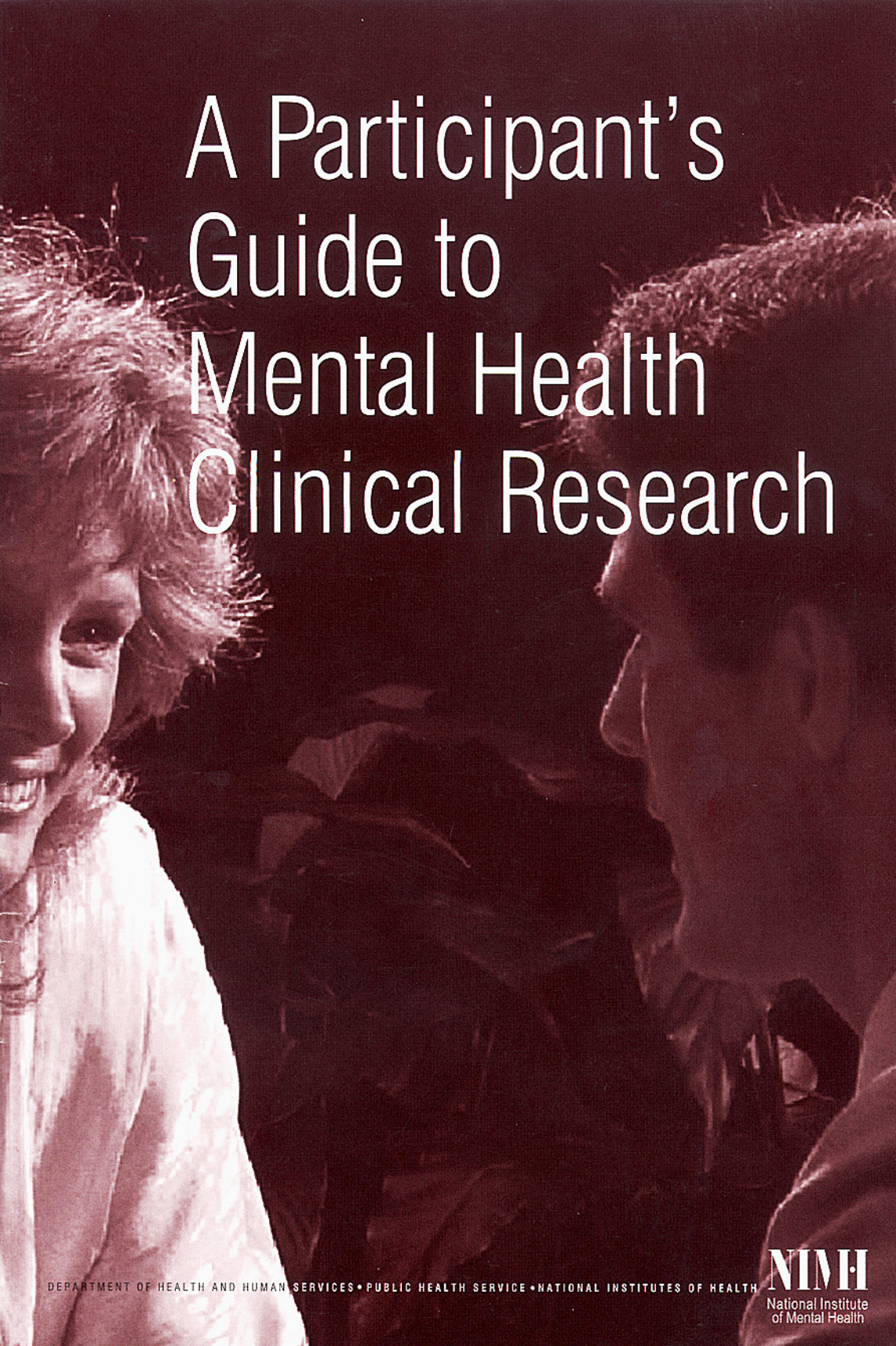
A Participant's Guide to Mental Health Clinical Research



DEPARTMENT OF HEALTH AND HUMAN SERVICES • PUBLIC HEALTH SERVICE • NATIONAL INSTITUTES OF HEALTH

NIMH
National Institute of Mental Health

Through the ages, disorders of the mind have been among the most devastating and feared illnesses of humanity. Today, thanks to ambitious and productive research on mental illnesses and to the willingness of many persons to participate in research, highly effective treatments for mental illnesses exist. As a result of these treatments, many thousands of persons who have brain diseases such as depression, manic-depressive illness, schizophrenia, and anxiety disorders lead fulfilling and productive lives.

Just as the pace of progress to date would not have been possible without the participation in research of patients with mental illness and other volunteers, neither will the advances of tomorrow be realized without their continued participation. It is important to note that just as research on treatments has evolved and become more effective, so too has our society's attentiveness to the well-being of research volunteers grown. Procedures now in place to protect volunteers are more effective than ever before.

The National Institute of Mental Health (NIMH) recognizes the Nation's debt of gratitude to research participants, and is striving to maintain the trust that human subjects place in the excellence of the research enterprise. Thus, we prepared this booklet to highlight some of the questions a person may have in thinking about joining a research study. We hope that by anticipating some questions and helping persons better understand why they might consider participating in mental illness research, all Americans will benefit in the years ahead.

Steven E. Hyman, M.D., *Director*

In research on mental illness, as in other areas of medical science, volunteers are all-important. Thanks in large part to their help, clinical researchers are learning more and more about the causes of mental disorders and are finding new and better treatments.

If you wonder whether to take part in a mental illness-related research study, this booklet may help. (It also may be useful as you help a family member or friend with this decision.) Anything you decide will, of course, be personal and will depend upon your interests, needs, and expectations about research. In coming to your decision, you need to understand your rights as a research volunteer. Because your rights and well-being as a subject in research come first, this booklet will review the safeguards designed to protect you.

You also should know how scientists study mental illness. Research volunteers are not merely "subjects" of research, but actively take part in the search for knowledge. When you do participate, you deserve to understand a few of the most important requirements for good clinical research.

We encourage you to review the information in this booklet and discuss it with others whom you trust. The topics are in a question-and-answer format. As you read, make notes of any additional questions you have for the director of the research project you are considering. We hope this will help you to get the facts, raise your concerns knowledgeably, and decide then about taking part in a research study.

Why Do Patients Participate in Research on Mental Disorders?

Although remarkable progress has been made in defining and treating mental illnesses, some treatments are not effective for all persons or may have significant side effects. Thus, most people who agree to take part in studies of mental illness hope the research will produce knowledge about the disease itself – for example, the role of genetics in illness – or about treatments that will benefit them directly.

Research may allow you to try a new treatment before it is widely available. Even if the aim of a study is not to test the effectiveness of a new treatment, the research may offer a degree of care that you might not get otherwise. Such care may allow the investigators to monitor your symptoms very closely to be sure of your diagnosis.

Medical, psychological, and behavioral research are our best hope for better understanding of and treatments for mental illnesses. Although most who take part in research hope to benefit themselves, they may also simply wish to help others, which is a reward in itself.

What Is Mental Health Clinical Research?

Scientists study and try different ways to diagnose, treat, and prevent human disease more effectively. The needed research may take place in a basic science laboratory, a clinic, or in the community.

In *mental health clinical research*, the term "clinical" means that the research involves persons in actual patient care settings. These may be **inpatient** settings (for patients whose illness requires hospitalization) and **outpatient** settings (for those who live in the community).

Some clinical research may examine how well a new treatment works – perhaps a drug or other type of therapy. In other instances, a clinical study might explore factors that affect mental disorders. These factors might include the role of genes and their interactions with life experiences in ways that might alter the chemistry of the brain and lead to illness.

In making your decision to participate in a research study, you should discuss the purpose of the research with the study director. Ask where the research will take place and how long it will last. What does the research involve? What are the potential benefits of participation? What are the risks? Does the research involve treatment of your illness? You will probably have many other questions for the researcher. Again, it may be helpful to write them down.

In the search for new knowledge, both you and the researcher will be trying out new things. If you do not know about the many safeguards that exist to protect research subjects, you may overestimate the risks of research. On the other hand, if you expect to receive only the most advanced new treatments, you may become disappointed.

How Will Treatment in a Clinical Research Study Differ from Treatment Your Own Doctor Provides?

Clinical research often involves providing treatment. Yet, treatment ***research*** is different from the care that you would get from your own doctor. Usually, when you go to a doctor, you want help with a particular problem. You count on your doctor to do what is best for you. You know that anything your doctor suggests is meant to make you well.

A treatment research project, however, is different. The investigator wants to learn about your illness, and not just treat you. Of course, a researcher will try very hard to see that you benefit from the treatment research and that any risk will be small. Yet one goal remains the most important: learning how well a new treatment works for someone with your illness.

In research, the design of a study may call for *standardized procedures*. For instance, when a researcher studies a medicine, or drug, the research plan may require that **only** the drug under study be available to you. It may mean that you will receive it only in a fixed dose; that is, the researcher cannot tailor the amount of a medication to your immediate needs. Or, standardized procedures may mean that you will receive a medication only in one specific way – for example, by a shot or as a pill.

In such a study, or *drug trial*, the treatment you will receive likely will be based on your *random assignment* to a particular medication or, sometimes, to an inactive pill (a placebo). You should be told what is known about the relative benefits and risks of each treatment used in the research study. You should also be told what is known about

alternative treatments that might be given outside a research project. In contrast, treatment outside of a research study seldom uses random choice of treatment and never uses a placebo; your doctor will always prescribe a treatment that he or she believes would be good for you. However, situations remain where no one may know what treatment is best, and that is one instance where the importance of research is clear.

It should help to know that even investigational treatments are well-tested for safety before their use in a clinical study. Also, remember that you **always** can decide to withdraw from a study. You, or someone close to you, should know whom to contact if you want to do so at any time.

How Are Clinical Studies of Mental Disorders Designed?

Clinical researchers call the standard scientific approach for trying out treatments a *double-blind, randomized, controlled clinical trial*. Understanding this term, and knowing how and why this approach is used, should help you to decide whether to become a research volunteer.

An important part of scientific research is comparison. Clinical research often will compare an investigational treatment to one that is used frequently and thus has familiar, or predictable, effects. To make the comparison useful, the investigator must try both methods on similar groups of subjects.

Researchers call the treatment with the predictable or known effect the control. The control may be a standard, commonly used treatment, or it may be a *placebo*. A placebo is something that does not directly affect the illness or symptoms under study in any specific way.

(You may have heard a placebo described as a "sugar pill.") Some studies use both a standard treatment and a placebo as controls.

The control helps an investigator find out if any changes seen in patients in the experimental group are, in fact, due to the new treatment.

The term *randomized* means how a researcher assigns each patient to a particular treatment under study. Researchers assign patients by chance either to a group taking the new treatment (called the treatment group) or to a group taking a standard treatment or a placebo (called the control group). This method, called randomization, helps avoid bias: having the study's results affected by human choices or other factors not related to the treatments being tested. In some studies, researchers do not tell the patient whether he or she is in the treatment or control group (called a single-blind study). This approach is another way to avoid bias, because when people know what drug they are taking, it might change the way they react. For instance, patients who knew they were taking the new treatment might expect it to work better and report hopeful signs because they want to believe they are getting well. This could bias the study by making the results look better than they really were.

Random assignment helps to make sure that those in the group who receive an investigational treatment are similar to those in the group who receive the control treatment. By making certain that all who take part are similar, random assignment helps a researcher to make better conclusions.

The term *double-blind* in research design means that neither you nor the researcher will know if you are assigned to the experimental or to the control group. The aim is to avoid letting either the investigator's hopes or expectations about a particular treatment or your hopes and expectations influence the manner in which he or she views improvements and side effects.

Your random assignment to a particular treatment group usually will occur after the researcher decides that you can be in the study, and after you agree to join the research by signing an informed consent form. Informed consent, which is key to the successful conduct of all clinical research, is discussed later in this pamphlet.

What Is a “Placebo Control” in a Medication Trial?

Studies of new drugs often compare the effects of an investigational drug with the effects of a *placebo*. If you are considering whether to take part in a drug trial, the director of the study must tell you if the study will use a placebo control. The informed consent form that you will sign if you agree to join the study must also explain any plans to use a placebo control.

The reason for using a placebo control is that the benefits from taking medications are not always due to the drug itself. These benefits are called "*placebo effects*." An example is when an investigator’s enthusiasm about a new medication sometimes influences the patient’s response.

A researcher must be able to separate placebo effects from the actual effects of the drug being studied. When equal numbers of patients receive either a placebo or another standard drug that will help treat their symptoms, the researcher can better judge the actual effects of the drug being tested.

In a "double-blind, placebo-controlled" research design, the doctors and nurses working directly with patients in the study will not know which group patients are in. Only members of the research team not involved in providing day-to-day clinical care will know which

patients are receiving an active treatment or a placebo. This information is shared only when there is a medical necessity to do so to protect the patient and at the end of the study.

Some scientists have questioned the use of placebo controls in clinical research. They argue that if any drug is effective in treating a given condition, then only that drug, and not a placebo, should be given as the control. Other researchers, however, believe that without a placebo control, it is harder to know whether an investigational medication is better than existing drugs. The choice depends on what is being studied, the medicine, and the illness.

If, during a study, an investigational drug seems to work very well, the researcher may stop using the placebo. In some instances, as discussed in a later section, participants may have a chance to use the investigational drug after a study is completed.

It is important that the director of a medication trial explain thoroughly any planned use of a placebo. Ask how the researcher plans to keep track of your symptoms. Also, ask if there is a possibility that your symptoms could become severe during the research project. If your symptoms worsen, at what point will the researcher decide to remove you from the study and provide standard treatment? In talking about these possibilities with the researcher, you must remember that participating in a study does not guarantee that you will receive a promising new medication. Indeed, you must consent to that fact. Also, you should remember that even if you receive an investigational drug, it may not be helpful for you. Remember you can always withdraw from a study.

What Is the Investigator's Responsibility if a Patient Has a Clinical Crisis?

You read earlier about the differences between clinical research and the care you receive from your personal doctor. In most research, an investigator will try to follow the research design: Following a research plan that has met all of the conditions described in the next section of this pamphlet – conditions meant to ensure that any proposed clinical research has scientific merit and is fully attentive to participants' well-being – takes precedence over "tailoring" treatments to a patient's unique needs. However, a patient who becomes much worse during a study will be withdrawn from the project and given immediate personal care, even though the worsening may not be related to the treatment being given.

You and, if it is appropriate, your legally authorized representative should discuss with the investigator the possibility that your illness could worsen during the research study. Then you can decide how to handle any emergencies that might arise during the study.

Among the issues you may wish to discuss is how the researcher will judge the nature and severity of your symptoms. Another issue could be that, under certain conditions such as a medication washout or a pharmacologic challenge, you might decide to reject all treatment. If you are seriously ill, you might not recognize how dangerous that decision could be. Thus, you should agree in advance on how to handle this situation.

What Protections Exist for Research Subjects?

Many "checkpoints" ensure that research meets strict scientific guidelines and follows rules that protect the subject. Several groups who are not part of the research team examine both the scientific plan and procedures to protect the interests of participants before an investigator may begin the research.

Each proposed study, including its provisions for the protection of human subjects and its consent form, must be approved by an *Institutional Review Board (IRB)*. Every organization that conducts research, for example a university or hospital, must have an IRB. The membership of these boards includes scientists, persons who are not scientific experts, and at least one "public" member who is not associated with the organization.

An important IRB responsibility is to review the *informed consent* materials that an investigator develops for those who take part in the study. This information allows the IRB and – more critically – you to judge the value, risks, and potential benefits of a research project. If an IRB has concerns about any part of the research proposal, the committee will tell the director of the study. The researcher must attend to these concerns before submitting the research proposal to a funding agency.

A funding agency, such as the National Institute of Mental Health (NIMH), provides the next review of human subject provisions for clinical research proposals. The funding agency also judges the scientific importance of a research proposal, and how the researcher will learn from it. Both the IRB and the funding agency conduct regular reviews to be sure that the researchers are meeting all the rules for the protection of human subjects.

You can be certain that a range of persons, both scientists and others, have reviewed any IRB-approved research that you may be asked to join. Nonetheless, having a general understanding yourself of how scientists conduct clinical research will help you feel more confident when talking about the project with the research director.

Does Research Involve Special Risk?

Well before a clinical study begins, the researcher has attempted to reduce any risk of physical discomfort or harm to you and others who take part. The effort likely began with preclinical, or basic, laboratory research that probably included animal studies, for example, to test the safety of a new drug. Yet, for research to be absolutely "risk-free," every possible outcome would have to be known – and if it were, then the research would not be necessary.

In fact, various different causes or forms of discomfort could result from a particular research study. A patient/subject may have to take off from work, or pay for some of the treatment. These requirements could be inconvenient or expensive. As you will see in the next section describing informed consent, you will be told about any foreseeable risks or discomforts that may occur in the research before you agree to participate.

Naturally, the chance that there might be pain or harm worries most people who are thinking about joining a clinical research project. Some discomforts may be like what you are used to in routine health care, such as a needle prick when blood is drawn for testing purposes. However, sometimes a research design may call for more uncomfortable procedures, procedures with known risks, or procedures for which the risk may not be fully known. These could include, for example, being deprived of sleep, receiving injections, having a spinal tap, receiving a

small dose of a radioactive substance needed for a brain scan, or treatment with an investigational drug.

Remember, nothing is without risks, including illness itself, and risks in clinical research are minimized as best as possible. Also remember that the research plan is reviewed by an IRB to insure the protection of people who participate in the research study, and any known risks should be described in the consent form.

What Is Informed Consent?

Federal regulations have been created to protect the well-being and rights of volunteers in biomedical research. These regulations (Title 45 Code of Federal Regulations Part 46 or 45 CFR 46) say no investigator may involve anyone as a subject in research without getting that person's *informed consent*, either directly or from the person's legal representative.

A researcher must ask you to sign a written informed consent form in which you agree to take part in a certain study. The form contains a description of the study, possible risks, and benefits of the research. The director of the research must prepare the form and an IRB must approve it. The researcher must then go over this form with you and get your permission to enter you into the study.

Having a mental disorder does not necessarily mean that a person cannot understand and see the value and risks of taking part in research. Most people, therefore, who enter research studies on mental disorders can provide informed consent. Additional guidelines and safeguards exist for patients who are not able to give their permission with full understanding. In those cases consent is obtained both from the participant and the legally authorized representative.

Informed consent is not a one-time event, but a continuing process. Throughout a study, the research team must continue to provide information about participating in the study. They must respond to any questions you have about the research and inform you if any new risks are identified. You may, at any time, reappraise your decision to take part in the project and withdraw your consent. It is advisable to discuss any concerns with the director of the study.

Every informed consent form developed by an investigator and submitted to an IRB for approval must include eight basic parts. These parts are:

- A statement that the study involves **research** and that tells what its goals are, how long the research will last, and what methods will be used.
- A description of any reasonably foreseeable **risks** or discomforts you could experience as a result of the research.
- A description of any **benefits** that the research may be reasonably expected to yield to you or to others.
- A description of **alternative courses of treatment**, or therapies, if any, which might help you.
- A statement describing how the researcher will protect the **confidentiality**, or privacy, of your medical records.
- For research in which risk is somewhat more likely than you would expect in routine health care, an explanation and description of the availability of **compensation or medical treatments** if injury occurs.
- The name and phone number of the **person to contact** about the research and your rights, and whom to contact in case the research causes an injury.
- A statement that your taking part in the research is **voluntary**, and that if you change your mind, or quit later on, you will **not be penalized in any way, or lose any benefits** you have coming to you.

The informed consent process must include the following items when they apply to you:

- A statement that the particular treatment or method used may not work as planned and may be risky for you.
- The reasons why the investigator might have to drop you from the study without asking you first.
- A list of any extra charges you may have to pay to take part in the research.
- A description of what would happen if you decide to drop out of the study, and what the researcher will do to make sure you keep receiving appropriate treatment if you do drop out.
- A statement that you will be told of any important results of the research which may help you to decide whether to continue taking part in the study.
- Approximately how many subjects are in the study.

Clinical researchers try to write informed consent forms that are brief and understandable by people without scientific or medical training. Even so, some informed consent forms appear long and complicated. Thus, it is important that you are given the opportunity to read the form thoroughly, perhaps discuss it with a family member or a trusted friend, and raise any questions you have with the investigator. We hope you will feel comfortable talking to the investigator or other members of the research team and asking questions until you are satisfied that you understand the informed consent form.

Some investigators prepare additional material to help research subjects understand the contents of an informed consent form. These might include, for example, a videotape that describes the illness under study, the research project, and the methods it will use. There may be a short quiz you can take to help identify issues you wish to discuss further with the researcher. You may be able to complete such a quiz at home at your convenience. If these ideas sound useful, ask the director

of the research if these or similar items are available. You can ask for a copy of the protocol to take home to discuss with family members, your physicians and others.

Involvement of Family Members and Others

You may wish to involve family members in some parts of a research study. For example, you might consult with a family member about taking part in the study, or you may wish to look over this booklet with a family member or close friend and discuss being a research subject with that person. If you are a parent or otherwise legally authorized representative of someone who might be a research subject, you may wish to involve other concerned family members in any decision you make.

Many family members welcome the chance to make sure, along with the research team, that no one will take advantage of you during the study. This role is clear if a family member is a patient's formal legally authorized representative; but even lacking such legal status, families usually do all they can to protect a family member who is ill.

Remember that Federal regulations protect your right to privacy in the handling of your records throughout (and following) a study. You must give clear permission if you wish the researcher to share personal information about you with family members. Still, you should be aware that, with your consent, your family members or other friends may have several opportunities to provide information during the study.

Will You Have Access to Those Drugs That Work After a Trial Is Complete?

Understandably, if an investigational drug helps you, you may wish to continue to take it after the trial has been completed. In some instances, a medication that is being investigated for use in treating your illness may have been approved by the Food and Drug Administration (FDA) for other uses. If you find that you benefit from such a medication, your own doctor can prescribe it for you.

Often, the company developing a new drug may try to see that you can continue to get it, even before the FDA has approved it for sale. You may be able to do this under what is termed a *compassionate plea basis*. This means that because the new drug has been so helpful, the manufacturer can give it to a physician, who may then prescribe it for you.

While companies often make such a new drug available, there may also be good reasons why a company cannot. Perhaps only a very small amount of a drug was prepared for the research project, and no more is available for use afterwards. Then again, a manufacturer may want to further test the drug under certain conditions, or to examine the results of a research study more fully before releasing it for *compassionate plea use*. A company would be especially careful if a new medication required that the doctor who prescribed it have some special knowledge or skill to monitor its safe use.

You and any family members interested in your well-being should discuss with the director of the research your questions about *compassionate plea* use. Each case is different, so the agreement has to be between the drug manufacturer and your own doctor.

Obtaining Care After a Research Project Has Ended

If you decide to take part in a research study – and, especially one that takes place in a hospital – you may find that you will have to stop, or interrupt, the care you now are getting for a mental disorder. Doing that, even temporarily, may result in your losing access to a program of personal care that had been expensive and hard to come by. The director of research on your study often will help you to get back into a program of care when the study is finished. The investigator's institution may assist in arranging for follow-up care.

Learning About the Results of Research

In most informed consent forms, the researcher promises to share what is learned from the study with you. These results will sum up the responses of everyone who took part in the study. In addition, the researcher will discuss with you any results that relate to your diagnosis or that may be useful in deciding on the best treatment for your disorder.

Be sure to ask the director of research when you can expect to hear about the results. Ask how you will get this information. Will the researcher write an article describing the study, or will those who took part be invited to a meeting with the study director when all the results are in? If you have questions about the results when you receive them, ask the researcher who can help you to understand what they mean.

A frustrating thing about research is that it often takes years before the results of a study are available. This is because of the time it takes to conduct the study, including getting enough people in the study to make the results meaningful. Be patient, but remember to ask for the results if you have not received them when you expected them.

Checklist of Questions

So you have been asked to take part in a research study! This can be a very satisfying experience, allowing you to help yourself now and to help others in the future. After all, without research, treatment cannot improve, and without those who take part, there would be no research! You are the one who makes research possible.

But how you do know if you want to take part? What questions should you ask? The researcher should answer these basic questions clearly for you. Others undoubtedly will arise during the discussion.

Q: Why do you want me in your study?

Q: What is the research about? How will this research help in treating or understanding my disorder?

Q: What do I need to do and how much time will this take?

Q: How might this study help me, my relatives, or other people with my disorder?

Q: What possible risks are there to me or my relatives if I take part?

Q: How will this be different from the care I am getting now, and do I have other options or choices?

Q: Could my illness become worse during the study? What will happen if it does?

Q: What will happen to me at the end of the study?

Q: What should I do if I want to drop out of the study?

Q: May I get back to you after I discuss this with my family/friend/case manager/doctor?

Remember to ask again if you do not understand the explanation to any question you have. And, if you forget the answers to these questions during the study, just ask them again.

For More Information on Research into the Brain, Behavior, and Mental Disorders Contact:

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Web site address: http://www.nimh.nih.gov

This is the electronic version of a National Institute of Mental Health (NIMH) publication, available from http://www.nimh.nih.gov/publicat/index.cfm. To order a print copy, call the NIMH Information Center at 301-443-4513 or 1-866-615-6464 (toll-free). Visit the NIMH Web site (http://www.nimh.nih.gov) for information that supplements this publication.

To learn more about NIMH programs and publications, contact the following:

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Phone numbers:
301-443-4513 (local)
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National Institute of Mental Health. Title. Bethesda (MD): National Institute of Mental Health, National Institutes of Health, US Department of Health and Human Services; Year of Publication/Printing [Date of Update/Revision; Date of Citation]. Extent. (NIH Publication No XXX XXXX). Availability.

A specific example is:
National Institute of Mental Health. Childhood-Onset Schizophrenia: An Update from the National Institute of Mental Health. Bethesda (MD): National Institute of Mental Health, National Institutes of Health, US Department of Health and Human Services;
2003 [cited 2004 February 24]. (NIH Publication Number: NIH 5124). 4 pages. Available from: http://www.nimh.nih.gov/publicat/schizkids.cfm