ECRI
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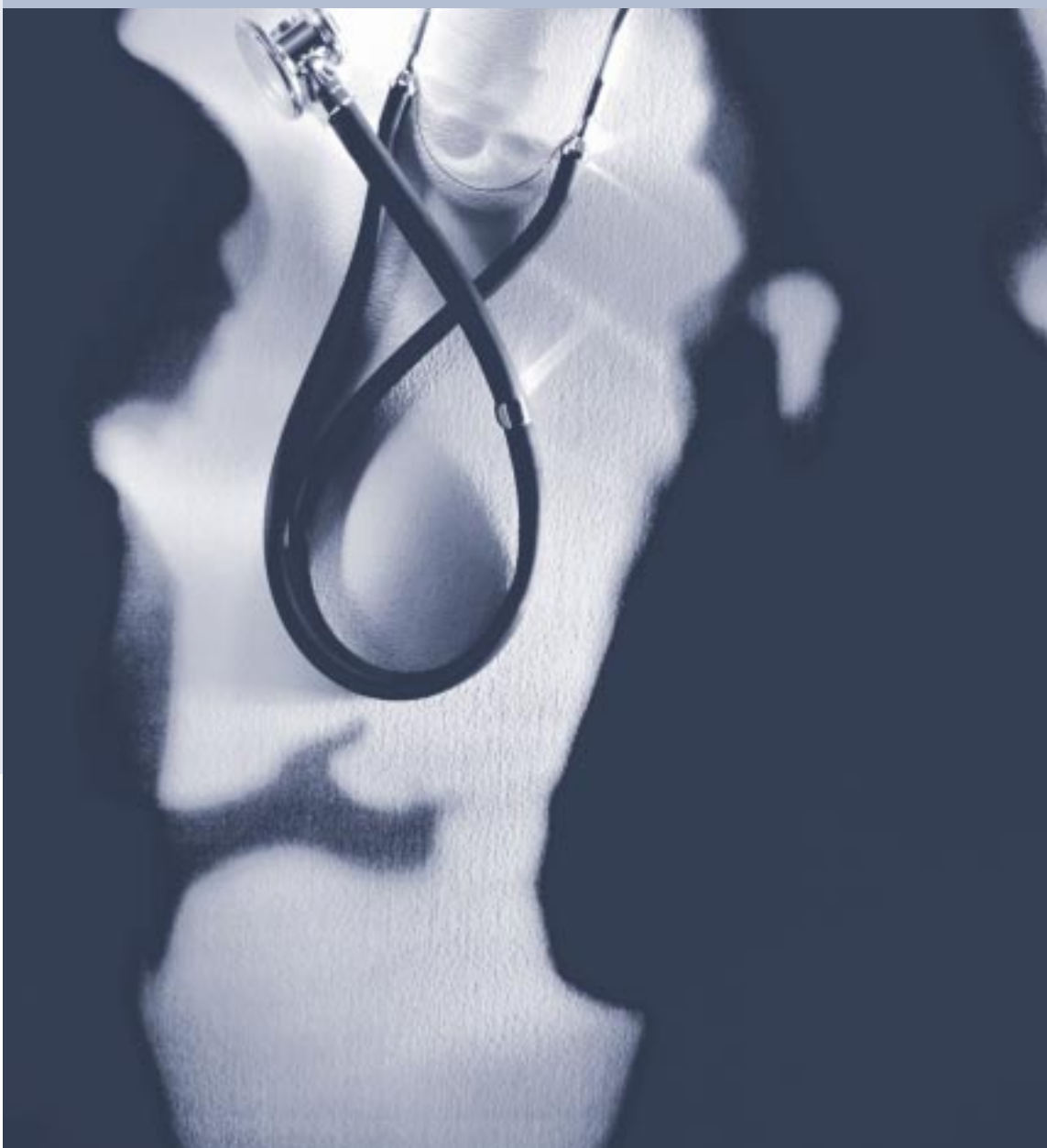
Should I Enter a Clinical Trial?

A Patient Reference Guide for Adults with a Serious or Life-Threatening Illness

A Report by ECRI Commissioned by AAHP



American Association of
HEALTH PLANS®

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ECRI acknowledges AAHP's initiative in the development of this guide. AAHP recognized the need for a resource that is objective, independent and useful for patients, health care professionals, and health plan purchasers. Their involvement has allowed us to create this guide and has assured it will be widely available for all of these audiences.

ECRI is solely responsible for the contents of this Patient Reference Guide. This Patient Reference Guide was funded by an unrestricted educational grant from Pfizer, Inc. to the American Association of Health Plans. Neither AAHP nor Pfizer, Inc. was involved in the research, writing, or conclusions ECRI reached. AAHP provided information to ECRI about health plan participation in clinical research, sponsorship of clinical trials, and state mandates on coverage of clinical trials.

Policy Statement

ECRI is solely responsible for the content of this Patient Reference Guide. The information in this Guide—including the conclusions—should be interpreted judiciously. This information is provided with the understanding that ECRI is not rendering any medical or legal advice or decisions on healthcare coverage or the provision of care to individual patients. This Patient Reference Guide includes a summary of ECRI's technical report that evaluated the available research evidence about (1) why patients enter clinical trials and (2) how well patients who receive medical care in a clinical trial do compared to patients treated for the same health condition outside a clinical trial. The information in this Guide is based on the available published scientific and medical literature as of June 2001. Scientific and medical knowledge evolves and may change over time as new research is published. You are urged to discuss the material in this Guide and the issues it raises with your medical doctors. This Guide does not include a complete description of the analytical methods ECRI uses to reach its conclusions on a particular topic. Those methods are fully described in ECRI's technical report.

How to Obtain Additional Copies of This Guide

This Guide is available online and in a limited print edition from the American Association of Health Plans (AAHP). You can download it for free from the "patient information" area at ECRI's Web site, http://www.ecri.org, and from AAHP's Web site at http://www.aahp.org. If you want a hard copy and cannot access the Guide online, please contact AAHP or your health plan to find out whether it has a print copy available.

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About ECRI and Its Healthcare Technology Assessment Process

ECRI (formerly known as the Emergency Care Research Institute) is a 35-year-old independent, nonprofit health services research organization. It is 1 of 12 centers in North America designated by the U.S. Agency for Healthcare Research and Quality as an Evidence-based Practice Center. As such, ECRI research staff evaluate the published medical literature and other information sources to assess how well drugs, devices, biologics, and procedures (generally termed healthcare technology) work. This is called healthcare technology assessment. As a 501(c)(3) nonprofit organization, ECRI accepts foundation grants and other charitable contributions to continue its research and dissemination of information to the public.

ECRI is also a Collaborating Center of the World Health Organization in Healthcare Technology Assessment. The Commonwealth of Pennsylvania recognizes ECRI as a Center of Excellence for Healthcare Technology Assessment under its Ben Franklin Partnership program.

ECRI is widely recognized by the healthcare community as the world's leading independent organization committed to analyzing the safety, efficacy, and cost-effectiveness of healthcare. ECRI provides information services and technical assistance to thousands of hospitals, healthcare organizations, professional medical societies, state and federal government agencies, ministries of health, and accrediting agencies worldwide. ECRI disseminates the results of its healthcare technology research and assessment through its more than 30 databases and publications. ECRI's interdisciplinary staff of 240 in the United States and abroad includes basic medical scientists, biomedical and clinical engineers, nurses, physicians, physicists, computer scientists, molecular biologists, healthcare policy analysts, medical editors, and technical writers.

To maintain independence and objectivity, ECRI and its staff adhere to strict conflict-of-interest policies that keep them at arm's length from medical device and pharmaceutical manufacturers. No gifts, grants, or contracts are accepted directly from these industries. Employees may not own stock in these companies or in individual health plans. ECRI's funding comes from the sale of its publications and databases and from grants and contracts from foundations, government agencies, and organizations. ECRI publications carry no advertising. Consumer versions of ECRI's work are distributed free to patients and their families through ECRI's Web site, http://www.ecri.org.

To develop this Guide, ECRI established a volunteer expert Advisory Committee to provide guidance and review. ECRI also established an External Review Committee. The Advisory Committee members and the External Review Committee members who gave ECRI permission to publicly acknowledge them are listed separately in this Guide; some members wished to remain anonymous. Advisory Committee members came from leading national healthcare consumer and patient advocacy groups, academic organizations in the public health and health services research fields, the medical profession, industry, and government agencies providing public health education information. We are indebted to them for their advice in producing this Guide.

This Guide differs from ECRI's previous technology assessment work in that we did not evaluate one specific medical technology. Rather, we assessed studies on patient outcomes of care within and outside clinical trials. We also analyzed studies on the reasons that patients have given for deciding whether to enter a clinical trial. In the Guide, we summarize the results of those assessments in two sections: *8. Do patients treated in clinical trials have better outcomes than similar patients treated outside clinical trials?* (p. 33) and *13. What reasons do patients give for participating and not participating in clinical trials?* (p. 53) . The ECRI research analyst leading the work on this assessment is a cognitive psychologist whose own primary research focused on how patients make decisions in healthcare. ECRI also consulted studies and other information about the many issues that a patient with a serious illness faces when deciding whether to enter a clinical trial.

About the American Association of Health Plans

The American Association of Heath Plans (AAHP) is the leading organization of health plans in the United States. It represents more than 1,000 plans that provide coverage and healthcare for 160 million Americans. Member plans include health maintenance organizations, preferred provider organizations, other network plans, and utilization review organizations. AAHP is the only association that speaks for the entire community of health plans. AAHP's mission is to create an environment in which its members can thrive by doing what they do best: promoting innovative, evidence-based, cost-effective coverage and care. It also initiates and supports research, compiles and distributes information about what's working and where, and, on a daily basis, presents managed care's case to policymakers, the media, and the public.

AAHP is a membership organization—an active alliance of individual health plans working together for the greater good. Its members guide AAHP policy, serve on key committees and task forces, and shape its campaigns and state-of-the-art education programs. AAHP, in turn, offers a multidimensional range of services to its members, from effective advocacy in Washington, D.C., to assistance with state and local issues, from strategic communications to state-of-the art education programs; and from legal expertise to public policy research. It also promotes continual quality improvement and breakthrough initiatives to systematically enhance the nation's health through preventive care and disease management.

In 2001, AAHP published *Health Plan Guide to Clinical Trials* to help member plans sort through the complexities of enrolling patients in clinical trials. The guide provided health plans with a checklist of important issues and information to consider as they assess whether to participate in a specific clinical trial. This Patient Reference Guide is a complementary effort to increase member access to well-designed, high-quality clinical trials that benefit patients, and it is at the core of AAHP's interest in and support of that effort.

AAHP received an unrestricted educational grant from Pfizer, Inc. and allocated it to support ECRI's research and writing of this Patient Reference Guide. Neither AAHP nor Pfizer, Inc. was involved in the research, writing, or conclusions ECRI reached. AAHP provided information to ECRI about health plan participation in clinical research and sponsorship of clinical trials and a summary of state mandates on coverage of clinical trials.

Advisory and External Review Committee Members

The volunteer Advisory Committee comprised leaders from national healthcare consumer and patient advocacy groups, academic organizations in the public health and health services research fields, the medical profession, industry, and government agencies providing public health education information. These members provided ECRI with valuable consultation, reviews, and advice about this Guide. We gratefully acknowledge their contribution.

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The volunteer External Review Committee comprised 10 members. Among them were patients and loved ones who had made a personal decision about whether to enter a clinical trial, clinical researchers, an institutional review board member, a health services researcher, patient advocates, and representatives from the National Cancer Institute and the U.S. Food and Drug Administration. Each person critically reviewed one or more drafts of this Guide to provide valuable advice. ECRI gratefully acknowledges those who consented to be listed here; some reviewers wished to remain anonymous.

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Introduction

The knowledge gained through clinical research-trials that test the use of new drugs and medical devices in humans—is at the core of advances in patient care. The results of clinical trials bring us new diagnostic tests and new treatments that improve our health and prolong our lives. The amount of research being done has increased dramatically in the past 10 years as drug and medical device companies in the private sector and National Institutes of Health researchers and others strive to develop and bring more new diagnostic tests and treatments to the public than ever before. In 2001, more than $42 billion dollars was spent on clinical research—about 52% by the private sector and 48% by federal agencies. Thus, more patients than ever before are needed to participate in the trials that evaluate new diagnostic tests and treatments.

Recently, some clinical research and some institutions conducting research have come under public fire in the popular press and on television. Several renowned institutions and medical centers have been in the news because of some serious adverse events and, rarely, unexpected deaths during trials. Although these situations represent a very small fraction of the current research, they have shaken public trust. Patient safety and adequate explanations to patients about the benefits and risks of trials have been key issues.

At the heart of clinical research are individuals who, by volunteering to participate in a trial, benefit future patient care by helping researchers learn what works in medicine. Most patients with a serious illness who enter a clinical trial naturally hope that the new experimental treatment will improve their immediate condition. Understandably, the desire to benefit patient care in the future is usually secondary. Thus, a necessary tension exists between the ultimate aim of clinical research (future benefit) and the hope of individual patients (present benefit). Although researchers cannot promise patients an immediate personal health benefit from participating in a trial, patients have described to us other kinds of immediate benefits from trial participation.

As one patient with cancer in a clinical trial summed it up, "Tremendous support and benefit comes from being part of a group of patients who are just like you. You feel tremendous medical team support because the researchers are worried about your specific disease and are devoted to treating your disease. They know more than anyone else about it. Then, you receive attentive care and intensive follow-up by a team of experts—not just one doctor—who discuss your care and what to do." Another patient noted that, even though she might not experience an immediate health benefit from the trial, she felt great satisfaction that her children or grandchildren might benefit from the knowledge gained from the trial.

Among the important issues patients must consider when thinking about entering a trial is understanding what will happen to them during and after the trial and how it may affect their quality of life. Other issues include whether patients are given sufficient information about the benefits and risks of a trial and other treatment alternatives during the consent process, who bears responsibility for protecting patients in clinical trials, who bears the costs of trials, and who is responsible for treating complications from treatment in a trial. What potential conflicts of interest exist among trial sponsors, researchers, and institutions carrying out the trial, and how do they affect patients? What are patients' rights for withdrawing from a clinical trial? What are researchers' ethical obligations to patients in trials?

This Guide takes a patient perspective to address these and other issues, but it takes no position on whether one should enter a trial—that is a uniquely personal decision. Our hope is that this Guide helps any adult with a serious illness who is thinking about enrolling in a trial to make a decision that he or she feels as confident as possible about. We dedicate this Guide to the patients and their loved ones who are facing this important decision and also to those who benefit us all by participating in a trial.

Chapter 1— Who Should Use This Guide?

This Guide is for adults with a serious or life-threatening illness who may seek treatment in a clinical trial. It is also for their loved ones and the healthcare professionals who support them during their decision-making process and treatment.

Thinking about taking part in a clinical trial may be one of the most difficult decisions you've ever faced. Fear of the unknown, uncertainty, and anxiety about the loss of control over what's happening are just some of the feelings that may be experienced by someone in this situation. It is hard to think of all the right questions to ask so that you feel as confident as possible about the decision you make. The path you take to make this decision is uniquely yours, based on personal preferences, your comfort level with the possible benefits and risks of a treatment that is under investigation versus standard treatment options, and, often, a "gut" feeling about what is right for you.

How can this Guide help me?

This Guide offers carefully researched, objective information about the world of clinical research today—the study of new (also called experimental or investigational) treatments in humans. The Guide explains how and why clinical research is conducted. It answers questions about many of the issues that affect patient participation. It discusses the roles and responsibilities of federal agencies such as the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), and Office for Human Research Protections in protecting patients. Most, but not all, clinical research has some oversight by a federal agency. FDA oversees clinical trials on new drugs and devices that companies have developed and want to bring to market. Companies must get FDA approval before they can market new products. NIH oversees much of the federally funded clinical research—which may involve development of new drugs and devices as well as new procedures that use already approved drugs and devices. Clinical research that is privately funded and focuses on already approved drugs and/or medical devices that pose no significant new risks to patients is not overseen by any federal agency, but is overseen by the institution where the research is being conducted.

How should I use this Guide?

The Guide is divided into sections that address common questions, as shown in the Table of Contents. This format will help you find the information that is most important to you now. Not all sections may interest you at once because of where you are in the decision-making process and what you already know or need answers for. Patient checklists appear at the end of many sections. You can use these checklists to help assess whether you have received all the information and asked all the questions you wanted. The checklists can also be used as a way to discuss information with your doctors, researchers, and your family and friends. A separate brief summary has been published for those who don't wish to read the full Guide. Since many issues in this Guide are interrelated, we cross-reference concepts in each section that are discussed more fully in other sections.

A list of Additional resources provides information on how to find out about clinical trials that are seeking patients to enroll. A Glossary defines the terms a patient might hear while talking with researchers about trials. We have carefully researched these terms to give you definitions that are most commonly used. The Appendixes at the end include some of the documents we refer to on ethical guidelines for the protection of human research participants, state laws about health insurer and Medicare coverage of trials, and information about some new federal patient protection initiatives.

We encourage you to share the Guide with loved ones and your doctors as you explore options about entering a clinical trial. The Guide can serve as a springboard for discussion of the issues that are most important to you.

We also urge you to take a trusted family member, friend, or patient advocate with you to your physician consultations about entering a clinical trial. (Many trials and medical centers have patient advocates—people who are trained to look out for patients' interests in trials.) Hearing information about your medical situation, a clinical trial, and treatment options can be overwhelming. It's very difficult to recall later everything that you were told. You or a loved one can take notes or tape-record physician consultations so that you can review information later when you are thinking about what you want to do. Of course, you should always tell your doctor in advance if you want to tape your discussions to help you recall the information you are given.

Does this Guide leave out anything I need to know?

This Guide covers what our research and discussions with patients revealed as the most critical issues that adults should consider when deciding about entering a clinical trial. One Guide cannot address every issue. This Guide does not address issues concerning trials for preventing disease, trials involving healthy volunteers, trials for children, or trials for patients who are unconscious or not mentally competent to make a decision about entering a trial. This Guide touches on, but does not address in great detail, special issues related to minority participation, participant age, or cultural issues in clinical trials. However, you will find references to other sources addressing these issues in *Additional resources* on p . 69.

Chapter 2— How Do We Know What Works in Medicine?

The surest way to learn what works in medicine is through well-designed and carefully conducted clinical research—studying the use of drugs and medical devices (healthcare technology) in humans—at a university, medical center or hospital, private research institution, or doctor's office. Ideally, a clinical trial is carried out in a controlled, methodical way so that researchers can carefully observe the effects of treatment on patients. Ironically, the effects of many standard medical practices have never been carefully studied in trials. Practicing medicine based on what the clinical research shows about how well a treatment works is a relatively recent concept called "evidence-based medicine."

Not until the mid-20th century did the idea of doing carefully designed human trials on healthcare technology take hold as a framework for determining safety and efficacy. The first randomized controlled clinical trials in modern medicine began in the late 1940s. Before that, we gained knowledge about what worked best by individual doctors' observations of their patients in day-to-day medical practice. However, the conclusions drawn from this "anecdotal" evidence are often misleading, simply mistaken, or incomplete.

Clinical trials that changed medical practice show why it is important to study a sufficiently large group of patients with the same medical condition and similar patient characteristics in a step-by-step process. These examples also illustrate why proper scientific and statistical methods are needed to design a trial, compare different treatments, and analyze and interpret the results. (See *What is a clinical trial?*, p. 7.)

The first reported randomized clinical trial: Effective treatment for TB

In the early 1940s, animal studies and encouraging results from trials on a few small series of patients had suggested that the new antibiotic streptomycin might be effective for treating an often-fatal condition, pulmonary tuberculosis (TB). The drug, made by a U.S. manufacturer, was not readily available in Great Britain, and doctors did not welcome the responsibility of deciding which TB patients should and should not get a promising *but not yet proven* new drug. To try to find out how well the new drug really worked and on whom, two British doctors designed what is thought to be one of the first truly randomized controlled trials. Randomization, a new concept, determined who would get the experimental drug—four injections a day for four months. The trial tested the new antibiotic against the standard care of the day in Great Britain—bed rest. No placebo was given because doctors felt it would be too painful (several intra-muscular injections daily) for patients not actually receiving the experimental drug. Ninety-seven patients with severe TB were randomly assigned to receive either the drug injections or hospital bed rest. Neither doctors nor patients knew beforehand which treatment a particular patient was going to receive. The patients were evaluated for six months. The results were published in 1948 in the *British Medical Journal*. They showed that 51% of the 55 patients in the treatment group had significant improvement after six months compared to only 8% of 52 patients in the bed rest (control) group. Streptomycin went on to become a proven standard of care in Great Britain, the United States, and elsewhere.

Study: Medical Research Council Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment for pulmonary tuberculosis. British Medical Journal 1948; 2: 769-782.

How do clinical researchers decide what to study to get the answers we need?

Today, clinical trials on testing new drugs and devices in humans cannot begin until researchers test the drug or device first in the laboratory and/or in animals (called preclinical studies). In a well-designed trial, researchers start with an idea that they are going to test (a hypothesis). An example of a hypothesis might be to test a certain heart medication to see if giving it during a heart attack significantly reduces the risk of sudden death after a heart attack. Researchers decide which outcomes (for example, patient survival, improvement in angina pain) the experimental treatment should affect and record observations about those outcomes after treatment. In this way, researchers test whether the treatment has a positive effect.

If results of preclinical studies show promise, a new (experimental or investigational) treatment is tested in humans during a sequence of trials called phase I through phase IV trials. (See *What is a clinical trial?*, p. 7.) Each phase must produce results that outweigh the risks of the experimental treatment before the treatment being studied can progress to the next phase of testing. Each phase typically involves a greater number of patients. Phase I may have as few as 10 or 20 patients. By phase III, several hundred or more patients may be enrolled. In the United States, a majority of trials are overseen by a federal agency (such as the National Institutes of Health or the U.S. Food and Drug Administration), and the clinical trial plans for each phase are submitted to the appropriate agency for review. To proceed, virtually all trials—regardless of federal agency oversight—must have approval from the institutional review board (IRB) for the medical facility where the study will occur. An IRB is a diverse group of professionals and laypeople who are responsible for protecting patient safety and rights at any facility conducting a trial. They review the plans (trial protocol) for every trial in their facility and must approve the protocol before the trial can begin. (See *What is an institutional review board?*, p. 49.) Please see the box article for examples of recent landmark trials that led to important gains in patient care.

Two recent landmark trials

Virtually all patients with a serious illness who enter a clinical trial hope it will improve their own health. Many patients also hope it will also improve medical knowledge and treatment for others in the future. Tens of thousands of clinical trials have been conducted during the past 50 to 60 years. Usually, it takes results from more than one trial to clearly show the benefits and risks of a treatment. Doctors don't usually change the way they practice medicine based on results from just one trial. Yet some individual trials have made a big difference in patient care. Whether it takes one trial or several trials to show how well a treatment works, medical knowledge is gained only by the participation of individual patients. Every clinical trial participant makes an important contribution to the whole.

Delaying disability and death from complications of diabetes

In 1993, researchers who conducted a large trial on controlling the complications of diabetes published landmark results that doctors worldwide have been able to use to improve the lives of patients with diabetes who need daily insulin. The Diabetes Control and Complications Trial Research Group enrolled thousands of people with Type 1 diabetes. The trial tested whether keeping blood sugar levels as close to normal as possible would prevent the life-threatening long-term complications of the disease. These complications include heart disease, nerve disease, blindness, kidney disease, and premature death. The researchers found that patients who took insulin several times a day based on frequent checks of their blood sugar levels slowed and sometimes halted the development of these terrible complications. This trial has given doctors the information they need to prolong and save lives and to help patients slow the life-threatening consequences of diabetes Type 1.

Study: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. New England Journal of Medicine. 1993 Sep 30;329(14):977-86.

Accumulating the evidence: Tamoxifen for preventing breast cancer in healthy women at high risk

Progress in medicine is often made in small steps over many years rather than as a result of one clinical trial. The use of tamoxifen to prevent breast cancer in healthy women who are at high risk of breast cancer is one such case. The drug tamoxifen was proven effective more than 20 years ago for preventing the recurrence of breast cancer in many women who have completed treatment and are in remission. In the 1990s, researchers began investigating tamoxifen as a potential treatment for preventing the first-time occurrence of breast cancer in healthy women at high risk for the disease. Radical and disfiguring surgeries such as mastectomy and removal of ovaries were available as preventive options for women at high risk. But tamoxifen offered the promise of a noninvasive preventive approach.

By 1998, three randomized controlled trials reported results on the effectiveness of tamoxifen for preventing the first-time occurrence of breast cancer. In these trials, women with high risk factors received tamoxifen or placebo in tablet form for five to six years (at the time of publication of results). The results of these trials begin to offer some insight into the usefulness of tamoxifen in this situation, but we are far from knowing the overall effects of the drug on survival and possible unwanted side effects, such as other types of cancer. Longer-term data are needed. ECRI did an analysis and found that for now, a certain group of healthy women will benefit most from tamoxifen to prevent breast cancer—healthy women aged 35 to 49 years old who are known to be at high risk for breast cancer. However, because we don't yet have long-term evidence, preventive therapy should be limited to five years' duration. Two of these three trials are continuing to collect longer-term data. It is hoped that these data will help find out more about the benefits and risks of long-term tamoxifen use in women of different ages and with different medical characteristics.

Fisher B, Costantino J, Wickerham D, Redmond C, Kavanah M, Cronin W, Vogel V, Robidoux A, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. Journal of the National Cancer Institute 1998 Sep 16; 90(18):1371-88.

Powles T, Eeles R, Ashley S, Easton D, Chang J, Dowsett M, Tidy A, Viggers J, Davey J. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomized chemoprevention trial. Lancet 1998 Jul 11;352(9122):98-101.

Veronesi U, Maisonneuve P, Costa A, Sacchini V, Maltoni C, Robertson C, Rotmensz N, Boyle P. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomized trial among hysterectomised women. Italian Tamoxifen Prevention Study. Lancet 1998 Jul 11; 352(9122):93-7.

Is a new, experimental treatment necessarily better than standard treatment?

No. In our culture, "new" often implies "better." In clinical research, however, one should avoid making this assumption. The very reason for conducting a trial of a new or experimental treatment is that we do not know how effective it is. We do not know whether it is equal to, better than, or more harmful than the standard treatment, even if it shows promise. Depending on the phase of the trial, we don't know all or even most of the possible side effects of the new treatment. To learn about why it's so important to test a treatment well in trials before it is widely used, see the box article at the end of this section, "Trials finally prove that 'new' wasn't 'improved'."

Trials finally prove that "new" wasn't "improved"

In our culture, the word "new" implies "better" or "improved." Yet, in medicine, this is not necessarily the case. Sometimes new turns out to be worse. That was the case with one of the highest-profile treatments to diffuse widely outside the research setting in the 1990s before there was good evidence about how well the treatment really worked. The treatment was high-dose chemotherapy (HDC) with autologous bone marrow transplantation (ABMT) for several kinds of solid-tumor cancers, such as breast, ovarian, and lung cancer.

The concept of the treatment arose from animal research in the 1960s. Researchers thought that giving higher doses of chemotherapy (up to 30 times higher than standard) might eradicate the cancer completely. The treatment was a "last hope" offered to many patients with advanced breast, ovarian, or lung cancer. HDC is toxic to the bone marrow, which produces the blood cells that fight infection. HDC can also permanently damage the patient's ability to make blood cells, so it is a high-risk treatment. It makes the patient very vulnerable to life-threatening infections that ordinarily do not cause problems in healthy people. To restore a patient's ability to make blood cells, ABMT and stem cell transplantation (SCT) were developed. The patient's bone marrow or stem cells were harvested before HDC and given back after HDC to restore the immune system.

Data from early-phase studies led some researchers to believe that the treatment was better than standard chemotherapy. They believed it was worth the increased risk of serious complications or death. However, well-designed studies that compared this new treatment to standard chemotherapy had not been done. The enthusiasm of many oncologists for the procedure—even at leading research institutions—made it very difficult to recruit women into the randomized controlled trials (RCTs). Many women were led to believe that the new procedure was better, so they wanted it and did not want to risk entering a trial that might assign them to the standard chemotherapy group instead of the HDC group. Women were led to believe that this experimental treatment was their only hope for a cure before the evidence was in. Many women sued their health insurers, which were reluctant to pay for a high-risk, unproven treatment, to obtain the treatment and succeeded.

At ECRI, in the absence of data from RCTs, analysts used statistical methods in 1994 and 1995 to analyze all the available published data from uncontrolled trials on HDC with ABMT/SCT. We then compared our analysis of survival and mortality rates to the survival and mortality of similar patients who had been in trials of standard chemotherapy. We found that HDC with ABMT/SCT not only produced worse outcomes than standard chemotherapy, but also had greater treatment risks and a significantly higher mortality rate than the most effective regimens of standard chemotherapy.

Patient demand and physician advocacy for the procedure grew during the mid-1990s. It was increasingly difficult to complete the RCTs because the treatment was readily available outside of clinical trials. (The treatment used already approved drugs, but in higher doses, so trials were not subject to FDA approval.) These trials took several years longer to complete than they should have because of patient recruitment problems. Finally, in 1999 and 2000, results of the RCTs comparing HDC to standard chemotherapy were published. Women who received standard chemotherapy did as well as those who received HDC with ABMT/SCT but had fewer complications and deaths. In the meantime, thousands of women had undergone the procedure outside of trials. Many suffered serious complications or died prematurely from the treatment itself, not from cancer.

The lesson here is that to protect patients and obtain timely information about a new treatment, the treatment should be studied in well-designed trials before being used widely in clinical practice. Patients and doctors can then consult the published results of trials and overall analysis of trials' results through databases and information provided by those who do healthcare technology assessment and by federal agencies such as the National Library of Medicine and the Agency for Healthcare Research and Quality. (See *Additional resources*, p. 69.)

Chapter 3— What is a Clinical Trial?

A clinical trial is the planned scientific study in humans of a drug, medical device, or procedure (generally called healthcare technology). A trial may be designed to study a completely new treatment or a new use of an existing treatment, or it may be designed to gain more information about the safety and efficacy of one treatment compared to others. From a patient perspective, it is important to understand that the main purpose of treatment in a clinical trial is different from the purpose of treatment outside a clinical trial. Ideally, the intent of a treatment in a clinical trial is to benefit society by advancing medical knowledge. The intent of treatment outside a clinical trial is to benefit the individual patient being treated. Patients have expressed different reasons for participating or not participating in clinical trials. ECRI formally assessed published studies about the reasons patients have given for enrolling or not enrolling in trials because knowing what other patients in a similar situation thought about it might help you clarify how you feel. We summarize the results of that assessment later in this Guide (see *What reasons do patients give for participating and not participating in clinical trials?*, p. 53).

Today, all clinical trials require a patient's voluntary consent to participate (or, in the case of a child or mentally compromised person, the consent of someone legally authorized to speak for that patient). Of course, standard medical treatment also requires patient consent, but that consent is often much less explicit than the consent required to participate in a clinical trial. A detailed discussion of the consent process is in the section *What is "informed" consent?* on p. 39. For any trial participant, it's important to remember that a patient can withdraw from a trial at any time. However, it is also important to communicate with the research team about leaving the trial so that they can record important data and account for what happened to each and every patient who entered the trial.

Several federal agencies play an important role in the conduct of most clinical trials. They make and enforce regulations for the protection of patients. These regulations are key to patient safety in trials and to gaining knowledge to improve medical practice. The U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), and Office for Human Research Protections (OHRP) are all parts of the U.S. Department of Health and Human Services. FDA requires companies researching new drugs and medical devices that have never been commercially marketed in the United States to provide data on human safety and efficacy before they are allowed to market their drugs or devices. Companies that want to market (and advertise) an already approved drug or device for a completely new use must also obtain FDA approval. The data that FDA requires must come from clinical trials conducted by the companies. Thus, FDA regulations and guidelines on conducting trials apply to a little more than half of the clinical research being done today—because that research involves new medical drugs and devices under development. New uses of already approved drugs or devices do not require FDA approval if they don't pose significant new risks to patients and if the company does not intend to advertise the new use or change the labeling of how the drug or device is used, so FDA does not oversee those trials. NIH oversees and funds close to half of clinical research. NIH research is done to develop new treatments that use new or existing drugs or devices. Some examples of NIH-funded research include trials for lung volume reduction surgery, different types of radiation treatment, high-dose chemotherapy, and gene therapy.

OHRP was established in the year 2000 to monitor federally funded clinical research to help protect patients in trials at more than 4,000 universities, hospitals, and other research institutions in the United States and abroad. OHRP also works with NIH and FDA to protect patients by sponsoring training of investigators and members of institutional review boards (IRBs), providing guidance and procedures for the patient consent process, and monitoring researchers' and sponsors' conduct in trials. (*Appendix C* on p. 94 provides more information about the role of federal agencies in clinical research.)

Why is it important to understand the different kinds of trials?

Patient safety, the protection of patients' rights in clinical trials, and the impact of trial participation on a patient's quality of life are the main reasons it's worthwhile to take the time to understand something about the different kinds of clinical trials. The section *What is randomization in a controlled clinical trial?* on p. 19 provides more information about trial design and what that means for a patient. While a trial is designed to gather scientific information about a treatment, and while there may be unknown risks, the safety of individual patients is the highest concern. Different kinds of trials offer different potential benefits and risks. Understanding the reasons for the trial design may help you understand more about the potential benefits and risks, your rights as a potential participant, and, if there is assignment to different treatment groups, why this is being done the way it is.

Different kinds of trials also require different levels of participation by patients. For example, a trial that is done on an outpatient basis may have a very different impact on a patient's lifestyle than a trial that requires hospitalization. Some trials may require follow-up tests that are time-consuming and/or invasive, such as a biopsy, and others may just require an office visit and quick exam. A person's desire and ability to participate may be affected by such factors.

Different kinds of trials may also have varying effects on patient quality of life in terms of the changes required in the patient's daily life, the degree of risk the trial poses and the patient's comfort level with that risk, and the possible side effects, even if they are deemed "minor" or "expected" by the research team.

As one cancer patient explained her thinking about entering a trial, she said, "I might not be as willing to enter a drug trial designed to identify the highest tolerable dose in humans as I would to enter a trial designed to find the lowest effective dose of a drug that has already been shown to work at a higher dose. One could have very different impact than the other on my quality of life."

Are trials only for people with no other alternatives?

No. Although a person with a serious illness may have tried every available treatment and may view a clinical trial as the only option left, some patients may consider a clinical trial when they are thinking about the first treatment for their condition. They may especially consider it if they have a condition for which there is no clear answer about which treatment is best. An example is prostate cancer. There are many choices for men seeking treatment for cancer confined to the prostate—different types of surgery, radiation, and hormone therapy. But many specialists treating the disease agree that we don't yet know which treatment, if any, is better than another. We simply do not have the long-term evidence to tell us. So, a patient with prostate cancer may decide to go into a clinical trial that compares two treatments. By so doing, he can expect to receive excellent medical care for prostate cancer in the clinical trial and contribute to the advancement of knowledge about prostate cancer treatment.

Are the doctors and nurses who deliver care during the trial different from other doctors and nurses?

In some ways, yes. They are supposed to undergo special training on how to conduct clinical research. They should be interested in advancing medical knowledge for patients as a whole by running a well-designed clinical trial and collecting data for analysis. The main objective of a doctor who does not do research is to care for each individual patient using standard (accepted as efficacious) treatments to obtain the best result for that patient. For more information about the differences between the roles of practicing physicians and research physicians, see *What are the ethical issues in clinical research?* on p. 65.

Many professional staff are typically involved in the care given during a clinical trial. They include the principal investigator(s), often referred to as the "PI." The PI is usually a medical doctor whose credentials have been evaluated and approved by the IRB and trial sponsor. FDA and NIH also look at PI credentials when reviewing trial protocols. Nurses also have a key role in research. They usually have the most contact with trial participants during the trial. A research coordinator is typically a nurse. When it is time for the scheduled checkups in the clinical trial, the research coordinator will take information, obtain body fluid or tissue samples, or run tests as required and ask the patient different questions about how he or she is feeling. The nurse may also take part in giving treatment, depending on what the treatment is. Other medical professionals, including resident physicians and interns, may be involved in the research. They may examine and take information from patients as the trial progresses. The research doctor(s) often evaluates each patient at each visit and reviews information collected by other research team members.

How does a trial begin?

It depends on who is sponsoring and conducting the trial. Privately sponsored trials that do not require FDA oversight usually must first obtain approval from the IRB of the facility where the trial is taking place. NIH-funded trials begin after the agency approves a grant for the clinical trial and after the IRB where the trial is being conducted gives approval for the trial. Trials for new drugs and medical devices typically involve more steps because trial sponsors are seeking FDA marketing approval and must meet FDA requirements for safety and efficacy by providing certain kinds of data. These trials begin after data from animal or laboratory testing (preclinical studies) have been collected to identify the effects of the new drug (toxicity/safety) or new device. Drug effects include how the dose affects the response; how the body uses and eliminates the drug; whether the drug can cause cancer, and how the drug might affect reproduction. Device effects include how the device works in or on the body and whether it functions consistently and as predicted.

To start a clinical trial on a newly developed drug or device, the sponsor (company or institution) has to file an application with FDA. Clinical trials to obtain marketing approval are conducted in three successive phases. FDA reviews the initial application, which includes a trial protocol, and allows the trial to proceed if no major safety issues are identified. In each successive phase, the sponsor files the trial protocol with FDA and the trial proceeds automatically, unless the sponsor receives notice from FDA within a specified time frame to hold off because of a safety concern. In the case of a drug, the application is called an investigational new drug application. In the case of a device, it is called an investigational device exemption. A similar application is made for biologics (products derived from living organisms or tissue). After marketing approval, a phase IV trial (also called a post marketing trial) may be done to continue studying the drug or device effects in the general population. (See *What are the differences in the phases of trials?*, p. 13.)

How does a trial end?

Overall, a typical trial ends when the research physicians have recruited enough patients (the number is decided when the trial protocol is designed to ensure valid results) and conducted all the planned follow-up to collect data. For the individual patient, the trial ends when he/she has received all the treatment and follow-up prescribed in the protocol or reaches a designated end point. Patients enter a trial at different times, so the trial isn't over for the researchers until the last patient who entered is accounted for and has received all the appropriate follow-up.

Sometimes the entire trial can end early. Researchers can stop a trial, an IRB can stop a trial, or a federal agency that has oversight of the trial can stop it. Trials have been stopped early for several reasons:

- Very positive results early in the trial that warrant giving the experimental treatment to everyone in the trial.
- Too many serious side effects and complications.
- Noncompliance with federal regulations to protect patient safety.
- A low probability that there will be a difference between treatment and placebo group results, even if the trial were to enroll all the patients intended (this situation is considered to be futile for patients and researchers alike).

Sometimes a trial can end early for a particular patient for various reasons, including:

- A patient's decision to withdraw.
- The researchers' decision to withdraw the patient for safety or other reasons. Safety reasons include very serious side effects or complications. Other reasons include the patient's inability to complete the trial treatment due to other health problems that require treatment and compromise further participation in the trial.

Very positive results early in the trial

Trials are sometimes stopped when it becomes clear that one treatment works much better than the alternative(s) being used in the trial. Discovering this depends in part on how many patients are in the trial. The number of patients needed for a trial and the duration of time required to get reliable results from the trial are determined before the trial begins. These factors are estimated on the basis of results from earlier phase studies. Earlier phase studies, however, cannot entirely predict the actual effect of the new treatment in a larger patient population. Because results are being monitored all during the trial, it sometimes becomes clear to researchers that one therapy is much better before the end of the trial. If a trial you are in is stopped for this reason, you would be informed immediately. Typically, the treatment that was found to be better is offered to all patients in the trial.

Too many serious side effects and complications

While a trial is ongoing, researchers periodically assess how it is progressing. In particular, they closely monitor the occurrence of side effects and complications (called adverse events)—especially unexpected adverse events. An adverse event is any harm, whether major or minor, that occurs during the course of the trial that might be caused by the therapy. These can include even minor events that can happen to people regardless of whether they are in a trial, such as headaches, nausea, indigestion, rashes, and insomnia.

Most adverse events that occur during the course of a trial are not related to the experimental treatment. Nearly everyone, for example, gets headaches from time to time. However, by carefully keeping records on how often all side effects occur among the clinical trial population, researchers can determine if headaches occur more often in

patients given the experimental treatment than would be expected. If so, headaches may be listed as a side effect related to the treatment. Sometimes adverse events that occur during a trial can be more serious and result in major discomfort, serious illness, hospitalization, or, rarely, death. By carefully recording the occurrence of all adverse events, researchers can tell whether any serious adverse effects are related to the experimental therapy. If they are, and if they put the patients' comfort or health at too great a risk, researchers may stop the trial.

The protection of the patients in the trial is the most important concern, even more important than finding out if the experimental treatment is effective. For this reason, if you are in a trial, it is important that you report everything that happens to you and that you answer honestly any questions that are asked about your health and your reaction to the therapy you've been given. Halting trials because of serious adverse events occurs rarely.

Noncompliance with regulations to protect patient safety

Trials may also be halted if FDA, NIH (or another federal agency with oversight), or an IRB finds a problem with the way the trial is being conducted. In a few cases during the past few years, entire clinical research programs have been temporarily shut down at prestigious academic institutions because of problems in one or more trials. Among the research centers that have been in the news in the past three to four years because they were shut down in whole or in part or had problems with clinical trials are the Veterans Affairs Medical Center in West Los Angeles, California; the University of Pennsylvania gene therapy program, Philadelphia; Duke University in Chapel Hill, North Carolina; the University of Illinois in Chicago; the University of Colorado; Johns Hopkins University in Baltimore, Maryland; and Fred Hutchinson Cancer Center in Seattle, Washington. Unexpected deaths occurred in a few of these cases. The tragic events were traced back to problems with adequate consent processes and noncompliance with trial protocols, among other issues. At most of these places, research resumed after the problems were investigated and resolved to the satisfaction of regulatory agencies and IRBs. However, parts of some research programs remain closed for the foreseeable future. Problems may be identified during an FDA or NIH site inspection, by an FDA Data Safety Monitoring Board, by an IRB, by patients, or because of unexpected adverse events. (A Data Safety Monitoring Board comprises community representatives and clinical research experts. The board may recommend revisions to or discontinuation of a clinical trial if the trial objectives remain unmet or safety concerns arise. The board may be set up by a clinical trial sponsor as an independent group to evaluate trial progress, safety data, and significant outcomes according to FDA regulations, or it may exist independently of a trial sponsor and the researchers.)

Researchers are also expected to adhere to explicit principles and ethical considerations as outlined in documents such as the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report (see *Appendix B*, p. 91). Also see *What are the ethical issues in clinical research?*, p. 65.

What would happen if my trial stops temporarily or ends early?

Patients in the trial are to be immediately notified if the trial is stopped early for any reason. Clinical researchers are also doctors who understand that continuity of patient care is essential. Researchers are morally and ethically bound to protect the patients in the trial. Someone from the research team will advise you what to do. The researcher will consult with any other doctor to whom your care is referred—be it your own doctor or someone else who you agree to see. If a trial ends early because of positive results, all patients in the trial may be offered the experimental treatment, even if it is not yet FDA approved, under special provisions, explained below.

Can I continue receiving a new treatment that is not yet FDA approved after the trial ends?

Perhaps. There is a way in which manufacturers and FDA make successful treatments available to trial participants after the trial while a drug or device is pending FDA approval. It is generally called "continued access." Continued access allows patients who are likely to benefit from an investigational new treatment to continue receiving it after the trial while the company is awaiting marketing approval. The researchers continue to monitor patients and collect data during this time, which in drug trials is sometimes referred to as an "open label" phase. The open label phase has no control groups; everyone in the original trial who might benefit receives the new treatment. This also ensures that patients who responded to the treatment can continue to receive it until it becomes commercially available (which could take up to several months after data have been submitted to FDA).

Chapter 4— What are the Differences in the Phases of Trials?

Generally, there are four phases of clinical trials. The first phase represents the earliest stage of testing in humans. Moving on to the next phase of research depends on the previous phase having sufficient efficacy (if it was evaluating efficacy) and no serious safety risks. For U.S. Food and Drug Administration (FDA) marketing approval of new drugs and devices, the sponsor (which is often a company) must complete and collect data from phase I through phase III trials and submit them to FDA for review. The fourth phase involves continued study of the medical treatment's use in patients after it is on the market and is often not required by FDA. Details of each phase are provided below. The potential risks and benefits differ in each phase and are explained to patients during the consent process before enrolling in a trial. (See *What is "informed consent?*, p. 39.) The institutional review board (IRB) of the facility conducting the trial is supposed to approve the trial, no matter what the phase. For patients, knowing the phase is important because there usually are more potential risks in earlier phase trials than in later-phase trials.

Phase I

Phase I is usually the first time a new drug or device is used in humans. The trial participants may be healthy volunteers. In circumstances in which the risks are justified, the new treatment may be given to patients with the disease who enroll in the trial. Often, no other treatment has worked for these patients, so a phase I trial is an opportunity to try something else. For example, with anticancer drugs, phase I trials are almost always conducted with patients whose cancer has not responded to the available standard treatments. Phase I trials of high-risk devices, such as artificial hearts, pacemakers, or other types of implantable devices, are usually conducted on seriously ill patients whose condition has not responded to other treatments.

Phase I studies are not always limited to "first-time-in-human" trials, though. "Secondary" phase I trials often evaluate new dosing schedules or combination therapies using drugs, radiation, or devices already on the market. These phase I trials may also assess drug toxicity or device function in different patient populations (for example, children) that were not studied before.

In phase I drug trials, the drug doses typically start very low and increase over time as more patients enter the trial and are treated. The results from early patients affect the dosing of subsequent patients as researchers try to determine the best dose for humans. The low starting dose is based on preclinical test results about toxicity. A standard measure of toxicity in preclinical testing is the percentage of animals (rodents) that die from the drug. The starting dose in humans is one-tenth the dose at which rodents died, although the dose may be even lower if other animals tested (such as dogs) were more sensitive to the drug. In cancer trials, patients with different types of cancer may be in the same phase I trial because researchers are trying to learn whether the drug has any effect on these cancers. In the case of devices, the device settings are put at minimum levels to begin with and adjusted according to the responses observed.

Phase I trials have no control groups. (A control group consists of patients in the trial who receive a treatment other than the experimental treatment or, depending on the type of trial, a placebo. Then comparisons are made between groups.) A phase I trial is therefore an "uncontrolled" trial. The number of patients in a phase I trial is usually small—from 10 to 80. The studies are usually of brief duration—several weeks to a few months.

Phase I device trials may involve a "crossover" or "on/off" periods in which the device is actively used in the patient for a period and then not used for a prescribed period to evaluate its effects. However, this method may not be used for all devices, such as heart pumps or valves, which are used for life-threatening conditions.

Will I benefit from a phase I trial?

A key issue for a patient to understand is that *a phase I trial can offer no assurance of a benefit of treatment to an individual patient*. While there is hope that it may provide some benefit, the trial's purpose is to test safety and toxicity. At this early stage of development, no evidence has accumulated in humans indicating that the treatment will be effective. Several published articles that have reviewed the therapeutic outcomes of patients in phase I cancer trials have found that the actual therapeutic benefit in these trials ranges from 3% to 5% of patients.

Sometimes a phase I trial is offered to a patient as a "last hope" because no other treatment has worked and a doctor has no other standard treatment to offer. Hope is very important. It is also natural for patients to want to try anything available and for their doctors to want to offer something else, especially if the patient wants to undergo more treatment. As the husband of a cancer patient told us, "Even if the doctors had told us she had only a 1% chance of benefit, we would have done the trial. She was young, we had children, and she wanted to take any chance at all."

Phase I trials are extremely important in these situations—and the patients who enter them are benefiting future patients by helping to advance medical knowledge. These trials are the only way that new treatments can be developed. If patient expectations are high for health improvement in a phase I trial, patients and their loved ones may feel very disappointed when it does not happen. Because the risks are generally greater in early-phase trials, patients may want to consider the potential impact of a phase I trial on their quality of life (such as treatment side effects, time commitment, travel requirements) and how they want to spend their remaining time.

So before a patient agrees to enter a phase I study, he or she should understand that *these trials carry the least potential for benefit and the greatest potential for risk because the only evidence at this point is from animal or laboratory studies or from results of the treatment for some other disease.*

Phase II

If a phase I trial has shown no serious risks or problems for patients, the sponsor designs and submits a protocol for a phase II trial to the appropriate federal agency (such as FDA or the National Institutes of Health [NIH]) and the IRB for approval to begin the next phase. A protocol is a detailed plan about how the trial is to be carried out and how the data are to be analyzed. In phase II trials, a control group may be included to start evaluating how well the treatment works (efficacy). A controlled trial enables the experimental treatment to be compared to standard therapy, a placebo, or, in the case of devices, sham (simulated) therapy. For *life-threatening* diseases, placebos and sham devices are rarely used. A control group consists of patients with similar characteristics who get some other treatment instead of the experimental treatment. A control can also mean giving the same patients different treatments at different points in the trial to compare their responses to the different treatments. Whether there are controls and what type of controls is to be used are determined based on FDA or NIH requirements (if either has oversight) and on ethical principles and guidelines in human research (the Declaration of Helsinki, the Nuremberg Code, and the Belmont Report; see *Appendix B* on p. 91). Then researchers use scientific principles about how to design a trial so it can yield the data they need to answer questions about safety and efficacy.

The impact of proposed control groups on patient welfare is also considered by the IRB reviewing the protocol. For example, placebo-controlled trials are considered unethical if effective, lifesaving, or life-prolonging treatment is available. Such trials are also unethical if patients assigned to a placebo group would likely suffer serious harm compared to those receiving an experimental treatment. These concepts are discussed further in *What is randomization in a controlled trial?*, p. 19.

In a phase II trial, the criteria used to determine patient eligibility (inclusion and exclusion criteria) are usually more specific than those in phase I. In phase II, the patients usually have similar medical characteristics and the same medical condition. If you are considering a phase II trial, you may want to look carefully at the protocol to ask questions about aspects that may be unclear to you. (See the checklist at the end of this section, *What should a protocol description for a trial tell me?*) Phase II trials typically take several months to several years to complete (depending on what is being studied). Phase II trials include more patients than phase I trials—usually from 50 to a few hundred patients.

Will I benefit from a phase II trial?

Perhaps. By phase II, some of the risks of the drug or device under investigation have been better defined. Some preliminary data on possible efficacy may be available from the phase I trial. Keep in mind that the main purpose of a phase II trial is to study efficacy and further refine the optimal drug dose, device use, or procedure technique. The likelihood of benefit, however, is still limited.

In a phase II trial, the concept of a control group and random assignment to a group may arise for the first time (although many phase II trials do not include a control group). Random assignment is a scientific method of assigning patients to different groups in a trial so that valid results can be obtained for comparison of treatments. The concept of randomization is often misunderstood or poorly explained to patients. See *What is randomization in a controlled trial?*, p. 19. The idea of being randomly assigned to treatment groups in a trial can be unsettling because some people feel that it involves giving up some personal control over which treatment they get. Some also feel that it gives up access to experimental treatment, but the reason the trial needs to be conducted is that no one knows if the experimental treatment works as well as, better than or worse than standard treatment. If there are no control groups, all patients will get the experimental treatment.

One family's only hope: an early-phase trial

F.S., age 55, spouse of Maria, father, and professional engineer.

My wife, Maria was 40 years old, athletic, and very well fit, but a heavy smoker. One cold January day she started to feel a "wheeze" in her chest, which increasingly became stronger, and went to see our family doctor. Chest x-rays showed a shadow that made him believe that she had an infection. He prescribed antibiotics, but she didn't feel any better. A few weeks later, the doctor ordered a computed tomography scan of her chest. It detected a "mass." A biopsy revealed that she had advanced non-small-cell lung cancer. This type of tumor is not treatable with traditional chemotherapy. We went to doctors at the renowned Fox Chase Cancer Center. They told us the tumor's location made it impossible to remove by surgery. The only option was a very aggressive series of radiation treatments. Because of her relative youth and otherwise good health, the doctors went "for the cure." She underwent 30 radiation sessions. Very shortly after some initial relief, her condition deteriorated from all the undesirable side effects of treatment

Maria carried an oxygen tank for more than three months to help her breathe. She never showed desperation, never complained. Not even during those long nights when she was coughing without relief. One Monday, after a terrible night and against her will, I called her oncologist. He asked me to take her and meet him at the emergency room. Once there, he said, "Maria, I have to treat you, and the only chance that you may have is Taxol, an experimental 'miracle drug' that has been successfully used for other types of cancer. It is now being tried for non-small-cell tumors like yours. There is still not much data about it."

It was an early-phase trial. The doctor explained to us that the patients would be randomly assigned to different protocols and types of drugs. We didn't ask too many questions. We were afraid, but we explained the situation to our two daughters (then 9 and 14 years old). I told my wife that the decision had to be hers, but I would give my opinion if she wanted it. I told her that most of all I was going to support her all the way, whatever her decision. She decided to enroll in the trial—she wanted any chance at survival. We were happy to learn that she had been assigned to the group to be treated with the maximum doses of Taxol.

When drops of the "miracle drug" started to run through her veins, we held out hope against all odds. Although we knew there was almost no chance, my wife, our girls, and I never, ever lost hope. She recovered slightly after her first treatment, but two days before the second session she started to cough heavily. I took her to the emergency room again. Soon after, they began her second round of Taxol, but it had to be interrupted. She was put on a respirator. The heavy cough seemed to come from her "good" lung. An emergency biopsy revealed that her other lung was compromised too.

As I write these words on the eighth anniversary of my wife's death, I ask myself if we did the "right" thing. The answer is absolutely yes. On the other hand, I ask myself if I would make the same decision if I had to go through that one more time? I don't know. We did what we felt was right at the time.

Phase III

Based on positive results from earlier phase trials, the sponsor designs a protocol for a phase III trial. Again, if applicable, FDA, NIH, or any other federal agency associated with the trial will look at the protocol. The IRB for the medical facility conducting the trial must approve the protocol before the trial can proceed. The possible benefits and risks of the treatment are better defined by phase III—but still not entirely known.

Phase III trials usually include control groups and use of randomization procedures for assigning patients to groups. Phase III may also include blinding—which means not revealing to patients and/or researchers which treatment group a patient is in. Phase III trials typically enroll hundreds to thousands of patients and may last several months to several years. The purpose is to obtain data on a wider spectrum of use by more patients. These trials further establish the efficacy, optimal doses, and routes of administration of a drug and optimal performance characteristics of a device. These trials also provide the opportunity to identify less-common side effects because more people are in the trial.

Will I benefit from a phase III trial?

A patient can enter a phase III trial with more expectation than in earlier phase trials of a possible therapeutic benefit—yet it's important to remember that efficacy is still not well established and not all risks have been identified. For example, if a drug is going to cause a rare adverse event, that means the event may happen only once in every 1,000 patients who get the drug. So it will only be seen after a large number of people have received the drug. Also, even if a new treatment has some efficacy, not all patients may respond. So, there is a chance of receiving little or no therapeutic benefit in a phase III trial, even if the therapy has been shown to work in other patients. If you are considering a phase III trial, you may want to use the protocol checklist in this section to see whether you have received complete information about the trial.

Phase IV

This phase of study is typically conducted after FDA has given marketing approval for the new drug or medical device. This phase is also termed a postmarketing study. These are usually large studies and are sometimes required as a condition of FDA approval. The point of further study is to see how well the treatment works in a broader mix of patients and to gain more information about side effects and their frequency—especially ones that were serious but not seen too often in smaller, earlier phase trials. Companies may also conduct these trials to compare their drug or device with a competitor's and see if it has any clinical advantages over the competition. By phase IV, risks are much better defined and a body of evidence on efficacy has accumulated. However, not all risks have been defined.

Checklist:
What should a protocol description for a trial tell me?

This checklist may help you determine whether you have received all the information you need about the trial. Having all the information is important so that you can assess how the trial might affect you and those in your social support system if you entered the trial. This information also helps your loved ones understand and discuss with you the type of support you might need during the trial and when.

- ✔ Purpose and phase of the trial
- ✔ Name and qualifications of each researcher involved in the study
- ✔ Location of the clinical trial site(s)
- ✔ Patient eligibility (inclusion and exclusion) criteria
- ✔ Number of patients that will be recruited into the study
- ✔ Study design (controlled or uncontrolled)
- ✔ Whether the study is randomized and blinded
- ✔ Randomization and blinding methods
- ✔ Treatments the control groups get
- ✔ Details of all the aspects involved in the treatment throughout the trial
- ✔ Study end points
- ✔ Duration of patient treatment and follow-up
- ✔ Types of follow-up exams and tests to be done after treatment

When discussing the protocol, you may also want to talk to the researcher about:

- ✔ How the treatment and follow-ups are scheduled
- ✔ Whether there is any flexibility in the scheduling
- ✔ Whether the treatment or follow-up medical procedures are time-consuming, invasive, or painful
- ✔ Whether patients who are successfully treated will be able to continue treatment when the trial ends

Chapter 5— What is Randomization in a Controlled Trial?

Randomization is a process for assigning patients to the experimental treatment group or the group(s) against which the experimental treatment is compared—the control group(s). The purpose of randomization is to ensure even distribution of patient characteristics in each group in a trial. It is also done to prevent researchers from influencing (consciously or unconsciously) which group patients are assigned to. This section explains how randomization works and the different types of controls (standard treatment, placebo) used in trials, the reasons for having controls, "masking" or "blinding" so that group assignment is not revealed to patients or researchers, and the implications of being in a control group.

Even though the purpose of clinical research is to benefit society, the main reason most people enter a trial is that they hope to improve their health. Hoping to improve one's health is a perfectly valid reason for participating. The whole point of treatment, regardless of whether it's given in a trial, is to help the patient. However, some patients who think about entering a trial stop when they learn that they may not receive the experimental treatment. This is unfortunate because studies have shown that patients in clinical trials fare better on the whole than similar patients who receive treatment outside a trial. (See *Do patients treated in clinical trials have better outcomes than similar patients treated outside of trials?*, p. 33.) *It is important to remember that as a participant in a clinical trial, you can expect to receive excellent medical care, regardless of which group you are in.*

What is a control group?

A control group consists of patients in a trial who do not get the experimental treatment. *In controlled trials of new treatments for life-threatening diseases, placebos are very rarely used.* The control group usually receives the best-known standard (accepted as efficacious) treatment at the time. Although many trials have no control group, researchers prefer having a control group whenever it is ethically possible because the results from trials with control groups are more reliable than results from trials with no control groups. Patients in a control group receive the same close monitoring and follow-up as patients receiving the experimental treatment. Even though it is rare for a trial for treatment for a life-threatening disease to use a placebo, we discuss below what placebos are and when and why they are used.

What is a placebo, and when is it used?

A placebo is any inactive treatment. It is often designed to look exactly like the real treatment. Although a placebo is often thought of as a pill—which it may be for a drug trial—it can also be an injection, a physical manipulation, a device that is inactive, or whatever harmless procedure is deemed an appropriate placebo for the trial. The important thing is that the placebo should have the same appearance as the real treatment. *A placebo is given only in trials in which the patient will not suffer any serious or long-term harm from receiving the placebo or sham (simulated device) treatment instead of active treatment.* Thus, placebos are not used in trials in which patients have a life-threatening illness.

Patients who receive a placebo receive the same attention and follow-up as patients in the other groups of the trial. Their health conditions are carefully watched for any signs that things are worsening. If a patient's condition worsens significantly, the researcher may take the patient out of the trial and find out what treatment group the patient was in. If it was the placebo group, active treatment may be given. However, for many trials conducted in critically ill patients for whom there is no effective treatment, patients are usually not switched from one group to another. Again, it is important to remember that placebos are not used in situations where the patient would be harmed by not receiving active treatment for the duration of the trial.

In some trials, researchers may want to compare the effects of treatment and placebo in the same patients. So a group may get treatment and placebo—but at different times during the trial. Patients cross over from the experimental treatment to placebo as determined by randomization, but they (and perhaps the researchers) may not know which they are receiving at a given time. One reason for crossover design is to determine whether there are any differences between the groups as well as within each group. Another reason might be to see if the disease varies over time—if there is a natural course of remission and relapse, as is the case, for example, with a form of multiple sclerosis. In such a trial, each group serves as both an experimental and a control group. Other trials may have a placebo group and control groups, receiving different standard treatments. The intent is to compare results of the new treatment to known treatments and to placebo.

Why use a placebo?

If, by definition, a placebo is not treatment, why give it? Why not simply do nothing and compare that to the treatment group? The reason placebos are better than nothing is because of the "placebo effect." For years, researchers have repeatedly observed that patients given a placebo often improve because of psychologic effects rather than because of treatment effects. In other words, a treatment may have two effects: a psychological effect and a physiologic effect. Patients may believe they are better simply because they believe they are receiving effective treatment. To determine whether the treatment is effective, researchers need to subtract the impact of the placebo effect. When researchers give the control group a placebo (and the close medical monitoring that is part of the clinical trial), they can subtract the placebo effect when the results of the experimental and control groups are compared.

Will I know if placebos are going to be used in a trial?

Yes. This is explained during the consent interview. However, if you enter a randomized placebo-controlled trial, it almost certainly will be "blinded" so that you will not know which group you are in and whether you are receiving the placebo. The placebo effect can be significant and unpredictable. Whenever possible, patients are not told what treatment they are being given until the trial is over. In this way, there is less chance that bias will be introduced from patients knowing which treatment they got. In fact, in many cases, the trial is designed so that the researchers themselves will not know which patients are in the experimental or control groups. This helps reduce possible biases that could affect results. Biases are factors that can affect the results of a trial independently of the effect of the treatment.

Is it better to be in the experimental treatment group than the standard treatment group?

Not necessarily. Publicity might surround an experimental treatment suggesting that it is a breakthrough, but the reason it is being tested in clinical trials is because there is a hope that it will prove to be better than current treatments. That hope is based on theoretical considerations, preclinical testing, and results from previous clinical trials. However, early signs and hopes do not always pan out. The reality is that, until the clinical trial is conducted and the results are analyzed, the experimental treatment is still unproven. *No one knows whether it will be better*

than, the same as, or worse than standard treatment until that happens. The technical term for this is "equipoise," meaning that our knowledge is equally balanced between thinking that the experimental treatment might be better and not knowing whether it really is. Any researcher talking to you about the treatments being tested in the trial should maintain a position of equipoise. He or she should not give you the idea that one treatment is better than the other. Whichever group you are in, you can expect to receive excellent medical care.

Why is randomization used to assign patients to groups?

Randomization is used because it is usually the preferred scientific process for ensuring that all patient characteristics, whether known or unknown to the researchers, will be represented, or balanced, in each group in the trial.

There are other ways that assignment to treatment groups could be done. For example, researchers might choose to give the experimental treatment to the patients they think could benefit the most and standard treatment to others. While this sounds logical, there are problems with this approach because at this point, researchers don't know how well the treatment works or in whom it works best. Researchers would really be guessing if they did this. Different researchers might choose different patients for the experimental treatment, and the results would differ and still not tell us how well the treatment works and on whom.

For example, a trial opens for enrollment and the first 100 people with a particular medical condition who come in and enroll are given the experimental treatment. The next 100 people with the same condition who enroll are given the standard treatment. The results of the treatments given to the groups are compared. Is the comparison valid? Not really. There could be some differences between groups that were not accounted for. For instance, the first 100 people might have been more eager to receive the treatment, perhaps because they are the sickest, so they enrolled first. So you might have different patient characteristics in the groups. These differences could affect the trial's results independently from the effectiveness of the treatment itself. Results from the first group of patients might seem worse than results from the second group simply because the first group was sicker at the outset, not because the experimental treatment did not work.

Differences in the characteristics of people selected to be in different treatment groups are called patient selection bias. This bias might yield misleading results about in whom the therapy works best. Randomization gets rid of this bias and helps ensure that researchers gain an accurate picture of a treatment's effects. Sometimes the differences in patient characteristics between groups in a trial affect the results more than the treatment itself if proper randomization methods are not used.

What is blinding or masking?

Blinding (also called masking) can be part of the randomization process to prevent patients and/or doctors from knowing which group a patient is assigned to. A trial is "double blind" when both the patients and researchers are unaware of which group a patient is in. A trial is "single blind" when only the patients are unaware of which group they're in. There are many methods for making random assignments in a blinded trial with two or more groups. Often, a computer program is used to generate the assignment for each successive patient who enrolls. Typically, a letter or number is used to designate each group in the trial, and patients are identified by a code of some sort—often a number. The treatment given to patients in each group appears identical so that no one can tell which treatment a patient is receiving. For example, in a trial on hormone replacement therapy, there may be a placebo group plus three treatment groups (groups A, B, C, and D). Each patient gets placebo or a different hormone dosage, but everyone receives the same directions and identical-looking pills to take.

Researchers conduct blinded trials on some types of treatments because the placebo effect can be very significant (with drugs tested for pain or depression, for example). In addition, patients may change how they behave depending on what group they're in. Or researchers' observations may be affected by their attitude (such as enthusiasm) toward a new treatment when they know a patient's group assignment. These conditions might not give reliable results. Patients have also been known to infer their treatment group status by the actions (sometimes unconscious) of the medical staff.

If you are in a blinded trial, you might be very curious about which group you're in. Most people try to guess, or to make the medical staff tell them, or to find out in some other way. This is natural and expected, although it rarely works. Because it is important that the trial fairly reflect only the effect of the experimental treatment, researchers conducting a blinded trial go to great lengths to mask the patient assignment groups—even from themselves.

What if someone tells me which group I'm in, even though I'm not supposed to know?

It's common for a patient to come to believe that he or she knows which group he or she is in. Possibly someone on the research team you trust believes he or she knows your assignment and tells you. Or you might see another patient receiving a different treatment and figure it out. Or you might believe you can tell by how you feel and the effect treatment is having on you. In any of these cases, the chances are very likely that you will not be able to tell which group you are in. In double-blind trials, the trusted source may not actually know which group you're in. The same medication may have different appearances. The effect you feel may be due to something else instead of treatment. Even if you think you are certain you know, continue in the trial as before.

What if I am assigned to a group that I don't want to be in?

If group assignment is not blinded, some patients decline further participation when they find out which group they're in. Usually this occurs because the patient has been assigned to a control group rather than to the experimental group. There may be other reasons as well. Participation in a clinical trial is voluntary. If you no longer wish to participate at any time, for any reason, you may withdraw. No one should talk you into continuing to participate if you don't want to, although the researcher will want to understand why you are withdrawing. If you do withdraw, you may still wish to participate in follow-up visits, if you are asked to. Sometimes researchers want to follow up with patients who have left the trial after receiving even partial treatment.

If you are assigned to the control group and feel disappointed, remember these two points before deciding to withdraw from the trial:

- Every participant in a clinical trial can expect to receive excellent medical care for the condition being treated in the trial, whichever group he or she is in.
- It is not known whether the experimental treatment actually is better than, the same as, or worse than standard treatment.

Can I talk to other patients in the same trial about my experience?

Certainly. Patients who have participated in a trial have reported receiving support and comfort from being part of a group of patients with the same disease or condition. However, there are some topics it would probably be better to avoid talking about with patients in the same trial. Comparing notes with other patients in the trial about your treatment responses may not be helpful because responses to treatment can vary greatly. Also, in a blinded randomized controlled trial, patients don't know which groups they are in, so you wouldn't know what another patient was receiving. In addition, the differences between people receiving even the same treatment can be striking. Sometimes thousands of participants may be needed just so researchers can understand the variability of human responses to the treatment.

As a practical matter, it is natural that patients will exchange views on their experiences of the treatment during the trial. It is important to remember that what happens to you may not be at all typical. The same applies to what others might tell you about their experiences. So it is usually better to not focus on comparing treatment effects with others in the trial. If you have specific concerns, talk to the trial's research coordinator or to the patient advocate, if the trial has one.

What about trials that aren't controlled or blinded?

Many trials are not controlled or blinded and are still very valid trials. Each clinical trial is designed to answer particular questions, and those questions differ for each trial. Depending on what the new treatment is, and depending on the stage of investigation, different types of trials are available for participation. Although the double-blind randomized controlled trial is the gold standard in clinical research, this type of trial may not always be possible or even preferable. Some trials may be gathering preliminary data to see if a treatment is safe enough to warrant a full-scale trial and may have no control group. Another trial may examine a treatment for a serious condition that has no alternative treatment, and randomization would be unethical. In cases like these, the particular question the trial is designed to answer may preclude using randomization or a control group. Trials like these might instead compare the results of the experimental treatment with the results of past trials that used a different treatment for the same condition.

Sometimes there is no need to use randomization because patients serve as their own controls. For example, a trial may be trying to determine the best way to administer a particular treatment for a condition that varies greatly among patients. Individual diabetic patients, for example, can have very different responses to drugs that regulate their blood sugar levels. Each patient may be given two (or more) different drug regimens during the trial, so comparisons can be made within each patient.

If the experimental treatment involves a device or surgical procedure, it can be impossible to create a look-alike or sham treatment. It may be awkward or unethical to give a sham treatment. Also, the effects of treatment using a device might be apparent to the patient—such as use of an electrical stimulation device that creates a certain sensation that cannot be duplicated in sham treatment. In any event, participation in a trial should be tailored to provide the maximum protection to patients as well as to gather the maximum amount of useful data from the trial.

Chapter 6— How Do I Find Out About Available Clinical Trials?

What do I need to know about online databases, doctor recommendations, and advertising?

There are many ways to find out about clinical trials that you may be eligible for. Some publicly and privately funded Web sites that have very useful information are listed here. More information about these Web sites and who manages them can be found in *Additional resources* on p. 69.

- **Acurian:** http://www.acurian.com
- **AIDS Clinical Trial Information Service (ACTIS)** http://www.actis.org/index.html
- **CenterWatch:** http://centerwatch.com
- **Coalition of National Cancer Cooperative Groups** http://www.ca-coalition.org
- **HopeLink:** http://www.hopelink.com/index.jsp
- **National Cancer Institute (NCI):** http://cancertrials.nci.nih.gov
- **National Institutes of Health (NIH):** http://www.clinicaltrials.gov
- **Pharmaceutical Research and Manufacturers of America:** http://www.phrma.org
- **Radiation Therapy Oncology Group (RTOG):** http://www.rtog.org

Your doctor may tell you about some trials. Doctors for patients who are receiving care at a specialized medical center devoted only to a certain disease (such as cancer or heart disease) tend to refer patients to trials sponsored at that center. Most doctors are not aware of all the available trials for your condition because of the time it takes to keep current on all available trials for all the patients that a doctor sees. Sometimes, a doctor who does not do research may be uncomfortable referring you to clinical trials as an option. Some doctors have concerns about losing control of the care of their patients. If you are interested in trials and your doctor seems to resist the idea, this Guide may be helpful for opening up discussion. Nearly every doctor has the patient's best interests at heart, so ask your doctor if there is any medical reason that you should not participate in a trial. If your views on participating in clinical trials differ, you may want a second opinion from another doctor you trust.

Talking with family and close friends about trial options may also be very important for your decision making. Depending on the trial you are considering, you may need additional support from them to do the things you usually do yourself, such as running errands; providing transportation; shopping, cooking, or cleaning; caring for other family members, such as children or elders; or caring for pets. You may also need more of their emotional and moral support at various times if there are especially difficult parts of treatment in a trial.

Some of the Web sites listed here provide matching services for patients and trial sponsors. Patients can register with a database and be contacted about trials that may be suitable. The databases are set up so that you can search by disease or condition and other factors. Some of these matching services are for-profit businesses that receive payment for each match they make. Also, for-profit listing services for clinical trials may list only the trials run by the companies that pay for listing and matching services. Therefore, patients should check more than one database to find out about as many trials as possible. You may also see ads for trials in newspapers and on television or hear them on the radio. U.S. Food and Drug Administration (FDA) regulations govern what these ads can state. To protect patients, the institutional review board (IRB) overseeing each trial also reviews ad content.

One patient's decision to enter a six-year-long trial

Many trials last a year or two, but others are long term because researchers are looking at how a treatment affects survival, and that usually cannot be determined in a trial that only lasts one or two years. Also, some treatments are given over a long period of time, with more intense treatment at some points and little or no treatment at other points. The level and length of trial participation you are willing to consider may depend on several factors. One patient aptly described to us her decision to enter a six-year-long trial.

"When I found out about participating in a clinical trial, I discussed this decision with my healthcare providers as well as my husband and several friends. Since the trial included several drugs that could potentially make me very sick, I needed to be sure I had support around to help me in daily activities. My husband and friends needed to understand that I would require additional care when I underwent treatment. Since the trial lasted six years, with most intensive therapy occurring in the first two years, it was critical to have this support to provide respite for my husband and to provide my friends with a direct way to help out. To their credit, everyone I asked to assist me was more than willing to help out. We still laugh about some of the funny things that happened during the trial. Because my family and friends understood the implications of the clinical trial, it made compliance easier, and it helped me adhere to the protocol."

What kind of information will I find in an ad or listing on the Internet?

When patients respond to databases and ads, they can expect to find basic trial information, including the title and purpose of the study, a brief protocol summary, basic eligibility criteria, a list of study site location(s), and how to contact the research site for further information. NCI's cancer clinical trial listing and trials posted by the government-sponsored ACTIS are two examples of trial listings. For-profit companies like Acurian also have trial listings. Some professional specialty cooperatives, such as RTOG, also sponsor and list clinical trials. If a database allows recruiters to add more descriptive information about a trial, prior IRB review and approval should ensure that this information does not promise or imply a certainty of cure or other benefit beyond that stated in the trial's protocol and consent document.

What do I need to know about advertising to recruit patients?

FDA regulations pertain to direct advertising to the public for research participants in trials FDA oversees. FDA allows direct advertising for new drugs and devices under investigation. This advertising includes newspaper ads, radio announcements, television broadcasts, Internet listings, bulletin boards, posters, and flyers that are intended for prospective participants. Direct advertising does not include (1) communications intended to be seen or heard only by health professionals, such as "Dear doctor" letters and doctor-to-doctor letters (even when soliciting for study participants) (2) news stories; and (3) publicity intended for other audiences, such as financial-page advertisements directed at prospective investors.

Can I trust the information I see in an ad for a trial?

IRB review and FDA regulations offer some protection for consumers regarding the kind of information in ads. FDA guidelines state that ads should be accurate and not misleading. (See the Checklist at the end of this section.) FDA considers advertising for trial participants to be the start of the consent and patient-selection process. (See *What is "informed" consent?* on p. 39.) IRBs are supposed to review and approve ads when they first receive a study protocol package, as well as any ads produced after a trial has started. FDA wants IRBs to review ads before release to make sure that the ads do not pressure potential participants or promise a certainty of cure beyond that contained in the consent form and trial protocol. This is especially critical when a trial involves participants who may be vulnerable to "undue influence." Such participants include patients with no treatment options or patients lacking health insurance who are enticed by free care or payment offered in a trial. FDA also does not want ads to promise "free medical treatment," when, in reality, the trial sponsor means that participants will not be charged for taking part in the trial. Ads are allowed to state that participants will be paid, but the ads should not emphasize the payment by using large or bold type. (See *What costs will I incur in a clinical trial?* p. 59 and *Are patients ever paid for being in a trial?* on p. 63.)

FDA wants ads to make no claims that an experimental treatment is safe or effective for the purposes under investigation. FDA also prohibits claims that the test treatment is equal to or better than any other treatment because these claims would mislead the public and would also violate regulations about the promotion of investigational drugs and devices. Recruitment ads are supposed to avoid terms such as "new treatment," "new medication," or "new drug" if they don't explain that the test item is investigational. FDA believes that phrases like "receive new treatments" lead trial participants to believe that they will be getting newly improved drugs or devices of proven worth.

Checklist: Information that should be included in study recruitment ads

This checklist can help you determine whether an ad for a clinical trial is misleading. The Food and Drug Administration, which developed this list, believes that any ad to recruit trial participants should limit information to that needed by patients to determine their general eligibility and interest.

- ✔ Name and address of the clinical investigator and/or research facility
- ✔ Condition under study and/or the purpose of the research, in summary form
- ✔ Criteria that will be used to determine eligibility for the study
- ✔ Brief list of participation benefits, if any (e.g., a no-cost health examination)
- ✔ Time or other commitment required of participants
- ✔ Location of the research and person or office to contact for further information

Chapter 7— How Do I Enter a Clinical Trial?

When you find out about a trial that interests you, you will need to find out if you really are eligible. Every trial has patient eligibility (inclusion and exclusion) criteria. These criteria, which were set by researchers when the trial was designed, are used to determine who is eligible for the trial. The criteria state what medical and other characteristics a patient must have to enter the trial. These characteristics might include restrictions on age, health status, disease stage, previous treatment, and other coexisting health conditions. It is advisable to look at a trial's general criteria to see if you meet them before contacting anyone associated with the trial so that you don't spend time pursuing a trial you can't enroll in. Also, if you succeeded in enrolling in a trial in which you knew you did not meet the criteria, it could add to your health risk.

Why can't anybody with the disease be in the trial?

Even when people have the same disease, there can be important differences among patients. For example, patients may have different stages of the disease. This might mean that they should get different treatment. Or patients may have other health conditions that exclude them from the trial. Among the main reasons for inclusion and exclusion criteria are:

- Ensuring patient safety
- Meeting the study objective by enrolling appropriate patients to gather data on specific endpoints

Researchers need to be able to sort out and account for everything that might affect treatment and results. For example, if a patient just finished one kind of chemotherapy and then entered a clinical trial for another kind of cancer treatment, researchers might not be able to sort out the effects of the experimental treatment from the effects of the previous chemotherapy. Thus, some types of previous treatment preclude entry into a trial.

How will I know if I am eligible for a trial?

General criteria are listed in trial databases and ads; detailed criteria are spelled out in the study protocol. If you meet general criteria, you can ask for the complete criteria when you first make contact with someone about the trial. A patient wishing to enroll in a trial might have to undergo some "screening" so that researchers can tell if the patient meets the inclusion criteria. If screening is required, the researcher must get the patient's consent for trial participation before doing any procedures that are performed only to determine the patient's eligibility for research. These clinical procedures may include withdrawal from medication (washout) in anticipation of or in preparation for the research, or diagnostic tests such as x-rays or blood tests.

Consent for participation in the trial is not needed for procedures the patient needs, such as those to diagnose or treat a disease, regardless of whether the patient enters the study. The results of such procedures can be used for determining eligibility. If the doctor talking to you about the trial orders any tests, ask whether they are required for your medical care or whether they are being done only to determine eligibility for the trial.

Any clinical screening procedures to determine eligibility are part of the patient-selection and recruitment process and part of the study protocol. Certain screening tests, such as those for HIV infection, may have state requirements about (1) the information that must be provided to the participant, (2) the organizations with access to test results, and (3) whether a positive result has to be reported to the health department. If you are undergoing eligibility testing for a trial, the researcher must tell you in advance of any such requirements. Whatever the test results, they should not affect your employment or health insurance.

Will a researcher pressure me to be in a trial?

No one should pressure you to enter a trial, and most researchers, though excited about their research, will not. It's natural for a researcher to be enthusiastic about his or her research. However, any researcher who is talking to you about participating in a trial that is comparing an experimental treatment to a standard treatment should frankly acknowledge that it is simply not known which treatment is better. The researcher should not advocate that one treatment is better than the other. Sometimes, maintaining a balanced position, or "equipoise," can be difficult for a researcher who has put a lot of his or her intellectual energy and career into developing a new treatment. If you sense that a researcher is much more enthusiastic about one treatment than the other in a clinical trial, get another opinion. Discuss the treatments being studied with a physician who is knowledgeable about them but not directly involved in the trial. Also see *What are the ethical issues in clinical research?* on p. 65.

Can I get a new drug or device that is not yet FDA approved if I don't meet trial eligibility criteria?

Yes. It can be very disheartening to decide to enter a trial and, after being evaluated for enrollment, be excluded from entering. There are ways, however, for some patients to gain access outside a trial to drugs or devices that have not yet been approved for marketing. The U.S. Food and Drug Administration (FDA) refers to the use of unapproved drugs or devices for patients not in a trial as "expanded access." It is also commonly called "compassionate use." The main ways in which manufacturers and FDA make new drugs and devices under investigation (i.e., unapproved drugs and devices) available to patients outside trials are through "emergency use," "single-patient use," and "special exception." Each is discussed below.

Emergency Use

Emergency use is the use of an investigational drug or device for a single patient with a life-threatening or severely debilitating medical condition for whom no standard acceptable treatment is available and for whom there is no time to obtain institutional review board (IRB) approval before treatment. FDA defines "life-threatening" as diseases or conditions for which the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes for which the endpoint of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the patient must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible. FDA defines "severely debilitating" as diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness; loss of arm, leg, hand, or foot; loss of hearing; paralysis; or stroke.

The emergency use of an unapproved drug or device requires that an investigational new drug or device exemption (IND or IDE) application be on file with FDA. If the intended patient does not meet the criteria for an approved study protocol, the doctor who wants to use the drug or device contacts the manufacturer to see if the drug or device can be made available for emergency use under the company's IND or IDE status. The doctor then files an emergency IND or IDE application for that patient. If there is no time to submit a single-patient IND or IDE application (see below) and the manufacturer has agreed to provide the drug or device, FDA can authorize shipment of the drug or device in advance of the IND or IDE application filing. The researcher or other doctor can request authorization by telephone or other rapid means of communication. Emergency use does not require prior approval by the institution's IRB, although the IRB must be informed of the situation. Some manufacturers will only agree to use of the experimental treatment if they receive an IRB "approval letter" before they ship the drug or device. The patient must also be informed about the drug or device and consent to be treated with it.

Single-Patient Use

Single patient use is the use of a new drug or device under investigation outside a clinical trial for a single patient or a few patients with a serious medical condition. The physician wishing to treat the patient(s) contacts the manufacturer to see if the investigational drug or device can be obtained. The physician must also obtain IRB approval to use the drug or device. If the manufacturer agrees to provide the drug or device, the physician then faxes a request by means of a written single-use IND or IDE application to FDA. FDA reviews it within a few days and, if approved, the manufacturer ships the drug or device. This type of access differs from emergency use in that it is less urgent (it takes several days instead of several hours from the time of the request to approval and use), and time is taken to file a written application before treatment begins.

Special Exception

Special exception applies to new drugs under investigation and allows access for patients who do not meet strict trial inclusion criteria but for whom the treating doctor believes that the investigational treatment would provide a benefit. The patient is treated according to the study protocol. This provision is approved for individual patients and small groups, and the treatment is administered during the time that the clinical trial is being conducted. Although the patient is not "officially" in the trial, follow-up is conducted and data are collected as though the patient were in the trial. As in the case of single-patient use, the manufacturer must agree to provide the drug or device, the doctor must get prior IRB approval and file appropriate paperwork with FDA, and FDA must agree to the use. The criteria that must be met for this use are presence of a serious disease or condition and failure of other treatment options.

Is patient consent needed to use an investigational drug or device outside a trial?

Yes. Even for emergency use, the investigator must obtain consent from the intended recipient or that recipient's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all the following:

- The patient is confronted with a life-threatening situation necessitating the use of the test article.
- Consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- Time is not sufficient to obtain consent from the subject's legal representative.
- No alternative method of approved or generally recognized treatment is available that provides an equal or greater likelihood of saving the patient's life.

FDA expects any doctor using an investigational drug or device outside a clinical trial to follow as many patient-protection procedures as possible, including:

- Obtaining an independent assessment by an uninvolved physician.
- Obtaining consent from the patient or a legal representative.
- Notifying institutional officials as specified by institutional policies.
- Notifying the IRB.
- Obtaining authorization from the IDE holder, if an approved IDE for existing device use.

Access to clinical trials: FDA and NIH guidelines on sex, age, and race

Guidelines developed during the past 10 years have sought to encourage minority participation in clinical trials. There must be a sound scientific reason for excluding potential participants on the basis of sex, race, or age. The U.S. Office of Minority Health provides information about issues affecting minority enrollment in trials (http://www.omhrc.gov). The National Institutes of Health (NIH) Office of Research on Minority Health (http://www1.od.nih.gov/ormh) focuses on research issues affecting minorities and has published guidelines requiring the inclusion of minorities and women in NIH-funded clinical studies whenever possible. Until the early 1990s, women of childbearing age had been routinely excluded from studies. In July 1993, FDA published its *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*. It developed this guideline amidst growing concerns that the drug-development process did not provide adequate information about the effects of drugs or biologic products in women. There was a general consensus that women should be allowed to decide for themselves the appropriateness of participating in early-phase clinical trials.

NIH guidelines stipulate that:

- NIH-funded studies must ensure that women and minorities and their subpopulations are included in all human-subject research.
- Women and minorities and their subpopulations must be included in phase III clinical trials in numbers adequate to allow for valid analyses of differences in the treatment's effect.
- Cost is not an acceptable reason for excluding these groups.
- NIH must initiate programs and support for outreach efforts to recruit and retain women and minorities and their subpopulations as volunteers in clinical studies.

The FDA guideline presents the following critical changes that drug and biologic study protocols are now supposed to reflect:

- The restriction is lifted that prevented most women with childbearing potential from entering phase I and early phase II trials. Women's participation is now encouraged. FDA believes that early drug and biologic trials can be safely conducted in women even before completion of all animal reproduction studies through protocol designs that include monitoring for pregnancy and measures to prevent pregnancy during the trial. FDA recommends pregnancy testing, and women must be counseled about using reliable contraception or abstaining from intercourse while participating in the clinical trial. It is important that investigators have access to gynecologic consultants who can provide information about contraceptives and advice for female study participants.
- Sponsors are directed to collect gender-related data during research and development. FDA wants the data analyzed for gender effects, in addition to other variables, such as age and race. FDA requires sponsors to include a fair representation of both genders as participants in clinical trials so that clinically significant gender-related differences in response can be detected. The guideline also underscores the importance of collecting data on how the drug is used in the body in terms of demographic differences (age, sex, race), beginning in the phase I and II studies, so that relevant study designs are developed for later trials.
- The guideline identifies three specific issues that drug companies should study, when feasible, with respect to gender: (1) the effect of the stages of the menstrual cycle; (2) the effect of hormonal treatment, including oral contraceptives; and (3) the effect of the drug or biologic on how oral contraceptives work in the body.

Chapter 8—Do Patients Treated in Clinical Trials Have Better Outcomes than Similar Patients Treated Outside Clinical Trials?

There is some evidence that patients treated in phase II or phase III trials survive longer than patients who are not treated in trials. The answer to this question came from ECRI's analysis of four studies of cancer patients and one study of heart disease patients. We briefly describe the analysis below, which ECRI has published elsewhere as a health technology assessment report.

In trying to answer this question, ECRI researchers searched for published studies that compared the treatment outcomes of patients in phase II, III, or IV trials to outcomes of patients who were eligible for those trials but did not participate. (Patients treated outside the trials did not necessarily receive the same treatment as patients in the trials.) Our searches identified only phase II and III studies. We then selected studies that compared treatment outcomes for adults with serious or life-threatening conditions. The treatment outcomes that may be of greatest interest to patients are survival and quality of life (QOL), so we only assessed data from trials that reported on at least one of these outcomes. We excluded trials that reported only laboratory results of cell counts or results of imaging studies such as computed tomography or magnetic resonance imaging scans because these measures don't tell us about survival or QOL.

There were 10 studies that reported on patient survival. One of these studies also reported on QOL. We examined these studies to see whether researchers controlled for patient characteristics (e.g., age, sex, disease stage, coexisting health conditions) that could distort their results—in other words, yield misleading results. For example, it would be important to know if patients who participated in the trials were much younger than those who did not because one would expect better survival from younger patients because they are likely to live longer. In this situation, if one compared the survival of patients who did and did not participate, it would not be clear whether a difference in survival was due to the age difference, to trial participation, or both factors. Because of such difficulties in interpretation, we only considered the results of studies that took differences in patient characteristics into account. The study reporting on QOL did not account for these differences and so, provided no meaningful data for analysis and interpretation.

Effect of trial participation on survival

Of the 10 relevant studies we found, 9 reported differences in the characteristics of patients who did and did not enter clinical trials. The 10th study was on patients with ovarian cancer and found no differences in the characteristics of patients in that study. Of the 9 trials that found differences in patient characteristics, only 4 accounted for these characteristics when they compared the survival of patients in trials to that of patients outside trials. Thus, we analyzed only the results of these 4 studies and the study of ovarian cancer patients to compare survival outcomes of patients treated inside and outside trials.

Four of the five studies found that patients in clinical trials survive significantly longer than patients who were eligible for, but did not participate in, the trials. All four of these studies enrolled patients with cancer. The fifth study (which enrolled patients with heart disease) reported a survival difference in the direction of improvement over patients not in the trial, but this difference was not statistically significant.

Thus, there is some evidence that patients in phase II or phase III trials survive longer than patients who are not in trials. This apparent advantage may be due to better treatment, better patient monitoring by medical personnel, or other factors. However, since there were only five studies available for analysis, we cannot conclude that these results apply to all patients inside and outside trials. Larger studies that control adequately for various important patient characteristics are necessary to confirm these results.

Chapter 9—What Kind of Care Can I Expect During a Clinical Trial?

You can expect to receive excellent medical care for the condition you are being treated for in a clinical trial. Typically, patients in clinical trials are more closely monitored than patients treated outside clinical trials. This is because the trial protocol requires detailed collection of data and frequent patient checkups to assess how patients are doing. In addition, the research doctors typically come from among the clinicians who are most knowledgeable about the disease or condition under study—it's the focus of their work. Trial sponsors, the institutional review board (IRB) (see *What is an institutional review board?* on p. 49.) for the institution where the trial is being conducted, the U.S. Food and Drug Administration (FDA), the National Institutes of Health, and any other federal agency that has some oversight of the trial also review the principal investigator's credentials for his or her qualifications. Sponsors and other funding agencies also have high standards that must be met, and they usually inspect clinical trial sites to make sure that the standards of the clinical trial can be met, especially with regard to patient care and safety.

Another important aspect to consider about your care during a trial is your care outside the trial. Will you have the social support system you need to help you during the trial? Having a good support system in place outside the trial can affect how well you feel emotionally, how well you can comply with the trial protocol, and whether you complete the trial. Depending on the trial you are considering, you may need additional support from family and friends to do things you usually do yourself, such as running errands; providing transportation for errands and clinical trial treatment and checkups; shopping, cooking, or cleaning; caring for other family members, such as children or elders; or caring for pets. You may also need more emotional and moral support from family and friends at different times during the trial if the treatment is more difficult to tolerate at one time than another.

Whom do I tell if I feel as though something is going wrong with my treatment in the trial?

The consent form you sign must list the name and contact information of a person on the research team you can contact 24 hours a day if you think you are having a serious side effect or complication. If you are concerned about some other aspect of the trial and how it is affecting you, there are a few choices of people you (or a loved one, if you are unable) can discuss it with. Try talking with the research coordinator or someone on the research team (other than the lead investigator); a patient advocate for the trial, if one is available; or a patient advisor from the IRB, if there is one. (See *What is an institutional review board?* on p. 49 for information on the membership makeup of IRBs.)

What if I have side effects and want to withdraw from the trial?

You have the right to withdraw from a trial at any time. It is important to report any side effects to the research team, even if you withdraw, so that they can collect important safety and efficacy information to analyze. Also, the research team needs to know why a patient has withdrawn so that they can account for what happened to all patients and assess effects of the treatment on patients. Even if you withdraw, your participation up to that point provides important information.

Who treats side effects or complications from treatment in a clinical trial?

Ultimately, the research team is responsible for dealing with side effects and complications. Practically speaking, the location for receiving treatment depends on where the patient is when a side effect or complication occurs. If the side effect does not require urgent attention and the patient has time, he or she should go to the research facility for treatment. If the event is serious, the patient (with the help of a family member or friend) should seek care at the nearest available medical facility and should let the treating doctors know whom to contact in the trial. The treating doctors will need vital medical information from the research team about you and your trial treatment so that the necessary consultations can take place to treat the complication or side effect appropriately. The consent form should explicitly state who is responsible for treating unexpected side effects and who will bear the cost of treating them. (See *What is "informed" consent?* on p. 39.)

What if my condition worsens during the trial?

You and/or a family member should talk frankly with the research doctor if your condition worsens. Unfortunately, the worsening of a patient's condition is not an unusual event if the patient has a life-threatening condition and the disease has progressed. Research doctors closely monitor each patient to observe the effects of treatment during the trial to see how well it is working. If the treatment itself is believed to be causing unexpected deterioration, research doctors will do everything possible to halt or reverse that effect—including withdrawing the patient from the trial. Again, keep in mind that you can withdraw from a trial at any time.

What if the treatment has an unexpected effect that they didn't tell me about?

Some uncertainty and risk are always part of clinical research. Also, remember that uncertainty is often part of the picture in standard medical practice. Unfortunately, no one, not even the researchers who designed the trial, know all the possible side effects or complications. The very reasons for doing medical research are to detect the risks as well as the benefits of treatment. Unexpected complications and side effects can happen, especially in early-phase trials, when the basic safety and efficacy data are just being collected. The more people on whom a new treatment is tested, the more we learn about side effects and how often they occur. Detecting rare side effects requires studying a lot of people—1,000 or more—simply to detect the effect. Long-term safety isn't really known for any treatment until that treatment has been used for a while on a large number of patients.

What happens if I don't do something that I'm supposed to do in the trial?

You should quickly contact the person designated on the consent form if you miss your treatment schedule or do something that is "off-protocol." It's not possible in advance to know what the consequences would be of doing something off-protocol. But it is very important that the researchers know about it as soon as possible so that your health and safety are ensured. You should write down what happened, when, and why, so you can remember and can tell the research team. No one will be angry with you for making a mistake, for whatever reason. Clinical trials not only find out how well a new treatment works, they also find out how easy or difficult it is for patients to follow the treatment regimen. If many patients have the same difficulty, the researchers may realize that they need to revise some aspect of treatment or instructions about how to follow the regimen. Thus, it is important to be honest about how well you can comply with what is asked of you.

What can I do to improve my own safety in a trial?

Make sure the research doctor has your medical records and knows who your other doctors are. You should confirm that the research doctor and your other doctors are communicating about what's happening to you in the clinical trial and outside the trial in terms of any care you receive. Also, promptly report any side effects to the researcher. Finally, let someone on the research team know if you have done anything that the protocol said not to do.

Tragedy for a patient who did not inform all his doctors about his health

A 65-year-old male patient with severe heart disease was enrolled in a high-risk phase I trial on gene therapy for coronary artery disease. The trial was testing whether the gene therapy could induce the growth of new blood vessels in the heart to do what his diseased vessels no longer could. The patient lived in the Midwest and traveled to Boston to undergo treatment in the trial. However, not all the patient's medical records were shared between his doctors at home and the doctors running the trial. Shortly before enrolling, the patient had a chest x-ray at home to diagnose other symptoms. The x-ray showed a suspicious mass in his chest, which, through further testing at home, was confirmed by the patient's doctors to be lung cancer. But the clinical trial researcher did not have that x-ray at the time of enrollment; if he had, the patient would have been excluded. Cancer was a very important exclusion criterion for the gene therapy trial because the researcher knew that the gene therapy could cause any cancer to grow more aggressively. If the researcher had seen the x-ray, the patient would not have been enrolled in the trial. In fact, the patient's lung tumor grew much more aggressively, and the patient died shortly after administration of a course of the gene therapy. The researcher stated that he was not aware of the tumor until after he had given the patient the gene therapy. Although the researcher should be responsible for obtaining all medical records and communicating with a patient's other doctors, patients also must be alert to make sure all their doctors are aware of all of all their health conditions, test results, and participation in a trial. The tragic death of this patient caused FDA to shut down the research for several months until an investigation was completed and FDA was sure that mechanisms were in place to prevent such events in the future.

Chapter 10— What is "Informed" Consent?

Informed consent is the term commonly used to refer to the consent process and the form a patient signs indicating that he or she agrees to participate in a trial. In this Guide, we will simply refer to these as the consent process and the consent form. The consent form is a patient's written agreement to participate in a trial based on full disclosure by the researcher about the trial, its potential risks and benefits, and other treatment options. Voluntary consent is required for anyone entering a clinical trial. The trial and its possible risks and benefits are explained to the patient orally and in writing by the researcher or research coordinator of the trial. Sometimes, videotapes are also used to help patients understand. When this discussion (also called a patient interview) is finished, the patient is asked if he or she understands the information and has the chance to ask questions. If the patient decides to enter the trial, he or she signs the consent form. This form should explain everything that was discussed during the consent interview. The patient receives a copy because it contains important information that he or she may need to refer to during the trial. The National Institutes of Health (NIH), U.S. Food and Drug Administration (FDA), and other federal agencies funding clinical research have regulations about what must be included in the consent interview and document. The institutional review board (IRB) of the facility conducting the trial also reviews consent documents to ensure that they contain everything required by federal regulations. (See *What is an institutional review board?* on p. 49.)

Researchers usually go to great lengths to explain a trial to a patient during the consent process. However studies of patient understanding of consent forms for trials have revealed some problems. Patients may believe that they understand the risks and benefits and feel satisfied with the consent process but often don't realize there are some things they have not understood. A recently published study of 207 cancer patients who enrolled in phase I or phase II trials in three Boston medical centers looked at patient understanding of the trials after completing the consent process. (Quality of informed consent in cancer clinical trials: a cross-sectional survey. *Lancet* 2001 Nov 24.) Researchers found that less than 40% of the patients who enrolled realized that receiving an experimental treatment might increase their risk or discomfort compared to standard treatments. However, virtually all patients were highly satisfied with the consent process. The study noted several things that contributed to greater patient understanding:

- Reading consent forms carefully.
- Having a nurse present during the interview.
- Taking the time to consider the enrollment decision carefully. (This will likely involve taking the consent form home, at least overnight.)
- Receiving a simplified consent form based on a model recently published by the National Cancer Institute.

Why is consent required?

First and foremost, the consent process is intended to protect human subjects (healthy volunteers and patients) who are participating in clinical trials. The underlying idea is that those who agree to take part in clinical research know what is going to happen to them during the trial. They have a right to be told about all the possible known risks and benefits because they are volunteering for an experiment that, by its nature, includes uncertainty. Every published guideline on the conduct of modern clinical research upholds a volunteer research subject's right to make an informed choice about whether to participate in the research.

Although clinical research has been conducted for decades, consent was not always an explicit part of the patient enrollment process, despite the existence of ethical guidelines like the Declaration of Helsinki and the Nuremberg Code (see *Appendix B*, on p. 91). Concerns about consent processes voiced during the last 35 years often refer to a landmark article, "Ethics and Research," published in 1966 in the *New England Journal of Medicine*. Henry Beecher, Harvard University professor, cited 22 examples of clinical investigators who had risked the lives or health of patients in trials without informing them that they were in a trial or obtaining their permission to participate in a trial. His article led to hearings by the Department of Health, Education, and Welfare (now the Department of Health and Human Services) to develop better-detailed guidelines for research on human subjects. These guidelines were published in 1979 as *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*.

Does consent involve more than getting my signature on the consent form?

Yes. Many clinical researchers use the consent form as a guide when they orally explain the trial to prospective participants. The patient's signature documents his or her agreement to participate, but it's only one part of the consent process and does not necessarily mean that "informed" consent was actually obtained.

Several federal agencies have consent regulations and guidelines for trials, including NIH and FDA. The checklist of FDA's requirements for a consent form at the end of this section may be useful to you when looking at a consent form.

The entire consent process involves:

- Giving the patient adequate information concerning the study.
- Providing adequate opportunity for the patient to consider all options.
- Responding to the patient's questions.
- Ensuring that the patient has understood this information.
- Obtaining the patient's voluntary agreement to participate.
- Continuing to provide information as the patient or situation requires during the trial.

Does the consent information differ according to sex, adult age, or race?

It might. If animal studies on the effects of an experimental treatment on reproduction and the fertility of future generations have not been completed before the first studies begin in humans, trial participants should be told that the potential effects on conception and fetal development are not known. All trial participants should be given any new information arising from ongoing preclinical studies as it becomes available. Consent forms should be updated with new information, when appropriate. Drugs may exert different effects on the body due to patient age, sex, or other demographic factors. Trial participants should be told about any new clinical data on general safety and effectiveness, including effects that affect people differently according to sex, age, or race. There are specific rules (which we do not cover here) that apply to trials enrolling minors or incapacitated patients or patients in emergency or trauma situations. Information on issues concerning participation of minorities in trials can be obtained from the federal Office of Minority Health Resource Center (see *Additional resources* on p. 69). Information about FDA and NIH guidelines on including minorities in trials can be found at the end of the section titled, *How do I enter a clinical trial?* on p. 29.

Does the consent form differ from place to place in a multicenter trial?

Today, many trials are multicenter—that is, the same trial takes place at several different medical facilities across the country and/or in many countries. Although the same information should be included in all consent forms, the forms may vary among centers involved in multicenter trials. This is due in part to the requirement to have the consent form reviewed and approved by the IRB that oversees and approves research at each institution. (See *What is an institutional review board?* on p. 49.)

What if I don't understand the consent form?

As a mentally competent adult, you should not enroll in a trial if you do not understand the information and the form on which you are asked to give consent. Enrolling a patient without consent or with inadequate consent violates federal regulations and ethical rules. Any researcher who does this risks severe penalties or may even be barred from doing more clinical research, so researchers are very interested in having patients understand the consent form for the patient's sake as well as their own. (Children or patients who are not mentally competent cannot be enrolled unless someone with the legal authority to speak for them gives consent.) Don't hesitate to take enough time with a researcher to ask questions and get the answers you need. It's the researcher's job to make sure you do understand so that you can make an informed decision. You may want to take the consent form home with you to read over and discuss with family members and trusted friends. This will also help the people who will be supporting you through the trial understand more about what will be happening to you. In that way, they may know how to support you best in the ways that you need.

Can I bring someone with me to the interview at which I'm asked to give consent?

Yes. When you are ready to receive the consent information, consider taking along a trusted family member or friend who is a good listener so that he or she can hear the same information you are hearing. Then you can talk it over with that person as well as with the research team. The friend or family member can also take notes or use a tape recorder during the interview while you put your full attention into listening. This person may also have good questions that are different from the questions you might think to ask. You should not sign a consent form if you don't feel comfortable with the information you have been given or don't understand the benefits and risks that have been explained to you. The person who conducts the consent interview should be knowledgeable about the study and able to answer all your questions. FDA does not specify, by title, who this person should be. Some trial sponsors and IRBs require the clinical investigator to personally conduct the consent interview.

How can I be sure I've been told everything I need to know?

Sometimes, it is hard to know what questions to ask because you aren't aware of what you don't know. Using the checklist in this section about the information that should be contained in a consent form may be helpful. A good way to test yourself on whether you understand the trial is to first explain to the researcher in your own words what you think will happen to you in the trial, how long you will be in the trial, and what the risks and benefits are. Then, ask the researcher if your understanding is complete and accurate.

Who else can I talk to about this?

There are several people who may be helpful as a sounding board when you think about the consent information and entering a trial. You do not have to sign the form at the time it is given to you. You can take it with you, take time to think, and talk it over with others. For some trials, however, the patient eligibility criteria stipulate that a patient must enter the trial within a certain time frame. The researcher should make this time frame clear to you without pressuring you if you are uncertain.

The following people may be helpful:

- *Your significant other.* It's important for the people closest to you—family and friends—to understand as best as they can what you are going through and what to expect when you are in the trial. This is especially important for the person most likely to care for you in an emergency (i.e., the person most likely to observe a side effect or complication and obtain medical care for you). Understanding what the trial will require of you can also give them an idea of the kind of support you are likely to need and when, so they can plan accordingly. (See *What costs will I incur in a clinical trial?* on p. 59 for a discussion of the intangible costs of being in a trial.)
- *A patient advocate for the trial.* A patient advocate is someone outside the research team who has been designated and trained to look out for patients' best interests and serve as an additional resource and means of support for patients in the trial. Not all trials have patient advocates. Among those that do, the patient advocates have even helped researchers design the trials to make them work better for patients who will enroll. When you make the first contact to get information about a trial, ask if the trial has patient advocates as a resource for trial participants.
- *Your primary care doctor.* It's important to let your primary care doctor know you are participating in the trial for appropriate coordination of care. Also, if your doctor knows you well and has no vested interest in whether you enter the trial, he or she may be able to help you weigh options.
- *A spiritual advisor or therapist.* You may want to talk with your pastor, priest, or other spiritual leader and/or a therapist, if any of these people have served as resources for you before. Also, some patients who may never have used such resources before may find them helpful when talking about different aspects of a trial and impact on quality of life. The husband of one patient going into a cancer trial told us that the family therapist he, his wife, and his daughters had begun seeing during his wife's illness helped them cope with the stresses of a poor prognosis and was very helpful as they weighed treatment options.

Who should be there when I sign the consent form?

You may want to bring a friend or family member. Officially, federal agencies such as FDA do not require a third person to witness the consent interview or signing unless the patient isn't given the opportunity to read the consent document before signing it. An IRB may decide that it wants a third party to observe the consent process in a particular trial, so a person appointed by the IRB may be there on your behalf to ensure that you understand the information and are voluntarily signing the consent form.

Can I give consent by telephone?

No. An oral approval does not satisfy regulatory requirements for a signed consent document. However, FDA states that it is acceptable to fax the consent document to a patient and then conduct the consent interview by telephone if the patient can read the consent form while it is being discussed. If the patient agrees, he or she can sign the consent and fax the signed document to the clinical investigator.

Who should be listed on the consent form as the contact to answer my questions?

The contact for questions about the research, patients' rights, and reporting of a research-related injury should be a knowledgeable person from the research team other than the principal investigator (the doctor heading the research). If the principal investigator is the only contact, some patients may not be comfortable reporting concerns and/or possible problems.

Can I leave a trial after I've signed a consent form?

Yes. You can leave a trial at any time. No one can or should force you to stay in a trial you are not comfortable with. If you decide to leave a trial, tell the research coordinator so that the researchers can account for what happened to all patients and so that they know why you withdrew from the trial. What's happening to you might have an impact on what's happening to other patients in the trial, so the researchers need to know.

If English is not my native language, will the consent form be in my language?

Federal regulations require that the consent document be in a language the patient understands. If the prospective participant speaks fluent English and the consent interview is conducted in English, the consent document should be in English. When potential participants include non-English-speaking people and the researchers or IRB think that the consent interviews are likely to be conducted in another language, an accurately translated consent form must be prepared. A copy of the translated consent form must be given to each participant who needs it. While a translator may be translating during a consent interview with a trial participant, FDA prohibits translating the consent form while talking with the patient as a substitute for a written translation. This is just one issue affecting minority patients in clinical trials. Please see *Additional resources* on p. 69 for resources about enrollment of minorities in clinical trials.

Are regulations about consent forms the same for all federal agencies that oversee trials?

Most, but not all. There are some differences, for example, between the regulations of the U.S. Department of Health and Human Services (DHHS) and FDA. FDA, but not DHHS, provides for an exception from the consent requirements in emergency-use situations (when an experimental treatment is used outside a clinical trial before it has FDA approval for marketing). Another example is that FDA explicitly requires consent forms to inform trial participants that the agency may inspect the records of the study as part of FDA oversight of the trial. While DHHS has the right to inspect the records of studies it funds (such as those by NIH), it does not require this to be stated in the consent form. FDA also explicitly requires that consent forms be dated as well as signed by the subject or the subject's legally authorized representative. The DHHS regulations do not explicitly require consent forms to be dated.

What are the biggest problems with consent processes today?

A lot of research has looked at how understandable and complete consent information is. Common problems with consent documents are wording that is often too technical, sentences that are too long, and documents that are hard to read because of the type size and layout. Sometimes, documents are very long because of all the information they must include. Patients may be able to read them but may not understand the content very well. Other problems are ethical and concern disclosure of conflicts of interest by the researcher. (See *What are the ethical issues in clinical research?* on p. 65 for a discussion of conflicts of interest related to consent processes.)

To address some of these problems, the National Cancer Institute, the Office for Human Research Protections, and Food and Drug Administration formed an Informed Consent Working Group to propose solutions. In 1998, the group issued its recommendations for researchers and IRBs and mailed this packet to thousands of IRBs, hospitals, patient groups, and researchers. It includes sample consent forms in English and Spanish. This information packet is available online at: http://cancertrials.nci.nih.gov/researchers/safeguards/consent/recs.html.

During the consent process, some responsibility lies with the patient to tell the researcher what he or she does not understand. In your own words, tell the person conducting the consent interview what you think was said, and ask "Is my understanding correct?" Read over information, and ask for definitions of terms that are unfamiliar. You may feel rushed to make a decision about treatment because of your situation. For your protection, it is worth taking time to read all the information, ask questions, talk it over with loved ones, and test out your understanding. Pay special attention to the parts of the consent form that talk about risks, potential side effects, possible complications, what is NOT known about the treatment, and who will be responsible for treating and paying for any trial-related complications. If you really want to know about the risks of the trial (although some people may not want to focus on this), ask the researcher, "Can you tell me all the worst things that this treatment could possibly do to me?"

Tragic events from inadequate understanding during the consent process

Some of the tragic incidents that have happened recently in clinical trials have to do with inadequate explanations of risks and benefits during the consent interview. A big question is whether all the important risks can be identified beforehand. Unfortunately, researchers cannot foresee all risks—especially in early-phase studies. Research necessarily involves some uncertainty. In phase I trials, the risks of what is not known about an intervention can be grave. Of course, deaths that occur in healthy volunteers in phase I trials are shocking. These incidents have received more attention than the loss of seriously ill patients in phase I trials because the purposes and study populations differ so much. The loss of a patient with a serious illness in a phase I trial is not entirely unexpected because of the severity of the disease itself.

Nonetheless, the loss of relatively healthy young volunteers in phase I studies raises important issues for anyone thinking about being in a trial. The parents of a healthy 17-year-old man, Jesse Gelsinger, who died in a phase I safety study on gene therapy, have expressed anger that they did not fully understand the risks of the trial. Jesse had a rare genetic defect that was being managed by diet and medication when he entered the trial. Allegations have been made that the trial researcher let his desire for professional recognition, financial gain, and career advancement outweigh his obligations to trial participants' welfare. Indeed, the director of the Institute for Gene Therapy at the university research center held an ownership interest in the company, which he later sold for $13.5 million. The university settled the case out of court for an undisclosed sum several weeks after the tragedy. Another patient, who suffered no physical harm in the trial, claimed mental distress from participating and has filed a lawsuit.

A phase I trial testing an asthma drug on healthy volunteers at a highly reputable university research center resulted in the death of a healthy young woman. Preliminary investigation into that trial suggests that appropriate approvals to study the drug being tested were not obtained because the drug under study was not new—but the way it was being used was new. The risks in the consent document touched on some potentially serious effects but did not suggest a potentially lethal effect of the drug. The volunteers said they did not know the degree of risk of the trial.

New initiatives in May 2000 from the DHHS on the protection of human subjects in clinical trials should help to improve the consent process and the work of IRBs to ensure that the process is properly conducted for the best patient understanding. *Appendix D* on p. 105 summarizes these efforts.

Checklist: What should a consent form include?

This checklist can help you assess whether a consent form you are reviewing contains all the kinds of information it should. If it doesn't, or if you don't understand it, ask the research coordinator to provide more information or explain the form to you.

The consent form should include:

- ✔ A statement that the study involves research.
- ✔ An explanation of the purposes of the research.
- ✔ The expected duration of the patient's participation.
- ✔ A description of the procedures to be followed.
- ✔ Identification of any procedures that are experimental.
- ✔ A description of any reasonably foreseeable risks or discomfort to the participant.
- ✔ A description of any benefits to the participant or others.
- ✔ Disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the participant.
- ✔ A statement describing the extent to which confidentiality of the participant's records will be maintained. In the case of trials overseen by FDA, the consent form must state that FDA may inspect the records. (Other agencies with trial oversight may also inspect the records but don't require that information to be stated in the consent form, so you may want to ask.)
- ✔ An explanation regarding whether any compensation and/or medical treatments are available if injury occurs and, if so, what they consist of, or sources of further information.
- ✔ Information on whom to contact with questions about the study and the participant's rights.
- ✔ Information on whom to contact in the event of a research-related injury.
- ✔ A statement that participation is voluntary and that the participant may refuse or discontinue participation at any time without penalty or loss of benefits.
- ✔ Any costs to the subject as a result of participation.
- ✔ Any financial interests the researchers and institution have in the research.

What additional information should be included, when warranted?

- ✔ A statement that the procedure or treatment may involve unforeseeable risks to the subject, or to the embryo or fetus, if the subject were to become pregnant.
- ✔ The anticipated circumstances under which the investigator may terminate the participant's participation without regard to the participant's consent.
- ✔ The consequences of a participant's decision to withdraw and procedures for withdrawal.
- ✔ A statement that significant new findings that may relate to the participant's willingness to participate will be provided.
- ✔ The approximate number of participants involved in the study.
- ✔ A summary of results of earlier phase studies that led to the current study.

Chapter 11—Is There Patient Confidentiality in a Clinical Trial?

In the age of the information superhighway, most of us have become concerned about privacy, especially regarding health matters and who can access our medical records. Some of the reasons for concern include fear of stigmatization because of a serious illness and possible employment or insurance discrimination.

Is my medical information kept confidential in a clinical trial?

Not always—it depends on the situation. First, it is important to note the difference between confidentiality and anonymity. In many cases, patient names are masked and patients are identified in records by a numbering system so that anyone looking at individual patient information does not see a name. Thus, the patient is anonymous. Officials from various federal agencies overseeing trials may inspect and copy clinical records to verify information submitted by a sponsor. The U.S. Food and Drug Administration (FDA) requires that the consent forms let patients in trials know that complete privacy does not apply in the context of research involving FDA-regulated drugs and devices. The U.S. Department of Health and Human Services does not require that patients be informed of this as part of the consent process, so if you don't see a privacy statement in the consent form for a trial sponsored by the National Institutes of Health or other federal agency, you may want to ask. FDA generally will not copy a trial participant's name during a site inspection unless a more detailed study of the case is required or there is reason to believe that the records do not represent the actual cases studied or results obtained.

The consent form should not state or imply that FDA (or another federal agency with oversight of the trial) needs clearance or permission from the clinical researcher, the patient, or the institutional review board (IRB) to access medical records. When clinical researchers conduct trials whose data will be submitted to FDA, they agree to give FDA access to trial records. Consent forms should clearly explain that when a patient participates in research, the patient's records automatically become part of the research database. Patients do not have the option to keep their records from being audited or reviewed by FDA or other federal agencies with trial oversight.

When an individually identifiable medical record (usually kept by the clinical researcher, not by the IRB) is copied and reviewed by FDA, proper confidentiality procedures are followed within FDA to protect patient privacy. Identifying names are blocked out. However, the laws relating to public disclosure of information and the enforcement responsibilities of FDA make it impossible to guarantee absolute confidentiality.

If the results of the study are published in a medical journal, is my identity protected?

Yes. Trial participants are not identified personally in published articles. Patients are anonymous, and articles that report individual patient data typically refer to individuals by a letter or number. Information about the sex and age of patients and medical characteristics is often included, but nothing identifies an individual patient.

Chapter 12—What is an Institutional Review Board?

An institutional review board (IRB) is a group of people formally designated to review and monitor clinical research to help ensure the protection of any person thinking about trial enrollment and those actually participating. Every university medical research center has its own IRB. Community hospital and nonuniversity research centers (such as cancer, transplantation, or heart centers) also have IRBs. Clinical research done in places other than university and nonuniversity medical research centers, community hospitals, and independent research institutions is still subject to IRB approval. Such places might include physician offices. Typically, an independent (also called central) IRB approves such research. The two IRB systems are discussed below. Federal regulations, first established in the 1970s, specify IRB responsibilities. They give IRBs the authority to approve, require modifications of, or disapprove clinical trial protocols. IRBs must approve federally funded research and research done by companies seeking U.S. Food and Drug Administration (FDA) marketing approval for their new drugs and devices. Many institutions require all clinical research occurring on their premises to undergo IRB scrutiny and approval. This is because most institutions believe that any person enrolling in a research trial is entitled to the same protections, regardless of whether a federal agency is overseeing the research.

How does an IRB protect patients?

An IRB protects patients by reviewing proposed research to assess the safety and welfare of human research subjects who might participate in the trial. An IRB assesses the ethics and validity of the trial design and the risks it poses to patients. If the risks are deemed to be too great, the IRB will not approve the research or will ask for changes to lower the risks. An IRB also evaluates the consent document and any recruitment ads for the trial to ensure that they provide patients with appropriate and understandable information about the trial. The IRB looks particularly at how the consent form explains the risks and benefits so that patients can make an informed decision about participation. IRBs also want to ensure that a clinical trial conforms to federal regulations. IRBs assess whether researchers might have a conflict of interest that could affect patients in the trial. (See *What are the ethical issues in clinical research?* on p. 65.) IRBs use a group process to review research protocols and consent documents and related materials. Every clinical trial protocol must have IRB approval before the trial can begin. (Of course, the National Institutes of Health (NIH) must also approve research it funds, and FDA must approve any trial for an investigational new drug, device, or biologic.)

Who sits on an IRB and represents the patient's perspective?

An IRB is supposed to have a balance of scientific and nonscientific members. Federal agencies like FDA have requirements about the makeup of the IRB. FDA requires at least one IRB member to have primary concerns in the scientific area and at least one member to have primary concerns in the nonscientific area. Most IRBs include physicians and Ph.D.-level physical or biological scientists to satisfy the requirement for at least one scientist. When an IRB reviews study protocols involving science beyond the expertise of its members, IRBs can use consultants to assist in the review. IRB members must come from diverse fields and include members with little or no scientific or medical training or experience, such as lawyers, clergy, and ethicists. Some members have training in both scientific and nonscientific disciplines, such as an attorney/nurse. However, a nonscientific member is supposed to be someone who is clearly nonscientific—not someone in a dual role. The IRB is also supposed to have a member who represents the patient perspective.

Can a patient contact the IRB for independent advice if the patient perceives problems in a trial?

Yes. Patients can report perceived problems to the IRB. Today, more and more IRBs are facilitating these interactions by having an independent patient advisor as one of the board members. The patient advisor provides support to patients experiencing problems during a trial. During the consent interview, you can ask whether a patient advisor is a member of the institution's IRB.

Can a clinical researcher be an IRB member?

Yes, but IRB members can't review protocols for their own research. For example, FDA cautions that IRB members who are routinely involved in research may not serve the IRB well because they would need to abstain from review and voting to avoid a conflict of interest and thus hinder the review procedure.

Are IRB members paid?

It depends on the type of IRB. Most IRB members for university medical research centers are volunteers, but regulations do not preclude paying members for services rendered. There are also IRBs (called central or independent) that are not associated with universities or research institutions, and they pay their members as professionals for their services (see below). Typically, payment to volunteer members covers travel expenses or honoraria (a small sum of money as a token to honor the time they have volunteered), and payments are not directly related to the time spent on review. FDA emphasizes that any payment to IRB members should not be tied to a favorable decision for approval of a trial.

Is there more than one kind of IRB?

Yes. There are two IRB systems in the United States. The first is the local IRB system. Local IRBs are established by university medical research centers and by other facilities conducting federally funded clinical research. These IRBs make up a large, loosely coordinated national network of IRBs. The federal Office for Human Research Protections (OHRP) (see the box at the end of this section) oversees IRBs and regulates institutional research. The second IRB system consists of central or independent IRBs. Companies sponsoring clinical trials established these IRBs in the private sector to oversee research done, for example, in physician offices or community hospitals not affiliated with a university. Central IRBs focus almost entirely on reviewing research protocols for compliance with FDA regulations about the protection of patients in clinical trials.

If a large clinical trial is being conducted at many medical centers across the country (also known as a multicenter trial), then each university's local IRB must approve the trial. If a company sponsors a multicenter trial, that does not involve university-affiliated medical centers, one central IRB oversees the activities at all research sites.

What determines which kind of IRB reviews a trial?

Most institutional IRBs have jurisdiction over all trials conducted within that institution. A central IRB may become the IRB of record for such trials only by written agreement with the administration of the institution or the in-house IRB. If a trial is conducted outside an academic institution with a private sponsor, then an independent or central IRB reviews the protocol.

Does it matter which kind of IRB reviewed the trial I'm considering?

There is some controversy about the use of central (independent) IRBs versus academic research IRBs. Some question the independence of central IRBs that are contractors whose services are purchased by companies whose focus is getting FDA marketing approval for their drug or device. However, the independence of university medical center IRBs has also been questioned regarding whether the interests of the institution take priority over the interests of patients. Also, academic medical centers engage in a lot of research that is paid for by drug and medical device companies. A 1999 report by the independent public interest group Public Responsibility in Medicine and Research (see *Additional resources* on p. 69) examined issues surrounding the IRB system controversy. The report concluded that neither type of IRB had a greater amount of pressure from industry than the other. This report also found no evidence that one type of IRB dealt "better or worse with such pressures."

Whatever type of IRB oversees a trial, the IRB must comply with all applicable requirements of the federal agencies that oversee the trial because these agencies do periodic inspections of IRB records and procedures to determine compliance with regulations.

The IRB system has been heavily criticized in the past few years because of serious problems in some clinical trials at prestigious research centers. Many of these problems stem from the tremendous increase in the amount of clinical research now being conducted and the fact that for many trials, IRB members are volunteers with many other pressing demands on their time. Please see the box article at the end of this section on IRB problems that affect patients.

Does an IRB or institution have to compensate a participant for an injury that occurs in a trial?

Institutional policy determines whether compensation and medical treatment(s) are offered and any conditions that might be placed on the trial participant's eligibility for compensation or treatment(s). However, FDA does require the consent form to address this issue, so patients are aware of what will happen. Furthermore, FDA requires that any statement that compensation is *not* offered must avoid appearing to waive the participant's rights or appearing to release the researcher, sponsor, or institution from liability for negligence.

If I am hurt in a trial, can I sue the IRB for not protecting me?

In 2000, for the first time in the United States, individual IRBs were named as defendants in malpractice lawsuits brought by patients who participated in clinical trials. (Patients have also brought suits against trial sponsors, researchers, and the facilities conducting the research.) These cases are still in litigation and are being watched closely for the precedents they will set about the liability of IRBs. FDA regulations do not address the question of IRB or institutional liability in the case of malpractice suits. FDA does not have the authority to limit the liability of IRBs or their members, so theoretically, they can be sued. Compliance with FDA regulations may help minimize an IRB's exposure to liability—as well as protect patients.

Do IRBs actively audit and monitor research to see if patients are adequately protected?

This has been a controversial issue. IRBs are not expected to observe consent interviews or the conduct of the study or review study records routinely. They can do this, however, if they wish. When and if an IRB is concerned about the conduct of the trial or the process for obtaining consent, the IRB may consider whether, as part of providing adequate oversight of the study, an active audit is needed. IRB time and resources are limited for actively monitoring ongoing trials, and the extent of continuing monitoring of trials by IRBs has been the subject of debate at many conferences during the past few years.

Does anyone inspect IRBs for adherence to regulations?

Yes, a sample of IRBs are reviewed. Specific IRBs may be reviewed in response to specific complaints. FDA's Division of Scientific Investigations at the Center for Drug Evaluation and Research maintains an inventory of IRBs that have been inspected, including dates of inspection and classification. The Division also now includes inspection results from FDA's Center for Biologics Evaluation and Research and FDA's Center for Devices and Radiological Health. Since FDA regulates slightly more than half the clinical research conducted today, this covers a lot. Anyone can access this information through Freedom of Information Act (FOIA) procedures. Once an investigational file has been closed, the correspondence between FDA and the IRB and the narrative inspectional report are also available under FOIA. FDA routinely posts much of this information on its Web site (http://www.fda.gov), including warning letters to companies, individual researchers, and institutions.

The U.S. Department of Health and Human Services (DHHS) also now maintains a registry of IRBs. That registry houses information about individual IRBs, their members, and their qualifications. Registration of IRBs is not mandatory, but DHHS strongly encourages it. IRBs overseeing federally funded research, such as NIH trials, would be registered here.

If an IRB rejects a study protocol and a researcher sends it to another IRB, is the second IRB told of the rejection?

Yes. When an IRB does not approve a study, it must provide a written statement of the reasons for its decision to the researcher and institution. If the study is submitted to another institution's IRB or to a central IRB, a copy of this written statement must be included with the study documentation so that the new IRB can make an informed decision about the study.

Problems with and solutions for IRBs

In the late 1990s, the Department of Health and Human Service's (DHHS) Office of Inspector General (OIG) investigated how well IRBs were functioning. Those investigations resulted in the issuing of four reports in June 1998 that described problems with the current IRB system in the United States and made recommendations for reforms. (Web site addresses to obtain the full reports are listed in *Additional resources* on p. 69.) One of the key problems identified involved the limited efforts by IRBs to conduct continuing review of research in progress, which directly relates to the safety of patients participating in clinical trials. OIG identified many reasons why ongoing IRB review is hampered and offered recommendations for reform. Federal agencies, patient advocacy groups, and the private sector have put a lot of effort into improving patient protection and reforming and improving the IRB system since 1998. Much work remains to be done. In response to the 1998 reports and congressional hearings, DHHS took action to strengthen the protection of participants in clinical trials. In May 2000, DHHS Secretary Donna Shalala said the new initiatives were "designed to further strengthen government oversight of all biomedical research, including gene transfer research." She also said the efforts were intended to "reinforce institutions' and researchers' responsibility to follow internationally accepted ethical standards and federal guidelines."

One of these initiatives was the creation of the Office for Human Research Protections (OHRP) in 2000. OHRP monitors federally funded clinical research to help protect patients in trials at more than 4,000 universities, hospitals, and other research institutions in the United States and abroad. OHRP also works with NIH and FDA to protect patients by sponsoring training of investigators and IRB members, providing guidance and procedures for the patient consent process, and monitoring researcher and sponsor conduct in trials. The IRB problems and recommendations identified by the reports, along with DHHS initiatives to address them, are summarized in *Appendix D*, on p. 105.

Chapter 13— What Reasons Do Patients Give for Participating and Not Participating in Clinical Trials?

Many studies have looked at the reasons adult patients with a life-threatening or serious illness give for having entered or not entered a clinical trial. Knowing what other patients have decided about participating may help clarify your thinking about why you do or do not want to enter a trial.

ECRI performed a formal systematic assessment to identify the most common reasons. First, ECRI conducted searches to identify all published English-language articles on this topic. We found 18 studies, but 4 of them did not report information about the percentages or numbers of patients giving each reason, so we could not analyze them. This left 14 articles with data for ECRI to evaluate. ECRI conducted various statistical analyses, grouping these studies together to try to identify the most common reasons given by patients. Results varied widely from study to study, and the differences in results could not be explained by differences between patients or by differences in study methods. After analyzing all the studies together, ECRI was able to give some estimates of the most common reasons given. We summarize these results below.

Reasons for participating

The three most commonly cited reasons that patients gave for participating in a clinical trial were:

1. Hope of some personal therapeutic benefit (reported by 16% to 100% of patients in different studies)
2. Confidence in their physician's recommendation to enter a trial (reported by 0% to 63% of patients in different studies)
3. Hope of benefiting others (reported by 0% to 65% of patients in different studies)

ECRI used statistical methods to try to estimate the typical percentage of patients who cited these reasons over all the studies. ECRI found that an estimated 45% of patients cited personal benefit, 30% of patients cited physician influence, and 21% of patients cited a desire to benefit others.

Other reasons for participating cited by patients varied widely. They included:

- No other alternative
- Family/friend influence
- Better to do something than having no treatment
- Free care and medication
- Better monitoring of condition
- Pressured to enroll by research trial personnel
- Nothing to lose
- Have the time to do it
- Trust in institution, doctors, nurses
- Don't know why, just did it

Reasons for not participating

Patients' most common reasons for not participating in trials were:

- Fear of placebo or randomization (reported by 1% to 31% in different studies)
- Too far to travel (reported by 11% to 37% of patients in different studies)
- Desire to have the physician choose the treatment (reported by 0% to 18% of patients in different studies) rather than accept a process that uses randomization to assign patients to a treatment group

Notice that the percentage did not exceed 37% for any one reason. When ECRI used statistical methods to estimate the prevalence of reasons given for not participating in a trial, the highest percentage was for travel concerns (23%) and the lowest percentage was for the desire to have the physician choose the treatment (11%).

Other reasons given for not participating (in no particular order of frequency) were:

- Preference for receiving standard treatment
- Fear or dislike being treated like a "guinea pig"
- Lack of insurance coverage for clinical trials
- Complex consent process
- Unable to give consent
- Doctor objected
- Family objected
- Not interested
- Condition deteriorating
- Inconvenient
- Dislike focusing on disease
- Not enough time

These reasons raise a number of questions for patients to consider when thinking about entering a clinical trial. Many of these issues are addressed in different sections of this Guide. Concerns about randomization, placebos, and treatment choice are in the section *What is randomization in a controlled trial?* on p. 19. Concerns about insurance coverage and the tangible and intangible costs of being in a trial to patients and their loved ones are discussed in *What costs will I incur in a clinical trial? Will my health insurer pay?* on p. 59. Issues about consent and the patient's right to enroll or to withdraw from a trial are in the section *What is "informed" consent?* on p. 39. Issues about the need for patient support during the trial are discussed in *What kind of care can I expect during a clinical trial?* on p. 35 and *How do I enter a clinical trial?* on p. 29.

Chapter 14—Will the Kind of Healthcare Facility Conducting the Trial Affect My Care?

Clinical trials are conducted at many kinds of medical facilities—university medical centers; community hospitals; specialized centers for cancer, heart disease, and organ transplantation; government hospitals; independent research institutes; and doctor's offices. The kind of healthcare facility should not make a difference in the quality of a trial or the quality of care you receive. There are differences among the settings in which clinical trials are conducted. No matter where a trial is conducted, research is subject to the same regulations to protect patients. Some people believe that a large medical center at a university is more desirable because of its reputation, experience, and resources. However, trial sponsors see great value in having physicians in private practice participate in trials because these doctors represent "the real world" of medical practice. Companies like to test the treatment in a broader mix of patients and settings than just one type of clinical setting.

Where a trial is conducted often depends on the trial's size and complexity. Large trials require resources that a community hospital or physician's office cannot provide because a large infrastructure is needed and is costly to maintain. Trained study coordinators, adequate research nursing staff, biostatisticians, data management personnel, a complex financial support system, and an investigational pharmacy to track the delivery of the test drugs are needed. The size of this infrastructure and the setting at a university medical center permit more checks and balances on how the research is being conducted than in a doctor's office or community hospital. So, one advantage of this setting is that more people are involved in the research, looking over each other's shoulders, and witnessing the care of each patient.

Nonetheless, a lot of pharmaceutical research is now being conducted in private doctors' offices and community hospitals. One of the reasons private doctors give for wanting to be involved in research is to make new drugs available to their patients earlier than would be possible otherwise. For example, private practitioners who treat HIV infection are carrying out trials on new HIV drugs.

Another reason private practice doctors are joining clinical research is that the research is another source of income, just as research has long been a major source of income for academic medical research centers. Trial sponsors pay costs for each patient enrolled in the study. The payment is intended to cover the cost of care, patient follow-up, data collection, analysis, and the cost of the staff and space required to support the trial.

What do I need to consider about where a trial is done and who is doing it?

The experience and training of the researchers are important. Once there may have been a presumption that university medical centers provided the best care in a research setting, but that is not necessarily the case today. Please see the *Checklist: What should I know about the place and people conducting the clinical trial?* at the end of this section.

What about reports in the news recently about problems in trials at reputable research centers?

Headlines in newspapers or television have pointed out things that have gone wrong at some prestigious research institutions in this country. Public trust has been shaken in clinical research. Several medical research centers at universities and cancer centers have had serious problems or unexpected adverse events, including deaths, during clinical trials. Overall, unexpected deaths resulting from participation in a clinical trial are very rare. Some of the recent events that have made headline news were especially tragic because they involved deaths of young, relatively healthy volunteers participating in phase I trials. These events also pointed out problems that need to be addressed to make all trials safer for patients. It's also important to remember that, unfortunately, healthcare providers and hospitals have made mistakes that have caused a significant amount of injury and death in routine care—so getting care outside a clinical trial also has risks and uncertainty.

The National Institutes of Health and the U.S. Food and Drug Administration (FDA) have taken strong corrective actions to address problems in clinical research. These include barring certain researchers from clinical research, shutting down some types of research for the foreseeable future at some institutions, closer oversight of trials by Data Safety Monitoring Boards, and better education and training for researchers and members of institutional review boards. Data Safety Monitoring Boards are set up by a clinical trial sponsor to evaluate trial progress, safety data, and significant outcomes according to FDA regulations. Community representatives and clinical research experts are board members and can recommend revisions to or discontinuation of a clinical trial if the trial objectives remain unmet or safety concerns arise. In addition, the Department of Health and Human Services reorganized and strengthened the federal agency now known as the Office for Human Research Protections. Patient advocacy groups have also strengthened their roles in clinical research. They have increased efforts to get well-trained patient advocates on institutional review boards. Some groups, such as the National Breast Cancer Coalition, are working alongside researchers to design clinical trials and consent processes from a patient perspective as well as a research perspective.

Checklist: What should I know about the place and people conducting the clinical trial?

Whether a university medical center, community hospital, or doctor in private practice conducts the trial, here is a list of questions you may want to ask. Note that a doctor in private practice is putting on a different hat when he or she takes on the role of researcher in addition to caregiver. Consider getting a second opinion about your participation in the trial from a doctor who is neutral about the trial before you enroll. There are some potential conflicts in changing from the role of doctor to clinical researcher. See *What are the ethical issues in clinical research?* on p. 65 for more about this.

- ✔ What experience does the research team have in doing trials?
- ✔ What is your (and the institution's) financial interest in this trial?
- ✔ What problems have you (or the institution) had conducting trials in the past?
- ✔ How were those problems identified and resolved?
- ✔ What resources are available to care for me if I have any side effects or complications, and how quickly will I be taken care of?
- ✔ What checks and balances are in place to ensure ethical conduct?
- ✔ What do you do to monitor patient safety throughout the trial?
- ✔ Who will keep in touch with my other doctors about my other healthcare needs during the trial?
- ✔ How will you feel about treating me if I don't want to be in the trial you are running?
- ✔ What will happen to our relationship if at some point I want to withdraw from the trial?

Chapter 15— What if I Need Other Medical Care While I'm in a Trial?

You can get the care you need from your usual doctors. However, if you are entering a trial, tell all your other doctors that you are in a clinical trial. Coordination of care among all the doctors treating you—both inside and outside of a clinical trial—is essential for your safety. Be sure to give all your doctors permission to share medical information with any healthcare provider caring for you. In this way, all of your healthcare needs can be appropriately coordinated. Problems have arisen in trials when research doctors lack full information and records from other doctors treating the patient—especially if the patient has traveled to another medical facility for the trial.

Another reason it's important to keep all your healthcare providers informed is that if you experience a new "unrelated" condition, it may actually be caused or made worse by the trial treatment. Also, even routine treatment for another condition might interact in some important way with the clinical trial treatment.

Some issues arise when a patient in a trial at one institution is admitted to another place. Here are two examples to illustrate some key points. When a patient receives treatment or hospitalization at a different healthcare facility from the one conducting the trial, the facility conducting the trial is to have procedures in place for rapidly identifying test drugs and devices (e.g., an emergency contact number and unblinding procedure) that a patient is using. If a patient is in a trial in which he or she does not know which treatment group she is in (a blinded trial), the researchers will "break" the blinding to reveal the treatment the patient was receiving. The doctor treating the patient at the nonresearch facility decides, after appropriate consultations with the researcher, whether to continue the test treatment while the patient is there. The researcher where the clinical trial is being done remains responsible for test-drug administration and follow-up and therefore needs to know about any hospitalization. The researcher also may need to report the patient experience as an "unexpected adverse incident" if it is possibly related to the experimental treatment.

If a patient needs anticipated, routine care for health conditions other than the one being treated in a trial, the researchers discuss it with the patient and treating physician before the patient starts the trial to set up the necessary care. The research facility's institutional review board (IRB) should be aware that other facilities or healthcare providers will be providing medical care. The IRB is responsible for ensuring that adequate reporting and safety systems regarding all patient care are in place before they approve a trial.

Whether the need for additional care is expected or unexpected, the local treating physician should obtain all necessary information from the clinical researcher to safely continue the experimental treatment from the trial while providing other care. Also, you should not need to sign a new consent form to continue receiving the trial treatment while at another facility that is treating you. The information conveyed should include a description of treatment procedures, warnings of possible adverse reactions, emergency procedures, and a copy of the signed consent form (which is a research summary as well as a consent form).

Chapter 16—What Costs Will I Incur in a Clinical Trial? Will My Health Insurer Pay?

A patient's costs can vary and may affect your decision about participating. Many health insurers now pay for costs of routine care given in the context of a clinical trial. Routine care costs typically include the medical care a patient would need whether he or she was in a trial. Examples of a routine care cost might be the tests that are needed for diagnosis and staging of the disease or some of the patient check-ups needed to monitor disease status.

You may have few out-of-pocket costs depending on the type of study you have entered, or there may be some fees associated with the treatment. Decisions about charging trial participants for investigational drugs and devices are guided by professional ethics, institutional policies, and Food and Drug Administration (FDA) regulations. In drug trials, there is rarely any cost to the patient for the investigational drug—the sponsor absorbs the cost of this as part of its research and development costs unless FDA has given the company special approval to charge for the drug. For trials that involve a device, there often is a cost for the device. Health insurance coverage for clinical trials is discussed later in this section.

Whatever the costs, any patient enrolling in a trial must be informed of those costs. Regulations require that the consent form outline all costs for care that will be billed to patients or their insurance companies as a result of participation in the study. FDA does not prohibit charging participants for treatment or services in a trial. The institutional review board (IRB) overseeing the trial has the responsibility to ensure that any such charges are appropriate and fair.

What charges might there be for investigational medical devices and radiation treatments?

The FDA's Investigational Device Exemption (IDE) regulations, which govern trials on experimental devices and radiation treatments, let sponsors charge for an investigational device. However, the charge should not exceed the amount needed to recover the costs of manufacture, research, development, and handling of the investigational device. A sponsor must justify to FDA what it intends to charge. This must be included in the IDE application submitted to FDA asking for approval to conduct the trial. The application must state the amount to be charged and why the charge does not constitute commercialization. FDA usually allows sponsors to charge researchers for the device, and the researchers can pass this cost on to trial participants.

What charges might there be for investigational drugs?

FDA's Investigational New Drug regulations let a sponsor charge for an investigational drug only under the conditions set forth below. In a clinical trial, the charge should not exceed an amount that is necessary to recover the costs related to the manufacture, research, development, and handling of the investigational drug or biologic. This also applies in cases where a patient gains access to an investigational drug outside the clinical trial (see the discussion of "expanded use" in the section *How do I enter a clinical trial?* on p. 29). FDA may stop letting a sponsor charge a fee if FDA finds that the conditions underlying the reason for the charge no longer exist.

A sponsor needs FDA's written approval to charge for an investigational drug or biologic in a clinical trial. To get approval, the sponsor must explain to FDA why providing the product without charge should not be considered part of the company's normal cost of conducting a trial.

A sponsor may charge for an investigational drug or biologic if access is granted outside of the trial. To do this, the sponsor must show that:

- There is adequate enrollment in the ongoing clinical investigations.
- Charging does not constitute commercial marketing of a new drug for which marketing approval has not yet been granted.
- The drug or biologic is not being commercially promoted or advertised to patients and doctors.
- The sponsor is actively pursuing marketing approval.

What costs are associated with being in a clinical trial?

There are tangible and intangible costs that patients may want to consider. Some tangible costs for clinical trial participation may also be "indirect" but very important to consider. These include the costs for travel, lodging, and additional lost time from work when participating in a trial. If you have a loved one or friend who travels to and from your appointments with you, or if the trial is in a town far away and someone accompanies you, they will also incur these types of expenses. The clinical trial research coordinator or a patient advocate from the trial may be able to help you determine what those costs would amount to over the full course of the trial. They may also have resources for lodging arrangements geared for patients participating in a trial and their loved ones. You should also ask who is responsible for paying the costs of treatment for any complications or side effects caused by trial participation should they occur.

Intangible costs include those such as separation from loved ones during the trial and other quality-of-life issues in terms of how the trial affects a patient's activities of daily living. For example, side effects from treatment, even if they are deemed "minor" and "temporary," such as nausea, can significantly affect a patient's activities and feelings. Also, in studies analyzed by ECRI, the need to travel to participate in a trial was the most common reason patients gave for not participating. So, it is important to consider the potential impact of the trial on your activities, quality of life, and relationships with loved ones.

Are trial costs covered by health insurance?

Costs of routine care (as described above) in many clinical trials, especially phase III trials, are now covered by many health insurance plans and Medicare. When you know which trial you are interested in, check with your health insurer about coverage. Health insurers often consider these requests on a case-by-case basis. It will be to your advantage to have the trial protocol in hand with other details about who is conducting and funding the trial. In some states, laws have been passed requiring health plans to cover various costs associated with care given in a clinical trial. The American Association of Health Plans (AAHP) tracks these state laws. Their chart summarizing which states had laws or mandates requiring health insurers to provide clinical trial coverage as of December 2001 is in *Appendix A* on p. 84.

A 1999 report by the U.S. Government Accounting Office, *NIH Clinical Trials: Various Factors that Affect Patient Participation*, found that most of the health plans they interviewed paid for some costs in clinical trials and determined coverage on a case-by-case basis. The report stated that once coverage was approved, insurers typically agreed to pay the standard, non-experimental care costs associated with the trial. Of course, "non-experimental care costs" are subject to some interpretation, so payments vary from health plan to health plan. These costs might include additional office visits and tests to monitor the patient's condition.

Many health plans have decided to collaborate in clinical research with sponsors or to allow patients to enter trials that meet certain criteria. AAHP provided information about health plan clinical research initiatives for this Guide. This information can be found in *Appendix E* on p. 107.

Recently, Medicare was mandated to cover some of the costs of patient care in clinical trials. For patients with Medicare coverage, most routine costs in federally funded or federally approved clinical trials are covered. The clinical trial investigators must also register the trial with Medicare. If the trial is not federally funded or approved, it must seek coverage approval from Medicare. If you are a patient with Medicare coverage, ask the investigator of the clinical trial you are considering whether the trial is covered by Medicare. *Appendix F* (p. 108) lists the detailed Medicare decision regarding coverage for clinical trials.

Chapter 17— Are Patients Ever Paid for Being in a Trial?

Sometimes, but not usually in cases of trials for patients with a serious or life-threatening illness. Federal agencies such as the Food and Drug Administration (FDA) and National Institutes of Health regulate the conditions under which this occurs. Most often, when payment is given, it is for healthy volunteers in phase I trials of a new drug or device under investigation. Payment is also sometimes given for studies of drugs that are already on the market—these may be phase IV studies, also known as "postmarketing surveillance" studies. For example, a phase IV study may involve study of a new dosing schedule for an existing drug (e.g., once-a-day dosing versus three-times-a-day dosing).

Payment to research subjects for participating is not considered a benefit. It is thought of as a recruitment incentive. Financial incentives are often used when health benefits to subjects are remote or nonexistent in the trial. The amount and schedule of all payments proposed by a trial sponsor are presented to the institutional review board (IRB) during initial review of the trial protocol. The IRB reviews both the amount of payment and the proposed method and timing of disbursement to ensure that neither are coercive or could unduly influence someone to participate. (Please see *What is an institutional review board?* on p. 49.)

Any amount of money being paid to a patient should accrue as the study progresses. For example, FDA says payment should not depend on the patient completing the entire trial. Typically, payment to patients who withdraw from a trial is made at the time they would have completed it (or a phase of it) had they not withdrawn. For example, in a trial lasting only a few days, an IRB may allow a single payment date at the end, even to patients who withdrew before that date.

While the entire payment should not depend on completing the trial, FDA allows payment of a small proportion before or during the trial as an incentive to complete the trial, providing that the incentive is not coercive. The IRB determines whether any bonus paid for completion is reasonable and not so large as to unduly influence patients to stay in the trial when they would otherwise have withdrawn. All information about payment, including the amount and schedule of payment(s), must be included in the consent document.

Can a trial sponsor offer as payment a coupon for a discount on the purchase price of the drug or device once it has been approved?

No. FDA states that this presumes, and wrongly conveys to trial participants, a certainty of favorable outcome of the study and prompt approval for marketing. Also, if the drug or device is approved, the coupon may financially coerce the patient to use that drug or device, even if it may not be in his or her best interest. If a coupon for a drug or device is given to a patient, he or she should inform a patient advocate (if the trial has one) or the IRB overseeing the trial.

Chapter 18— What are the Ethical Issues in Clinical Research?

Ethical issues in the conduct of clinical trials have existed for as long as trials have been conducted. Three main documents—the Declaration of Helsinki, the Nuremberg Code, and the Belmont Report—present the overarching principles guiding the ethical conduct of modern clinical research and the creation of regulations to protect research patients and can be found in *Appendix B*. New technologies, such as stem cell research, gene therapy, animal tissue transplantation into humans and the way they are being developed raise a host of new ethical dilemmas. For patients, the core of the dilemma is trust in physicians. Frances Miller, a professor of public health and law at Boston University, and an institutional review board (IRB) member at three Harvard teaching hospitals, sums it up this way in a recent article, "Trusting Doctors," in the Boston University Law Review:

"As new technology and pharmaceuticals have brought doctors expanded scope for simultaneously treating patients and making money, many physicians have discovered creative ways to align their self-interest, financial and otherwise, with patient therapy." Miller further points out, "Research physicians realize that success depends upon their ability to produce reliable scientific results which can be published or otherwise used to obtain professional advancement. Reliable scientific results are also the key to [Food and Drug Administration] FDA approval, federal research dollars, and future funding from drug and device manufacturers." And because there can be no trial without patient volunteers, this climate raises issues for patients, trust of doctors, and consent processes.

Cases in the news media of problems in some trials have spawned intense activity in federal oversight of clinical trials since the late 1990s. The federal government's Office for Human Research Protections and FDA have temporarily shut down clinical research at several leading academic research centers since 1999 because of concerns about patient safety and ethical conduct of research. New federal policies on patient protection were initiated by various government agencies with clinical trial oversight after the Office of Inspector General reported in 1998 on serious problems with the IRB system. This Guide cannot address many ethical issues affecting clinical trial research today. But it touches on a few key issues directly affecting patients in clinical trials: financial and intellectual conflicts of interest and the blurring role of physicians and researchers.

It may be difficult to have a frank discussion with the researcher about potential conflicts of interest, especially financial investments in companies for which he or she is conducting research. If you are not comfortable asking the researcher directly, there are some options. A friend or loved one could inquire on your behalf, or you could ask a different member of the research team. If you want to know, you have a right to know. But only you can decide your comfort level with the information you gain during these inquiries.

What is a conflict of interest in a clinical trial?

Conflict of interest is best thought of as a problem that arises when one person's professional obligation to someone else conflicts with his or her personal interests. As humans, we all have conflicts of interest. Recently, the medical research community, the public, federal agencies, private industry, and bioethicists have paid much attention to conflicts of interest in clinical research. The increased interest arises from the skyrocketing amount of clinical research being done and huge increases in sponsorship by private companies. By the late 1990s, annual medical research spending by private-sector businesses surpassed National Institutes of Health research spending by several billion dollars. That trend is expected to continue. This industrialization of clinical research has added to the potential for conflicts of interests in clinical trials. Academic research institutions now partner with companies to conduct their research. Companies now exist whose sole business is to run clinical trials for sponsors in private doctors' offices and community hospitals. These companies are called contract research organizations. These relationships create tension among the interests of institutions, researchers, doctors, and patients. From a patient's perspective, being able to trust the doctor offering a trial is the key issue.

A conflict of interest in a clinical trial exists when the interests of the researchers and/or institutions conducting the research are at odds with their professional obligation to patients in the trial. The obligation of researchers also includes maintaining the integrity of the research to achieve valid results—whether positive or negative.

Conflicts of interest are inevitable. Their existence does not mean that someone has done something wrong. What matters is the way a researcher or institution handles a conflict of interest. The key moral question is whether the person with the conflict of interest has fulfilled his or her obligation to the patient or compromised it to promote self-interest. The tension in a conflict of interest comes from the need to balance self-interests and patient welfare. If the researcher is unable to be objective about the research or look out for what is best for the patient, there is a moral and ethical problem.

For example, take the case of a researcher who developed a new gene therapy and headed the phase I research in clinical trials. He owned 20% of the stock of the small biotechnology company that bought the rights to his development. The hospital where the research was being done owned another 20% of the stock of the small biotechnology company. The researcher and hospital have a conflict of interest between obtaining positive results from the research to get a return on their investment and maintaining the welfare of patients in the trial. Most people would agree that the researcher and hospital have an obligation to tell patients about their financial interest in developing the gene therapy. Of course, even with financial interest at stake, it is theoretically possible to put patient welfare first, although even the best of intentions can be influenced unconsciously by self-interests.

A different sort of conflict of interest arises in the case of a researcher in an academic institution who is up for promotion in his department as a result of success in obtaining large research grants, recruiting patients into clinical trials, and publishing journal articles based on the research. Although there is no direct financial conflict of interest, the conflict exists between the researcher's self-interest for career advancement and his reputation and patient welfare in recruiting potential participants without unduly influencing them to participate. The researcher might present an excessively rosy picture of what a trial can offer a patient. This might not be deliberately misleading, but rather it may come from the researcher's enthusiasm for and commitment to his work.

How might conflicts of interest affect me?

A conflict of interest might mean that a research doctor subtly persuades you through enthusiasm or by downplaying the risks to enroll in a trial. Although this can be unconscious on the part of the researcher, the balance is upset between the researcher's interests and patient welfare. The researcher may overemphasize the promise of the new treatment because of a desire for positive outcomes and perhaps also a wish to be able to offer the patient something when all other options are gone.

A conflict of interest might also mean that a researcher's clinical observations about how well you are doing differ from your perception of how you feel. The researcher might downplay reporting of side effects. He or she might record observations that suggest you are doing better than you are. If this happens, the researcher's observations compromise the integrity of the research. The researcher's interest in positive results outweigh the individual patient's welfare. In any case, for patients, it's important to remember that early phase trials can promise no therapeutic benefit and to carefully consider the risks that are explained.

What do researchers have to disclose to patients about conflicts of interest?

There has been much controversy over what researchers should disclose to trial participants, especially regarding financial interests in companies sponsoring the research. Researchers are supposed to disclose potential financial conflicts of interest to the institution in which their research is being conducted. It is the institution's responsibility to decide what to do with the information. Sometimes IRBs are given the information, but often they are not. A recent article in the *New England Journal of Medicine*, "Conflict-of-interest policies for investigators in clinical trials" (November 30, 2000) found that the policies at 10 leading academic medical centers varied widely about disclosure of financial interests in drug, device, and biotechnology companies. Some researchers feel insulted that anyone would think that their financial interest would be greater than their concern for patient welfare. On the other hand, those who want to reduce potential conflicts of interest feel that, despite the Hippocratic oath and other guiding ethical principles, doctors are only human and can be tempted by the same things that tempt us all—money, recognition, and power.

What conflicts exist between the role of physician and the role of researcher?

You might learn about a clinical trial through your own physician. Physicians caring for patients are asked more than ever to help recruit patients for clinical trials. Physicians may be paid for each patient they recruit to a trial and this serves as a source of additional income. Physicians in private practice outside academic medical centers are participating as researchers more than ever because of the enormous amount of research being conducted by the private sector—more than $20 billion in the year 2001 alone. This combined role can be confusing for patients because the purpose of medical research is to benefit society, and this differs from the purpose of treating individual patients, which is to offer the standard treatment that is known to work best.

It is also sometimes difficult for doctors who are explaining to patients various standard treatment options and unproven treatment options in clinical trials. The doctor must grapple with allegiance to each patient and allegiance to the research. In a clinical trial, the research doctor is constantly balancing patient care and safety with the goal of advancing the research. This can be more challenging for doctors in private practice who usually spend most of their time offering standard care to patients, not conducting research. It can be helpful to get more than one medical opinion about your condition, standard treatment options, and clinical trials.

Trust is key to sorting out what a doctor/researcher recommends for you. Only you can decide whether you trust the doctor and the researcher. Generally, trust is built when a patient feels respected, listened to, and genuinely cared for and when questions are answered openly and honestly by the doctor/researcher. Because the goal of treatment differs in standard therapy and research, this necessarily alters the doctor-patient relationship and interactions.

In her article "Trusting Doctors," Professor Miller of Boston University, concludes that doctors' significant financial conflicts should routinely be disclosed to patients during the consent process. She writes, "Disclosure of such information will not deter most potential subjects from participating ... because the medical profession still enjoys a high degree of trust from most people… . Trust between research physicians and patients is a precious commodity, which must not be squandered in the…pursuit of commerce—or even science."

Checklist: What should I ask about conflicts of interest?

Learn whatever you can about the researcher's interests in the trial by asking questions during the consent interview. Here is a checklist of some questions you might want to ask.

- ✔ What are the researcher's reasons for doing the trial?
- ✔ What is the researcher's relationship with the company whose drug or devices are being tested in the trial?
- ✔ Is he or she a paid consultant to any company sponsoring any part of the research?
- ✔ Does he or she own stock in the company?
- ✔ Are bonuses given by the sponsor to the institution or researcher for reaching certain patient recruitment goals for the trial?
- ✔ Are there plans to publish a paper about the trial results?
- ✔ Does publication depend on positive results of the trial?
- ✔ Does more funding depend on positive results of this trial?

Chapter 19— Additional Resources

Where can I learn about trials that are recruiting patients?

Aside from ads for trials in newspapers and on the radio and television, many private companies, organizations, and federal agencies list currently ongoing clinical trials. Some of these services also "match" patients and clinical trials. However, patients should know that many database listing and matching services are paid a fee for each patient enrolled. Also, these services might list only the trials of the sponsors and companies paying for listing and matching services.

Acurian

http://www.acurian.com/
This is a for-profit company that links the biopharmaceutical and pharmaceutical companies that sponsor clinical trials with qualified physician investigators who are needed to conduct the trials and the patients who are needed to participate in the trials. There is no fee to patients searching for clinical trials. The site provides detailed information on clinical trials and new medical therapies that allows patients to search a proprietary database of more than 42,000 clinical trial sites. Patients search by medical condition and state to find out what trials are currently available. The site also provides detailed drug information from development through approval processes and links to articles from medical and clinical research resources.

AIDS Clinical Trial Information Service (ACTIS)

http://www.actis.org/index.html
The U.S. Department of Health and Human Services provides this clinical trial database. The site is a central resource for federally and privately funded HIV/AIDS clinical trial information. The site also provides information on the newest drug treatments, research on vaccines, and links to other relevant databases.

CenterWatch

http://centerwatch.com/
This for-profit company offers information related to clinical trials, including a listing of more than 41,000 industry- and government-sponsored clinical trials. It also provides information on new drug therapies recently approved by the U.S. Food and Drug Administration (FDA). The site is designed to be a resource both for patients interested in participating in clinical trials and for research professionals. CenterWatch offers patients and their family and friends free and confidential e-mail messages every time a new clinical trial is listed on the CenterWatch Web site. The site also assists patients in finding and applying to participate in clinical trials. There is no fee to patients.

Coalition of National Cancer Cooperative Groups

http://www.ca-coalition.org/
This nonprofit organization's stated mission is to "improve the quality of life and the survival of people with cancer…by raising awareness of cancer clinical trials and by working with all interested organizations to ensure the continued opportunity for cancer patients to participate in high quality clinical trials." Trials listed on this site are those sponsored by members of the Coalition of National Cooperative Groups, Inc., including the American College of Surgeons Oncology Group (ACOSOG), Cancer and Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), Gynecologic Oncology Group (GOG), North Central Cancer Treatment Group (NCCTG), Radiation Therapy Oncology Group (RTOG) and the National Surgical Adjuvant Breast and Bowel Project (NSBP).

HopeLink

http://www.hopelink.com/index.jsp
HopeLink is a for-profit healthcare information technology company that provides Web-based products and services for companies in the clinical trial industry as well as for patients. HopeLink brings together groups from the healthcare, high-technology, and nonprofit sectors to improve clinical trials awareness and accelerate patient enrollment in trials. The site offers information for cancer patients about clinical trials currently open for enrollment, trial sites, patient inclusion/exclusion criteria for each open trial, and contact information for the organization conducting the trial. The service is free to people searching for clinical trial information. The directory currently includes cancer trials from both government and industry sponsors. The site began offering information on trials for other diseases in 2001.

MyCure

http://www.mycure.com/
This is a for-profit patient and clinical trial matching service that provides patients with information about possible research therapies for their condition and informs the public about select ongoing clinical trials. Patients can register for information about relevant clinical trials and matching services online. There is no charge to patients.

National Cancer Institute (NCI)

http://cancertrials.nci.nih.gov/
This is a federal government-sponsored site providing cancer information from the National Cancer Institute (NCI), which is part of the National Institutes of Health. Links at the site provide information and news about cancer research, some of the latest published articles from medical journals on cancer research developments, and trials listed in PDQ®, (Physician Data Query) NCI's database of about 2,000 clinical trials.

National Institutes of Health (NIH)

http://www.clinicaltrials.gov
NIH has developed this site to provide patients with current information about federally funded clinical trials for a wide range of diseases and conditions. It is broader in scope than the NCI cancer trials site. The site provides general information about clinical trial participation, and you can search the site by disease/condition, trial sponsor, or geographic site.

Office of Research on Minority Health (ORMH)

http://www1.od.nih.gov/ormh/mhi/research
This NIH agency lists clinical trials that specifically address minority health issues. Trials that are recruiting patients are listed mainly by disease category (e.g., cancer, diabetes, cardiovascular disease, kidney disease, hematology).

Pharmaceutical Research and Manufacturers of America (PHRMA)

http://www.phrma.org
PHRMA represents the United States' leading research-based pharmaceutical and biotechnology companies. The Search for Cures section of their Web site features New Medicines in Development. This is a database containing information about new drugs being researched in clinical trials. You can search the database by disease, drug name, company, or indication for the drug's use. You can also sign up online to receive free updates on new drugs in development and pharmaceutical policy issues.

Radiation Therapy Oncology Group (RTOG)

http://www.rtog.org
This site was developed by a national cooperative research organization under the auspices of the American College of Radiology whose focus is on clinical trials that involve radiation therapy either alone or in conjunction with surgery and/or chemotherapeutic drugs. This cancer study research group is funded by the NCI and comprises 250 of the major research institutions nationally and in Canada. In 2001, it had more than 40 active studies that involve radiation therapy either alone or in conjunction with surgery and/or chemotherapeutic drugs.

Links to federal agencies and federal reports on clinical trial issues and human subject protection

Department of Health and Human Services (DHHS)

http://oig.hhs.gov/oei/summaries/b275.pdf
This directly links to the 1998 Office of Inspector General report on the institutional review board (IRB) system, *The Emergence of Independent Review Boards*. You will find information on the development of independent (also called central) IRBs and their role in ensuring protections for human participants in clinical research.

http://www.dhhs.gov/progorg/oei/reports/a276.pdf
This directly links to another 1998 Office of Inspector General report on the IRB system, *Institutional Review Boards: A Time for Reform*. It includes recommendations aimed at several federal agencies that have clinical trial and IRB oversight.

http://www.dhhs.gov/progorg/oei/reports/a273.pdf
This directly links to another 1998 Office of Inspector General report on the IRB system, *Institutional Review Boards, Their Role in Approving Research*.

http://www.hhs.gov/oig/oei/reports/a459.pdf
This directly links to the June 2000 Office of Inspector General report on *Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research*.

http://oig.hhs.gov/oei/reports/a447.pdf
This directly links to the full text of the April 2000 Office of Inspector General report, *Protecting Human Subjects: A Status of Recommendations*. This updates NIH's and FDA's response to recommendations made in the 1998 reports criticizing the IRB system.

http://www.hhs.goc/news/press/2000pres/20000523.html
This links to a DHHS press release describing new initiatives beginning in May 2000 on the safety of human research subjects.

Food and Drug Administration (FDA)

Cancer Liaison Office

http://www.fda.gov/oashi/cancer/trials.html
This site offers consumer information about cancer, trial listings, and other information about cancer trials by disease category. It also provides links to NCI-designated cancer treatment centers.

Center for Drug Evaluation and Research (CDER)

http://www.fda.gov/cder
This links to one of the three main divisions of FDA. This site provides information for consumers, healthcare professionals, and clinical trial sponsors about the drug approval process, drug warning letters, drug interactions, safety alerts, and consumer information on FDA activities.

Center for Devices and Radiological Health (CDRH)

http://www.fda.gov/cdrh/
This links to one of the three divisions of FDA. This division provides information for consumers, healthcare professionals, and product sponsors on medical device approval processes, product warning letters, other medical device related information and guidance, and consumer information.

Center for Biologics Evaluation and Research (CBER)

http://www.fda.gov/cber/index.html
Information about CBER's regulatory requirements and activities, the biological products regulated by the agency, and consumer information.

National Cancer Institute (NCI)

http://cancernet.nci.nih.gov
This is NCI's gateway to current and accurate cancer information. Among the many information resources at this site are disease descriptions and testing information, treatment options, cancer literature, and links to the NCI clinical trials database.

http://info.nih.gov/handbook/handbook/
NCI is one of the institutes of NIH. This links to the full text of the *Investigator's Handbook*, a manual that explains the policies and procedures of the Division of Cancer Treatment and Diagnosis (DCTD) with respect to the clinical use of its investigational drugs.

National Human Research Protections Advisory Committee

http://ohrp.osophs.dhhs.gov/nhrpac/nhrpac.htm
The National Human Research Protections Advisory Committee provides expert advice and recommendations to the Secretary of Health and Human Services, Assistant Secretary for Health, the Director of the Office for Human Research Protections, and other departmental officials on a broad range of issues pertaining to the protection of human research subjects.

National Institutes of Health (NIH)

http://www.nih.gov (general Web site)

Office of Human Subjects Research (OHSR)

http://ohsr.od.nih.gov/
OHSR operates within the Office of the Deputy Director for Intramural Research of NIH. NIH's Intramural Research Program (IRP) is located in Bethesda, Maryland. Researchers there conduct and collaborate on many different kinds of research including research involving human subjects. The OHSR was established to help IRP researchers understand and comply with the ethical guidelines and regulatory requirements for research involving human subjects. OHSR's overall goal is to promote and support the IRP's efforts to conduct innovative research that protects the rights and promotes the welfare of human subjects.

http://grants.nih.gov/grants/guide/notice-files/not97-010.html
This link shows the criteria NIH uses for rating new clinical research grants requesting funding.

Office of Human Research Protection (OHRP)

http://ohrp.osophs.dhhs.gov/
OHRP is a federal agency in DHHS that provides guidance documents for IRBs, registration for IRBs, news of upcoming federally sponsored conferences about the ethical and safe conduct of clinical trial research, and information for researchers about complying with federal regulations when conducting trials.

Office of Minority Health Resource Center (OMHRC)

http://www.omhrc.gov
OMHRC provides free information on various health issues affecting U.S. minorities, including cancer, heart disease, HIV/AIDS, and diabetes. They also provide information about participation of minorities in clinical trials and clinical trial issues that affect minorities, in particular.

Office of Research on Minority Health (ORMH)

http://www1.od.nih.gov/ormh
ORMH leads the federal effort at NIH in stimulating new research ideas for improving the health status of minorities in America from birth to the end of life. ORMH supports studies and programs as pilot projects managed by its partners, NIH and other federal agencies. ORMH was created by NIH in 1990. One of its five major areas of focus is to promote the inclusion of minorities in clinical trials. The site provides a searchable list of trials that are recruiting minorities.

Links to other agencies and organizations of interest

Agency for Healthcare Research and Quality (AHRQ)

http://www.ahrq.gov

AHRQ's National Guideline Clearinghouse™

http://www.guideline.gov
This federal agency sponsors and conducts health services research that provides evidence-based information on healthcare outcomes, quality, cost, use, and access. The information is used by patients and clinicians, health system leaders, purchasers, and policymakers to make more informed decisions and improve the quality of healthcare. AHRQ's Web site provides access to the health technology assessments performed by its 12 Evidence-based Practice Centers in North America (of which, ECRI is one) and links to databases such as the National Guideline Clearinghouse (NGC). NGC is a Web-based resource that provides online access to evidence-based clinical practice guidelines. NGC helps healthcare professionals and health system leaders select appropriate treatment recommendations by providing full text or an abstract of the recommendations.

National Academies of Science Institute of Medicine (IOM)

http://www4.nationalacademies.org/iom/iomhome.nsf
IOM's mission is to advance and disseminate scientific knowledge to improve human health. The Institute provides to the government and the public objective, timely information and advice concerning health and science policy. IOM publishes reports from its research on various health policy issues. A recent report on clinical research is *Preserving Public Trust: Accreditation and Human Research Protection Programs*, published in April 2001. The full report can be accessed directly online at http://www.nap.edu/books/0309073286/html/. Another report of interest is on Medicare coverage of clinical trials. E*xtending Medicare Reimbursement in Clinical Trials* can be accessed at http://www.nap.edu/catalog/9742.html.

National Library of Medicine (NLM)

http://www.nlm.nih.gov
A part of NIH, NLM is the world's largest medical library. The Web site hosts NLM's many databases of health information for healthcare professionals and consumers. One of its most used databases is PubMed, which contains bibliographic citations and abstracts of millions of medical journal articles that have been published in thousands of medical journals. The site is also a gateway to many other health information resources provided by the federal government.

Public Responsibility in Medicine and Research (PRIM&R)

http://www.primr.org/aahrppupdate.html
Since its founding in 1974, PRIM&R has been committed to advancing strong research programs and to the consistent application of ethical precepts in medicine and research. Through national conferences and published reports, PRIM&R addresses a broad range of issues in biomedical and behavioral research, clinical practice, ethics, and the law. Topics addressed include: the ethical and procedural issues surrounding the operation of IRBs; educating researchers and others about the responsible conduct of research; the range of problems affecting AIDS research and treatment; reproductive and other technologies and their effects on patient care; healthcare ethics committees; scientific integrity and conflicts of interest; and the general range of questions surrounding academic/industrial relations. This link provides an update on PRIM&R's plan for developing an accreditation system for human research protection programs and the formation of the Association for Accreditation of Human Research Protection Program (AAHRPP).

Chapter 20—Glossary

This glossary defines terms a patient might encounter when considering participation in a clinical trial. The sources ECRI consulted to develop these definitions are at the end of this Glossary:

Academic medical center: A medical center affiliated with a university that teaches medical students and conducts basic research (preclinical research) and clinical trials. Also called university medical center.

Active treatment: In a clinical trial, treatment that is intended to reduce or eliminate the disease in a patient.

Adjuvant treatment: Additional treatment given with the main treatment to improve the overall effects of treatment. For example, adjuvant chemotherapy is given after surgical removal of cancer to improve the chance of controlling or curing the disease.

Adverse drug reaction (ADR): A harmful response to a medicine.

- **Unexpected ADR:** an unanticipated harmful response to a medicine.

Adverse event (AE): An undesirable health event that occurs in a participant during a clinical trial. It may or may not be related to the treatment itself.

- **Serious AE:** any health problem a clinical trial participant experiences during the trial that is life-threatening, requires hospitalization, results in disability, causes a birth defect, or results in death.
- **Treatment-related AE:** an undesirable and unintended result of treatment given to a patient during a clinical trial.
- **Unexpected AE:** an unanticipated harmful response to treatment during a clinical trial.

Altruistic behavior (altruism): Voluntary behavior that involves some risk or self-sacrifice, has no external reward, and is intended to help others.

Anecdotal evidence: Informal observations of treatment results in individual patients. Doctors make such observations in their day-to-day practice of medicine.

Assurance: In a clinical trial, a formal written, binding commitment that is submitted to a federal agency by an institution in which the institution agrees to comply with regulations for research with human subjects. It specifies the procedures through which compliance will be achieved. The federal Office for Human Research Protections accepts, reviews, and issues "Assurances" for clinical trials.

Belmont Report: A report on ethical principles and guidelines for protecting human subjects of research, written by the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and published in 1979.

Bias: In a clinical trial, any factor or idea that distorts observations, results, and conclusions and thus jeopardizes the validity of the study and/or its results.

- **Selection bias:** bias that results from choosing patients for participation in a trial without taking into account patient characteristics that can skew the results.
- **Unconscious bias:** an unintended distortion because an investigator holds preconceived notions that he or she is unaware of.

Biologic: A product derived from a living organism that is used in the diagnosis or treatment of disease. Examples include gene therapy, allergy shots, vaccines, and blood products.

Biotechnology: Any and all products used in the diagnosis and treatment of disease that were derived from living organisms or biological systems.

Blinded or blinding: A method used in a clinical trial to prevent participants and/or researchers from knowing whether the patient is receiving the experimental or control treatment in a trial. Also referred to as "masking." Single blinding is when only the patient does not know which treatment he or she is receiving. Double blinding is when both the patient and researcher do not know which treatment the patient is receiving.

Carcinogens: Cancer causing substances; investigational new drugs are tested in animals and in the laboratory to determine if they cause cancer and at what dose.

Carry-over effect: A treatment effect that continues after treatment has stopped.

Center for Biologics Evaluation and Research: The division of the FDA that safeguards the public health through regulatory control of the research and marketing of biological products such as blood, vaccines, therapeutics, and related drugs and devices.

Center for Devices and Radiological Health: Division of FDA that safeguards the public health through regulatory control of the research and marketing of medical devices, devices that deliver radiation therapies, and radioactive products used in healthcare.

Center for Drug Evaluation and Research: Division of FDA involved in regulating new drug development and approving new molecular entities for research and commercial marketing. FDA also conducts generic drug review, over-the-counter drug review, and postmarketing surveillance of drugs approved for marketing. This agency is responsible for reasonable assurance of the safety, effectiveness, and labeling of all drug products for human use.

Chemotherapy: Drugs used to treat illness; often refers to drugs for cancer treatment.

Clinical research: Studies performed in humans that are intended to increase knowledge about how well a diagnostic test or treatment works in a particular patient population.

Clinical research coordinator (CRC): A person who handles the administrative responsibilities in a clinical trial. The CRC coordinates communication between the trial site, the sponsor, and federal agencies and reviews all data before visits from anyone (sponsor, FDA, NIH) monitoring the trial. Also called trial coordinator, study coordinator, research coordinator, clinical coordinator, research nurse, or protocol nurse.

Clinical trial: A prospectively planned scientific study of the effects of a diagnostic test or treatment on selected patients, usually with respect to safety, efficacy, and/or quality of life.

Clinically significant: A treatment effect that has a meaningful impact on a patient's health. Some trials may find statistically significant results of a treatment, but those results might not make a difference in the patient's health.

Combined therapy: Using two or more agents or treatments together with the intent of achieving results that are superior to those that would be achieved by either treatment alone.

Community hospital: A hospital that delivers routine, standard, healthcare services in a community setting. Unlike academic medical centers, teaching medical students and research are usually not a major part of community hospital activities.

Compassionate use: One of the mechanisms by which FDA expands the availability of investigational new products that are not yet approved for marketing to very ill patients who have no other treatment options. (See expanded access.)

Compensation: Payment for or provision of care to a clinical trial participant for a research-related injury. Also, payment to patients for participation in a trial.

Conflict of interest: In a clinical trial, a situation in which the interests of the researcher or research institution are at odds with patient welfare.

- **Financial:** the conflict between a researcher's or research institution's financial interests in a company sponsoring the research and their obligation to patient welfare.
- **Intellectual:** the conflict between a researcher's self-interests (achieving positive results and personal recognition, maintaining his or her reputation, advancing career) and his or her obligation to uphold the integrity of the research.
- **Potential:** conflict of interest that could affect patient welfare or the integrity of research results due to conflicting interests of the researcher or research institution.

Consent: (See informed consent.)

Continued access: One of the ways that FDA makes investigational new products available to patients. Continued access allows patients who are likely to benefit from a new treatment to receive it in an open-label trial, while the company is awaiting marketing approval, after the controlled clinical trial has been completed and yielded positive results. See open-label trial and expanded access.

Contract research organization (CRO): A company with whom a drug or device manufacturer or sponsor contracts to perform clinical trial related activities. CROs may contract to develop protocols, recruit patients, collect and analyze data, and prepare documents to submit marketing applications to the FDA.

Contraindication: A circumstance or condition under which the administration of a treatment is known to be harmful to the patient.

Control group: In a clinical trial, the patient group(s) that does not receive the experimental treatment. The control group receives the standard treatment, placebo, or no treatment, in accordance with the trial design, and the results of the control group(s) are compared to the results from the experimental group.

Controlled trial: A prospective clinical trial comparing two or more treatments, or placebo and treatment(s) in similar groups of patients or within patients. The trial typically takes the form of a placebo and/or standard treatment against which the effects on the experimental treatment are compared. A controlled trial may or may not use randomization to assign patients to groups and it may or may not use blinding to prevent them from knowing which treatment they get.

Crossover trial: A trial in which patients first receive either the treatment or control (placebo or standard treatment) and after a predetermined amount of time, are given the other intervention. In this way, patients serve as their own controls because treatment and control effects are compared within the patient. Also known as an "on/off" design.

Data: Recorded observations about patients in a trial.

- **Baseline data:** information that describes the patients at the start of the trial.
- **Demographic data:** information about patient sex, age, race, geographic location, etc.
- **Objective data:** information that is measurable and quantifiable using a test or evaluation tool (e.g., laboratory finding, imaging study, rating scale).
- **Quality-of-life data:** objective and subjective information that is gathered about patients by researchers or from patient perceptions. The information concerns the effect that an individual's health status has on how well the patient performs activities of daily living and how the patient feels about his or her ability to fulfill social, familial, and personal roles.
- **Raw data:** observations, measurements, and activities recorded before performing statistical analysis or drawing conclusions.
- **Subjective data:** patients' feelings and perceptions about their health status and functioning (e.g., patient satisfaction).
- **Survival data:** measurements of who remains alive at certain time points after treatment, usually expressed from the date of diagnosis or from a starting point of a treatment.

Data Safety Monitoring Board (DSMB): A board set up by a clinical trial sponsor to evaluate trial progress, safety data, and significant outcomes, according to FDA regulations. This committee, comprising community representatives and clinical research experts, may also recommend revisions or discontinuation of a clinical trial if the trial objectives remain unmet or safety concerns arise.

Department of Health and Human Services (DHHS): Federal agency established to protect the health of the U.S. population. FDA, NIH, Centers for Disease Control and Prevention, and Centers for Medicaid & Medicare are under DHHS's umbrella.

Device (medical): An instrument, apparatus, implement, machine, invention, implant, in vitro reagent, or other article intended for use in the diagnosis, treatment, or prevention of disease. A device is intended to affect the structure or function of the body, but it does not function through chemical action within or on the body.

Disclosure: Made known.

- **Financial disclosure:** making known the facts about an individual's income sources and investments.

Dose: a measured amount of a therapeutic substance.

- **Effective:** the dose that produces the desired clinical result.
- **Maximum-tolerated:** the highest dose that can be administered without having toxic or lethal effects in humans.

Double-blind trial: A clinical trial in which neither the patients nor the researchers giving the treatments know which group (control or experimental) the patients are in and which treatment a patient is receiving.

Effectiveness: The degree to which a diagnostic test or a treatment produces a desired result in patients in the daily practice of medicine.

Efficacy: The degree to which a diagnostic test or a treatment produces a desired result in patients under the idealized circumstances of a clinical trial.

Emergency use: One of the mechanisms by which FDA makes investigational new products available before they are approved for marketing. Doctors can request permission from FDA and a manufacturer to use such a product on an emergency basis for a patient in a life-threatening medical situation for which no standard treatment is available.

End point: In a clinical trial, the designated point that researchers will measure in patients after the completion of treatment within the trial. Example: 5-year survival, 35 sessions of radiation therapy, 6 courses of chemotherapy.

End-stage disease: The phase of a disease that precedes death.

Enroll: To register in writing to join a group (e.g., enroll in a clinical trial).

Equipoise: A state of true uncertainty on the part of a researcher about which treatment (investigational or standard) will achieve a better result.

Equity: Fairness in the allocation of resources or treatments among individuals or groups.

Ethical violation: Breach of an established rule of moral behavior.

Ethics: Conforming to an accepted standard of human behavior.

Ethics committee: In the context of clinical trials, an independent group of medical professionals and lay persons who deliberate on the ethics of a trial design with regard to the safety and protection of clinical trial participants and their rights.

Evidence-based medicine: An approach to practicing medicine that involves consideration of results of clinical trials that are relevant to the disease or condition being treated when making decisions about how to treat patients.

Exclusion criteria: Factors used to determine whether an individual is ineligible for a study.

Expanded access: The mechanism by which FDA makes it possible for doctors to use investigational new products for gravely ill patients outside the context of a clinical trial and before a product has received marketing approval.

Experimental: Investigational, unproven.

Experimental treatment group: The group that receives the investigational treatment in a trial; the group to which the control group results are compared. The experimental group is sometimes referred to as the "treatment" group in a clinical trial.

FDA: Food and Drug Administration.

Federal Food, Drug and Cosmetic Act: Federal act passed in 1938 that required companies manufacturing drugs to submit reports of clinical investigations about the safety of new drugs.

Follow-up: A doctor's or researcher's examination of patient signs and symptoms after a test or treatment has been given.

Food and Drug Administration (FDA): The federal agency accountable for guaranteeing the safety and effectiveness of all drugs, biologics, vaccines, and medical devices used in the diagnosis, treatment, and prevention of human disease.

Functional status: A person's ability to perform age-appropriate self-care tasks related to social, psychological, and physical functions.

Generalizable: The extent to which the results of a clinical trial can be applied to patients being treated in routine medical practice outside the trial. (See validity, external.)

Health-related quality-of-life measure (HRQOL): Any of a variety of tools (i.e., questionnaires, rating scales, or surveys) used to assess the effect of an individual's health on how well he or she performs activities of daily living and fulfills social, familial, and personal roles.

Healthcare technology: Any drug, medical device, or procedure used in the care of patients.

Healthcare technology assessment: A multidisciplinary field in which scientists, clinicians, biomedical engineers, and others evaluate the effectiveness of healthcare technology and behavioral health interventions (e.g., psychological therapy, behavior modification) by statistically analyzing the results of published studies on the technology or intervention of interest.

Helsinki Declaration: Guidelines, adopted in 1964 by the 18th World Medical Assembly (WMA) (Helsinki, Finland) and revised in 2000 by the 52nd WMA General Assembly, for physicians conducting biomedical research. This declaration outlines clinical trial procedures required to ensure patient safety, adequate consent and ethics committee reviews in human subjects.

Heterogeneous: Mixed, not of the same kind. For example, a heterogeneous patient population is made up of people with different characteristics (these can be medical or demographic characteristics).

High-risk: Particularly subject to potential danger or harm.

Homogeneous: Of the same kind, alike.

Hypothesis: An unproven idea or proposition that is formed and used in clinical research to explain the relationship between or among variables that a researcher intends to study.

Hypothetical: Assumed without proof.

Inclusion criteria: The factors used to judge a participant's eligibility for inclusion in a trial. There is an underlying rationale for the criteria selected. The rationale relates to the questions that the researchers are trying to answer by conducting the trial.

Informed consent: A patient's oral and written agreement to participate in a clinical trial. Consent is based on full disclosure about the treatment, its potential risks and benefits, alternative treatments, and any other information the patient needs to make the decision. All patients enrolling in clinical trials must sign a consent document that explains what will happen to them in the trial.

Institutional review board (IRB): A specially constituted group of people established or designated by a research institution or clinical trial sponsor to protect the welfare of human participants clinical research and ensure trials adhere to federal regulations on the conduct of clinical research. In the United States, all clinical research requires approval from the relevant IRB. IRBs, in turn, must adhere to federal regulations. The IRB consists of physicians, statisticians, researchers, community advocates, and others who review and approve or disapprove research protocols, consent forms, and promotional materials for a trial.

Invasive: In healthcare, the puncture or incision of the skin using a medical device (e.g., needle, scalpel, laser).

Investigational: Experimental, unproven.

Investigational device exemption (IDE): FDA permission for a company or sponsor to use its new medical device in a clinical trial evaluating the safety and efficacy of the device. An IDE is not yet FDA approved for marketing, but must be investigated in clinical trials to gather data that FDA will consider for the marketing approval application.

Investigational new drug (IND): A novel chemical substance used to affect the function of the mind or body with the intention of diagnosing, preventing, or treating a disease, a condition, or its symptoms. An IND is not yet FDA approved for marketing to treat a particular condition, but must be investigated in clinical trials to gather data that FDA will consider for the marketing approval application.

Investigator: A researcher responsible for conducting a clinical trial at a trial site.

- **Principal investigator (PI):** An individual that leads a team of investigators at a trial site; also referred to as principal investigator.
- **Sponsor-investigator:** An individual, company, institution, or organization (sponsor) that is responsible for conducting a clinical trial at a trial site.

In vitro: Outside the body.

In vivo: Inside the body.

Landmark study: In clinical research, a study of such importance that it historically marks the discovery of a new way to diagnose or treat a disease or condition.

Legally authorized representative (LAR): A person or agent authorized under law to consent, on behalf of another person, to an individual's participation in a clinical trial.

Malpractice: Negligence by a professional in the exercise of his or her professional duties.

Medical device approval process: The process by which medical devices are approved by FDA for legal marketing in the United States. Congress passed the Medical Device Amendments of 1976 to grant FDA broad powers to regulate the manufacture and distribution of medical devices. FDA subsequently developed two mechanisms by which manufacturers can bring a new product to market: premarket notification (510[k]) and premarket approval. FDA's premarket approval process requires manufacturers to conduct clinical trials and collect data on safety and efficacy of their devices for submission to FDA in a premarket approval application. Premarket notification does not usually require clinical trials because the devices are considered similar to devices already on the market.

Medicare: A federal program of reimbursement to hospitals and physicians for healthcare provided to persons 65 years of age and older, persons eligible for Social Security disability payments for at least two years, and selected workers who need kidney transplantation or dialysis services.

Mentally competent: Having the capacity to understand information, make decisions, and act reasonably.

Metastatic: Cancer that has spread from its original site to other organs or tissues.

Monitor: An individual employed by a sponsor or contract research organization who helps to plan, conduct, analyze and interpret data from a trial.

Monitoring: Activities to check patients' health status during a trial. Also, activities to oversee the progress of a trial to ensure a researcher's compliance with the protocol and regulatory requirements.

Morbidity: Rate of sickness often expressed as the ratio of sick to well people in a given population.

Mortality: Death rate.

Multicenter trial: A clinical trial conducted at multiple sites using a common protocol.

National Institutes of Health (NIH): A federal agency consisting of many separate research institutions, such as the National Cancer Institute. NIH conducts research in its own facilities and funds billions of dollars in research in other facilities in the United States and abroad.

New drug application (NDA): An application made to FDA that requests a license to market a new pharmaceutical in the United States. The application must include all appropriate clinical data from phase I through phase III clinical trials.

Nuremberg Code: Code of human research ethics devised in 1947 after World War II. Nazi physicians were found guilty of crimes against humanity for conducting experiments on humans without patient consent. This code forms the foundation for current law and ethics on consent for participation in clinical trials.

Off-label use: The use of a device for an indication different from the specific one for which it received marketing approval. Off-label use is usually not illegal and arises from a clinician's decision to use a device or drug for a purpose other than that specifically indicated on the product label that was FDA approved. FDA regulates manufacturing methods, distribution, and advertising of medical products but not physician practice. Physician use may be bound by what health plans and Medicare and Medicaid are willing to cover.

Office for Human Research Protections (OHRP): A federal agency under the umbrella of the Department of Health and Human Services to help ensure the protection of humans participating in clinical research. OHRP issues "Assurances" and supervises compliance with regulatory requirements by research institutions receiving federal funding. This agency also provides initiatives on ethical issues in clinical research and coordinates interaction among federal agencies on these issues.

Open design: A clinical trial design in which both the investigators and research subjects know the treatment groups to which subjects are assigned.

Open-label trial: A trial in which all patients are receiving the investigational new drug after the completion of a controlled trial that had positive results. In this way, FDA allows patients who are likely to benefit to receive the new drug while the company awaits FDA approval to commercially market the drug.

Outcome: The ultimate result of a medical test or treatment given to patient. Examples of general, patient-oriented outcomes are overall survival rates, disease-free survival rates, treatment-related morbidity, and mortality. Indirect (also called surrogate) outcome measures are tumor response rates, laboratory tests, and imaging studies. (Examples of surrogate measures are a man's prostate-specific antigen level after treatment for prostate cancer or a computed tomography scan after radiation treatment.) Indirect outcome measures do not tell us directly about how well a patient is—although some indirect measures may be correlated with health improvements.

Patient characteristic: The medical or demographic qualities or traits of a patient. Examples of medical characteristics are disease, stage of disease, blood pressure, weight, hormone receptor status, and prior treatments. Examples of demographic patient characteristics are age, sex, and race.

Phase I, II, III, IV trials: Studies conducted in humans on investigational new devices, drugs, biologics, or procedures.

- **Phase I:** Studies safety and toxicity in a small group of healthy volunteers or patients with the disease of interest.
- **Phase II:** Studies safety and efficacy, typically in 50 to 300 patients with the condition or disease that the investigational treatment is intended to treat. Trial may take up to two years.
- **Phase III:** Studies safety and efficacy in a larger group, perhaps in a 1,000 or more patients to demonstrate safety and efficacy in a larger population and to look for uncommon adverse reactions. This phase trial may last several years.
- **Phase IV:** Studies the use of a drug or device after it has been approved for marketing to determine longer-term effectiveness and identify rarer adverse reactions.

Physician influence: A doctor's power to sway a patient decision based on the patient's trust in the doctor and the doctor's reputation and position.

Placebo: An inactive substance or treatment, such as a sugar pill, injection of sterile water, or sham medical device, that is given under the guise of treatment to separate the effects of the actual agent or treatment being evaluated from psychological or other effects.

Placebo effect: A health effect from administration of a placebo. This may occur because of patient belief that a treatment is working and because of the attention given by healthcare providers to the patient in the clinical trial.

Preclinical study: A laboratory or animal study that is done using a drug, device, or procedure to find out if the new treatment shows enough promise to be studied in humans.

Prevalence: The total number of cases of a specific disease or condition in a given population at a given time.

Prognosis: A forecast of the probable result of a medical condition or disease in a patient.

Protocol: The formal plan for the conduct of a clinical trial that defines the design, purpose, length, patient selection, methods, treatment, follow-up, clinical end points, and outcomes to be measured.

Provider: In healthcare, an individual or group (e.g., physician, hospital) that provides healthcare services.

Quality of life: A standard of living; in healthcare, it applies to the patient's expressed satisfaction with his or her quality of life as affected by health status. (See health-related quality-of-life measure.)

Randomization: Any of the many methods used to assign subjects to an experimental group or control group so that assignment is not influenced in any way by those making the assignments or by the researchers conducting the trial. Random assignment reduces the potential for bias in a study.

Recruitment: Processes used to attract and enroll trial participants according to inclusion and exclusion criteria. (See inclusion criteria, exclusion criteria.)

Regulations: With respect to clinical research, the federal statutes, codes, and laws that govern the conduct of federally funded clinical trials and privately sponsored clinical trials for new drugs, devices, biologics, and procedures.

Remission: A period of time during which the signs and symptoms of a disease or condition diminish or disappear.

Research coordinator: See clinical research coordinator.

Research team: In clinical trials, the group of healthcare professionals who conduct the trial. A research team typically includes, among others, a principal investigator, a subinvestigator, and a clinical research coordinator.

Resident physician: A medical school graduate who is receiving required on-the-job training at a healthcare facility.

Results: An analysis of the data collected during a clinical trial.

- **Preliminary:** Results reported before the end of a clinical trial. Also refers to results reported from early phase studies.

Risk: In a clinical trial, the probability of discomfort or harm to participants in a clinical trial.

- **Acceptable risk:** a risk that is deemed to be reasonable, given the purpose of the trial and its potential benefits for patients in the trial.
- **Unreasonable risk:** a risk that is deemed to far outweigh any potential benefit for the patient in the trial.

Screening for eligibility: Methods (e.g., phone interview, medical tests) used to determine which patients are eligible for a trial. (See inclusion/exclusion criteria.)

Sham treatment: An inactive device or device/procedure that mimics the actual device and can be used as a placebo in a clinical trial.

Side effect: Undesired effect of a treatment. Investigational new drugs and devices are evaluated for immediate and long-term side effects.

Sign: Any objective evidence of a disease (as detected by a test or clinical examination by a doctor).

Specialist: A physician trained in a particular field of medicine or surgery, such as oncology, cardiology, neurosurgery, gynecology, urology, or pulmonary medicine.

Sponsor: An individual, company, institution, or organization that initiates, manages, and finances a clinical trial.

Sponsor-investigator: An individual who both initiates and actually conducts a clinical investigation. (Corporations, agencies, or institutions do not qualify as sponsor-investigators.)

Stage of disease: The extent or severity of disease as designated by numerals or letters. For example, in cancer, disease is often designated as stage I (earliest stage), II, III, or IV (most advanced stage).

Standard treatment: The treatment that is currently thought to be effective in medical practice.

Statistical significance: An index of how probable it is that an observed difference is the result of chance rather than of the experimental treatment. This is expressed as a "p" value. Convention holds that the p value should be <0.05 to call an effect statistically significant. A value of <0.05 means that there is a <5% probability that the observed results were due to chance. A statistically significant result does not always mean that the finding has clinical importance. (See clinically significant.)

Subject: An individual who participates in research.

- **Vulnerable subject:** Individuals whose willingness to voluntarily participate in a clinical trial may be unduly influenced by their expectation of benefit or fear of retaliation if they don't participate.

Survival: A state of remaining alive.

- **Disease-free survival:** living without signs or symptoms of a disease state.
- **Overall:** living without taking into account the disease state.
- **Progression-free survival:** living with no progression of disease.

Symptom: Any evidence of disease perceived by the patient; a symptom may not necessarily be detected by a test or clinical examination by a doctor.

Terminally ill: Life-threatening, incurable disease or condition.

Toxic: Poisonous to a living organism or person; ability to cause grave harm or death.

Treatment IND: See treatment use and investigational new drug.

Treatment outcome: See end point, outcome.

Treatment use: A way in which FDA makes investigational products that have demonstrated some efficacy available to very ill patients outside a clinical trial before the product has been approved for marketing. (See expanded access.)

Uncontrolled trial: A trial that has no control groups, so no comparisons between treatments or treatments and placebo are made. These are also sometimes called case series.

University medical center: A healthcare institution that is part of a university that teaches medical students and conducts basic research (preclinical research) and clinical trials. Also called an academic medical center.

Validity: The extent to which the results of a study can be believed.

- **External validity:** The extent to which a trial's results can be applied to patient populations or settings outside those of the trial. (See generalizable.)
- **Internal validity:** The extent to which a trial's results can be attributed to the treatment in the trial rather than to flaws in the study design. A study with internal validity allows you to draw valid conclusions about the way one variable affects another in that study. A study can be internally valid (i.e., the intervention works for the study population or in the setting studied) and yet have no validity for populations or settings outside the study.

Variable: Any attribute or characteristic that can change or that may have more than one value over time (e.g., height, weight, religion, age, medical characteristics).

Voluntary: Free of coercion, duress, or undue inducement. In a clinical trial, refers to a participant's decision to enroll.

Washout period: Time in the course of a clinical trial when participants receive no treatment for the indication under study.

Withdraw: In a trial, to end a patient's participation before he or she reaches the designated end point.

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Chapter 21—Appendixes

A. SUMMARY OF SELECTED PROVISIONS OF STATE LAWS REQUIRING COVERAGE OF CLINICAL TRIALS* (DECEMBER 2001)

State Laws: To date, 15 states have enacted laws addressing insurance coverage of clinical trials. More than half of these laws have been enacted within the past two years. The laws typically outline the type of costs that insurers are required to cover. These costs include services that would have otherwise been provided under the contract for standard therapy and typically do not include costs normally paid for by the trial sponsor. Additionally, most bills specify the type of trial insurers are required to cover.

Federal Activity: In 2000, the Health Care Financing Administration (now known as the Centers for Medicare & Medicaid Services [CMS]) issued a national coverage decision requiring insurers participating in the Medicare program to cover the routine costs associated with certain clinical trials. The coverage decisions include some guidance on what are and are not considered routine costs and also specifies the type of trial that qualifies for coverage. For example, trials funded by the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the agency for Healthcare Research and Quality (AHRQ), CMS, the Department of Defense (DoD), the Veteran's Administration (VA), centers or cooperative groups of those agencies, and the U.S. Food and Drug Administration (FDA) automatically qualify for Medicare coverage. Additionally, a mandate for private plans to cover the routine costs associated with clinical trials is one of the provisions common to both the Senate- and House-passed patients bills of rights.

STATE, CITE, AND YEAR ENACTED	COSTS REQUIRED TO BE COVERED	TYPE OF TRIAL REQUIRED TO BE COVERED	OTHER PROVISIONS OF NOTE
Arizona 20-826.01 (2000)	Patient costs include any fee or expense covered under the contract that is for a service or treatment that would otherwise be required if the patient were receiving usual and customary care. Patient costs do NOT include costs of any drug or device provided in a Phase I trial; any investigational drug or device; non-health services that might be required for an individual to receive treatment; managing research of the trial; and service or treatment that would not otherwise be covered under the contract; or treatment provided out of state.	Phase I to IV cancer clinical trials conducted in the state and approved by NIH; an NIH cooperative group or center; FDA; DoD; VA; a qualified research entity that meets criteria established by the NIH for grant eligibility; or a panel of qualified, recognized experts in clinical research with academic health institutions in the state.	

* Insurers in New Jersey have voluntarily agreed to cover routine patient care costs associated with cancer clinical trials. All phases of cancer trials sponsored by the NIH, FDA; DoD, and VA are eligible for coverage under the agreement.

STATE, CITE, AND YEAR ENACTED	COSTS REQUIRED TO BE COVERED	TYPE OF TRIAL REQUIRED TO BE COVERED	OTHER PROVISIONS OF NOTE
California SB 37 (2001)	Routine patient care costs include costs associated with provision of healthcare services, including drugs, items, devices, and services that would otherwise be covered under the contract. Includes coverage for services that are typically provided absent a clinical trial; that are required solely for the provision of the trial; that are required for the monitoring of the trial; that are provided for the prevention of complications arising from the trial; and that are needed for the reasonable and necessary care arising from the trial, including the diagnosis or treatment of complications. Routine patient care costs do NOT include costs of drugs or devices that have not been approved by FDA; non-healthcare services that might be required for an individual to receive treatment; services provided solely for data collection; services that are otherwise specifically excluded under the contract; or services customarily provided by trial sponsors.	Phase I to IV cancer clinical trials approved by NIH, FDA, DoD, or VA.	• Applies to Medi-Cal.

STATE, CITE, AND YEAR ENACTED	COSTS REQUIRED TO BE COVERED	TYPE OF TRIAL REQUIRED TO BE COVERED	OTHER PROVISIONS OF NOTE
Connecticut SB 325 (2001)	Routine patient care costs include medically necessary services incurred as a result of the trial that would otherwise be covered under the contract. Includes services rendered by a physician, diagnostic or laboratory tests, hospitalization or other services provided to the patient during the course of the trial, including those for complications, that is consistent with the usual and customary standard of care and would be covered if the individual were not enrolled in the trial. Routine patient care costs do NOT include costs of the investigational drug or device; non-healthcare services that might be required for an individual to receive treatment; facility, ancillary, and professional services and drug costs paid for by grants or funding for the trial; services that are inconsistent with widely accepted and established regional or national standards of care or that are performed specifically to meet the requirements of the trial; services that would not otherwise be covered, including exclusions; and transportation, lodging, food, and other expenses.	Cancer clinical trials conducted under the auspices of an independent peer-reviewed protocol that has been reviewed and approved by NIH, an NCI-affiliated cooperative group, FDA, DoD, or VA.	• Makes clear that the law does not require coverage for any single institution cancer clinical trial conducted solely under the approval of an Institutional Review Board (IRB).
Delaware SB 181 (2001)	Patient costs include items and services that are otherwise generally available to the individual. Patient costs do NOT include costs of an investigational item or service, items or services provided solely for data collection, or items and services customarily provided by research sponsors.	Trial must be approved or funded by NIH; an NIH cooperative group or center, including but not limited to the NCI Clinical Cooperative Group and the NCI Community Clinical Oncology program; VA; DoD; an IRB of a state institution that has a multiple project assurance contract approval by the Office of Protection for the Research Risks of NIH; or a qualified research entity that meets the criteria for NIH Center Support eligibility.	• The trial must meet certain requirements specified in the law, including therapeutic intent and support of scientific evidence. Additionally, the trial must not test exclusively for toxicity and must not unjustifiably duplicate existing studies.

STATE, CITE, AND YEAR ENACTED	COSTS REQUIRED TO BE COVERED	TYPE OF TRIAL REQUIRED TO BE COVERED	OTHER PROVISIONS OF NOTE
Georgia 33-24-59.1 (1998)	Routine patient costs include medically necessary costs of blood tests, x-rays, bone scans, magnetic resonance imaging (MRIs), patient visits, hospital stays, or other similar costs generally incurred in connection with the trial that would otherwise be covered. Routine patient costs do NOT include costs of: any trial therapies, regimens, drugs; or any costs of services that are generally furnished without charge in connection with a trial. The law is not meant to relieve sponsors of financial responsibility for the accepted costs of the trial.	Phase II to III prescription drug clinical trials for the treatment of children's cancer conductedin the state and approved by FDA or NCI and certified by the Pediatric Oncology Group, the Children's Cancer Group, or the Commissioner.	• Applies to state employee plans. • Mandate is limited to dependent children diagnosed with cancer prior to their 19th birthday.
Illinois 215 ILCS 5/356y (1999)	Routine patient care includes costs of blood tests, x-rays, bone scans, MRI, patient visits, hospital stays, or other similar costs generally incurred in standard cancer treatment. Routine patient costs do NOT include costs of any trial therapies, regimens, or drugs; any costs of services that are generally furnished without charge in connection with a trial; or any costs provided primarily for the convenience of the individual. The law is not meant to relieve sponsors of financial responsibility for the accepted costs of the trial.	Phase II to IV cancer clinical trials for the terminally ill that are approved by HHS; NIH; FDA; a qualified nongovernmental cancer research entity as defined by NIH; or a peer-reviewed and approved cancer research program defined by DHHS.	• This law is a mandatory offering law. • Sets an annual benefit limit of $10,000.
Louisiana 22:230.4 (1999)	Patient costs include costs of healthcare services, treatments, or testing that are incurred as part of the protocol treatment. Patient costs do NOT include costs of non-healthcare services that a patient may be required to receive as a result of the treatment; management of the research data; investigational drugs or devices; or services not otherwise covered by the contract.	Phase II to IV cancer clinical trials approved by NIH; a cooperative group funded by NIH; FDA; VA; DoD; a federally funded general clinical research center; or the Coalition of National Cancer Cooperative Groups.	• Applies to the state employee plans.

STATE, CITE, AND YEAR ENACTED	COSTS REQUIRED TO BE COVERED	TYPE OF TRIAL REQUIRED TO BE COVERED	OTHER PROVISIONS OF NOTE
Maine 4310 (2000)	Routine patient costs do NOT include costs of tests or measurements conducted primarily for the purpose of the trial or that are reasonably expected to be paid for by trial sponsors.	Trials for life-threatening conditions approved and funded by DHHS, NIH, or a cooperative group or center of the NIH.	
Maryland 15-827 (1998)	Patient costs include costs of medically necessary healthcare services that are incurred as a result of the treatment. Patient costs do NOT include the costs of an investigational drug or device; non-health care services that a patient may be required to receive as a result of the treatment; management of the research; or services that would not otherwise be covered under the contract.	Phase I to IV cancer clinical trials and other trials for life-threatening, degenerative, or permanently disabling conditions approved by NIH; an NIH cooperative group or center; FDA; VA; or an IRB of an institution in the state that has a multiple project assurance contract approved by the Office of Protection from Research Risks of NIH.	
New Hampshire 415:18-1 (2000)	Routine patient care costs include costs of medically necessary services incurred as a result of the trial and that are regularly reimbursed by the insurer under the contract. Routine patient care costs do NOT include costs of investigational drugs or devices; non-healthcare services that an individual might require; services that are clearly inconsistent with widely accepted and established regional or national standards of care; management of the research; or services not covered under the contract.	Phase I-IV cancer clinical trials and trials for other life-threatening conditions approved by NIH; an NIH cooperative group or center; FDA; VA; DoD; or an IRB of an institution in the state that has a multiple project assurance contract approved by the Office of Protection from Research Risks of NIH.	• Permits coverage for Phase I to II to be decided on a case-by-case basis. • Plans and providers shall develop a mutually agreed-upon process to share aggregate clinical and financial data on the progress and outcome of trials.

STATE, CITE, AND YEAR ENACTED	COSTS REQUIRED TO BE COVERED	TYPE OF TRIAL REQUIRED TO BE COVERED	OTHER PROVISIONS OF NOTE
New Mexico 59A-22-43 (2001)	Routine patient care costs include services that would otherwise be covered under the contract and drugs approved by FDA. Routine patient care costs do NOT include costs of investigational drugs, devices, or procedures; non-healthcare services that the individual is required to receive as a result of the treatment; management of the research; services not otherwise covered by the contract; tests necessary for the research; services paid or charged for by the trial sponsors.	Phase I to IV cancer clinical trials approved by NIH; an NIH cooperative group or center; DoD; FDA; VA; or a qualified research entity that meets the criteria established by NIH for grant eligibility.	• Sunsets in July of 2004. • Applies to Medicaid. • Specifies that plans shall not provide benefits that supplant a portion of the trial costs that are customarily paid for by government, biotech, pharmaceutical, or medical device industry sources.
North Carolina SB 100 (2001)	Patient costs include medically necessary costs of healthcare services associated with participation in a covered clinical trial, including those related to the healthcare services typically provided outside a clinical trial, the diagnosis and treatment of complications, and medically necessary monitoring-only to the extent that such costs have not been or are not funded by national agencies, commercial manufacturers, distributors, or other research sponsors of participants in clinical trials. Patient costs do not include costs of non-FDA-approved drugs; services that are not healthcare services; those provided solely to satisfy data collection and analysis needs; those related to investigational drugs and devices; and those that are not provided for the direct clinical management of the patient.	Phase II to IV trials. Trials must involve determinations by the treating physicians and relevant scientific data and opinions of experts in relevant medical specialties. They must also be approved by centers or cooperative groups that are funded by NIH, FDA, CDC, AHRQ, VA, and DoD. Trials must be conducted in a setting and by personnel that maintain a high level of expertise because of their training, experience, and volume of patients.	• Health benefit plans may also cover trials sponsored by other entities. • In the event a claim contains charges related to services for which coverage is required, and those charges have not been or cannot be separated from costs related to services for which coverage is not required, the health benefit plan may deny the claim.

STATE, CITE, AND YEAR ENACTED	COSTS REQUIRED TO BE COVERED	TYPE OF TRIAL REQUIRED TO BE COVERED	OTHER PROVISIONS OF NOTE
Rhode Island 27-41-55 (1997)	Not specified.	Phase II to IV cancer clinical trials approved by NIH in cooperation with NCI; community clinical oncology programs; FDA; VA; or a qualified nongovernmental research entity as defined by NCI cancer center support grant guidelines.	• Any portions of a phase II trial which are customarily funded by government, biotech, pharmaceutical, or device industry sources shall continue to be funded by such sources.
Vermont 4088B (2001)	Routine patient care costs.	Cancer clinical trials conducted by the Vermont Cancer Center or the Norris Cancer Center; or administered by a Vermont hospital.	• This law establishes a pilot program that sunsets after three years. • Few details provided in statute. Requires Commissioner to issue rules. • Cancer centers and four largest insurers are to participate in an analysis of cost data at end of second year to determine the financial impact on premiums. • Applies to Medicaid.
Virginia 38.2-3418.8 (1999)	Patient costs include costs of medically necessary healthcare services that are incurred as a result of the treatment. Patient costs do NOT include costs of non-healthcare services that a patient may be required to receive as a result of the treatment; management of the research of the trial; or investigational drugs or devices.	Phase II to IV cancer clinical trials approved by NCI; an NCI cooperative group or center; FDA; VA; or an IRB of an institution in the state that has a multiple project assurance contract approved by the Office of Protection from Research Risks of the NCI.	• Coverage of routine patient care costs is voluntary for Phase I cancer clinical trials. • Applies to state employee plan.

B. THE DECLARATION OF HELSINKI; THE NUREMBERG CODE; THE BELMONT REPORT

THE DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic Principles for All Medical Research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional Principles for Medical Research—Combined with Medical Care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

THE NUREMBERG CODE

1. The voluntary consent of the human subject is absolutely essential.

   - This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

   - The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seemed to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable [sic] cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

THE NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS

THE BELMONT REPORT

Office of the Secretary, Ethical Principles and Guidelines for the Protection of Human Subjects of Research of Biomedical and Behavioral Research, April 18, 1979

Ethical Principles & Guidelines for Research Involving Human Subjects

Scientific research has produced substantial social benefits. It has also posed some troubling ethical questions. Public attention was drawn to these questions by reported abuses of human subjects in biomedical experiments, especially during the Second World War. During the Nuremberg War Crime Trials, the Nuremberg code was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. This code became the prototype of many later codes intended to assure that research involving human subjects would be carried out in an ethical manner.

The codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted. Three principles, or general prescriptive judgments, that are relevant to research involving human subjects are identified in this statement. Other principles may also be relevant. These three are comprehensive, however, and are stated at a level of generalization that should assist scientists, subjects, reviewers and interested citizens to understand the ethical issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects. This statement consists of a distinction between research and practice, a discussion of the three basic ethical principles, and remarks about the application of these principles.

A. Boundaries Between Practice and Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

For the most part, the term "practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective.

When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is "experimental," in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.

Research and practice may be carried on together when research is designed to evaluate the safety and efficacy of a therapy. This need not cause any confusion regarding whether or not the activity requires review; the general rule is that if there is any element of research in an activity, that activity should undergo review for the protection of human subjects.

B. Basic Ethical Principles

The expression "basic ethical principles" refers to those general judgments that serve as a basic justification for the many particular ethical prescriptions and evaluations of human actions. Three basic principles, among those generally accepted in our cultural tradition, are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.

1. **Respect for Persons**—Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

   An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.

   However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated.

   Some persons are in need of extensive protection, even to the point of excluding them from activities which may harm them; other persons require little protection beyond making sure they undertake activities freely and with awareness of possible adverse consequence. The extent of protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations.

   In most cases of research involving human subjects, respect for persons demands that subjects enter into the research voluntarily and with adequate information. In some situations, however, application of the principle is not obvious. The involvement of prisoners as subjects of research provides an instructive example. On the one hand, it would seem that the principle of respect for persons requires that prisoners not be deprived of the opportunity to volunteer for research. On the other hand, under prison conditions they may be subtly coerced or unduly influenced to engage in research activities for which they would not otherwise volunteer. Respect for persons would then dictate that prisoners be protected. Whether to allow prisoners to "volunteer" or to "protect" them presents a dilemma. Respecting persons, in most hard cases, is often a matter of balancing competing claims urged by the principle of respect itself.

2. **Beneficence**—Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. Such treatment falls under the principle of beneficence. The term "beneficence" is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.

   The Hippocratic maxim "do no harm" has long been a fundamental principle of medical ethics. Claude Bernard extended it to the realm of research, saying that one should not injure one person regardless of the benefits that might come to others. However, even avoiding harm requires learning what is harmful; and, in the process of obtaining this information, persons may be exposed to risk of harm. Further, the Hippocratic Oath requires physicians to benefit their patients "according to their best judgment." Learning what will in fact benefit may require exposing persons to risk. The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.

The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research. In the case of particular projects, investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation. In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.

The principle of beneficence often occupies a well-defined justifying role in many areas of research involving human subjects. An example is found in research involving children. Effective ways of treating childhood diseases and fostering healthy development are benefits that serve to justify research involving children-even when individual research subjects are not direct beneficiaries. Research also makes it possible to avoid the harm that may result from the application of previously accepted routine practices that on closer investigation turn out to be dangerous. But the role of the principle of beneficence is not always so unambiguous. A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.

3. **Justice**—Who ought to receive the benefits of research and bear its burdens? This is a question of justice, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Another way of conceiving the principle of justice is that equals ought to be treated equally. However, this statement requires explication. Who is equal and who is unequal? What considerations justify departure from equal distribution? Almost all commentators allow that distinctions based on experience, age, deprivation, competence, merit and position do sometimes constitute criteria justifying differential treatment for certain purposes. It is necessary, then, to explain in what respects people should be treated equally. There are several widely accepted formulations of just ways to distribute burdens and benefits. Each formulation mentions some relevant property on the basis of which burdens and benefits should be distributed. These formulations are (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit.

   Questions of justice have long been associated with social practices such as punishment, taxation and political representation. Until recently these questions have not generally been associated with scientific research. However, they are foreshadowed even in the earliest reflections on the ethics of research involving human subjects. For example, during the 19th and early 20th centuries the burdens of serving as research subjects fell largely upon poor ward patients, while the benefits of improved medical care flowed primarily to private patients. Subsequently, the exploitation of unwilling prisoners as research subjects in Nazi concentration camps was condemned as a particularly flagrant injustice. In this country, in the 1940's, the Tuskegee syphilis study used disadvantaged, rural black men to study the untreated course of a disease that is by no means confined to that population. These subjects were deprived of demonstrably effective treatment in order not to interrupt the project, long after such treatment became generally available.

   Against this historical background, it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures, justice demands both that these not provide advantages only to those who can afford them and that such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

C. Applications

Applications of the general principles to the conduct of research leads to consideration of the following requirements: informed consent, risk/benefit assessment, and the selection of subjects of research.

1. **Informed Consent**—Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

   While the importance of informed consent is unquestioned, controversy prevails over the nature and possibility of an informed consent. Nonetheless, there is widespread agreement that the consent process can be analyzed as containing three elements: information, comprehension and voluntariness.

   Information. Most codes of research establish specific items for disclosure intended to assure that subjects are given sufficient information. These items generally include: the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research. Additional items have been proposed, including how subjects are selected, the person responsible for the research, etc.

   However, a simple listing of items does not answer the question of what the standard should be for judging how much and what sort of information should be provided. One standard frequently invoked in medical practice, namely the information commonly provided by practitioners in the field or in the locale, is inadequate since research takes place precisely when a common understanding does not exist. Another standard, currently popular in malpractice law, requires the practitioner to reveal the information that reasonable persons would wish to know in order to make a decision regarding their care. This, too, seems insufficient since the research subject, being in essence a volunteer, may wish to know considerably more about risks gratuitously undertaken than do patients who deliver themselves into the hand of a clinician for needed care. It may be that a standard of "the reasonable volunteer" should be proposed: the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.

   A special problem of consent arises where informing subjects of some pertinent aspect of the research is likely to impair the validity of the research. In many cases, it is sufficient to indicate to subjects that they are being invited to participate in research of which some features will not be revealed until the research is concluded. In all cases of research involving incomplete disclosure, such research is justified only if it is clear that (1) incomplete disclosure is truly necessary to accomplish the goals of the research, (2) there are no undisclosed risks to subjects that are more than minimal, and (3) there is an adequate plan for debriefing subjects, when appropriate, and for dissemination of research results to them. Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator.

   Comprehension. The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice.

   Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information. While there is always an obligation to ascertain that the information about risk to subjects is complete and adequately comprehended, when the risks are more serious, that obligation increases. On occasion, it may be suitable to give some oral or written tests of comprehension.

Special provision may need to be made when comprehension is severely limited-for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disable patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest.

Voluntariness. An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence. Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance. Also, inducements that would ordinarily be acceptable may become undue influences if the subject is especially vulnerable.

Unjustifiable pressures usually occur when persons in positions of authority or commanding influence-especially where possible sanctions are involved-urge a course of action for a subject. A continuum of such influencing factors exists, however, and it is impossible to state precisely where justifiable persuasion ends and undue influence begins. But undue influence would include actions such as manipulating a person's choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitle.

2. **Assessment of Risks and Benefits**—The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research. Thus, the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. For the investigator, it is a means to examine whether the proposed research is properly designed. For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate.

   The Nature and Scope of Risks and Benefits. The requirement that research be justified on the basis of a favorable risk/benefit assessment bears a close relation to the principle of beneficence, just as the moral requirement that informed consent be obtained is derived primarily from the principle of respect for persons. The term "risk" refers to a possibility that harm may occur. However, when expressions such as "small risk" or "high risk" are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm.

   The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Unlike, "risk," "benefit" is not a term that expresses probabilities. Risk is properly contrasted to probability of benefits, and benefits are properly contrasted with harms rather than risks of harm. Accordingly, so-called risk/benefit assessments are concerned with the probabilities and magnitudes of possible harm and anticipated benefits. Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.

Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society). Previous codes and Federal regulations have required that risks to subjects be outweighed by the sum of both the anticipated benefit to the subject, if any, and the anticipated benefit to society in the form of knowledge to be gained from the research. In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected. Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.

The Systematic Assessment of Risks and Benefits. It is commonly said that benefits and risks must be "balanced" and shown to be "in a favorable ratio." The metaphorical character of these terms draws attention to the difficulty of making precise judgments. Only on rare occasions will quantitative techniques be available for the scrutiny of research protocols. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible. This ideal requires those making decisions about the justifiability of research to be thorough in the accumulation and assessment of information about all aspects of the research, and to consider alternatives systematically. This procedure renders the assessment of research more rigorous and precise, while making communication between review board members and investigators less subject to misinterpretation, misinformation and conflicting judgments. Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit, especially where there is no alternative to the use of such vague categories as small or slight risk. It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.

Finally, assessment of the justifiability of research should reflect at least the following considerations: (i) Brutal or inhumane treatment of human subjects is never morally justified. (ii) Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures. (iii) When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject-or, in some rare cases, to the manifest voluntariness of the participation). (iv) When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits. (v) Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

3. **Selection of Subjects**—Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.

   Justice is relevant to the selection of subjects of research at two levels: the social and the individual. Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research. Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions.

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects.

Some populations, especially institutionalized ones, are already burdened in many ways by their infirmities and environments. When research is proposed that involves risks and does not include a therapeutic component, other less burdened classes of persons should be called upon first to accept these risks of research, except where the research is directly related to the specific conditions of the class involved. Also, even though public funds for research may often flow in the same directions as public funds for health care, it seems unfair that populations dependent on public health care constitute a pool of preferred research subjects if more advantaged populations are likely to be the recipients of the benefits.

One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.

C. THE ROLE OF FEDERAL AGENCIES IN CLINICAL TRIALS

Department of Health and Human Services (DHHS)

DHHS is the principal federal agency whose mission is to protect the health of all Americans and provide essential human services. DHHS programs are administered by 11 operating divisions, which include 8 agencies in the Pubic Health Service (PHS) and 3 human service agencies. The U.S. Food and Drug Administration (FDA) is one of the main PHS agencies with oversight of clinical trials; the National Institutes of Health (NIH) is another. Extensive regulatory processes (federal statutes, laws, and codes) govern the conduct of trials for new drugs, devices, and biologics. Many of these regulations are key to patient safety during the trial.

FDA

FDA was formed in 1931. A healthcare crisis about one particular drug in the late 1930s gave rise to the idea of testing drugs that were on the market. A liquid form of a sulfa drug had caused more than 100 deaths in a short period. At that time, most drugs in the United States had never undergone human testing before being brought to market. So, in 1938, Congress passed the Federal Food, Drug and Cosmetic Act. This Act required companies manufacturing drugs to submit reports of clinical investigations about the safety of new drugs. In 1962, an amendment to that Act added a requirement that drug manufacturers provide data on their drug's efficacy for the first time.

Today, FDA requires developers of new drugs and medical devices to submit evidence of safety and effectiveness from controlled clinical trials, according to the Code of Federal Regulations. Three different centers at FDA regulate healthcare products: the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health. A treatment consisting of a combination of drugs, biologically derived products, and/or devices is called a "combined therapy" or "combined product." Different centers at FDA are required to work together on oversight of these trials.

NIH

NIH began in a one-room laboratory in 1887. Today, NIH comprises 27 institutes and centers. Among them are the National Cancer Institute, the National Heart Lung and Blood Institute, the National Institute of Allergy and Infectious Diseases, the National Human Genome Research Institute, and National Institute of Diabetes and Digestive and Kidney Diseases. All the institutes and centers conduct research in their own laboratories and fund basic science and clinical research at universities, medical schools, hospitals, and research institutions throughout the United States and abroad.

NIH also trains research investigators. NIH's primary concern is to wisely invest the tax dollars earmarked for clinical research. Most of the funds go to grants and contracts supporting research and training of more than 50,000 researchers at more than 2,000 research institutions.

NIH also has a special panel, the Recombinant DNA Advisory Committee, that provides oversight and a public forum for discussing gene-transfer research. NIH research in the 21st century is focusing on better ways to prevent and treat diseases; improve the health of infants, children, women, and minorities; understand the aging process; and learn how behavior and lifestyle practices affect health.

Office for Human Research Protections (OHRP)

OHRP is a federal agency under the umbrella of DHHS that works with NIH, FDA, and other federal agencies funding clinical research to help ensure the protection of humans participating in that research. OHRP issues "assurances" and supervises compliance with regulatory requirements by research institutions receiving federal funding. An assurance is a formal written, binding commitment that is submitted to a federal agency by an institution in which the institution agrees to comply with regulations for research with human subjects. It specifies the procedures through which compliance will be achieved. OHRP also provides initiatives on ethical issues in clinical research and coordinates interaction among federal agencies on these issues.

Other DHHS divisions

Other DHHS divisions that conduct medical and social science research include the Centers for Disease Control and Prevention (CDC) and the Agency for Healthcare Research and Quality (AHRQ). CDC monitors and studies disease trends, investigates outbreaks of disease, fosters safe and healthful environments, and implements illness and injury control and prevention. AHRQ supports healthcare technology assessment, which evaluates data from published clinical trials to find out what works best in medical practice. ARHQ, in partnership with the American Medical Association and the American Association of Health Plans, also sponsors the National Guideline Clearinghouse™, which is a public database of evidence-based clinical practice guidelines.

D. INSTITUTIONAL REVIEW BOARD (IRB) PROBLEMS, SOLUTIONS, AND PROGRESS

In the late 1990s, the U.S. Department of Health and Human Services (DHHS) Office of Inspector General investigated how well IRBs were functioning. Those investigations resulted in the issuing of four reports in June 1998 that described problems with the current IRB system in this country and made recommendations for reforms. (Web-site addresses to the full reports are listed in Additional resources.) One of the key problems identified was IRBs' limited efforts in conducting continuing review of research in progress, which directly relates to the safety of patients participating in clinical trials. The Inspector General's office identified many reasons why ongoing IRB review is hampered and offered recommendations for reform. These are summarized below.

Problems

- Heightened workload pressure. IRBs, which consist of trained volunteers from academia and other professions, are flooded with research proposals for review. They simply do not have the resources or time to keep up with the increasing workload.
- Limited feedback on multisite trials. IRBs now review many trials that are large multicenter trials. The U.S. Food and Drug Administration (FDA) and DHHS often require these trials to be monitored by Data Safety Monitoring Boards and clinical audit teams; however, these groups rarely report their findings to IRBs. Thus, information about things that happen to patients in trials may not be communicated from one group to another in a timely way.
- Limited feedback on FDA actions against investigators. FDA rarely discloses information they take against researchers citing legal concerns under the Privacy Act. Thus, IRBs often learn of such actions only indirectly through media reports or other informal means.
- Limited scientific expertise. No single IRB can possibly have sufficient representation from all fields of medicine to assess every protocol. Although they can use consultants, IRBs may have difficulty finding people who are available and willing when they need them.
- Limited outside representation of patient interests. IRBs typically have minimal outside representation by people who can provide counterbalance on the interests of clinical trial participants compared to the interests of the research.
- Trust. The IRB process is rooted in trust and assumes the best intentions of investigators and sponsors. This tradition makes thorough continuing review suspect because the IRB's job as it currently stands is to ensure protections up front, not to be "watchdogs" or "police."

Recommendations

- Recast federal IRB requirements so that IRBs have greater flexibility and are more accountable for results. This can be done by lessening IRB procedural requirements and requiring IRBs to undergo regular performance-focused evaluations.
- Strengthen continuing protections for human subjects participating in research by requiring Data Safety Monitoring Boards for some multisite trials and by giving IRBs feedback on developments during multicenter trials and FDA actions. Increase IRB awareness of research centers' on-site practices in clinical trials.
- Enact federal requirements to ensure that investigators and IRB members are adequately educated and sensitized to human-subject protections by requiring research centers to have a program to train investigators on these issues. Also require investigators to show in writing their familiarity with and commitment to human-subject protections, and require IRBs to have ongoing education and training for IRB members.
- Help insulate IRBs from conflicts that compromise their mission to protect patients participating in research by, among other things, requiring more IRB members from outside of institutions and medical research.
- Recognize that IRBs have heavy workload pressures and require them to be able to access adequate resources as needed to conduct proper review.
- Reorganize the federal oversight process or the National Institutes of Health (NIH)/Office for Protection of Research Risks and require registration of IRBs.

What has changed?

Federal agencies, patient advocacy groups, and the private sector have put a lot of effort into improving patient protections and reforming and improving the IRB system since 1998. Much work remains to be done. In response to the 1998 reports and Congressional hearings, DHHS took actions to strengthen the protections of participants in clinical trials. In May 2000, DHHS Secretary Donna Shalala said the new initiatives were "designed to further strengthen government oversight of all biomedical research, including gene transfer research." She also said the efforts were intended to "reinforce institutions' and researchers' responsibility to follow internationally accepted ethical standards and federal guidelines." Those initiatives focused on the following five areas:

- Improving education and training of clinical investigators, IRB members, and associated IRB and institutional staff. NIH, FDA, and the Office for Human Research Protections are working closely to assure that those involved in approving and conducting research receive appropriate research bioethics training and human-subjects research training. The training is now required of all investigators receiving NIH funds and of all those who receive funding in the future. In addition, since late 1998, many research institutions have offered a special training course "IRB 101 On the Road" developed by the group, Public Responsibility in Medicine and Research. This nonprofit public interest group's main activity is sponsoring education conferences on biomedical and bioethical issues. The IRB course provides IRB members, clinical researchers, and research staff with basic knowledge of the ethical principles underlying clinical research, procedures for reviewing clinical research protocols, and the regulations governing IRB operations.
- Improving informed-consent oversight. NIH and FDA are to issue specific guidance on informed consent, clarifying that research institutions and sponsors must audit records for evidence of compliance with informed-consent requirements. For especially risky or complex trials, IRBs are expected to take additional measures, which might include third-party observation of informed-consent processes. Researchers are also required to go over informed consent again when any participant suffers a significant trial-related event that might affect his or her willingness to continue in the trial.
- Improving monitoring of phase I and II trials. NIH now requires investigators conducting these early-phase trials to submit clinical trial monitoring plans to NIH when funding is sought and to IRBs when trial approval is sought. The relationship between FDA Data and Safety Monitoring Boards and IRBs will be more clearly defined as to their independence, responsibilities, confidentiality issues, and qualifications for membership on the boards.
- Dealing with researcher conflicts of interest. NIH was ordered to issue more guidance on conflicts of interest. A conference on financial conflicts of interest and the protection of human research subjects was held in August 2000. Federal agencies, stakeholders from the private sector, and the academic research community participated. A draft interim guidance was issued in January 2001, based on the presentations made at the conference, public comments on the conference, and other documents. That draft guidance was released for comment and received extensive comments from the private sector, public interest groups, patients, and the academic research community. Those comments are under consideration and the draft was in revision as of late 2001.
- Imposing civil monetary penalties. DHHS is pursuing legislation to enable FDA to fine researchers for violations of informed consent-up to $250,000 per clinical investigator and up to $1 million per institution. Currently, FDA can impose sanctions that halt research. IRBs can also halt research. FDA's commitment to impose sanctions and halt research has been even more evident at leading research institutions since the year 2000, when entire research programs were temporarily shut down pending satisfactory resolution of problems identified by FDA.

E. EXAMPLES OF HEALTH PLAN RESEARCH INITIATIVES

Health plans are engaged in many clinical trial research initiatives, and the following list is by no means exhaustive. Rather, it gives you an idea of some of the ways various insurers are allowing their members to participate in trials and receive coverage for the costs.

Aetna Health Plans: Participated with the University of Pennsylvania in a trial on high-dose chemotherapy and bone marrow transplantation for advanced metastatic breast cancer. Since 1999, Aetna has supported the National Institute of Child Health and Human Development clinical trial on first-trimester screening for Down syndrome.

Harvard Pilgrim Health Care: This health plan currently has patients enrolled in trials of treatments for cancers of the breast, colon, gastrointestinal tract, female reproductive organs, prostate, brain, head, neck, lung, lymph nodes, male reproductive organs, Hodgkin's disease, leukemia, and bone marrow transplants.

Kaiser Permanente, Southern California: Kaiser Permanente has an extensive program of clinical trials research and, when medically necessary, refers patients to clinical trials conducted at local universities and other Kaiser Permanente facilities. In-plan clinical trial Centers of Excellence have been designated in the therapeutic areas of adult oncology, pediatric oncology, AIDS/HIV, allergy, neurology, cardiology, and cardiovascular surgery.

Oxford Health Plans: Oxford has referred patients to clinical trials studying high-dose chemotherapy with bone marrow transplantation or stem cell rescue for breast cancer and high-dose chemotherapy for small cell lung cancer.

United Health Care: This health plan has covered costs of care for eligible members enrolled in clinical trials of commercial and fully insured products. The health plan also pays for all phases of multicenter clinical trials sponsored by the Coalition of National Cancer Cooperative Group, Inc., a network of six of the National Cancer Institute's cooperatives.

Health Partners: This health plan has developed a set of criteria it uses to consider members' requests for coverage of clinical trial costs for unproven therapies for which there is growing evidence of benefit. The criteria take into account five elements: quality of the available evidence, health outcome, probability of success in achieving that outcome, cost, and strength of the conclusion.

Group Health Cooperative (GHC): GHC's Center for Health Studies research is funded primarily by the National Institutes of Health and foundations. It focuses on the prevention and treatment of major health problems. Study areas include cancer control, cardiovascular health, mental health, chronic illness management, women's health, immunization, health behavior, and complementary and alternative medicine. The center conducts trials in cancer prevention, chronic disease management, complementary and alternative medicine, mental health, smoking cessation, and women's health.

GHC physicians may provide access to experimental treatments as part of clinical trials sponsored by national collaborative research groups, such as Southwest Oncology Group and Children's Oncology Group.

Henry Ford Health System Health Alliance Plan: The Henry Ford Health Sciences Center serves as the educational and research arm of the Henry Ford Health System. The center conducts clinical trials in multiple areas including oncology, cardiology, neurology, surgery, internal medicine, gastroenterology, endocrinology, and infectious diseases. Its mission is to identify and test medical interventions to deliver the best care, investigate health system performance measures, and develop innovative models for training physicians. The Center is engaged in more than 1,500 studies in basic, clinical, and public health research, using research affiliations with Case Western Reserve School of Medicine, as well as collaborations with several universities nationwide.

F. MEDICARE COVERAGE OF CLINICAL TRIALS

As of September 19, 2000, Medicare began covering the routine costs of qualifying clinical trials. To qualify for coverage, trials must adhere to federal regulations on the protection of human subjects, and all parts of the trial must be conducted according to appropriate standards of scientific integrity. Trials that automatically qualify for Medicare coverage are those funded directly or supported by centers or cooperative groups that are funded by the National Institutes of Health, the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, the Centers for Medicare and Medicaid Services, the Department of Defense, the Veteran's Administration, and trials conducted under a U.S. Food and Drug Administration (FDA) new drug application reviewed by FDA.

The Medicare coverage decision for clinical trials also states that Medicare Choice organizations must cover the services regardless of whether they are available through in-network providers. Medicare Choice organizations can have reporting requirements to track and coordinate care when members participate in clinical trials, but cannot require prior authorization or approval. For the initial implementation of this policy, Medicare contractors are paying providers directly on a fee-for-service basis for covered clinical trial services for beneficiaries in Medicare Choice programs.

Routine costs of a clinical trial include all items and services that are provided in either the experimental or control arms of a trial and are otherwise generally available to Medicare beneficiaries provided that

- Medicare benefit category exists,
- the item or service is not excluded by statute, and
- Medicare does not have a national noncoverage policy.

Medicare considers routine costs in clinical trials to be

- Items or services that are typically provided for patient care outside a trial;
- Items or services required solely for the provision of the investigational item or service (e.g., administration of a noncovered chemotherapy drug), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; or
- Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service-in particular, for the diagnosis or treatment of complications.

Medicare does not cover

- The investigational item (i.e., the drug or device) or service;
- Items and services that are done solely to collect and analyze data and are not used for the direct clinical management of the patient (e.g., monthly CT scans for a condition usually requiring only a single scan); and
- Items and services that the research sponsors usually provide free of charge for any trial participant.

Trials must meet at least the three following requirements for coverage

- The purpose of the trial must be to evaluate an item or service that falls within a Medicare benefit category (e.g., physicians' service, durable medical equipment, diagnostic test) and must not be a statutorily excluded item or service (e.g., cosmetic surgery, hearing aids).
- The purpose of the trial must have a therapeutic intent; it must not be designed exclusively to test toxicity or disease pathophysiology.
- Trials of treatments must enroll patients with the diagnosed disease of interest-not healthy volunteers. Trials of diagnostic interventions may enroll healthy patients to have a proper control group.

Medicare states that to qualify, trials should have the following characteristics, and some trials (such as those funded or supported by those agencies listed above) are presumed by Medicare to meet these characteristics and automatically qualify for Medicare coverage:

- The trial's purpose must be to test whether the intervention potentially improves the participants' health outcomes.
- The trial is well-supported by available scientific and medical information or is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- The trial does not unjustifiably duplicate existing studies.
- The trial design is appropriate to answer the research question being asked in the trial.
- The trial is sponsored by a credible organization or individual capable of successfully conducting the trial.
- The trial complies with federal regulations on protection of human subjects in research.
- All aspects of the trial are conducted according to the appropriate standards of scientific integrity.

Selected References

ECRI consulted more than 1,000 published articles and references while researching the material to produce this Guide. The selected references below include those that ECRI used in its technical report on the reasons patients give for participating in trials and the outcomes of patients receiving care in clinical trials compared to outcomes of patients receiving care outside trials. Also included are those references that might hold the most interest for users of this Guide. You can obtain medical journal articles through local medical school libraries.

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