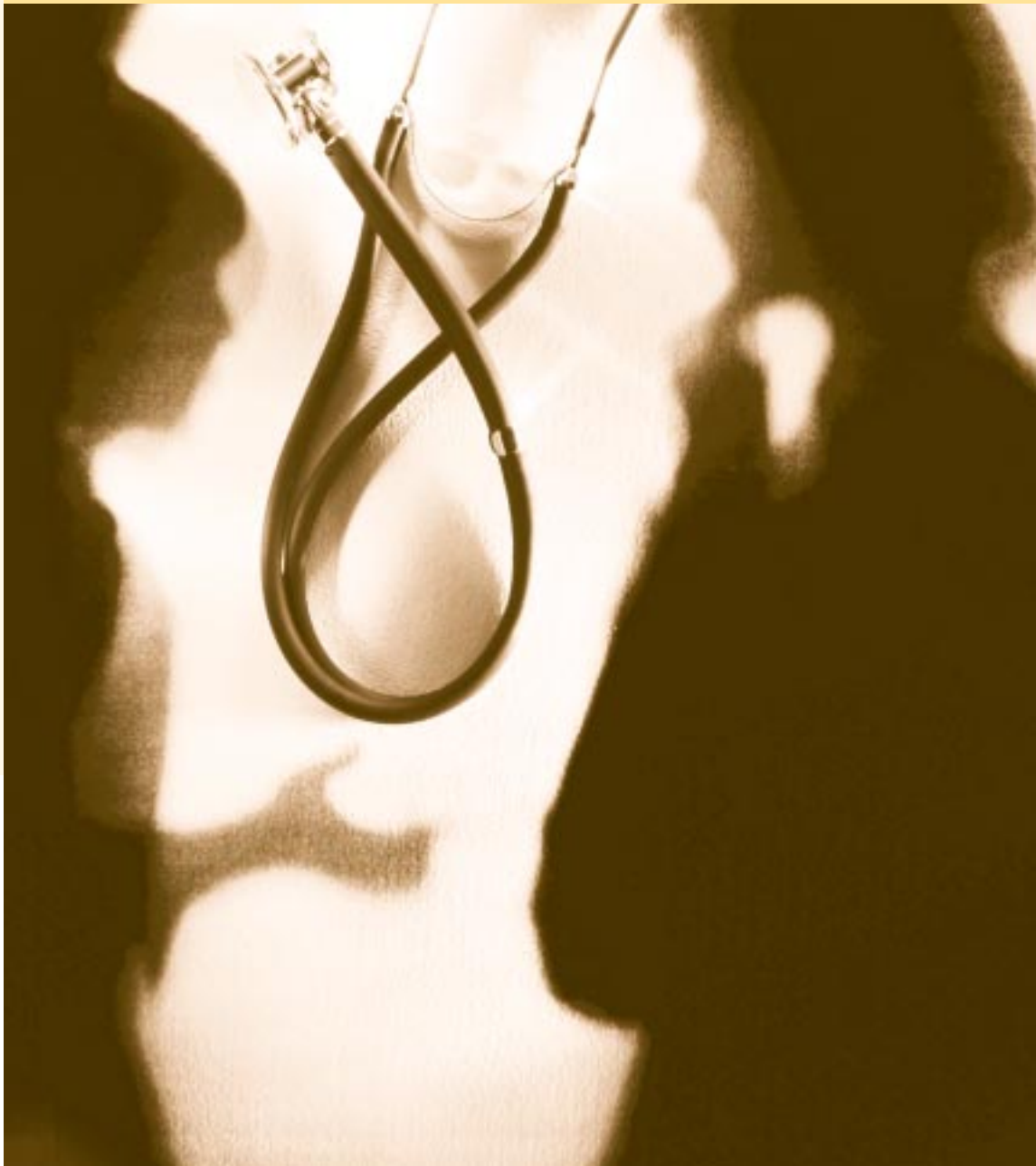
Summary of the Complete Patient Reference Guide

ECRI
A NONPROFIT AGENCY

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.

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Who Should Use this Summary?

This Patient Reference Guide Summary highlights key issues covered in the full Guide, *Should I Enter a Clinical Trial?*, for adult patients who are thinking about enrolling in a clinical trial and their loved ones. Words that appear in **bold** are defined in the *Glossary* at the end. We provide checklists that may be useful during your discussions with physicians and loved ones about whether to enter a trial. A list of Web resources shows where you can find information about clinical trials that are open for enrollment and more information about various issues related to clinical trials. The full Guide and Summary take no position on whether one should enter a trial—that is a uniquely personal decision. Our hope is that patients consult the full Guide to support their decision making about enrolling in a trial so they can feel as confident as possible about their decision. We dedicate this Guide to the patients and their loved ones who are facing this important decision and to those who benefit us all by participating in a trial.

You can access the full Guide on the Web at *www.ecri.org* or *www.aahp.org*. If you cannot access it online, please contact the American Association of Health Plans (AAHP) to request a hard copy. We encourage readers to obtain the full-length Patient Reference Guide, which provides more detailed information about participation in clinical trials.

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 the past 10 years as researchers in the public and private sectors strive to develop and bring to the public more new diagnostic tests and treatments than ever. Thus, more patients than ever are needed to participate in trials.

In the press and on television, some institutions conducting clinical research have come under public fire recently because of some serious **adverse event**s and, rarely, unexpected deaths during trials. Although these situations represent a very small fraction of the current clinical research, they have shaken public trust. Patient safety and adequate explanations to patients about the benefits and **risk**s 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. Researchers cannot promise patients an immediate personal health benefit from participating in a trial, but patients have described to us other kinds of immediate benefits from trial participation.

As one cancer trial patient 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." 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.

This Summary offers some basic information to consider when deciding to enroll in a clinical trial. *Should I Enter a Clinical Trial? A Patient Reference Guide for Adults with a Serious or Life-Threatening Illness* provides more detailed information on these topics and other questions important to patients and their families. *But the final decision about enrolling in a clinical trial rests with you and your loved ones. Being informed will enable you to make a decision that is right for you.*

Among the key issues covered in the full Guide are the following:

- How can patients make sure they receive adequate information about the risks of a trial when deciding whether to enroll?
- Where can patients find out about clinical trials that are recruiting patients?
- How can patients find out if they are eligible for the trial?
- Can patients get a treatment under investigation even if they are not eligible for the trial?
- What are the different types of trials, and why should patients take the time to understand those differences before making a decision?
- How might different trials affect a patient's quality of life?
- Who should a patient talk to about the trial before deciding to enroll?
- Who shares responsibility for protecting patients in clinical trials?
- What are the tangible and intangible costs to patients of being in a trial?
- Who is responsible for treating complications from treatment in a trial?
- What potential conflicts of interest exist among trial **sponsor**s, researchers, and institutions carrying out the trial?
- What are patients' rights to **withdraw** from a trial?
- What are researchers' obligations to patients in trials?

What is a Clinical Trial?

The very purpose of trials is to gain new knowledge about new treatments that might benefit future patients. But in the trial, the new treatment is still under investigation to see how well it works. Although "new" often implies "better" in our culture, the fact is that until clinical research on a new treatment is complete, we do not know if it is better, the same as, or worse than standard treatments. Sometimes, treatments publicized as "promising" or "breakthrough" do not fulfill their promise. The only way to find out is through well-designed and well-conducted clinical trials.

Is participating in a trial different from receiving treatment outside of a clinical trial?

Yes. 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. Treatment in a clinical trial is intended to *benefit society and future patients* by advancing medical knowledge. It is important to understand that individual patients may or may not benefit from the **experimental** treatment in a trial; this is why the trial is being conducted—to find out how well it works. However, patients may experience other types of immediate benefits, such as the comfort and support that can come from being part of a group of patients with the same condition being treated and closely monitored by a team of experts—the research doctors.

For patients in trials, there are risks associated with participating because researchers cannot guarantee that a treatment being tested will provide a benefit. In a trial, there is only the hope that it will. The very reason for doing the trial is to find out if the treatment works. Weighing the risks and benefits to make an informed decision about whether to participate can be complicated. In making an informed decision, it is necessary to understand something about the different types of trials, the right questions to ask, and patients' rights as trial participants.

What are the different types of clinical trials, and what do I need to know about them?

There are four general phases of trials in humans (phases I through IV). Human trials cannot begin until laboratory and/or animal tests on the new treatment under investigation have been completed in "**preclinical** studies." The results of each phase must show that there are no serious safety problems and that the experimental treatment holds some promise before it can be tested in the next phase. Each phase typically involves a greater number of patients. Phase I may have as few as 10 or 20 patients. Phase III may have several hundred or thousands of patients. The design of trials also changes as the phases progress. Later phase studies often compare results of the experimental treatment group to the results of standard treatment group (**control group**) in what are known as **controlled trial**s.

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 is worth taking the time to understand something about the different kinds of clinical trials. Different kinds of trials offer different potential benefits and risks; they 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. Some trials may last less than a year; others may last five years or longer. Factors like these may affect a person's desire and ability to participate.

Different kinds of trials also have different effects on patient feelings about risk and quality of life. As one cancer patient explained her thinking about entering a trial, "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. The risks involved and impact of one trial on quality of life could be very different." The different phases of the trials are as follows:

- **Phase I** trials assess safety and **toxicity** of the treatment in a small group of healthy volunteers or patients with the disease of interest. *Phase I trials are not designed or intended to be therapeutic.* These trials cannot promise individual patients any therapeutic benefit because very little is known at this point about the treatment's activity in humans. Phase I trials lay the groundwork for the next phases of trials that begin to test **efficacy** (how well the treatment works). Studies of phase I trials have shown that 3% to 5% of participants benefit from the treatment.
- **Phase II** trials further test safety and begin to test efficacy, typically in 50 to 300 patients with the condition or disease for which the treatment is intended. Phase II trials may take up to two years.
- **Phase III** trials study safety and efficacy in a larger group, perhaps thousands of patients, and look for uncommon adverse reactions. This phase may last several years. Phase III trials typically compare the new treatment to standard treatment(s) and perhaps a **placebo**, if it is ethical to use one (trials for life-threatening diseases rarely use placebos). Trials that compare treatments are controlled trials and may involve random assignment of patients to different treatment groups.
- **Phase IV** trials are sometimes done after a new drug or device has received **U.S. Food and Drug Administration (FDA)** approval and is being used by the general public. Phase IV trials determine longer-term **effectiveness** and identifies rarer side effects. FDA does not require this phase of trial for all newly approved drugs or devices—it depends on whether FDA believes some questions still need to be answered.

How will I learn about the risks and benefits of participating in a trial?

An eligible patient cannot enroll in a trial until the known benefits, risks, purpose, and plan for the trial have been thoroughly explained and all the patient's questions have been answered. This is called the **consent** process. It is also often called informed consent. It is very important to take the time to read and consider all the information provided and to ask questions. That often means taking the consent form home to read it again and discussing it with close family, friends, and advisors. Also, taking a trusted family member or friend along to the consent interview may be helpful so someone else hears the same information and you can discuss it later. It may also help to tape record the consent interview to review the information later—just let the doctor know if you want to do this. If a patient decides to enroll in a trial after the interview, he or she signs a consent form and keeps a copy for future reference. This document contains everything that was explained orally, including the contact information for someone on the **research team** who can answer questions and respond to emergencies.

Even after a patient enrolls in a trial, he or she can withdraw at any time for any reason. Should you choose to withdraw it is very important to let the researchers know why you are withdrawing so they can collect important **data** that may affect the way they are conducting the trial. Patient consent is an ongoing process throughout the trial. If important new information is gained about the experimental treatment during the trial, researchers are

required to share it with patients and reconfirm their consent to participate. Most patients may believe they understand risks and benefits and feel satisfied with the consent process, but often do not realize there are some things they have not understood.

The checklist provided here may help you determine whether you have received all the information you need for your decision making before signing a consent form.

Checklist: What to discuss with the researchers and close family and friends during the consent process

This checklist can help you determine whether you have received all the information you need to make your decision to enroll—and to keep you informed throughout the trial. You may want to take it with you to the consent interview to use as a basis for discussion and taking notes.

- ✔ Explanation that the trial involves research.
- ✔ Summary of results from previous trials that led to this trial.
- ✔ Purpose of the new research and what it is trying to achieve.
- ✔ Duration of the trial for the patient if he or she remains in it until the end.
- ✔ Detailed description of each test and treatment that will be given according to the trial protocol.
- ✔ Timing and location of those tests and treatments and how they are scheduled for the patient.
- ✔ Identification of any procedures that are experimental.
- ✔ Description of any foreseeable risks or discomforts (i.e., pain, minor and major side effects) from any test or treatment given.
- ✔ Description of any possible benefits to participants or others.
- ✔ Description of treatment alternatives that might help participants.
- ✔ Statement about the extent to which confidentiality of participants' records will be maintained.
- ✔ Explanation of whether any compensation and/or medical treatments are available if injury occurs from treatment in the trial. If so, what are they and who will provide them?
- ✔ Whom to contact with questions about the trial and the participant's rights.
- ✔ Whom to contact in the event of a research-related injury.
- ✔ Statement that participation is **voluntary** and that participants may refuse or discontinue participation at any time without penalty.
- ✔ Itemization of direct costs to the patient as a result of participation.
- ✔ Travel and lodging information for patients and loved ones accompanying them.
- ✔ Support that the patient might require from family and friends for daily activities or daily needs (e.g., transportation, assistance shopping, preparing meals, childcare) while in the trial.

How Can I Learn About Trials I Might be Eligible For?

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 below. More information about these Web sites and who manages them can be found in the complete Guide.

- **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 own 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 only 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. If you are interested in trials and your doctor seems to resist the idea, the Guide may be helpful for opening up discussion. 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 errands, transportation, shopping, cooking, cleaning, or caring for other family members or 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. As one patient explained, "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."

Will I be eligible for the trial I want to enroll in?

When you find out about a trial that you might be interested in, you will need to contact the researchers to find out if you are eligible. Every trial has eligibility criteria (also called **inclusion** and **exclusion criteria**). These criteria state what **patient characteristic**s make the patient eligible or ineligible for the trial, such as age, health, disease stage, previous treatment, and other coexisting health conditions. Even when people have the same disease, there can be important differences among patients. For example, patients may be in different stages of the disease, which might mean that they should get different treatment. Or, patients may have other health conditions that exclude them from the trial. So, there are several reasons for eligibility criteria. First, patient safety is a major concern. Second, the researchers have an objective. They are trying to gather data in the trial to answer some very specific questions. They need to be able to account for factors that can affect patient treatment and outcome. Some patient characteristics can get in the way of being able to tell if the treatment works or not; those characteristics may be excluded so that researchers will be able to answer the questions they set out to answer.

Once you know whether you are eligible for a trial, there are other important factors you may want to consider before deciding, such as the impact the trial might have on your daily activities and relationships with family and friends, and their ability to provide the support you need during the trial. Trials 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. The duration and location of the trial and whether it requires travel that will result in separation from loved ones are both important factors for patients. In published studies of patients' reasons for choosing not to enter a trial, travel inconvenience was the reason most often given for not participating. A person's desire and ability to participate may be affected by such factors.

If you have decided you want to enroll in a trial, you may have to undergo some "screening" before researchers can tell if you are eligible. While a researcher is allowed to discuss with a patient the availability of trials and the possibility of entry into a trial without first obtaining a signed consent form, the researcher must complete the consent process for clinical trial participation before conducting any clinical procedures on the patient that are performed solely to determine the patient's eligibility for research. If you are undergoing eligibility testing for a trial, the researcher must tell you in advance of any such requirements and how an unfavorable test result could affect employment or insurance before conducting the test.

Who ensures patient safety and the qualifications of the researchers and research organization involved in the trial?

Several federal agencies (among them, the **National Institutes of Health** [NIH], **Office for Human Research Protections** [OHRP], and FDA) and the **institutional review board** (IRB) where the trial is being conducted have different roles for protecting patient safety and rights in clinical trials. FDA has oversight of trials that are testing new drugs and medical devices before they are brought to market. NIH oversees trials that it funds at institutions throughout the country. OHRP works with FDA, NIH, and other federal agencies to provide training to researchers and IRBs, to sponsor conferences, and to help ensure patient protections according to federal **regulations**. IRBs review the trial protocol for virtually every trial conducted in their institutions and/or affiliated facilities.

An IRB is a group of people that has been formally designated to review and monitor clinical research to assure the protection of any person thinking about enrolling and those actually participating. Every university medical research center has its own IRB. Community hospital and non-university research centers, such as cancer, transplantation, or heart centers, also have IRBs. IRB members are medical professionals and lay volunteers who review research proposed within their medical facilities. An IRB assesses the research protocol for the safety and welfare of potential participants in the trial. An IRB also 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 it will ask for changes to lower the risks. An IRB also evaluates the consent form and recruitment ads for the trial to ensure that they provide patients with appropriate and understandable information about the trial. The IRB particularly looks at how the consent form explains the risks and benefits to patients to determine if it is as complete and understandable as possible. 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.

Among the ways that FDA and NIH ensure patient safety is to randomly inspect a sampling of clinical trial sites to check on adherence to the protocol and regulations for patient safety. For example, they look at whether the patients in the trial meet the stated enrollment criteria—because if they do not, patients could be at increased risk for harm from the treatment in the trial. FDA requires **Data Safety Monitoring Boards** for trials it oversees. This is an independent board set up by a clinical trial sponsor (company or institution evaluating a new and unapproved drug or device) to evaluate the trial's progress, safety data, and significant outcomes. This board comprises community representatives and clinical research experts that have the authority to recommend revisions or discontinuation of a trial if the trial objectives are unmet or safety concerns arise.

OHRP issues **assurances** (agreements made by facilities conducting trials that they will comply with regulations) and supervises compliance with regulations by those receiving federal funding for trials. OHRP also coordinates conferences for federal agencies to discuss topics such as ethical issues in clinical research.

Do all the patients in a trial receive the same treatment?

It depends on the type of trial. For trials that have more than one treatment group, scientific processes may be used to assign patients randomly to treatment groups. The purpose of **randomization** is to evenly distribute patient characteristics in each group in a trial to ensure valid results. It is also done to prevent researchers from influencing (consciously or unconsciously) to which group patients are assigned. Some patients have said that they do not want to enroll in a trial because they might be randomly assigned to a treatment group. They have expressed feelings that it takes away some control and choice about treatment. They also fear being assigned to the control group—the group that gets some other treatment and not the experimental treatment. Some patients believe the experimental treatment is better because it is new. Others fear being assigned to a group that receives placebo (**inactive treatment**). The following are some key points to keep in mind:

- *For patients with a life-threatening disease, the control groups virtually always consist of other treatments that have some proven efficacy. Placebos are very rarely used. Remember, the main point of the trial is to determine how well the experimental treatment works because no one knows yet if it is better than, the same as, or worse than standard treatment.* A control group is a group that receives some other treatment of known efficacy in the trial. Results from the experimental treatment group are compared to results from the control group to see how well it works. Placebo is an inactive treatment usually designed to look exactly like the real treatment. It is often thought of as a pill, but can also be an injection, a physical manipulation, a device that is inactive, or any other appropriate procedure that simulates the experimental treatment. There are stringent federal and ethical guidelines about when a placebo can be used—and it can only be used when there is no risk of harm to the patient who receives placebo instead of the experimental or standard treatment.

- *A treatment that is new and experimental is not necessarily better.* The experimental treatment may be the same as, better, or even worse than the standard treatment. Keep in mind that control groups often receive the current gold standard in treatment. The risks may be greater in the experimental treatment group because less is known about the treatment. Also, patients in the control group receive the same close **monitoring** and evaluation as those in the experimental group. So, no matter which group a patient is in, he or she will receive excellent care for the condition being treated by a team of researchers.
- Several studies have shown that patients participating in trials survive longer than similar patients who were eligible for a trial but chose to receive treatment outside a trial. The reasons for this are not clear, but some believe that this is because, typically, patients in a trial receive closer medical attention and more follow-up visits to monitor their condition than patients who are not in a trial.

Should I be concerned about any conflicts of interest of my personal physician or the research organization?

A conflict of interest in a clinical trial arises when a person's or institution's commitment to someone else conflicts with his or her professional obligation to the patient. The recent increased concern about conflicts of interest arises mainly from the skyrocketing amount of clinical research and huge rise in sponsorship by private companies. That trend is expected to continue. There are a variety of reasons for the potential for conflicts to arise 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 can strain the competing interests of institutions, researchers, doctors, and patients. Conflicts of interest are inevitable. Their existence does not mean that anyone has done anything wrong. What matters is whether the person with the conflict of interest has fulfilled his or her professional obligation to the patient or promoted self-interest.

For a patient in a trial, a researcher's conflict of interest might mean that he or she subtly persuades patients to enroll in a trial through enthusiasm or downplaying of risks. Although this can be unconscious on the part of the researcher, the balance is upset between the researcher's interests and patient welfare. A conflict of interest might also mean that a researcher's interest in obtaining positive results outweigh making objective clinical observations about how well you are doing. The researcher might even downplay reporting of side effects. Researchers might also have a financial conflict of interest if they own stock in the company for whom they do research or if they are a paid consultant for that company.

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 family member 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.

Doctors who conduct clinical research also may have a conflict. They want to further research and improve treatment for the future, but they are also deeply committed to helping the patients who are in the trial now. They are grappling with their allegiance to the research and allegiance to each patient. It is important for clinical research doctors to acknowledge this potential conflict so they can help trial participants distinguish research goals from individual treatment goals. Since more and more doctors in private practice are becoming involved in research in their own offices, this situation is coming up more often.

For patients, trust is key to sorting out what a doctor/researcher recommends to you. Only you can decide whether you trust what is recommended to you. You may want to get a second opinion from another doctor. Keep in mind that the goal of care given in a trial is different from the goal of care given outside a trial, whether that trial is conducted in a doctor's office or at a university medical center.

This checklist may help you in seeking the information you want about potential conflicts of interest.

Checklist: What should I ask my physician or the researchers about potential conflicts of interest?

- ✔ What are the researcher's reasons for doing the trial?
- ✔ What is the researcher's relationship with the company whose products are being tested in the trial?
- ✔ Is the researcher a paid consultant to any company sponsoring any part of the research?
- ✔ Does the researcher 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?

Will I incur Any Costs by Participating in a Clinical Trial?

There are tangible and intangible costs that patients may want to consider. Tangible direct costs may vary depending on the type of trial you have entered. Decisions about charging trial participants for experimental drugs and devices that are not yet FDA approved are guided by professional ethics, institutional policies, and FDA regulations. In drug trials, there is rarely a cost to the patient for the experimental 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. Whatever the direct costs of care, 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 trial. FDA does not prohibit charging participants for treatment or services in a trial. The IRB overseeing the trial has the responsibility to ensure that any such charges are appropriate and fair.

Some costs for clinical trial participation may also be "indirect," but very important to consider. These would include the costs for travel, lodging, and additional lost time from work when participating in a trial. If you have a loved one who accompanies you to regular appointments locally, or if the trial is in a town far away and someone goes with 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 figure out 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 of the trial include separation from loved ones during the trial and other quality-of-life issues affecting a patient's daily life activities. 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. In an analysis of why patients choose not to enroll in a trial, the need to travel in order to participate was among the top three reasons 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.

Will my health insurance pay?

Many health insurers and Medicare 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 or not he or she was in a trial. Examples of a routine cost might be the tests that are needed for diagnosis and staging of the disease or some of the patient checkups needed to monitor disease status. Patients will need to check with their insurers about what costs of trials are covered. Some states have mandated health insurers to cover some of the costs of participation in trials. Those mandates are included in the full Guide, which you can access on the Web.

Additional Resources

Where can I learn about trials that are recruiting patients?

Ads for trials appear in newspapers and on the radio and television, and many private companies, organizations, and federal agencies list open clinical trials. Some of these services also "match" patients to 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. This list implies no endorsement of these sites.

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 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.

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 new 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. The site is designed to be a resource both for patients interested in participating in clinical trials and for research professionals. Centerwatch offers patients 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, Inc.

http://www.ca-coalition.org/
Trials listed on this nonprofit organization's 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 company that provides Web-based products and services for companies in the clinical trial industry and for patients. The site offers information for cancer patients about clinical trials currently open for enrollment, trial sites, patient eligibility criteria for open trials, and contact information for the organization conducting the trial. The service is free to people searching for clinical trial information. The directory includes cancer trials from both government and industry sponsors and 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 treatments under investigation 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, 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. You can search the site by disease, 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 database contains information about new drugs being researched in clinical trials. Search the database by disease, drug name, company, or indication for the drug's use. You can sign up online to receive free updates on new drugs in development.

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 clinical trials that involve radiation therapy either alone or in conjunction with surgery and/or chemotherapeutic drugs. This cancer trial research group is funded by 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 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.

http://www.fda.gov
This links to FDA's main Web site, which is the gateway to its three divisions: drugs, devices, and biologics. This site provides information for consumers, healthcare professionals, and clinical trial sponsors about approval processes, warning letters, drug and device interactions, safety alerts, and consumer information on FDA activities.

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.

National Institutes of Health (NIH)

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

http://ohsr.od.nih.gov/ (Office of Human Subjects Research [OHSR])
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 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.

Office for Human Research Protections (OHRP)

http://ohrp.osophs.dhhs.gov/
OHRP is a federal agency in the DHHS that provides guidance documents and 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
The 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
The ORMH leads the federal effort at the 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 Health Care Research and Quality (AHRQ)

http://www.ahrq.gov

http://www.guideline.gov (AHRQ's National Guideline Clearinghouse™ [NGC™])
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 NGC.

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. IOM provides to the government and public objective and 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, Preserving Public Trust: Accreditation and Human Research Protection Programs, was 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. Extending 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 law. Topics addressed include the ethical and procedural issues surrounding the operation of IRBs; the education of 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).

Glossary

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

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.

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 governing 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.

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.

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.

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 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.

Compassionate use: One of the mechanisms by which FDA makes investigational new drugs and devices that are not yet approved for marketing available to very ill patients who have no other treatment options.

Conflict of interest: In a clinical trial, a situation in which the interests of the researcher or institution are at odds with their professional obligation to the patient.

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. Patients enrolling in clinical trials must sign a consent form that explains what will happen in the trial.

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 FDA.

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. 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.

Data: Recorded observations about patients in a clinical trial.

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. DHHS divisions include, among others, FDA, NIH, the Centers for Disease Control and Prevention, and Centers for Medicare & Medicaid Services.

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.

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

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

Enroll: To consent to and enter a clinical trial.

Ethics: Conforming to an accepted standard of human behavior.

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 trial.

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.

FDA: see U.S. Food and Drug Administration

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

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, consent and ethics committee reviews in human subjects.

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: see consent

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.

Investigational: Experimental, unproven.

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 it 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.

Medicare: A federal program of reimbursement to hospitals and physicians for healthcare provided to people 65 years of age and older, people 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.

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.

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 health research institutions. NIH conducts research in its own designated laboratories 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. This code forms the foundation for current law and ethics on consent.

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

Outcome: The ultimate result of a medical test or treatment given to patient. General, patient-oriented outcomes are overall survival rates, disease-free survival rates, treatment-related morbidity, and mortality.

Patient characteristic: The medical (e.g., disease, stage of disease, hormone receptor status, prior treatments) or demographic (e.g., age, sex, marital status, race) qualities or traits of a patient.

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 treatment being evaluated from psychological or other effects.

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

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.

Randomization (random assignment): 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 trial.

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

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

Results: Analysis of the data collected during a trial.

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

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.

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

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.

Toxicity: Degree of being poisonous to a living organism or person; ability to cause grave harm or death.

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.

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

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

Policy Statement

This Summary provides a brief overview of an in-depth Patient Reference Guide on this topic. ECRI is solely responsible for the content of this Summary. The information in this Summary—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. The information in this Guide Summary 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 Summary and the issues it raises with your medical doctors.

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 evaluates 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.

To maintain independence and objectivity, ECRI and its staff adhere to strict conflict-of-interest policies that keep an arm's length from medical device and pharmaceutical manufacturers. 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. ECRI received funding for this Patient Guide from the American Association of Health Plans (AAHP).

To develop this Patient Guide, ECRI established a volunteer expert Advisory Committee to provide guidance and review. Advisory Committee members came from leading national healthcare consumer and patient advocacy groups, academia in the public health and health services research field, the medical profession, industry, and government agency providing public health education information. ECRI also established an External Review Committee consisting of patients in trials, their loved ones, researchers, and consumer advocates. We are indebted to them for their advice in producing this Guide. Their names are listed in the text of the full Guide.

About the American Association of Health Plans

AAHP is the nation's leading organization of health plans, representing more than 1,000 plans that provide coverage and care for 160 million Americans nationwide. Member plans include health maintenance organizations (HMOs), Preferred Provider Organizations (PPOs), other network plans, and utilization review organizations (UROs). AAHP is the only association that speaks for the entire community of health plans. AAHP's mission is to create an environment in which our members can thrive by doing what they do best: promoting innovative, evidence-based, cost-effective coverage and care. We also initiate and support research, compile and distribute information on what's working and where, and, on a daily basis, we present 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. Our members guide AAHP policy, serve on key committees and task forces, and shape our 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 to assistance with state and local issues, from strategic communications to state-of-the art education programs, from legal expertise to public policy research. We also promote 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 is at the core of AAHP's interest in and support of this project.

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