Health Lawyers' Public Information Series

# MEDICAL RESEARCH: A CONSUMER'S GUIDE FOR PARTICIPATION

AMERICAN HEALTH LAWYERS ASSOCIATION

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# Medical Research: A Consumer's Guide for Participation

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## I. Introduction

Research is the process of going up alleys
to see if they are blind.
— Marston Bates

People take part in medical research for many reasons. Some want to learn more about a specific medical condition and treatment options. Others want access to the newest drugs or devices that may be available only through a research study. Still, others may believe the quality of care in a research study is better than what is otherwise offered.

Sometimes people agree to take part in research hoping to help others. Research can further science, attract more attention to a medical condition, or lead to new treatments for a specific condition. This may not benefit the participant directly but it may be the participant's hope that the experience will benefit future patients.

The goal of *Medical Research: A Consumer's Guide to Participation* (*Guide*) is to help you consider the issues related to participating in research. The *Guide* describes many of the different kinds of research and how research can expand options for healthcare. It explains why some research does not offer any benefit directly to participants and explains the legal protections available to research volunteers. It discusses the responsibilities of the researcher and the participant and addresses insurance and payment issues.

Most importantly, this *Guide* will help identify questions to ask and factors to consider before and during the research study. There can be risks, as well as benefits, associated with volunteering for medical research. If you or a family member is thinking about taking part in a research study, a good understanding of these risks and benefits is vital.

# II. The Basics of Medical Research

## A. Translational vs. Clinical Research

Volunteers can take part in two types of medical research: translational and clinical. The participation of volunteers is critical to the success of both types of research.

1. Translational Research

Translational research is often referred to as "bench to bedside" research because it tries to take the discoveries that were made in the laboratory and apply them to humans (clinical application). Translational research uses tissues and body fluids from volunteers so that scientific discoveries can be applied to medical conditions. For example, a newly discovered receptor (the part of a cell that binds to certain types of molecules) in skin or saliva may play a role in cancer. By studying tissue and body fluids that do or do not contain that receptor or substance, the researcher can begin to discover whether or not there is a link with cancer.

Scientists study both healthy and diseased tissue, often using tissue that is left over after a medical procedure. Studying healthy tissue helps scientists understand how normal cells work and what effect substances like drugs and chemicals may have. Studying a removed tumor helps researchers understand the properties of cancer cells and improve treatments. Tissue research also reveals new ways to diagnose health problems through biomarkers which are molecules in the blood that indicate health or illness. For most translational research, there is no direct risk to research volunteers.

Tissue research in the area of genetics—the study of proteins or genes that affect cell development—is critical. It helps scientists learn how certain proteins or genes affect detection, diagnosis, or response to treatment. It also sheds light on the development of diseases that are passed from parents to children. Some doctors and scientists believe that many diseases have a genetic basis. If this is true, it might explain why medicines work well in some patients but do not work in others. Improved understanding of the role of genetics in health and illness may someday lead to medicines that are tailored to match the patient's genetic code.

Removed tissue may be studied immediately or be frozen or preserved for later use. Frozen tissue is stored in a tissue bank, also known as a biorepository. The stored tissue is identified by a number or code, not by the research volunteer's name. However, some clinical or medical information about the volunteer may be included to help researchers understand experiment results. This information can include general health and past or current medical treatments. Sometimes, additional information about the volunteer's health is collected for years after the volunteer has donated her tissue for research. Scientists study this information to better understand changes related to the aging process, health status and treatments the person has undergone.

Researchers collect tissue for research according to a document called a protocol. The protocol describes in detail the research design and how the study will proceed. For tissue research, the protocol describes how donations will occur, the type of tissue that will be collected, how the tissue will be preserved, and the research that will be performed. In most cases, informed consent will be required. Informed consent refers to the agreement of a person to take part in research after being told about its risks, potential benefits, and alternatives. In other words, the researcher asks permission to collect and study a person's tissue or bodily fluids. A form is used to record this information, which describes the type of research that will be performed and explains a participant's right to revoke consent and end her participation. A volunteer always has the right to revoke consent. In some cases, the volunteer's tissue may be removed from the research study but in others, because of the way the tissue is stored, the tissue remains in the study but no more information about the volunteer is collected.

A protocol is also usually developed so that tissue from a tissue bank can be used. The protocol will describe the plan for research using the tissue. Often, the informed consent that is used to collect tissue allows the tissue to be used for any kind of research. Sometimes, however, the informed consent will limit the kind of research that can be done. Researchers respect these limitations. To protect research volunteers, a group of people called an institutional review board (IRB)at the research institution conducting the research will review and approve the protocol.

2. Clinical Research

In clinical research, doctors and scientists test new ideas about ways to prevent, diagnose and treat diseases. Another name for clinical research is clinical trial. In clinical trials, a drug, medical device, biologic (e.g., vaccine), blood product, gene therapy or surgical procedure is tested to answer the following questions:

- Is it effective and safe for use in humans?
- Should it be approved for wider use?
- If it works well for one condition, does it also work for another condition?
- Is there a common or existing treatment that is better?
- How does it compare to standard care or against a placebo?
- Can a standard treatment that has already been approved be used differently to make it more effective, easier to use, and/or to decrease side effects?
- Can an existing treatment be used in a new way, or on different groups of people such as children or the elderly?
- Is there a better way to prevent a disease in those who never had it or to keep a disease from returning?
- How can comfort and quality of life for those with a chronic condition be improved?
- How do genetic characteristics change diagnosis or treatment of a disease?

There are different kinds of clinical trials based on the purpose of the research. A treatment trial studies new treatments or combinations of existing treatments. A prevention trial studies how a disease can be prevented through medicine, exercise, diet, or other changes. Diagnostic and screening trials look for better ways to diagnose diseases or those at risk for disease. Quality of life trials focus on how to improve comfort and quality of life for those suffering from chronic or untreatable conditions.

### B. Regulation of Medical Research

Regulation of medical research in the United States is a patchwork of federal and state laws. There is no federal law that applies to all clinical research. Federal laws and regulations only apply to research that is funded or supported by the United States government or research that involves certain drugs or devices.

Most, but not all, medical research performed in the United States is regulated by agencies of the U.S. Department of Health and Human Services (HHS). These agencies include the Food and Drug Administration (FDA) and the National Institutes of Health (NIH). Several years ago, HHS developed regulations for research supported by HHS agencies. Many other government agencies now use this regulation, called the "Common Rule," to protect research volunteers.

The Common Rule codifies three basic ethical requirements for conducting human research:

- Respect for Persons – People have the right to be given information about the risks and benefits of research. People also have the right to make their own decisions about participating in research. The agreement to take part in research should be voluntary and free of coercion. There are some groups of people, such as children, who are considered vulnerable or especially at risk of being coerced or unfairly convinced to take part in a research study. Special protections apply for these situations.
- Beneficence – Researchers must keep risks as small as possible and make benefits as likely as possible. This is accomplished through careful research design, careful review of data, and stopping studies if they unexpectedly seem to be doing more harm than good.
- Justice – The benefits and burdens of research must be shared fairly. Those most likely to benefit should also shoulder the greatest burden. Certain groups should not be selected to participate simply because they are more convenient or easily convinced. If public funds are used to support research on new therapies, those therapies should be made available even to those who cannot afford them.

For research supported by the United States Public Health Service (which comprises all agency divisions of the HHS, including the NIH, the Centers for Disease Control & Prevention (CDC), and the Agency for Healthcare Research and Quality (AHRQ)), the Common Rule is enforced by the Office for Human Research Protections (OHRP).

It is important to remember that a great deal of research conducted in the United States is not supported by federal agencies and, therefore, is not covered by the Common Rule. Such research sponsors may include commercial drug and device manufacturers, non-profit foundations, and research institutions. Many of them, but not all, voluntarily comply with the Common Rule requirements.

Research involving drugs and devices is usually regulated by the FDA no matter who is funding the research. In addition, some research institutions are accredited by a non-profit organization called the Association for the Advancement of Human Research Protection Programs (AAHRPP). AAHRPP sets standards for the conduct of clinical trials and other research and requires participating institutions to apply equal protections to all research volunteers regardless of how particular projects are funded.

The Common Rule, FDA regulations, and AAHRPP standards establish similar requirements including:

- Oversight of the research by an ethics committee or institutional review board (IRB). IRBs have at least 5 members with different skills and backgrounds. For example, IRBs include at least one layperson and at least one individual who has no relationship with the research institution.
- IRB policies that govern review, approval, and ongoing oversight of human research.
- Research designs that minimize risks and enhance possible benefits of the research. Research should include only risks that are reasonable compared to the possible benefits.
- Fair recruitment and selection of potential research participants and, absent a waiver approved by the IRB, voluntary, informed consent of those who have agreed to participate.
- Privacy protection.
- Special protections for children and, under the Common Rule and AAHRPP standards, pregnant women, neonates, and prisoners.

When requirements for human research are discussed throughout this Guide, we are referring to these standards. If you are asked to participate in a research study, you should know who is funding the research and whether the research involves a drug or device. You may also want to ask whether the organization conducting the research is accredited (accreditation generally means that the organization or institution performing the research has been recognized and approved as having conformed with certain standards). The answers to these questions can help you understand your research volunteer protections.

## C. How Are Clinical Trials Conducted?

Most medical researchers are dedicated scientists and healthcare providers who want to improve health and find good ways to prevent and treat illness. The researcher in charge of a study is called the principal investigator. In clinical trials, the principal investigator is often a doctor but in other studies, she may be another type of healthcare professional such as a nurse, psychologist, audiologist, or physical therapist. The skills needed to be a principal investigator are determined by the study details.

The principal investigator leads a research team. Usually, each member of the research team has received special training in research activities. Research teams often include research nurses, research coordinators and assistants. Some teams include research pharmacists who have special skills related to combining drugs and working with new drugs.

Sometimes clinical trials are developed and funded by companies that make the product being tested. These companies are called sponsors. Sponsors have duties to help make sure the clinical trial is conducted as the law requires. Sometimes, sponsors can also be individuals, government agencies, doctors, and non-profit foundations.

1. Basics of Clinical Research Design

Clinical trials are conducted according to the research plan described in the protocol. When developing a research plan, the researchers pose questions that they hope the research will answer. Research design is important. A well-designed research plan protects research volunteers and also improves the chance that the data from the research will answer important questions.

One way to make sure the research answers important questions is to control variables. A variable is an event or factor that changes, manipulates, or influences research outcomes. A common saying in science is that “correlation is not causation.” In other words, the fact that two things are seen together does not mean that one causes the other. When there are too many variables, it is hard to tell which variable was most important.

2. Controlling Outside Factors

All research studies try to control outside factors that might affect the results. One outside factor is the hope of research volunteers and researchers that the product being studied will work. Science shows that if research volunteers or researchers strongly believe, hope, or expect that the item being studied will or will not work, their belief will influence their analysis of the data and more likely turn their belief or expectation into a reality. This effect is called bias. One of the ways researchers avoid bias is by using a single or double blinded study design.

In single blind studies, a duplicate or placebo of the study product is used. A placebo looks exactly like the study product but has no effect or therapeutic value. The use of placebos prevents bias from affecting research results. In a single blind study, the research volunteer does not know if she is receiving the study product or the placebo. In a double blind study, the details of whether the research volunteer is receiving the study product or a placebo is hidden from both the research volunteer and the research team.

Sometimes, it is not possible to conduct a blind a study. An open-label study is when both the patient and the research team knows that the actual study product is being used. For example, most studies that involve surgery are open label. Also, many medical device studies are open-label because it is difficult to create a placebo of the medical device (e.g., a prosthetic for the leg).

3. Randomized Trials

Some clinical trials are randomized. Randomizing is another way that researchers try to limit the impact of outside factors. In a randomized trial, participants are arbitrarily assigned to the control group or the experimental group. The control group receives no treatment or receives a placebo. The experimental group receives the treatment or product being studied.

Randomized trials can provide more objective results. Like double blind studies, randomized trials are considered more reliable and scientifically valid. There is no tendency to place certain individuals in the control group or experimental group based on how they will react to treatment. There can be risks with randomized or double blind studies because a research volunteer may be placed in the control group that receives no treatment or the group that receive the placebo. For serious illnesses like cancer, it can be risky to use a placebo if an effective treatment is available. To decrease this risk, research studies for serious diseases often provide some standard therapy in addition to the product being tested.

4. The Phases of a Clinical Trial

Most clinical trials are conducted in several different phases. First, the drug or device is usually tested on animals. Once the scientists know how the drug or device affects animals, human research is allowed to begin. When a device or drug is tested, many questions are answered in the laboratory bench phase and through animal testing which occur through proof of concept or feasibility studies, and pilot or pivotal trials (trials regarding a new device). Screening, prevention, diagnostic, and quality-of-life studies do not always follow this approach.

Phase I of clinical trials is the first step in testing a new drug or device on humans. Phase I testing helps scientists determine whether the new product is safe for humans. Researchers watch closely for harmful side effects. Different doses are tested to identify what dosage is safest and most effective. The dosage of the new drug is gradually increased as the scientists gain knowledge about the product. The goal is to identify the highest dosage amount for further testing. The ways in which a new drug or product is administered are also tested. Some different ways of administering drugs are by mouth (oral) or through shots (under the skin or into muscle). Phase I trials usually include a relatively small number (10-100) of participants and they often use healthy participants because the goal at this phase is to evaluate safety rather than determine whether the product is effective.

Phase II trials evaluate the safety and effectiveness of the new treatment or product. Phase II is the stage where scientists start to measure whether the product works in humans. The drug is tested on about 100 to 500 participants. Because this phase of testing looks at whether the drug is effective, Phase II participants often have the medical condition the product is intended to treat. Phase II may also include a control group of individuals who do not have the disease.

Phase III trials are the next step. Phase III studies gather more information about how effective the drug is. The research is designed to see whether, and how well, the drug improves the targeted medical condition. Researchers also continue to watch carefully for side effects and safety concerns.

Because Phase III trials focus on how well the drug works, participants usually have the disease the drug is intended to treat. Sometimes Phase III trials will compare the new drug to the current standard

therapy to assess safety and effectiveness. Other Phase III trials look at existing treatments to see if they are effective for a different condition. Phase III trials may also look at whether changing the dose or the way the drug is provided changes how well the treatment works.

In some Phase III trials, all participants receive the drug being tested. In others, participants are randomly assigned to different groups, usually by computer. This protects against bias and helps to ensure that human choices and outside factors do not influence the study's results. One group (Group A) receives the product being tested, and the other group (Group B) may receive standard therapy or a placebo. In a blinded study, neither the participant nor the research team knows if the participant is receiving the product being tested. In some trials, Group A and Group B switch places halfway through the trials so that each group receives the study product for one-half of the trial. This is called a cross-over design.

Studies generally move into Phase III only after the product has shown promise in Phases I and II. Phase III trials often involve large numbers of people (1,000 to 5,000) and are often conducted in several locations. Some Phase III trials take place in multiple countries. On average, it takes about seven years to complete Phases I, II, and III testing of a new treatment.

Phase IV trials evaluate the long term safety and effectiveness of a drug. Phase IV usually occurs after the drug has been approved for use by the FDA. Several thousands of individuals may participate in a Phase IV study. This level of participation is less common in Phase I, II or III. Phase IV studies are increasingly being required by regulators to assure long term safety and effectiveness after initial approval.

Medical devices are studied in a similar way. After a device is developed, an initial study called a feasibility study is conducted. Feasibility studies focus on evaluating whether the device is useful. A feasibility study is also called a pilot study. Wider testing of the device occurs in a pivotal study. Pivotal studies are similar to Phase II and Phase III studies in drugs. Even after a device is approved for use by the FDA, long term studies may be conducted.

5. Where Are Clinical Trials Conducted?

Clinical trials may be conducted at hospitals, in clinics, or through physician offices. Research can also be conducted at nursing homes, community cancer programs, and special research institutes. The choice about where to hold a clinical trial is partly based on the kinds of research activities required. Some procedures, for example, need to be done in a hospital, while others can be safely done in a clinic or physician's office. The location of the trial can also be based on the risks associated with the trial. In some cases, it is important to hold the study in a location that can handle surgical emergencies. Other studies may require that special medication be available. When planning a clinical trial, sponsors look for physicians who are experienced principal investigators, who understand the special requirements of clinical trials, and who have access to well-trained research support teams. Many academic medical centers and teaching hospitals have research as part of their mission, as do many community hospitals.

6. How Can I Find Out About a Clinical Trial?

Physicians often have information about clinical trials. Hospital websites also list research options. Clinical trials can be found in newspapers or through radio and television ads. There are several different resources on the internet. For example, the federal website www.clinicaltrials.gov lists many different kinds of clinical trials. Individuals can search for trials based on a certain disease or where the research is being conducted. In addition, patient support groups often have information on where clinical trials are being conducted for specific diseases.

# III. Protecting Research Volunteers

Research participants are volunteers. Special rules often exist to protect research volunteers. These rules may be based on:

- The policies of the hospital or research center where the research will occur.
- The fact that the research is supported by the federal government.
- The fact that the sponsor wants to use data from the research to be allowed to sell a new drug or device.

One very common way to provide this special protection is through an institutional review board (IRB). An IRB is a special ethics committee that oversees human research studies.

### A. What Is an Institutional Review Board?

The main purpose of the IRB is to protect clinical trial participants. When reviewing research, the IRB considers:

- Risk to research volunteers, compared to potential benefits.
- Activities that are only for research purposes and those that would occur anyway.
- Ways that researchers plan to keep risk as low as possible.
- Ways that researchers plan to protect the privacy of research volunteers.
- Information that researchers will give potential volunteers about the trial.
- Methods the researchers will use to get the informed consent of research volunteers.
- Whether the research answers an important question.

Once the IRB approves the research, it continues to oversee the study. It will require reports from the researchers about how the clinical trial is going. If there are harmful or adverse events, those must also be reported to the IRB. If the IRB thinks the risks are greater than the benefits, the IRB can order the research to stop.

Many research institutions have their own IRBs. Some institutions or principal investigators will arrange for an outside IRB to approve and review their research study.

IRB members are selected for their skills. Different skills and backgrounds help ensure that the IRB is able to protect the rights and welfare of research volunteers. An IRB usually has at least five members. These individuals possess different but necessary skills and interests. This helps balance the IRB's review. Members usually include scientists, non-scientists, and individuals with no relationship to the research institution or research.

When the IRB approves a research plan, it decides how often the IRB will review the progress or results of the study. Generally, research studies are reviewed once a year. Sometimes, the IRB will decide that the study should be reviewed more often. This can happen if a study involves several different risks. It can also happen if some of the risks are very serious.

When an IRB conducts its later reviews, it considers many of the same things as it does in its initial review. It also considers:

- What progress has been made in the research;
- How many volunteers are participating in the trial; and
- Any problems or adverse events that may have occurred.

If the study is going well and there are not many adverse events or other problems, the IRB usually allows the study to continue. The IRB may also decide to revise, suspend, or terminate the project. Suspension or termination may occur if certain rules are not being followed or if the research is causing unexpected harm to the volunteers. Sometimes the clinical trial may show early proof that the treatment or product being researched is safe and effective. In that case, the sponsor may try to end the study so that the treatment or product can be offered to more people.

### B. What is a Data Safety Monitoring Board?

Regular review of the research data is necessary to help protect research volunteers. By frequently reviewing the data, any new risks can be quickly identified. The frequency of data review is based on how much risk the research poses. Studies that pose serious risks to volunteers or studies that have many

different risks are subject to frequent and extensive data review. Studies that target serious diseases also have frequent data review.

The IRB reviews certain safety data based on reports of problems and the annual review report. In some cases, however, a data safety monitoring board (DSMB) is used. The DSMB is a special committee that monitors the safety of volunteers involved in a clinical trial. The DSMB includes experts on the disease that is being studied as well as experts on safety, ethics and statistics. DSMBs are usually used when there are many different sites or locations involved in the study.

There are several differences between an IRB and a DSMB:

- An IRB often only looks closely at the data from one site. A DSMB collects and reviews data from all of the sites where the study is being conducted.
- Safety data is often reported more frequently and in more detail when a DSMB is reviewing it.
- Conflicts of interest can occur in some cases if the IRB is influenced by the researchers. A DSMB can minimize any conflicts of interest because it is independent of the research sites.
- In some cases, the DSMB may include or be able to consult with experts that are less accessible to a local IRB or research institution.

### C. How Do I Make Sure My Decision is Voluntary?

A person's decision to take part in a research study is strictly voluntary. To help make sure the choice is really informed, ask the following questions:

- Do I understand the risks and possible benefits of the study?
- Do I understand exactly what I must do to be in the study?
- Do I understand which procedures are only needed because of the research and which procedures I would have anyway?
- How often do I need to be seen by my doctor during the study?
- What happens if I miss a follow-up visit?
- What are my options if I don't want to be part of the study?
- If my regular doctor is conducting the study, will our usual relationship change during the study or if I decide to stop participating?
- Have I had a chance to ask questions and have all my questions been answered?
- Have I had time and the opportunity to think about my decision?
- Do I feel like I am being pressured to take part in the study?

You are not required to volunteer for research to get or keep insurance coverage or to receive other benefits to which you are entitled. A choice not to volunteer will have no impact on your regular medical care. If any researcher ever suggests otherwise, you should talk to the IRB that is overseeing the research. Contact information for the IRB should be included in the informed consent form.

### D. What Is Informed Consent?

In most studies, a researcher must obtain informed consent before allowing a volunteer to take part in the study. Informed consent occurs when an individual makes a voluntary choice to enroll. Informed consent is not just about signing a document. The process of informed consent includes receiving verbal and sometimes written, videotaped or electronic information about the study. This includes information about the risks, potential benefits, and alternatives to the research. The consent process continues as long as the research continues. As changes are made to the protocol, you may be given more information about risks and benefits and you may be asked to sign a new consent form.

Researchers usually use an informed consent document to show that a volunteer has agreed to take part in a study. This document must be approved by the IRB. The informed consent document may vary among researchers and institutions, but it usually includes:

- A statement confirming the study is for research purposes.
- The purpose of the study.
- The length of time the study is expected to continue.

- A description of the procedure or treatment being studied.
- An explanation of any part of the study that is experimental.
- A description of any reasonably foreseeable risks or discomforts.
- A description of any possible benefits to the participant or others.
- Alternative procedures, treatments, or products that might be helpful to the participant.
- A statement describing how researchers will protect the confidentiality of research volunteer information.
- Information on whom to contact with questions and concerns.
- A statement that participation is voluntary and that the volunteer can leave the study at any time without penalty.

Some informed consent documents will include additional information. Sometimes, the IRB may waive some statements or elements. However, there are certain statements that cannot be included in the informed consent document. For example, the document cannot require the volunteer to waive or appear to waive legal rights, like the right to sue for malpractice that might occur during the study.

Informed consent forms should be easy to understand. For studies recruiting people who do not speak English or are blind, the forms should be translated to languages they can read and understand. The research team should explain the information in the informed consent form and answer any questions. After questions have been answered, the volunteer can decide whether to sign the form. It is important to remember that the informed consent document is not a contract. The volunteer is free to withdraw from the study at any time.

If the research volunteer is able to make medical decisions, the volunteer signs the informed consent form; however, some research involves individuals who cannot make medical decisions. In this case, the IRB usually requires the consent of a legally authorized representative. For children, this is usually a parent or guardian. Sometimes, adults cannot make medical decisions, so the legally authorized representative might be another adult or an organization, such as a court, permitted under state law to make decisions. A legal representative's authority to grant permission is based on state law. The requirements may vary among states.

Informed consent, or use of consent forms, may be waived or excused by the IRB. IRBs waive informed consent only after careful consideration. A waiver usually will be approved only when the study poses very little or no risk to the volunteer. A waiver won't be granted just because it is hard to get informed consent. A waiver may be approved if there is no reasonable way to get informed consent. This can occur when the researcher is only using information collected beforehand (e.g. through another study) – called a retrospective study. Another reason an IRB might approve the waiver is when simply knowing that one is participating in the study could change the results. For example, when the study only involves observation of the participant, knowledge of participation may change the outcome. Sometimes, researchers will tell participants about the research after the data collection is completed.

Some studies will involve information that is especially private or sensitive in nature. If the informed consent form is the only thing that would link a research volunteer to the research, the IRB may permit waiver of the documentation. In this case, information about the research will be given to the participant but the document does not have to be signed by the volunteer. This avoids making a connection between the volunteer and the results. The volunteer always has the right to ask for a copy of the consent form whether or not it needs to be signed.

Another way that confidentiality can be protected in research is through a Certificate of Confidentiality. These certificates are issued by the National Institutes of Health and they help protect against disclosure of sensitive information, even if a court orders disclosure. More information about the Certificate of Confidentiality program can be found at www.grants.nih.gov/grants/policy/coc/.

### E. How Are Vulnerable Populations Protected in Medical Research?

Federal regulations (the Common Rule) treat pregnant women, fetuses, prisoners, and children as vulnerable to possible coercion or to special risks of participation in research not encountered by others. Some institutions may consider other groups as vulnerable. For example, the elderly may be viewed as a vulnerable population. Special rules apply to these groups. For example, there are special informed

consent rules. The IRB may also have special duties to minimize risk and protect these volunteers. There are some kinds of research in which vulnerable populations cannot usually participate. These special rules are intended to provide extra protection to vulnerable individuals.

It is important to understand the definitions of each vulnerable population. Under the federal rules, a woman is considered "pregnant" from the time conception is confirmed until the child has been delivered. A "fetus" is the product of conception from implantation until delivery (from HHS regulations on the protection of human subjects). A "prisoner" is someone who has been confined or detained against her will in a penal institution or a similar facility. A prisoner can also be someone who is being held while awaiting arraignment, trial, or sentencing. A "child" is a person who is not yet old enough to legally consent – generally under the age of 18. In some states, teenagers are allowed to consent for certain kinds of medical care. Whether that confers the right to consent to research is a question of state law. If a child is a "ward" of the state, extra protections are provided. A ward is a child who is placed in the legal custody of the State, a child welfare agency, or an institution.

Other "at-risk" volunteers may include people who:

- Have limited ability to understand complex ideas.
- Have impaired ability to make decisions.
- Are at risk for suicidal behaviors.

There are no specific regulations to protect these at-risk populations but some researchers will offer special protections to these individuals.

# IV. Rights and Responsibilities of Research Volunteers

### A. What Documents Must I Sign?

Your medical information is confidential. This means that it can only be used or disclosed in certain cases. Rules about the use of confidential information are established by laws and by ethical standards. A federal law called the Health Insurance Portability and Accountability Act (HIPAA) created federal rules to protect the privacy of certain medical information. Many states also have additional rules about health information privacy.

Under HIPAA, your health information can be used for some things, like treatment and payment, without your written permission. Other uses of your health information are only allowed if certain requirements are met. Use of your health information for research usually requires your permission. If you decide to become a research volunteer, you may be asked to sign a special form called a privacy authorization. The privacy authorization explains exactly how your information can be used for the study. Sometimes the privacy authorization is part of the informed consent form. Sometimes the privacy authorization is a separate form.

The IRB may also serve as the Privacy Board of a research institution. A Privacy Board is a group of people that helps ensure compliance with privacy and confidentiality rules under HIPAA. Because the IRB is skilled at protecting the rights of research volunteers, the IRB is often also responsible for protecting privacy rights in research studies. This guidebook will use the term "IRB" even when it is referring to its role as a Privacy Board.

Sometimes, the IRB will decide that health information can be used for research without written permission. This is called a waiver of authorization. There are special rules for when the IRB can approve this approach. To approve a waiver of authorization, the researcher must show that:

- Identifiable information is needed for the research.
- The use or disclosure involves no more than minimal risk to privacy.
- The research could not realistically be done without the waiver

Under HIPAA, researchers can also use your private information without your written permission for reviews preparatory to research. This rule allows researchers to look at private information while the research project is being planned. For example, researchers may look at medical records to see if the research idea makes sense or if there are enough people who might be interested in the research to make it worthwhile.

Under HIPAA, your medical information remains private even after you die but there is a special rule that allows researchers to use the medical information of decedents without written permission. The researcher must get the approval of the IRB for this use. Researchers may decide to ask family members for permission to use the information. Usually one person is responsible for taking care of the affairs of the patient after death. That person can agree to the use of the patient's private information after death.

### B. How Is My Information Used?

Private information is often collected during a research study. This private information may include information about the volunteer's health, disease or condition, treatment, and life style. A good research study will limit its information collection to facts that will help researchers answer the research question. Research volunteers should understand what information is being collected and why.

The research information collected is called data. The data will be reviewed regularly. These reviews consider how the study is progressing, how the treatment or product is working, and whether the new treatment or product is safe and effective. Data is reviewed by the research team and the IRB. In some cases, data will also be reviewed by the DSMB as discussed earlier in this guidebook. The DSMB is a group of individuals who review research data to determine if the risks involved in the study are acceptable. The DSMB focuses on the safety of the study, while the IRB reviews each study to ensure that the rights of the research volunteers are protected.

Sponsors who fund studies may send a trained monitor to the research site. This individual will ensure that the collected data is accurate and complete and that private information is kept confidential. The monitor will compare the research data against the volunteer's medical record. This helps ensure there are no errors in the data and that the results can be reliably used to make decisions about product approval or future treatment standards. Often, research is done on new drugs or devices to

determine whether the product is safe and effective. In this case, the sponsor may submit the data to the FDA to obtain permission to market the product. If the sponsor wants to market the product in other countries, government agencies of those countries may review the data. The data may also be reviewed by other U.S. regulatory agencies like the Office of Human Research and Protections (OHRP) of the U.S. Department of Health and Human Services. OHRP is responsible for overseeing research volunteer protection for federally-supported research. Other agencies may review data for other purposes, such as an audit. An audit is a review of the research program's operations to ensure that research is being conducted safely and in compliance with the law. Research data may be published in a professional magazine or journal. This allows physicians, scientists, and other interested people to learn the results of the research. However, these publications will not include your name or other identifying information unless you give your permission.

### C. What Are My Privacy Rights?

Research often requires the use of very private information. State laws and HIPAA protect this personal health information. In some cases, other documents will be needed.

There are research methods that help protect the privacy of research volunteers. For example, the researcher may assign a unique number to identify each research volunteer. This allows the research team to record and analyze data based on the assigned number rather than by name. This preserves anonymity since only the number is released for data reviews, not the individual's name. The list of volunteers and their assigned numbers is kept by research staff in case a volunteer needs to be informed of certain information regarding her care.

Not everyone is required to protect a volunteer's personal information. Only "covered entities" are regulated by HIPAA. Physicians, hospitals, and health insurance plans are "covered entities" but other researchers and sponsors are not "covered entities and, therefore, not covered by HIPAA. Also, state privacy laws usually only apply to certain people and companies. Studies that are not conducted at a covered entity and which are not subject to the Common Rule or FDA oversight may have different duties regarding confidentiality. It is important for volunteers to understand who might see their information and whether that person or company is required to protect the volunteer's privacy. Private information can lose protection when it is disclosed to someone who is not subject to the privacy laws.

In assessing privacy risks, volunteers may want to ask the following questions:

- Do I understand the authorization form?
- Who will be allowed to see, use and share my personal health information? Are all of them subject to privacy laws?
- How long will the information be used or shared?
- What heath information is needed and why?
- Do I have the right to cancel my authorization? How do I cancel?
- What happens if I decide to not sign the authorization form?
- What happens to my private information after the study is completed?
- Have I had the opportunity to ask questions about the authorization and have they been answered?

### D. Who Can I Contact if I Have Complaints or Concerns?

The informed consent and authorization forms should provide information on whom to contact with concerns, questions, or complaints about the study. The contact person will usually be a member of the research team. This person could be the study coordinator or the principal investigator. Other points of contact include:

- The hospital or institution in which the research is taking or took place, the IRB that reviewed and approved the research plan, and the company or sponsor that made the treatment or product that is being tested;
- The FDA or the OHRP if federal money was used to support the study; or
- The state licensing board if the research volunteer wishes to file a complaint about a specific healthcare provider or researcher.

If a volunteer has questions or concerns, it is important to talk to someone. This brings the issue to the

research team's attention and may improve the research study going forward.

If a research volunteer believes her privacy was violated, she should inform the research team, principal investigator, and/or the hospital conducting the research. The volunteer can also contact the Office for Civil Rights at the U.S. Department of Health and Human Services.

### E. What Are My Responsibilities as a Research Volunteer?

The volunteer is responsible for carefully considering the informed consent information. If the information is not easy to understand, the individual should ask questions until she understands all of the parts of the research study.

It is important for the participant to follow all of the principal investigator's instructions. Even a minor change can impact the study. Participants should promptly report changes in her condition. This is especially true of any side effects, also called "adverse events." These events should be reported even if they do not seem related to the study.

A person may participate in a study while receiving treatment for an unrelated medical condition. Changes in therapy or treatment for that condition may have an impact on the study. Therefore, changes to a volunteer's medical treatment should be reported immediately to the research staff. If a volunteer is being treated by several doctors, she should inform all of them about her participation in the study. Regular physicians may want to discuss the details of the study with the principal investigator to ensure the patient's safety.

Many research studies will present risk. A risk is the possibility that something will go wrong or that the volunteer might be injured. Research involves risk because there are many unknowns in a study, especially during the earlier phases. Some risks in research are the same as the risks in normal medical care. For example, the risk of bruising that may occur when drawing a blood sample would be the same whether conducted for normal medical care or for research purposes. However, other risks are unique to the research study. For example, if the study involves the administration of a new treatment or product in which the side effects are not yet known, those side effects are a risk unique to the research.

Not all risks from a research study are physical. When private or sensitive information is collected, privacy risks exist if the data is misused. When genetic information is collected, there are risks linked with learning about the individual's genetic make-up. For example, the volunteer could learn that he is at risk for a genetically-based disease. Information about racial and ethnic heritage can also be revealed. When considering participation in such studies, the volunteer should ask questions about privacy protection and whether genetic information will be shared.

The volunteer should evaluate whether the research risk is acceptable as compared to the potential benefits. Three factors help with this decision: 1) the risks and potential benefits themselves, 2) the likelihood of the risk, and 3) how serious the risk would be if it occurred. In the blood drawing example, mild bruising that disappears in a day or two may be an acceptable risk. But, bruising is a more serious risk if the participant suffers from a bleeding disorder or takes medicine that affects clotting. Deciding on the acceptability of risk is a personal decision that must be made by the volunteer.

Potential volunteers should consider the benefits of a study. It is important to remember that the participant may not receive any direct benefit. The treatment or product being tested may not work. The participant may be assigned to the control group and receive no treatment or the standard medical therapy may be more effective in treating the participant's condition. Even so, the individual may feel that she benefited by contributing to the advancement of medicine and science. Enrolling in a study may provide a volunteer with access to treatments that may not be available to the public. Being a volunteer may also provide a heightened level of medical attention. The researcher and research team strive to understand how the study is affecting the human body, so medical care is paramount. Being a volunteer may also give an individual more control over her medical care. As with risks, identifying the benefits is a personal decision.

# V. Payment for Research Treatments

Health insurance coverage for some research may be difficult to obtain. When talking about insurance coverage for research, two different kinds of care must be considered. The first is care that is only provided because of the research study, sometimes called research-only care. This includes, for example, the product being studied and tests that are required only because of the research. The other is care that would have been provided for the volunteer even if the volunteer was not taking part in the research study. This is often called routine care.

### A. Who Will Pay for My Care While I Am a Research Volunteer?

Responsibility to pay for costs of care during research can vary. In translational research, there are usually no costs to the volunteer. The tissue and fluids are collected as part of the volunteer's medical care, and the volunteer is not required to have additional tests. In most clinical studies, some of the treatment provided will be experimental or investigational (provided only because of the research), and some will be routine care. Routine care is generally covered by insurance. Often, investigational and experimental care is not covered. In this case, research-only care may be paid for by the sponsor. There are some cases where even the routine medical care is covered or paid for by a sponsor. There are also some cases where the experimental care is covered by insurance. This is most common in cancer research and varies from state to state. Volunteers should discuss costs with the research team or principal investigator during the informed consent process.

Insurers often require therapeutic intent before even routine care is covered. Therapeutic intent is research that not only gathers data about a product's effectiveness but also tries to treat the disease or condition. The research will not be covered if it is merely to determine safety and proper dosage. This requirement can make obtaining insurance coverage for Phase I trials especially difficult but there are some cases where even Phase I trials meet this standard. For example, Phase I oncology trials usually have the potential for therapeutic benefit for active cancer patients enrolled in the study.

### B. Will My Insurance Plan Pay for My Care?

This is a complicated question that does not have an easy answer. A good place to start is the volunteer's health plan contract. Health plan contracts may provide a general outline as to what the insurance plan will cover during a research study. Understanding Medicare and the individual's state regulations for coverage will help in understanding the individual's health plan coverage.

### C. How Do Health Plans Define "Research"?

An individual's health plan contract will usually have definitions for "research," "investigational," and/or "experimental" care. Experimental care is usually not covered by insurance plans. Research or investigational care and/or routine care provided during a study may be covered, particularly under Medicare. There are no standard definitions for these terms. It is important to understand the individual health plan's definition for each. For example, some studies will involve research or investigation on a treatment that has not yet been approved by the FDA. In other cases, the research or investigation might involve a new use for a product that has been approved by the FDA for another purpose. Other studies could compare two treatments already approved by the FDA. Each of these can be treated differently by different health plans.

### D. Are the Costs Associated with Clinical Trial Participation Covered?

Clinical trials can be sponsored. Sponsors can be a pharmaceutical or device company, a federal agency like the NIH or U.S. Department of Veterans Affairs, or individuals such as a physician. The sponsor usually pays for certain costs associated with the research. These costs could include data collection and management, research team time, research tests, and the experimental treatment or product.

### E. Can Coverage Continue After the Clinical Trial Has Ended?

Some sponsors continue to provide the research treatment or product at no charge for a limited period after the trial. This occurs through a patient assistance program (PAP). PAPs are operated by the sponsors or through an independent organization. The clinical site hosting the clinical trial may also assist and cover the new treatment or product for a limited time. Volunteers should ask about the existence of such programs from the sponsor or clinical site if the treatment proves beneficial.

### F. Can Research Volunteers Be Paid for Participating in a Clinical Trial?

Volunteers are sometimes paid by sponsors for their participation in trials. This is especially true in the early phases of investigational drug, biologic, or device development. Payment for participation is a recruitment incentive. These financial incentives are used most often when health benefits to the volunteer are minimal or nonexistent. They may also be offered if the research requires many visits to the clinical site. Volunteers may be offered compensation for their time and any discomfort experienced during the trial. The amount of compensation is determined by the sponsor.

### G. What Will Insurance Plans Cover?

Sponsors generally do not subsidize all patient care costs linked with the clinical trial. Trial sponsors rely on insurers to pay for usual and routine patient care. This can include doctor visits, hospital stays, laboratory tests, and x-rays. These are generally costs related to treatment the patient would have received even if he had not volunteered for the study. But health insurance and managed care providers often do not cover what they consider to be extra care costs related to volunteering for research. Coverage varies by health plan and study. Some health plans may not cover clinical trials if the treatment or product being studied is considered experimental or investigational. If enough data indicates that the treatment or product is safe and effective, a health plan may consider it "established" and cover some or all of the costs. Whether an insurer will pay for medical care connected with research can have a significant impact on whether a patient volunteers for the research.

A health plan contract may have rules that a trial must satisfy to be covered. For example, the trial may have to be sponsored by a specific organization or be considered "medically necessary." A plan may require that the treatment not be significantly more expensive than other available treatments. Some plans only cover studies for diseases that have no standard or effective treatment. The facility and medical staff may have to meet the plan's standards to conduct certain procedures.

Health plans are less likely to have review processes in place for prevention and screening trials, so research participants may have difficulty obtaining coverage for those trial costs. In many cases, it is important to have someone from the clinical research team discuss the details of coverage with the health plan.

Many states have passed legislation or developed policies requiring health plans to cover the costs of certain clinical trials (see Appendix B).

### H. What is Medicare's Payment Policy for Clinical Trial Participation?

On June 7, 2000, President William J. Clinton issued an executive memorandum relating to Medicare payments during clinical trials. The memorandum directed the U.S. Department of Health and Human Services Secretary to "explicitly authorize [Medicare] payment for routine patient care costs… and costs due to medical complications associated with participation in clinical trials." Since then, regulations governing Medicare payment policy for clinical trial participation have evolved. This evolution has created confusion among Medicare beneficiaries and the contractors who manage the Medicare program.

After July 9, 2007, Medicare covers routine costs of qualifying clinical trials and "reasonable and necessary" items and services used to diagnose and treat clinical trial complications. Routine costs of a clinical trial include all items and services that are otherwise generally available to Medicare beneficiaries. These items and services can be provided in either the experimental or control arms of the clinical trial. The items and services must fall into a Medicare benefit category, not be statutorily excluded, and they must not be the subject of a national non-coverage decision. However, there are a few things that are not covered:

- The investigational item or service itself unless it is covered outside of the clinical trial;
- Items and services provided solely to satisfy data collection and analysis needs, or items and services that are not used in the direct clinical management of the patient (e.g., monthly CT scans for a condition that usually requires only a single scan); and
- Items and services customarily provided by the research sponsors free of charge for any enrollee in the trial.

Medicare defines routine clinical trial costs as:

- Items or services that are typically provided absent a clinical trial (e.g., conventional care);
- Items or services required solely for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapeutic

agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and

- Items or services needed for reasonable and necessary care, particularly arising from the provision of an investigational item or service for the diagnosis or treatment of complications.

This policy does not withdraw Medicare coverage for items and services that may be covered by local medical review policies (LMRPs) or the regulations on category B investigational device exemptions (IDE), described further below.

Medicare generally covers only the treatment of complications arising from the delivery of non-covered items or services and unrelated reasonable and necessary care. This even includes complications from items and services that may be statutorily prohibited. As long as the item or service is not subject to a national non-coverage policy, Medicare will cover routine costs of qualifying clinical trials. However, the non-covered item or service iteself will not be covered.

Medicare regulations require Medicare Advantage (MA) organizations to follow Medicare's national coverage decisions (NCDs). MAs are Medicare's managed care plans. The October 17, 2007 NCD confirmed Medicare coverage of routine care costs connected with clinical trials and the investigational item itself if covered outside the trial. This requires some modification of most MA organizations' rules governing provision of in and out-of-network items and services. MA organizations must now cover services provided in clinical trials regardless of whether they are available through in-network providers. MA organizations may also have reporting requirements to track and coordinate care of clinical trial participants, but MA organizations cannot require prior authorization or approval.

### I. What Payment Rules Apply if the Research Involves a Device?

There are special Medicare coverage rules about device use in an investigational device exemption (IDE). An IDE allows investigational devices to be used in clinical studies to determine safety and effectiveness. This data is required to support a Premarket Approval (PMA) application or a Premarket Notification (510(k)) for the FDA. Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)s require clinical data to support the application. This exemption includes clinical evaluation of modifications made to a current standard device or new uses of legally marketed devices.

The FDA categorizes devices with IDEs as either Category A or Category B devices. Category A devices are considered experimental. Medicare and commercial insurance rarely cover Category A devices in clinical trials. Category B devices are considered "next generation" versions of approved devices. Medicare and commercial insurance plans will frequently cover these devices.

An individual should ask her physician if the clinical trial device is under an IDE. If so, the individual should further question if the device falls into Category A or B. This will make a difference as to whether the device is covered by a health plan or not.

### J. What About Off-Label Uses of Drugs or Devices?

Many clinical trials study off-label uses of drugs. "Off-label" means a drug or device is used for a purpose for which the FDA has not approved. One example of an off-label use is prescribing a drug that has been FDA-approved to treat cancer to treat migraines instead. Even though physicians have discretion to prescribe a drug or device for off-label use, the physician should inform her patient when a prescribed drug or device is being used off-label. Some health plans will not cover off-label use, and patients should be aware of off-label use before agreeing to treatment. This is especially true with cancer and psychiatric disorders since these drugs are often prescribed off-label.

Medicare may cover anti-cancer infused drugs for off-label use. Off-label use may also be covered:

- If the proposed use is noted in one of several approved compendia that track evidence of efficacy for off-label uses; or

- If a Medicare contractor believes there is sufficient evidence of efficacy in peer-reviewed literature.

Many commercial insurers follow Medicare's lead in this area. A health plan might deny coverage of a treatment or product because it was used off-label. If the use is noted in a drug compendia or peer-review literature, the volunteer or patient should consider appealing the coverage denial and ask the physician to assist in the appeal. The physician should be willing and able to share with the patient's health plan evidence that was used to make the decision to prescribe the drug or treatment off-label.

### K. What Other Government Programs Help Pay for the Costs of Care?

Beneficiaries of TRICARE, the U.S. Department of Defense's health program, have coverage for medical costs related to some clinical trials. These trials include participation in National Cancer Institute (NCI) sponsored Phase II and Phase III cancer prevention and treatment trials. This includes screening and early detection for cancer patients. The U.S. Department of Veterans Affairs allows eligible veterans to participate in NCI sponsored prevention, diagnosis, and treatment studies. All phases and types of NCI sponsored trials are included.

Medicaid patients may have to pay for certain costs regarding care in clinical trials, but these policies vary by state. Medicaid is the federal government's state-administered health program for individuals and families of low incomes.

### L. Which States Require Coverage of Certain Costs Incurred During a Clinical Trial?

A growing number of states have passed legislation or instituted special agreements requiring health plans to pay the cost of routine medical care during a clinical trial. As with Medicare policy, these laws and agreements do not cover the research costs associated with the trial that includes research tests. In most cases, the research costs would be paid for by the sponsor, such as the NCI or a pharmaceutical or device company. States that mandate clinical trial coverage are listed in Appendix B.

### M. What Questions Should I Ask to Determine Whether Coverage Will Be Provided?

- Who is sponsoring the research: the physician or principal investigator, the hospital or academic medical center, a pharmaceutical or medical device company, or a federal agency such as the National Cancer Institute?
- In what phase of the research will I be participating?
- Will the research involve off-label use of an already approved drug or device, or will it involve use of an unapproved drug or device?
- Will the treatment that is being provided as part of the research protocol be covered by my insurance plan? If not, why not? What are my appeal rights regarding a non-coverage decision? If covered, specifically which services will be covered and not covered? What will my co-payment be for covered services?
- What are my options for continued coverage after the clinical trial is over?
- If I am a Medicare beneficiary, does the research involve off-label use of an anti-cancer drug or a device that falls under an investigational device exemption?
- Does my state law require that health insurance plans cover certain costs of clinical trials and off-label uses? What costs are covered?

## VI. Conclusion

Through medical research, scientists and clinicians improve prevention, diagnosis and treatment of disease, and improve the quality of life of those suffering from disease. The decision to volunteer to participate in a medical research program is an important decision. We hope this guidebook has provided you with information that will help you make that decision. We encourage you to ask questions, be informed, and be active in your healthcare.

## GLOSSARY

There are many special words that are used to describe and talk about research. To help you better understand issues related to medical research, a glossary of commonly used terms is provided below. While not all of the words in this glossary appear in this Guidebook, they are helpful to know as you decide whether or not to participate in a clinical trial.

**Assent:** The process of obtaining one's agreement to participate in research.

**Bench Research:** General scientific research that occurs in a laboratory.

**Bias:** Permitting expectations or hopes to influence decisions or analysis of data.

**Biologic:** A substance made from a living organism that is used to prevent, diagnose or treat a disease, such as a vaccine.

**Biomarker:** A protein occurring in the blood that indicates health or the presence of an illness.

**Biorepository:** A facility that collects and stores tissue and body fluids for research, also referred to as a tissue bank.

**Blinded:** A study design used to decrease bias. In a single-blinded study, the research volunteer does not know if she is receiving the study product. In a double-blinded study, neither the research volunteer nor the principal investigator knows who is receiving the study product.

**Case Reports:** A research and teaching approach that uses a detailed discussion of the clinical progress of one person or several people (case series) and follows the progress of the person's disease or treatment. Researchers hope to learn more about the disease and its treatment by examining how the disease progresses and what effect a given treatment has.

**Case-Control Study:** A research approach that compares detailed information about two very similar groups of people (one that has a disease and one that doesn't). Researchers use this technique to try to identify what causes one group to be sick and the other to be healthy.

**Case Report Form (CRF):** The form used to collect and submit information and data about a research study.

**Cells:** The basic functional units of the body. Groups of cells that perform common functions create tissues.

**Clinical Trial:** Research into how a new medical approach works in people. Clinical trials can study prevention, diagnosis, and treatment options. Also referred to as clinical research.

**Cohort Study:** A cohort is a group of people who have common characteristics. A cohort study looks at outcomes and compares groups of people who are alike in many ways but have some differences.

**Common Rule:** The term used for the regulations that were developed to guide research that is supported by the federal government and involves human volunteers as participants.

**Compassionate Use Trial:** A clinical trial that permits use of a new, possibly helpful treatment by people who have a serious disease but do not qualify to be included in a clinical trial exploring the treatment.

**Control Group** (also control arm): The group of people in a clinical trial that do not have the disease or do not receive the experimental product. Control group participants may receive a placebo, an alternate treatment, or no treatment.

**Controlled Clinical Trial** (also controlled study): A clinical trial that uses a control group as comparison to the experimental product.

**Cross-Over:** A study design where the experimental and control groups switch halfway through the trial so that each group receives the study product for one-half of the trial.

**Data and Safety Monitoring Board (DSMB):** A group of people who review data during a clinical trial to determine whether the risk/benefit ratio remains acceptable.

**Device:** A product that is used to prevent, diagnose or treat disease, but which does not work by a chemical reaction or metabolism. A device is often an item that is implanted or applied to the body.

**Diagnostic Trial** (also screening trial): A clinical trial that looks for better diagnostic tests for diseases.

**Dose:** The amount of drug or biologic given at one time.

**Dose-Limiting:** The dose at which side effects are so significant that no higher dose should be given.

**Dose-Dependent:** When the action or effect of a drug or biologic varies based on the dose.

**Drug:** Any substance (other than a food) that is used to prevent, diagnose or treat illness or symptoms of an illness; also, any substance that changes mood, thinking, or body function.

**Efficacy:** Effectiveness. How well a product works to prevent, diagnose or treat an illness.

**Eligibility Criteria:** The characteristics that must be present to be allowed to participate in a clinical trial.

**Experimental** (also investigational): A drug, device or biologic that has passed animal testing and can be tested in humans, but has not yet been recognized to be safe or effective. Some insurance companies and other payors distinguish between experimental, which cannot be covered, and investigational, which can be covered in some cases.

**FDA:** The U.S. Food and Drug Administration. The agency charged with ensuring the safety of food and safety and efficacy of drugs, devices and biologics.

**Feasibility Study** (also pilot trial): A preliminary study to determine the chance of success, costs and benefits of a research project.

**Follow-Up:** Continuing the monitoring of a person's condition after a clinical trial is completed. Follow-up is used to gather information about long-term effects of a study product.

**Gene:** The segment of DNA that passes on characteristics from parents to offspring based on how they are arranged.

**Good Clinical Practice:** The internationally-accepted ethical and scientific standards for conducting research involving human volunteers. GCPs are intended to assure that data is valid, reliable, ethically obtained, and volunteer participants are protected.

**Informed Consent:** The process that verifies a volunteer's willingness to participate in research after the volunteer has received and considered information about that research. Information provided for informed consent includes information about the research project; risks, benefits and alternatives; who can participate and how to end participation; and who to contact with questions. The informed consent process is ongoing throughout the research and includes updating the volunteer about newly discovered risks, benefits, and alternatives.

**Institutional Review Board (IRB):** A group of people, including physicians, scientists, and non-scientists, who review and oversee research that involves human volunteers. The IRB is responsible for ensuring that human research volunteers are protected and treated fairly.

**Investigational** (also experimental): A drug, device or biologic that has completed animal testing and is being tested in humans. An approved drug, device or biologic can be investigational if it is being studied for different uses at different dosages or given in a different way.

**Legally Authorized Representative:** The person or entity legally authorized to make decisions about participating in research for a person who cannot make those decisions for him/herself.

**Open-Label:** A study design where both the patient and the research team know that an actual study product, and not a placebo, is being used. Open-label studies are conducted when it is difficult or not possible to blind the study.

**Phase I Study:** The first human-based research project to evaluate a possible new product. Primarily determines absorption, distribution, dosing, toxicity and safety. In some cases, there may be therapeutic intent, especially in cancer trials.

**Phase II Study:** After successful conclusion of a Phase I study, this phase evaluates the safety of the product in a larger study group that typically has the disease or condition the product is intended to treat.

**Phase III Study:** Studies the safety and efficacy of a product in a larger study population. The study population consists of those with the disease or condition the product is intended to treat. If successful, this is typically followed by an application to the FDA for permission to market the product.

**Phase IV Study:** Studies the long-term safety and effectiveness of a drug or device. These studies usually involve thousands of individuals and occur after FDA approval has been received.

**Pilot Trial** (also feasibility study): The preliminary trial of a drug or device using a small number of animals. The goal is to gather general information rather than to obtain statistically significant results.

**Pivotal Trial:** The clinical trial of a new device.

**Placebo:** An inactive substance that is made to resemble the product being studied. Placebos are used when there is no effective treatment for the disease or condition being studied. Placebo is intended to prevent bias from affecting research results.

**Prevention Trial:** A clinical trial to study how a disease can be prevented through medicine, exercise, diet, or other changes.

**Principal Investigator:** The scientist or healthcare provider who is primarily responsible for the conduct of a research project. The principal investigator is responsible for making sure that the protocol is followed, only people who meet eligibility criteria are enrolled, and she oversees the safety of research volunteers. She works with the sponsor, the DSMB, and the IRB to make sure the research is safe, scientifically useful, and ethical.

**Proof of Concept Study:** A study intended to show that a hypothesis or concept is valid.

**Protocol:** The document that describes the research design for a given research project.

**Quality of Life Trial:** A clinical trial to study methods to improve the quality of life for individuals suffering from chronic conditions.

**Randomized:** A process where each volunteer in a study has an equal chance of being placed in the treatment arm or the control arm of the study. Randomization is intended to prevent bias from affecting the research results.

**Research:** A systematic study of an issue, intended to lead to generalizable results.

**Research Design:** The plan for conducting research in a way that makes it scientifically useful and ethical. The research design includes determining whether the study will be blinded, whether a control group will be used, and whether volunteers will be assigned to an arm randomly. The research design is described in the protocol.

**Revoking Consent:** The participant's decision to end her participation in the clinical trial. A volunteer always has the right to revoke consent.

**Risk/Benefit Ratio:** The comparison between the risks and the benefits of proposed research. Whether the risk/benefit ratio is acceptable depends on how serious the disease being studied is and whether another effective treatment exists for that disease.

**Screening Trial** (also diagnostic trial): A clinical trial to identify better ways to diagnose diseases or individuals at risk for a disease.

**Sponsor:** The individual or organization funding the research study. A sponsor can be the company that developed the product being tested or government agencies, doctors, or non-profit foundations that have a research idea.

**Standard Treatment** (also standard therapy): The treatment or therapy thought to be effective and usually used for a given disease or condition.

**Test Article:** The product that is being evaluated in a research study.

**Therapeutic Intent:** When a research study is intended both to gather data about the effect of a product and to treat a disease or condition.

**Tissue:** A group of cells that have similar structure and work together to perform a specific function.

**Tissue Bank** (also biorepository): A facility that collects, stores, and distributes tissues and cells for research purposes.

**Toxicity:** The degree of damage that a product can cause to an organism by chemical action.

**Translational Research:** Research that takes discoveries in the laboratory and applies them to humans.

**Treatment Trial:** A clinical trial to study new treatments or combinations of existing treatments.

**Variable:** A factor that can be changed or manipulated in an experiment to determine its effect on the research outcome.

**Vulnerable Group:** A group that is considered especially at risk of being coerced into taking part in a research study. Pregnant women, neonates, children and prisoners are often considered vulnerable populations. Special protections exist to protect these groups.

# STATES MANDATING INSURANCE COVERAGE OF CLINICAL TRIALS

## Arizona

**Legislation:** Senate Bill 1213

**Effective:** January 2001

**What clinical trials are covered?** Phase I, II, III, and IV clinical trials for treatment, palliation (supportive care) or prevention of cancer approved by one of the following:

- National Institutes of Health (NIH)
- NIH cooperative group or center
- U.S. Food and Drug Administration (under an Investigational New Drug application)
- U.S. Department of Defense
- U.S. Department of Veterans Affairs
- A qualified research entity that meets NIH criteria for grant eligibility.
- A panel of qualified clinical research experts from academic health institutions in the state.

**Who is required to pay?** Private insurers and managed care plans.

**Other key criteria:**

- Trial must be reviewed and approved by an Institutional Review Board of an institution in Arizona.
- Health professional must agree to accept reimbursement from the insurer as payment in full.
- There is no clearly superior, non-investigational treatment alternative.
- Excludes coverage for trials outside of Arizona.

## California

**Legislation:** Senate Bill 37

**Effective:** August 2001

**What clinical trials are covered?** Phase I, II, III, and IV clinical trials with a therapeutic intent for patients with cancer and recommended by a treating physician. Trial must either involve a drug exempt from a New Drug Application (NDA) under federal regulations or be approved by one of the following:

- National Institutes of Health (NIH)
- U.S. Food and Drug Administration
- U.S. Department of Defense
- U.S. Department of Veterans Affairs

**Who is required to pay?** All California insurers, including the state's Medicaid program and other medical assistance programs.

**Other key criteria:**

- Plan may restrict coverage to services in California unless protocol is not provided at a California hospital or by a California physician.

## Connecticut

**Legislation:** Senate Bill 325

**Effective:** January 2002

**What clinical trials are covered?** Clinical trials for treatment, palliation (supportive care), or prevention of cancer approved by one of the following:

- National Institutes of Health (NIH)
- National Cancer Institute cooperative group or center
- U.S. Food and Drug Administration
- U.S. Department of Defense
- U.S. Department of Veterans Affairs

**Who is required to pay?** Private insurers, including individual and group health plans.

**Other key criteria:**

- Prevention trials are covered only in Phase III and only if they involve therapeutic intervention.
- Insurer may require documentation of the likelihood of therapeutic benefit, informed consent, protocol information and test results, and/or a summary of costs involved.

## Delaware

**Legislation:** Senate Bill 181

**Effective:** July 2001

**What clinical trials are covered?** Clinical trials for treatment, palliation (supportive care), or prevention of cancer approved by one of the following:

- National Institutes of Health (NIH)
- NIH cooperative group or center
- U.S. Department of Defense
- U.S. Department of Veterans Affairs
- Institutional Review Board that has a Multiple Project Assurance (MPA) from the U.S. Department of Health and Human Services' Office for Human Research Protections.

- A qualified research entity that meets the criteria for NIH Center Support grant eligibility.

**Who is required to pay?** Every group or blanket policy.

**Other key provisions:**

- The trial must have therapeutic intent and enroll individuals diagnosed with the disease.
- The trial must not be designed exclusively to test toxicity or disease pathophysiology (the functional changes that accompany a particular syndrome or disease).

## Georgia

**Agreement:** Georgia Cancer Coalition agreement (for separate legislation, see following section on Legislation).

**Effective:** 2002

**What clinical trials are covered?** Phase I, II, III or IV cancer clinical trials for patients with cancer and recommended by a treating physician. The trial must either (1) involve a drug that is currently exempt under federal regulations from a new drug application or (2) be a trial that is approved by one of the following:

- National Institutes of Health (NIH)
- NIH-sponsored cooperative group or center
- U.S. Department of Defense
- U.S. Department of Veterans Affairs
- U.S. Food and Drug Administration
- An Institutional Review Board of any accredited school of medicine, nursing, or pharmacy in the state of Georgia

**Who is required to pay?**

- Kaiser
- BlueCross/BlueShield of Georgia
- United Health Care
- Aetna
- Humana
- Coventry
- OneHealth
- Cigna
- The Georgia Department of Community Health (which administers the State Health Benefit Plan, Medicaid, and PeachCare).

**Other key provisions:**

- The agreement also provides for the coverage of cancer screens and examinations in accordance with the most recently published guidelines and recommendations established by any nationally recognized healthcare organization.

**Legislation:**

- The Georgia Cancer Coalition agreement covers both adults and children. There is also a law in effect for children only. The law (Senate Bill 603) was passed in 1998 and requires all health plans in Georgia to reimburse the patient care costs associated with a dependent child's participation in a phase II or phase III cancer clinical trial that is testing prescription drugs. The child has to have been diagnosed with cancer prior to his or her nineteenth birthday, and the trial has to have been approved by the U.S. Food and Drug Administration or the U.S. National Cancer Institute.

## Louisiana

**Legislation:** Senate Bill 761

**Effective:** July 1999

**What clinical trials are covered?** Phase II, III, and IV clinical trials for the treatment, supportive care, early detection, and prevention of cancer. The trial must be approved by one of the following:

- Cooperative group funded by a component of the National Institutes of Health
- U.S. Food and Drug Administration
- U.S. Department of Veterans Affairs
- U.S. Department of Defense
- Federally funded general clinical research center
- Coalition of National Cancer Cooperative Groups

Also, the clinical trial protocol must have been reviewed and approved by a qualified Institutional Review Board operating within the state that has a multiple project assurance contract approved by the Office of Protection from Research Risks, U.S. Department of Health and Human Services.

**Who is required to pay?** Health maintenance organizations, preferred provider organizations, the State Employee Benefits Group Program, other specified insurers.

**Other key provisions:**

- There is no clearly superior, noninvestigational approach.
- The available clinical or preclinical data provide a reasonable expectation that the treatment will be as effective as the noninvestigational alternative.
- The patient has signed an IRB-approved informed consent form.

## Maine

**Legislation:** 24-A: Maine Insurance Code

**Effective:** 1999

**What clinical trials are covered?** Clinical trials enrolling individuals who have a life-threatening or serious illness for which no standard treatment is effective. Trial must be approved and funded by any one of the following:

- National Institutes of Health (NIH)
- NIH-sponsored cooperative group or center
- U.S. Department of Health and Human Services

**Who is required to pay?** Managed care organizations and private insurers.

**Other key provisions:**

- Participation must offer meaningful potential for significant clinical benefit to the enrollee.
- Referring physician must conclude that trial participation is appropriate.

## Massachusetts

**Legislation:** House Bill 4376 (Chapter 257)

**Effective:** January 2003

**What clinical trials are covered?** All phases of cancer treatment trials. Trial must be peer-reviewed and approved by one of the following:

- National Institutes of Health (NIH)
- NIH-sponsored cooperative group or center
- U.S. Department of Defense
- U.S. Department of Veterans Affairs
- U.S. Food and Drug Administration
- A qualified non-government research entity

**Who is required to pay?** All health plans issued or renewed after January 1, 2003.

**Other key provisions:**

- Insurers must provide payment for services that are "consistent with the usual and customary standard of care" provided under the trial's protocol and that would be covered if the patient did not participate in the trial.

## Michigan

**Agreement:** Michigan Consensus Agreement

**Effective:** February 2002

**What clinical trials are covered**? Phase II and III cancer clinical trials that are sponsored or approved by any one of the following:

- National Institutes of Health (NIH)
- National Cancer Institute
- U.S. Food and Drug Administration
- U.S. Department of Defense
- U.S. Department of Veterans Affairs
- Centers for Medicare and Medicaid Services
- Centers for Disease Control and Prevention
- The agreement also would cover any side effects from the clinical trial treatment, including hospitalization costs.

**Who is required to pay?** Private insurance plans, HMOs and the Michigan Medicaid Program.

**Other key provisions:**

- Coverage for Phase I trials is under consideration.

## Missouri

**Legislation:** Senate Bill 1026; Senate Bills 567 & 792

**Effective:** August 28, 2002 (S.B. 1026); May 12, 2006 (S.B. 567 & 792)

**What clinical trials are covered?** Phase II, III or IV clinical trials for the prevention, early detection, or treatment of cancer as approved or funded by one of the following:

- National Institutes of Health (NIH)
- NIH Cooperative Group or Center
- U.S. Food and Drug Administration
- U.S. Department of Defense
- U.S. Department of Veterans Affairs
- An Institutional Review Board in Missouri that has been approved by the U.S. Department of Health and Human Services
- A qualified research entity that meets the criteria for NIH Center support grant eligibility

**Who is required to pay?** All health benefit plans operating in the state.

**Other key provisions:**

- There must be identical or superior noninvestigational treatment alternatives available before

providing clinical trial treatment, and there must be a reasonable expectation that the clinical trial treatment will be superior to the noninvestigational alternatives.

- Requires coverage of FDA-approved drugs and devices used in cancer clinical trials even if those drugs and devices have not been approved for use in treatment of the patient's particular condition.
- Health benefit plans may limit coverage of routine care costs of patients in phase II trials to those facilities within the plans' provider network.
- For individually underwritten health plans, the phase II provision is not mandatory but must be offered as an option.

## New Hampshire

**Legislation:** Senate Bill 409

**Effective:** January 2001

**What clinical trials are covered?** Phase I, II, III, and IV trials for cancer and other life-threatening conditions, with coverage for Phase I and II trials to be decided on a case-by-case basis. Coverage is required for clinical trials that are approved by:

- National Institutes of Health (NIH)
- NIH cooperative group or center
- U.S. Food and Drug Administration
- U.S. Department of Veterans Affairs
- U.S. Department of Defense
- An Institutional Review Board of an institution in New Hampshire with a Multiple Project Assurance (MPA) from the U.S. Department of Health and Human Services' Office for Human Research Protections

Coverage is also required for reasonable and medically necessary services to administer the drug or device under evaluation in the clinical trial.

**Who is required to pay?** Private insurers and specified managed care plans.

**Other key provisions:**

- Trials are covered when standard treatment has been or would be ineffective or does not exist, or when there is no clearly superior noninvestigational alternative.

## Nevada

**Legislation:** Senate Bill 29

**Effective:** January 1, 2006 (extends legislation in effect since January 2004 to include phase I cancer clinical trials)

**What clinical trials are covered?** Phase I clinical trials for the treatment of cancer, and phase II, III, and IV clinical trials for the treatment of cancer or chronic fatigue syndrome that are approved by one of the following:

- National Institutes of Health (NIH)
- NIH cooperative group
- U.S. Food and Drug Administration (FDA)
- U.S. Department of Veterans Affairs
- U.S. Department of Defense

**Who is required to pay?** Private insurers and managed care plans.

**Other key provisions:**

- There is no medical treatment available that is considered more appropriate treatment than the treatment provided in the clinical trial.
- Trial must be conducted in Nevada

## New Jersey

**Agreement:** New Jersey Consensus Agreement

**Effective:** December 1999

**What clinical trials are covered?** All phases of cancer clinical trials run by:

- National Institutes of Health (NIH)
- NIH cooperative group or center
- U.S. Food and Drug Administration
- U.S. Department of Defense
- U.S. Department of Veterans Affairs

**Who is required to pay?** All insurers in the state, including those affiliated with the New Jersey Association of Health Plans.

## New Mexico

**Legislation:** Senate Bill 240

**Effective:** March 14, 2001

**What clinical trials are covered?** Phase II, III, and IV clinical trials for the early detection, treatment, palliation (supportive care), or prevention of recurrence of cancer. Trials must be approved by one of the following:

- National Institutes of Health (NIH)
- NIH cooperative group or center
- U.S. Food and Drug Administration (under an Investigational New Drug application)
- U.S. Department of Defense
- U.S. Department of Veterans Affairs
- Research entities meeting NIH grant standards.

**Who is required to pay?** Private insurers, specified managed care plans, Medicaid, and other state medical assistance programs.

**Other key provisions:**

- Legislation is effective through July 1, 2009 (as per Senate Bill 73).
- Trial must have therapeutic intent.
- There must be a reasonable expectation that treatment will be at least as effective as standard or noninvestigational cancer treatment.
- Payment is limited to in-state or in-network costs, unless the plan covers standard out-of-state or out-of-network treatment.

## North Carolina

**Legislation:** Senate Bill 199

**Effective:** January 2002

**What clinical trials are covered?** The law extends coverage to all people diagnosed with a life-threatening condition who choose to enroll in a Phase II, III, or IV clinical trial. Includes clinical trials approved and funded by any one of the following:

- National Institutes of Health (NIH)
- NIH cooperative group or center
- U.S. Food and Drug Administration
- Centers for Disease Control and Prevention
- Agency for Healthcare Research and Quality
- U.S. Department of Defense
- U.S. Department of Veterans Affairs

**Who is required to pay?** All health insurance plans and the teachers' and state employees' comprehensive major medical plan.

**Other key provisions:**

- Mandated coverage is effective for health plans that are in effect or renewed on or after March 1, 2002.
- Patients suffering from a life-threatening disease or chronic condition may designate a specialist who is capable of coordinating their health care needs as their primary care physician. The law also established an Office of Managed Care Patient Assistance.

## Ohio

**Agreement:** Ohio Med Plan

**Effective:** March 1999

**What clinical trials are covered?** National Cancer Institute-sponsored Phase II and III cancer treatment clinical trials for Ohio state employees enrolled in the Ohio Med Plan.

**Who is required to pay?** The state's Ohio Med Plan.

**Other key provisions:**

- Preauthorization is required for clinical trial participation.

## Rhode Island

**Legislation:** Senate Bill 2623; Senate Bill 1, House Bill 5062

**Effective:** 1995 (SB 2623); 1998 (SB1, HB 5062)

**What clinical trials are covered?** Phase II, III, and IV cancer clinical trials approved by one of the following:

- National Institutes of Health (NIH)
- A community clinical oncology program
- U.S. Food and Drug Administration
- U.S. Department of Veterans Affairs
- A qualified nongovernmental research entity, as identified by an NIH support grant.

**Who is required to pay?** Private insurers and specified managed care plans.

## Tennessee

**Legislation:** House Bill 837

**Effective:** July 2005

**What clinical trials are covered?** Phase I, II, III, and IV clinical trials for the treatment of cancer approved by one of the following:

- National Institutes of Health (NIH)
- U.S. Food and Drug Administration (FDA) through an Investigational New Drug application
- U.S. Department of Defense
- U.S. Department of Veterans Affairs

**Who is required to pay?** Any health benefit plan offered by an employer; excludes individually underwritten health insurance policies.

**Other key criteria:**

- The subject of the trial must evaluate a drug, medical device or service that falls within a Medicare benefit category.
- Limits coverage to those drugs, medical devices, and services that have been approved by the FDA and that are used in the clinical management of the patient.

## Vermont

**Legislation:** House Bill 6

**Effective:** February 24, 2005 (extends and modifies legislation in effect since March 2002)

**What clinical trials are covered?** Approved cancer clinical trials conducted under the auspices of the following cancer care providers:

- The Vermont Cancer Center at Fletcher Allen Health Care
- The Norris Cotton Cancer Center at Dartmouth-Hitchcock Medical Center

If no suitable trial is available at the above locations, the law covers approved cancer clinical trials being administered by a hospital and its affiliated, qualified cancer care providers in or outside the state of Vermont.

**Who is required to pay?** All health insurance policies and health benefit plans issued in Vermont, including the Vermont Medicaid program.

**Other key provisions:**

- Participants in cancer trials located outside Vermont must provide notice to the health benefit plan prior to their participation.
- Health insurers are permitted to require patients participating in a trial outside the provider network to receive routine follow-up care within the plan's network, unless the patient's cancer care provider determines this would not be in the best interest of the patient.
- Cancer care providers and the state's four largest health insurers are required to participate in a cost analysis to determine the impact of the program on health insurance premiums.

## Virginia

**Legislation:** Senate Bill 1235, House Bill 871

**Effective:** July 1999

**What clinical trials are covered?** Phase II, III, and IV cancer treatment trials, with Phase I trials covered on a case-by-case basis. Trial must be approved by one of the following:

- National Cancer Institute (NCI)
- NCI cooperative group or center
- U.S. Food and Drug Administration
- U.S. Department of Defense
- U.S. Department of Veterans Affairs
- An Institutional Review Board of a Virginia institution with a Multiple Project Assurance (MPA) from the U.S. Department of Health and Human Services' Office for Human Research Protections.

**Who is required to pay?** Private insurers, specified managed care plans, and public employee health plans.

**Other key provisions:**

- There is no clearly superior, noninvestigational alternative.
- Data provide a reasonable expectation that the treatment will be at least as effective as the alternative.

## West Virginia

**Legislation:** House Bill 2675

**Effective:** June 2003

**What clinical trials are covered?** Phase II, III, or IV clinical trials for the prevention, early detection, or treatment of cancer, or for the treatment of any other life-threatening condition.

The clinical trial must be approved by one of the following:

- National Institutes of Health (NIH)
- NIH-sponsored cooperative group or center
- U.S. Food and Drug Administration (FDA)

- U.S. Department of Veterans Affairs
- The Institutional Review Board (IRB) of an institution in West Virginia that has a Multiple Project Assurance contract approved by the NIH Office of Protection from Research Risks

**Who is required to pay?** Private insurers, managed care plans, Medicaid or state medical assistance, public employee health plans.

**Other key provisions:**

- The treatment must have therapeutic intent.
- There is no clearly superior, noninvestigational alternative.
- The available clinical or pre-clinical data provide a reasonable expectation that the treatment will be more effective than the noninvestigational treatment alternative.
- Does not require reimbursement for clinical trials intended to:
  - Extend the patent of any existing drug.
  - Gain approval of or coverage for a metabolite of an existing drug.
  - Gain approval or coverage relating to additional clinical indications for an existing drug.
  - Keep a generic version of a drug from coming to market.
  - Gain approval of or coverage for reformulated or repackaged version of an existing drug.

## Wisconsin

**Legislation:** Assembly Bill 617

**Effective:** Nov. 1, 2006

**What clinical trials are covered?** All phases of cancer clinical trials, as approved by one of the following:

- National Institutes of Health (NIH)
- NIH Cooperative Group or Center
- U.S. Food and Drug Administration
- U.S. Department of Defense
- U.S. Department of Veterans Affairs

**Who is required to pay?** All health benefit plans operating in the state, including self-insured plans.

**Other key provisions:**

- The cancer trial must have therapeutic intent, not exclusively testing toxicity or disease pathophysiology.

# ONLINE RESOURCES

### Protecting the Research Volunteer and Ensuring Voluntary Decision-Making:

**Monitoring the Safety of Clinical Trials**
www.cancer.gov/clinicaltrials/understanding/monitoring-safety-of-trials
(Although this website is hosted by the National Cancer Institute, the information it presents is extremely helpful and applies to non-cancer-related research as well as cancer-related research).

### Informed Consent:

**Informed Consent Checklist**
www.hhs.gov/ohrp/humansubjects/assurance/consentckls.htm

**Informed Consent Tips**
www.hhs.gov/ohrp/humansubjects/guidance/ictips.htm

**Informed Consent FAQ's**
www.hhs.gov/ohrp/faq.html

**Exculpatory Language in Informed Consent Documents**
www.hhs.gov/ohrp/humansubjects/guidance/exculp.htm

**Volunteering for a Research Study? Talk to Your Doctor about What You Should Know**
www.acponline.org/running_practice/ethics

**Guide to Understanding Informed Consent**
www.cancer.gov/clinicaltrials/conducting/informed-consent-guide
(Although this website is hosted by the National Cancer Institute, the information it presents is extremely helpful and applies to non-cancer-related research as well as cancer-related research).

**Should I Enter a Clinical Trial? A Patient Reference Guide for Adults with a Serious or Life-Threatening Illness**
www.ecri.org/Documents/Clinical_Trials_Patient_Reference_Guide.pdf

### Vulnerable Populations:

**Children**
www.hhs.gov/ohrp/researchfaq.html

**Prisoners**
www.hhs.gov/ohrp/prisonerfaq.html

**Pregnant Women and Fetuses**
www.hhs.gov/ohrp/faq.html

**More on Vulnerable Populations**
www.grants.nih.gov/grants/policy/hs/populations.htm

**Persons at High Risk for Suicidality**
www.nimh.nih.gov/health/topics/suicide-prevention/issues-to-consider-in-intervention-research-with-persons-at-high-risk-for-suicidality.shtml

**Persons with Impaired Decision-making Abilities**
www.grants.nih.gov/grants/policy/questionablecapacity.htm

**Informed Consent from Individuals with Impaired Decision-making Abilities**
www.hhs.gov/ohrp/faq.html

### Privacy Rights of the Research Volunteer:

**Letting Your Personal Health Information be Used and Shared for Research, NIH publication 05-5613**
http://privacyruleandresearch.nih.gov/patients.asp

**US Department of Health and Human Services Office for Civil Rights**
www.hhs.gov/ocr/privacy/psa/complaint/

**HIPAA Privacy Rule**
www.hhs.gov/ocr/hipaa

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