your current care provider is not able to answer all your questions. A list of resources for gathering information about clinical trials is included at the end of this section.

Once you have found a particular clinical trial you are interested in, you will probably want to consider specific information about the trial before making a final decision. Following is a sample list of considerations. You may want additional information.

- What is the purpose of the trial? Is the goal in keeping with your needs?
- What are the eligibility requirements? Are you likely to be eligible for the trial?
- Who will be in charge of your care?
- Will you be able to see your regular oncologist, or will you become someone else's patient?
- Who will monitor your care and safety?
- Where will you receive your care?

- How long will the trial last?
- What can you reasonably expect if you participate in the trial? What can you reasonably expect if you do not participate in the trial?
- What will your responsibilities be if you participate in the trial?
- What are the possible short-term benefits of the trial? What are the possible long-term benefits?
- What kinds of treatments, procedures, or tests will you have to undergo? Are they painful?
- What are the possible side effects? Are they any worse than the possible side effects from standard treatment? Are there any long-term side effects? Who will monitor you for these side effects?
- Is participating in the trial going to affect your daily life? If so, how?
- Will you have to pay for treatment? Will any of the treatment be free? Who will help you answer insurance coverage questions?
- Will participating in this trial prevent you from receiving other therapies now or in the future?
- What is the follow-up care plan for the trial?
- Whom can you call if you have problems during the trial?

More Information About Clinical Trials

To learn more about clinical trials in general or about specific trials currently available for people with lung cancer, call or contact one or more of the following organizations, or check with some of the on-line clinical trial locators.

National Cancer Institute (NCI)
Cancer Information Service
800-422-6237
www.cancer.gov/clinicaltrials

Food and Drug Administration (FDA)
Office of Special Health Issues
301-827-4460
www.fda.gov/oashi/cancer/cancer.html

SUMMARY

All new lung cancer treatments are made available because people have participated in clinical trials to prove the effectiveness and safety of those new treatments. Clinical trials offer another treatment option for people with lung cancer. There are potential advantages and disadvantages to participating in a clinical trial.

To determine if a clinical trial is right for you, talk with your health care provider. Gather the information you need to make a knowledgeable choice. Ultimately, each person must decide what the best treatment option is for his or her goals.