NIH Guidance on Informed Consent For Gene Transfer Research

Introduction to Guidance

NIH GUIDELINES: "How will the major points covered in Appendix M-II, Description of Proposal, be disclosed to potential participants and/or their parents or guardians in a language that is understandable to them?"

DISCUSSION
Since before the first clinical gene transfer trial began enrolling subjects, the National Institutes of Health (NIH) and its Recombinant DNA Advisory Committee (RAC) have sought to assist investigators in developing good consent forms and processes for clinical gene transfer research. Appendix M sections M-III and M-IV were added to the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) to address points and issues related to informed consent that would benefit from particular attention. These sections address issues unique to gene transfer, as well as issues that gene transfer has in common with other forms of clinical research.

The requirements of Appendix M were always intended to be complementary to and are consistent with other requirements, regulations, and guidance documents, including 45 CFR 46, 21 CFR 50, and 21 CFR 56, and other guidance from the Office for Human Research Protections and the Food and Drug Administration. However, even after the promulgation of Appendix M-III and M-IV, NIH has continued to seek ways to assist investigators and others involved in the consent process for gene transfer trials.

In 2002, the NIH Office of Biotechnology Activities (NIH OBA) formed a RAC Informed Consent Working Group - composed of members of the RAC, outside experts, and representatives of the Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) - to assist the in the development of a comprehensive, web-based guidance document to supplement Appendix M. After an extensive development process, the guidance document was endorsed by the RAC in December 2003.

IMPORTANT NOTE

This guidance document DOES NOT constitute policy, requirements, rules, regulations, or laws enforced by NIH OBA or any other component of the Federal government. It is NOT a part of the NIH Guidelines for Research Involving Recombinant DNA Molecules, nor does it amend Appendix M. Instead, it provides supplementary material that may assist investigators and others in applying relevant sections of Appendix M, but its contents are neither prescribed nor required.

All sample consent form language provided in the guidance has been made "generic" and is meant only to illustrate how various issues could be conveyed; the samples are not endorsed by the above entities, are not intended to stand in for complete sections of a gene transfer research consent form, and should not necessarily be used verbatim. It is important to make informed consent language specific to each study design, population, and purpose, as well as to the information and communication needs of potential participants. Investigators, in consultation with their IRBs and IBCs, are best positioned to determine the most appropriate consent form language for a given study.

The guidance provided here is intended to serve as a resource and learning tool for individuals involved in gene transfer studies and others with an interest in this field.

Intended Audience: This guidance is intended to be useful to a variety of audiences:

- Investigators when providing information to potential participants about, and preparing informed consent forms for, gene transfer studies
- Sponsors of gene transfer research when drafting model consent forms and advising investigators on the consent form and process
- Institutional review boards (IRBs) and institutional biosafety committees (IBCs) when reviewing gene transfer protocols and consent forms
- Potential participants when making a decision about whether to participate in a gene transfer study
- The general public seeking to learn more about the issues involved in gene transfer research

How to Access the Guidance: The guidance can be viewed on this website or downloaded and printed in its entirety as a pdf document. To view the guidance on the website, you may either start at the beginning and go through the

guidance page by page by clicking on the navigational arrow, or click on the headers in the navigational menu on the left of the page to be directed to the specific section that you want to read more about.

How to Maximize Utility of the Web-based Guidance: Each page of the guidance is devoted to a particular section of Appendix M. In general, each page has five components:

- Excerpts from the NIH Guidelines - exact language from the relevant section of Appendix M
- Discussion - narrative expanding on the Appendix M section. Bolded subheadings identify specific areas of discussion relevant to the page's topic.
- Main Points - summary of the major ideas conveyed in the Discussion
- Sample Language - examples of how to implement the points made in the Discussion in the consent form as well as examples of what not to say
- Tools & Background Materials - links to various consent tools, web pages, and articles for more information about the page topic

This guidance was designed to be interactive when used on the Web. You can scroll over and click on any underlined words to access further information on that item, particularly in the Tools & Background Materials and Sample Language boxes.

Appendix M-III-A

Communication about the Study to Potential Participants

TOOLS & BACKGROUND MATERIALS

- OBA Brochure, "Deciding Whether to Participate in Gene Transfer Research"
- NHF Brochure, "What You Should Know About Enrolling in a Gene Therapy Trial"
- ECRI Brochure, "Should I Enter a Clinical Trial?"
- CDC Brochure, "Taking Part in Research Studies: What Questions Should I Ask?"
- NCI Brochure, "A Guide to Understanding Informed Consent"
- Annas GJ. Reforming Informed Consent to Genetic Research. JAMA 2001.
- Brody BA. Making informed consent meaningful. IRB: A Review of Human Subjects Research 2001.
- FDA Guidance on Consent Process

MAIN POINTS

- Informed consent is a communication process, not a form.
- Various methods and tools exist to improve comprehension of information.

DISCUSSION

Informed Consent - A Process, Not a Form: Informed consent is much more than a document or obtaining a participant's signature on a consent form. Informed consent is a process of communication between an investigator and a potential research participant.

The purpose of the consent process is to:

- Ensure that potential participants understand that they are being asked to participate in research, and that they appreciate the differences between research and treatment
- Foster potential research participants' understanding of what to expect from participation in a study
- Encourage and respond to questions about study participation
- Facilitate discussion, reflection, and free and informed decision making

The consent form serves as a record of the information conveyed to the potential participant about participation in the study. The signing of the consent form provides documentation that the individual has agreed to participate in the study.

Improving Understanding and Voluntariness: A crucial outcome of the consent process is that potential participants understand pertinent information about the research. Another important outcome is that potential participants understand that the choice to participate is theirs and that refusal to participate will not jeopardize their clinical care. A number of techniques have been shown to increase understanding and voluntariness, including:

- Having the potential participant take information home
- Having a relative or friend present during discussions with the researcher
- Using videotapes, question and answer pamphlets, drawings, computer modules, or other educational tools to provide information about the research
- Having a research nurse or another qualified person also talk to the potential participant and offer to answer questions

A number of concepts that are crucial to improving understanding and voluntariness are discussed more fully in the Voluntary Participation, Time for Decision-Making, Consent Form, and Comprehensibility sections.

Appendix M-III-A-1

Conflicts of Interest

NIH GUIDELINES: "Which members of the research group and/or institution will be responsible for contacting potential participants and for describing the study to them? What procedures will be used to avoid possible conflicts of interest if the investigator is also providing medical care to potential subjects?"

DISCUSSION

Conflicts of interest, whether financial or non-financial in origin, may at times, if not examined and addressed, adversely affect participants' understanding of research, or the voluntariness of their participation. Some conflicts of interest may have the potential to affect participants' safety or data integrity as well. Potential research participants and the public are increasingly aware of and concerned about possible conflicts of interest and should be provided with appropriate information about them before they enter a study. In addition, researchers should attempt to eliminate, reduce, or properly manage such conflicts wherever possible.

Non-financial Conflicts of Interest: All researchers can be viewed as having non-financial conflicts of interest because they benefit from publications and grants, which are generally facilitated by positive research results. The resulting pressure to complete a study and publish impressive results could compromise the integrity of the research and the rights and safety of participants in various ways. Investigators need to be aware of the pervasive and subtle nature of such conflicts.

If an investigator is also the personal health provider of the potential research participant, there may be an additional conflict of interest. A physician's duty is to honor the best interests of the patient. An investigator must do what is best for the study. These two objectives are not always consonant. Further, potential participants may be reluctant to question the advice of a health provider on whom they depend for care.

Many participants in gene transfer research first learn of the study from an investigator as part of a therapeutic encounter. Therapeutic relationships may develop before, during or after the study. Such relationships may influence both participants' and researchers' understanding of the goals of the study. Researchers should address this nonfinancial conflict of interest both before and during the conduct of a

SAMPLE LANGUAGE

- Sample 1 - Non-financial Conflict of Interest
- Sample 2 - Financial Conflict of Interest
- Sample 3 - Financial Conflict of Interest Disclaimer

TOOLS & BACKGROUND MATERIALS

- NIH Guidance on Financial Conflicts of Interest
- ASGT Policy on Financial Conflict of Interest in Clinical Research
- AAMC Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research
- AAMC Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research
- AAU Report on Individual and Institutional Conflict of Interest
- Brody BA. Expanding disclosure of conflicts of interest: The views of stakeholders. IRB 2003.
- Levinsky NG. Nonfinancial conflicts of interest in research. New England Journal of Medicine 2002.

MAIN POINTS

- **Investigators may have conflicts of interests that may affect the communication and decision-making process.**
- **Investigators should inform potential participants of any possible conflicts of interests and take steps to**

trial in order to ensure that differences between research and treatment are understood.

Financial Conflicts of Interest: Investigators may have equity, patent and other commercial interests in the products they research and develop, thus creating a financial conflict of interest that could influence their communication with potential research participants and the conduct of the study.

Potential participants should be told who is sponsoring the research study, whether the investigators are receiving compensation from the sponsor to conduct the research, and whether there are any potential conflicts of interest. Investigators should be required to disclose possible financial conflicts of interest to their institutions and to potential participants. Investigators should consult their institutions' IRB to determine how much information should be provided regarding the existence, nature, and management of those conflicts. Institutions should have procedures in place to mitigate the influence that such conflicts have on the study and consent process.

Financial conflicts of interests can be addressed and managed by various means, such as divestiture and wider disclosure (e.g., to scholarly journals). Some professional organizations have made specific recommendations about managing and disclosing possible financial interests. These statements may prove helpful to investigators and institutional review boards. The National Institutes of Health (NIH) has issued guidance clarifying its regulations regarding possible financial conflicts of interest that apply to all NIH-funded research.

To address concerns about both financial and non-financial conflicts of interest, it may be useful to have a person who is not the health provider discuss the research study with the potential participant. A decision-monitoring plan may also be considered. Potential participants should always be told that they are free to participate in the study or not, and that a decision about study participation will not affect their clinical care.

SAMPLE LANGUAGE

Sample 1 - Non-financial Conflict of Interest

Your physician is a researcher in this study. As a researcher in this study, he/she is interested not only in your health and well being, but also in the results of this study. It is possible that sometimes these two goals may conflict with one another. Researchers protect the rights and interests of participants by carefully following the rules of the study.

You do not have to be in any research study offered to you by your health provider. When you are deciding if you should join the study, you may want to talk with someone not part of the study about your questions and feelings about joining. This could be s a family member, friend, or another health provider.

Sample 2 - Financial Conflict of Interest (adapt for specific circumstances)

The investigator of this study, [name], is an officer in the company that makes the gene transfer agent you will get if you join the study. The investigator also holds stock and options in the company. This means the investigator may make more money if the study shows that the gene transfer agent is helpful. Although the investigator is not supposed to let his/her financial interests affect the study, this may not be always possible.

Sample 3 - Financial Conflict of Interest Disclaimer

This research is sponsored by [name of sponsoring company, agency, or group]. This means that [name of sponsoring company, agency, or group] is paying the research team for the costs of doing the study. The researchers do not have a financial stake in the results of the study.

NIH GUIDELINES: "How will the major points covered in Appendix M-II, Description of Proposal, be disclosed to potential participants and/or their parents or guardians in a language that is understandable to them?"

- Simplification Guide to Medical Terms
- Dartmouth Informed Consent Evaluation Tool
- Telephone Evaluation Plan
- FDA Guidance on Non-English Speaking Subjects

MAIN POINTS

- **Investigators should be attentive to using language easily read and understood by potential participants.**
- **Various methods and tools exist to improve and assess comprehension of information.**
- **All verbal and written communication about the research study should be provided in language understood by the potential participant.**

DISCUSSION

Gene transfer research concepts are often difficult for potential participants to understand. Thus, particular care should be given to convey these concepts in the consent form in a readable and understandable manner. Readability and understandability are not synonymous; it is possible to make use of computerized readability scales and still have a consent form that is difficult to understand. Sometimes, reducing reading level without providing additional explanatory aids can lead to vagueness and oversimplification of scientific information, which is undesirable.

Improving Comprehensibility of the Consent Form:
Comprehensibility of the consent form is promoted by:

- A short summary paragraph or list at the beginning of the form introducing key concepts to potential participants, including that:
  - They are being asked to participate in research;
  - The principal goal of all research is to develop knowledge that could help others in the future;
  - They should ask questions and consult with others before deciding;
  - They do not need to enroll in research in order to obtain treatment for their condition;
  - They can refuse to participate without repercussions.

The text of the consent form can then provide detailed information about the particular study, and may repeat some of the summarized issues in the context of the particular study.

- Uncluttered documents, broken into sections with headings
- Use of second-person instead of first-person voice
- Short sentences written at no more than an eighth-grade educational level
- Attention to definitions
- Avoidance of technical jargon
- Consistent use of terms

Sometimes, "research" and "treatment" terms are used interchangeably in consent forms. Consistent use of terms is preferred, however, to help minimize the potential for confusion. For example, one term should be used to describe the experimental gene transfer intervention, instead of calling it, at various places, study injection, delivery of a modified virus vector, or gene shot. One term should be used to refer to the investigator (instead of using, for example, both "researcher" and "study doctor"), and one term should refer to participants (instead of using, for example, both "patients" and "subjects" to refer to those enrolled in the study).

Furthermore, consent forms should be written in the second person rather than the first person. Telling potential subjects, "This is what will happen to you if you are in this study" conveys information more clearly than "I have been told that if I join this study, this will happen to me" - a construction that can be awkward and confusing.

In addition, the use of emphatic and directive language should be avoided. A common example is "You understand that....". This construction should never be used in consent forms because it conveys a presumption about what the participants comprehend and detracts from the consent form's proper educational focus on providing information and explanations to potential participants.

Various tools exist to gauge the comprehensibility of the consent form before it is used with potential participants. Such tools include:

- Readability software programs, such as the Flesch Reading Ease score and Flesch-Kincaid Grade Level score (can be found in most versions of Microsoft Word), the Smog Readability Formula, and the Fog Index.

Because these readability measures use syllable count to calculate the score, you should be aware when using these programs that the score may be somewhat inflated because of unavoidable scientific language.

- Asking colleagues and/or lay readers to comment on the readability, understandability, and internal consistency of the consent form as a whole.

Improving Comprehensibility of the Consent Process: In some studies that are especially complicated or risky, or that propose to enroll especially vulnerable participants, it may be desirable to develop a communication evaluation plan to ensure that study personnel have clearly and thoroughly explained key information and that potential participants understand key issues. Such evaluation can take many forms, including:

- A communication monitor assigned to the study, or advocate chosen by the potential participant, may be present during discussions, review the consent form, and provide assistance to the investigator and potential participant to ensure comprehension.
- An evaluation tool (such as a short true-false questionnaire) may be used as part of the consent process so that the person obtaining consent can determine whether any parts of the study require further explanation. See Dartmouth Informed Consent Evaluation Tool as an example.
- A telephone follow-up plan may be devised in which a monitor assigned to the study asks potential participants scripted questions about key information after the consent process has occurred. The monitor can request a follow-up meeting with the investigator and potential participant to address any areas of concern. See Telephone Evaluation Plan for an example.

Communicating with Non-English Speakers: Federal regulations require that consent be provided in a language understood by the potential participant. For potential participants who do not understand English, it may be advisable for the consent form and any supplementary materials to be professionally translated and for the translation to be checked for scientific accuracy so that important nuances are properly conveyed. In addition, investigators, institutional review boards, institutional biosafety committees, and institutions should have appropriate plans in place for use of interpreters experienced with the translation of medical information in all verbal communication during the consent process and throughout the study.

Appendix M-III-A-3

Time for Decision Making

SAMPLE LANGUAGE

- **Sample 1**

MAIN POINTS

- **Potential participants should be given sufficient time to decide whether they want to enroll in the study.**

NIH GUIDELINES: "What is the length of time that potential participants will have to make a decision about their participation in the study?"

DISCUSSION
In order to make an informed decision concerning study participation, potential participants should be given ample time to review the consent form, to ask questions, and to discuss their decision with others as desired.

Many institutional review boards provide guidance to investigators on this issue, including recommendations that potential participants take the consent form home to discuss it with family members or primary care providers before making an enrollment decision.

Investigators and IRBs should consider the following:

- Participants in gene transfer studies may desire or require very different amounts of time to decide whether to participate in the study.
- Some potential participants may come to the consent process having already decided to participate - perhaps having already traveled and made plans or financial commitments. This possibility should be acknowledged in the consent process so that, when appropriate, the investigator can emphasize the significance of the

information conveyed in the consent form and process.

- Commitment to research participation is ongoing. It may be advisable to design a process for revisiting consent, reporting regularly to participants on significant developments that may affect their decision to remain in the study. Such a process may be used at intervals during participation and for long-term follow-up to reconfirm participation. It may also be required whenever new information is learned that could affect a participant's willingness to continue in the study, or that may have health implications for persons who have received the intervention.

SAMPLE LANGUAGE FOR CONSENT PROCESS

Process Sample 1

You may have already thought a lot about participating in this study. You may even have already made a decision about whether to be in the study. Even if this is true for you, it is important that we provide you with this information and talk about it before we start you in the study. Some information may be new or different. Some could even change your mind. It is always okay to change your mind about being in the study. And even if you don't change your mind, the information can help you understand the study better.

Appendix M-III-A-4

Assent

NIH GUIDELINES: "If the study involves children or persons with impaired decision-making capacity, how will the assent of each person be obtained?"

DISCUSSION

Gene transfer studies may enroll children or cognitively impaired persons if the investigator can provide justification for their participation in the study. In such instances, investigators must obtain permission from the legally authorized representative of the child or cognitively impaired person. Investigators must also obtain the assent of the potential participant when appropriate.

Permission from Legally Authorized Representatives: For potential participants who cannot give consent, investigators must obtain permission from a legally authorized representative of the potential participant. For children, this is usually the parent. For adults, it may be someone designated as health care proxy. The permission process should include instruction to the parents and/or legally authorized representatives regarding the difference between permission for treatment and permission for research participation. Legal counsel should be consulted to determine who is permitted to act as a legally authorized representative for research enrollment in the state(s) in which participants will be enrolled. It should be noted that authority for treatment decision-making does not always extend to decision-making about research participation.

Cognitively Impaired: If a potential participant is cognitively impaired and judged to be incapable of giving consent, the potential participant must still be asked and agree to participate in the study even though he or she may not fully understand its purpose, benefits, and risks - unless the impairment completely precludes any meaningful communication. The investigator should follow institutional guidelines for obtaining assent

TOOLS & BACKGROUND MATERIALS

- 45 CFR 46 Subpart D
- OHRP Guidance on Participation of Cognitively Impaired Persons in Research (1993)
- FDA Guidance on Assent of Children
- OHRP Guidance on Participation of Children in Research (1993)
- NBAC Report on Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity
- AAP Statement on Informed Consent, Parental Permission, and Assent in Pediatric Practice
- ACP Statement on Cognitively Impaired Subjects

MAIN POINTS

- **When a potential participant cannot give consent:**
  - **A legally authorized representative should be appointed to provide consent on the person's behalf**
  - **Assent should be obtained when possible**
- **Tailor assent form and process to the potential participant's capacities and needs.**
- **Minors who give their assent to participate in research must be approached for consent when they**

and addressing dissent from cognitively impaired individuals.

reach the age of majority, generally age 18.

Minors: Investigators should follow Federal regulations, namely, 45 CFR 46 Subpart D and FDA guidance on assent of children for enrolling minors (generally children under age 18) in research. Investigators should obtain parental permission, and the assent of the minor when appropriate. In addition, investigators should plan how dissent from minors should be addressed - a determination that is specific both to the age of the child and the design and purpose of the study. Information should be appropriate for the developmental age of the child. It is generally a good idea to approach individuals who assented to participate in research as a minor once they reach the age of majority for either continued participation in the study or continuation of long-term follow-up.

Appendix M-III-B

Consent Form

TOOLS & BACKGROUND MATERIALS

- NIH Office of Biotechnology Activities
- NIH Recombinant DNA Advisory Committee
- Appendix M of the NIH Guidelines
- FDA Guidance on Consent Forms

MAIN POINTS

- There should be a separate consent form for the gene transfer component when possible.
- If a separate consent form is not possible, the gene transfer component should be described separately within the consent form.

NIH GUIDELINES: "Submission of a human gene transfer experiment to NIH OBA must include a copy of the proposed informed consent document. A separate informed consent document should be used for the gene transfer portion of a research project when gene transfer is used as an adjunct in the study of another technique, e.g., when a gene is used as a "marker" or to enhance the power of immunotherapy for cancer.

Because of the relative novelty of the procedures that are used, the potentially irreversible consequences of the procedures performed, and the fact that many of the potential risks remain undefined, the informed consent document should include the following specific information in addition to any requirements of the DHHS regulations for the Protection of Human Subjects (45 CFR 46). Indicate if each of the specified items appears in the informed consent document or, if not included in the Informed Consent document, how those items will be presented to potential subjects. Include an explanation if any of the following items are omitted from the consent process or the informed consent document."

DISCUSSION

Appendix M-III-B strongly encourages use of a separate consent form for the gene transfer component of a study in which either additional investigational interventions or standard treatments are also used. This can help potential

participants assess the potential benefits and harms of gene transfer when it is combined with other interventions.

If a separate consent form for the gene transfer component of the study is not possible, the single consent form should describe the gene transfer component separately whenever possible, in order to give adequate attention to gene transfer's unique features. For example, separate sections or subsections addressing gene transfer aspects of the study may be placed throughout the consent form in such a way as to enable potential research participants to distinguish among the various components of the study.

The NIH Office of Biotechnology Activities (OBA), which staffs the Recombinant DNA Advisory Committee (RAC) and administers the NIH Guidelines, can be a resource for development and review of gene transfer research consent forms. Among the valuable resources available on the OBA website are a number of sources of information, data, and descriptions applicable to different gene transfer interventions, vectors, diseases and conditions, including:

- GeMCRIS Database - provides information on gene transfer trials. This resource may be useful to Investigators in the development of their consent form and to potential participants seeking information about trials similar to the one in which they are contemplating enrollment.
- Proceedings from Gene Transfer Safety Symposia and Policy Conferences
    - Safety Considerations in Cardiovascular Gene Transfer Clinical Research, December 2000
    - Safety Considerations in the Use of AAV Vectors in Gene Transfer Clinical Trials, December 2000
    - Internally Deleted, Helper-Dependent Adenoviral Vectors, March 2000
    - Lentiviral Vector for Gene Delivery, March 1998
    - Prenatal Gene Therapy: Scientific, Medical, & Ethical Issues, January 1999
- Reports and Other Documents of Interest
    - Letter to principal investigators conveying RAC recommendations regarding adverse events in a gene transfer trial studying X-linked SCID, March 2003
    - Assessment of adenoviral vector safety and toxicity, January 2002
    - Enhancing the protection of human subjects in gene transfer research at the National Institutes of Health, July 2000
    - Requirements for reporting serious adverse events: request for institutional review, November 1999
    - FDA letter to IND sponsors/principal investigators of gene transfer clinical trials regarding protocol submission and adverse event requirements, November 1999
    - RAC statement regarding in utero gene transfer research, March 1999
- Minutes and webcasts of past RAC meetings

Appendix M-III-B-1

Purpose

NIH GUIDELINES: "The subjects should be provided with a detailed explanation in non-technical language of the purpose of the study and the procedures associated with the conduct of the proposed study, including a description of the gene transfer component."

DISCUSSION

Potential participants should be given a succinct explanation of why they have been approached for the proposed study. In particular, they should be told whether they are being approached because of their disease or as a healthy volunteer [2]. The purpose section should also include general information about the study design (including phase and objectives), the nature of the disease, and a brief description of the gene transfer

SAMPLE LANGUAGE

- Sample 1 - Healthy Volunteer
- Sample 2 - Patient-subject Volunteer
- Sample 3 - Phase I
- Sample 4 - Phase I
- Sample 5 - Phase II
- Sample 6 - Phase III
- Problematic Sample 1

TOOLS & BACKGROUND MATERIALS

- Sample Gene Transfer Descriptions

intervention.

The greatest challenges to investigators in describing the purpose of the study include:

- Presenting the study and the science of gene transfer in a way that does not imply that the logic driving the hypothesis of the study is fact
- Describing the overall goal of the study in a way that does not imply that the long-term research goals (e.g., finding a new way to treat melanoma) are the goals of the current phase of the study (e.g., to determine a safe dosage)

- OBA Brochure, "Deciding Whether to Participate in Gene Transfer Research"
- NIH Backgrounder on Human Gene Transfer Research
- Sample Vector Descriptions

MAIN POINTS

The purpose statement should:

- **Not overstate the goals of the study**
- **Reflect the study phase**
- **Include an understandable explanation of gene transfer**

Placing emphasis on the research nature of the intervention and appropriately qualifying any statements or claims about anticipated outcomes and potential benefits of the current study are as important when describing the purpose as when describing or disclaiming any potential benefits. The purpose section of the consent form should be compared with the potential benefits section to avoid discrepancies and minimize possible confusion.

Study Phase: The purpose description should reflect the phase of the trial and should be based on pre-clinical and other clinical evidence. A brief description of classic study phases, reflecting the design and purpose of each, is included below as a reference. These descriptions could also be modified and adapted to use when informing potential participants.

Phase I studies are small studies of an experimental intervention and are usually the first time the intervention has been tried in humans. Their primary purpose is to test for safety, to see how the intervention affects the body, to test for harms and discomforts, and to see how the side effects change at different doses. Many phase I studies employ dose escalation designs.

Some, but not all, Phase I trials also attempt to reveal whether or not the intervention has any beneficial effects. Any Phase I trials with this additional purpose should be designed and powered appropriately. The hope for therapeutic benefit is not a sufficient basis for identifying efficacy testing as a secondary purpose.

Phase II studies are mid-sized studies of the experimental intervention and are designed to begin a more complete evaluation of the effectiveness of the intervention. The purpose of Phase II studies is to see if the intervention has any beneficial effects at a dose level thought to be safe based on earlier studies. Phase II studies also continue to test for harms, discomforts, and side effects resulting from the intervention.

Phase III studies are large studies of the experimental intervention for the purpose of gathering data on a larger group of participants in order to prove or disprove the safety and effectiveness of the intervention that has been tested in earlier studies. Phase III studies also reconfirm optimal doses and routes of administration. Phase III studies also provide an opportunity for investigators to recognize less-common side effects in a larger number of participants. The experimental intervention in Phase III studies may be compared to a standard treatment or to a placebo.

Relevant aspects of study design linked to phase - such as dose escalation in Phase I trials, and use of placebo groups, control groups, and comparison group designs in Phase III trials - should be briefly mentioned in the purpose section, and then explained in appropriate and relevant detail in the procedures section of the consent form.

Phase I/II Studies: Because investigators should build upon the knowledge gained in Phase I of their study, and so that potential participants considering enrollment in Phase II can benefit from knowing the outcomes of Phase I, it is important that Phase I and Phase II not be combined unnecessarily. The NIH Recombinant DNA Advisory Committee (RAC) reviews many Phase I/II studies and sometimes questions the appropriateness of a combined design. In the event that Phase I and Phase II must be combined, one consent form should be used for the Phase I portion of the trial and a second should be used for the Phase II portion of the trial to allow the different goals of the Phase I and Phase II components to be properly understood. If two separate consent forms are not possible, investigators should consider how potential participants are best informed of the differences between Phase I and Phase II and about the phase to which they will be assigned.

Describing Gene Transfer: A brief description of the gene transfer intervention should be provided to the potential participant. If the investigator's institutional review board approves, it may be desirable to create a scientific appendix to the consent form that briefly explains the scientific theory behind gene transfer and how that theory is to be applied in the current study.

The process of gene transfer is likely to be unfamiliar to most potential participants. Therefore, it is especially important that the investigator clearly and simply explain the gene transfer methodology used in the given study. Sample descriptions of different gene transfer methods are provided in this guidance. It is also important to use terms like "genes" and "DNA", especially if the gene transfer intervention is otherwise described by an acronym or other term that does not itself make an obvious connection to the introduction of new genes or new DNA into the body. Background material about basic genetics and the science of gene transfer research may be beneficial to some potential participants.

Describing Vectors: Most gene transfer requires a vector, often described as a transportation system to deliver the gene. Many descriptions use vivid analogies that compare the vector to a car and the gene to the passenger. For studies using a vector, descriptions of this sort may be helpful to lay readers. For those few studies not using a traditional vector (e.g., naked plasmid DNA), the description should discuss the method of delivery in plain language.

Sample vector descriptions for potential participants are included in this guidance. Investigators should pay particular attention to how adenoviruses are described since they are not just a common cold. Adenovirus can be better described this way: "Adenovirus is a common virus found in human respiratory systems. In its normal state, it can reproduce and cause a respiratory infection. Respiratory illnesses caused by adenovirus infections range from the common cold to pneumonia, croup and bronchitis."

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[2] Although use of healthy volunteers is uncommon in gene transfer research, it is not unknown. Healthy volunteers may be an appropriate population in selected studies.

SAMPLE LANGUAGE

Sample 1 - Healthy Volunteer

You have been asked to join this study as a healthy volunteer. This means that the investigators think that they can learn about a certain disease or condition that other people have from participation of healthy people like you.

Sample 2 - Patient-Subject Volunteer

You were asked to be in this study to help the investigators learn more about the type of disease you have. The investigators will try to keep the risks of harm to you from being in the study as low as possible. They believe that being in the study will not keep you from getting any treatments you may need for your disease.

This study will enroll people with your disease [CHOOSE WHICHEVER APPLIES]

- *Whose disease has been treated unsuccessfully by all standard means*
- *Who will continue to receive standard treatment*
- *Who can probably put off standard treatment during the study*
- *Who can probably stop or change standard treatment during the study*

Sample 3 - Phase I

This study is experimental. It is meant to investigate the safety, possible harms, and side effects of injecting your cancer with an experimental gene transfer agent called [X]. This is the first time that this gene transfer agent will be used in humans with your disease.

Sample 4 - Phase I

The investigator's goal is to find out the highest dose of the gene transfer agent that is safe. This is the first step in

studying whether it can be used to treat others with your disease in the future.

Sample 5 - Phase II

The purpose of this study to find out if repeated doses of the gene transfer agent, [xx,] are safe for research participants with your disease, and to see if any side effects cause problems for participants. This study is also being done to find out if giving [xx] can help lung disease in CF by making normal genes in the lung cells.

Sample 6 - Phase III

The purpose of this study is:

- *To find out if participants live any longer if the gene transfer agent is injected directly into their tumor(s)*
- *To find out if the intervention shrinks, stops or slows the growth of the tumor(s).*

We will also continue to check the safety of the gene transfer agent.

PROBLEMATIC LANGUAGE

Problematic Samples

You have been invited to participate in this study because your disease has progressed despite standard treatment.

You are eligible to participate in this study because there is no effective treatment for your disease.

Comments: For early-phase studies, these statements, standing alone, may foster the perception that research participants are likely to benefit from study participation, simply because nothing else has worked for them. In order to avoid creating this impression, descriptions of the targeted study population should focus on how risks can be minimized in and knowledge can be gained from the population, as illustrated in Sample 2 above.

SAMPLE GENE TRANSFER DESCRIPTIONS

- The gene transfer used in this study tries to provide corrected copies of one of your genes that does not function properly in your body [can be used in studies supplying corrected genes for monogenic diseases, or the p53 gene for some cancers]
- The gene transfer method used in this study tries to add copies of a gene that will alter the characteristics of the targeted cells [for example, when inserting the HSV-TK gene into tumor cells to make them susceptible to destruction by gangiclovir]
- The gene transfer method used in this study tries to add copies of a gene that increases the immune response against a tumor [use, for example, when inserting the gene for IL-2 or interferon gamma]

SAMPLE VECTOR DESCRIPTIONS

- A virus called [adenovirus, adeno-associated virus, retrovirus, other virus, i.e. fowlpox, vaccinia], which has been changed in the laboratory so that it is not likely to reproduce or cause an infection once it is in your body. [A short description of each virus used in the vector should be added, as illustrated by the adenovirus description provided in the section above entitled "Describing Vectors."]
- Loops of DNA containing the gene [naked plasmids].
- Loops of DNA associated with fat molecules [called liposomes] that help improve gene delivery.
- If another delivery system is used to introduce the gene modified cells or to deliver the recombinant DNA directly (e.g., a gene gun) to a human, a brief description should be included in the consent form.

Appendix M-III-B-1-a

Procedures

SAMPLE LANGUAGE

- Sample 1 - Dose Escalation Design
- Sample 2 - Randomization to Experimental or Control Arm

TOOLS & BACKGROUND MATERIALS

- Simplification Guide to Medical Terms

MAIN POINTS

- **The consent form should:**
  - **Describe the study procedures and timeline for these procedures**
  - **Distinguish between the research component and standard treatment**
- **Potential participants should be told how they and others will be assigned to study cohorts and, if applicable, their dose level.**

NIH GUIDELINES: "The subjects should be provided with a detailed explanation in non-technical language of the purpose of the study and the procedures associated with the conduct of the proposed study, including a description of the gene transfer component."

DISCUSSION

Potential participants should be provided a description of the design of the study, including a schedule of the study events and expected time commitments. The language in the procedure section of the consent form should not be overly scientific so that average lay readers can understand what they will experience as research participants. Breaking the procedures down into stages may make the information easier to understand. Timelines, including those presented in tabular or graphical format, may also be helpful.

Whenever applicable, the consent form and process should attempt to make clear to potential participants how research participation differs from being treated for health problems outside of the context of the study. This topic is also addressed in the Alternatives section.

Organization of Procedures Section: It is especially important in early-phase research, such as most gene transfer studies, to distinguish standard treatments from investigational interventions, and tests and measurements provided as part of clinical care from those related to the research study. Institutional review boards (IRBs) and institutional biosafety committees (IBCs) can provide guidance on how to differentiate between these activities. Using separate consent forms, or separate consent form sections, for the research component and standard treatment component is one reasonable way to distinguish between the two.

Avoiding Improper Language: Because gene transfer interventions, like other investigational interventions in early-phase trials, are unproven and have not yet been studied for efficacy, they should not be referred to as treatments.

Some examples of improper language are:

- *You will receive up to three treatments in this study.*
- *Your participation in this treatment program is entirely voluntary.*
- *Your illness will be treated using gene transfer.*

Alternative language reinforcing the experimental character of gene transfer should be chosen appropriately for a given protocol. Possible alternatives to the above examples might be:

- *Participants will get up to three gene transfer infusions in this study.*
- *Your participation in this research program is entirely voluntary.*
- *As part of this study, you will get a gene transfer injection.*

Dosing Group Designs and Cohort Assignments: Many Phase I studies utilize dose escalation to determine a safe gene transfer agent dosage amount. If the study involves dose escalation, the investigator should explicitly state to which dosage cohort the potential participant will be assigned, the dose level to be received, and any potential risk-benefit balance for that particular cohort. In providing this information, the investigator should describe and explain dose escalation designs for the following reasons:

- Potential participants should be told that the dose level selected for them is not based on a medical determination of what is best for their treatment; instead, the dose level is based on the order in which they enrolled in the study and/or how previous participants have reacted. During enrollment, they should be told about the experience of earlier enrollees when possible.

- The risks of harm and discomfort from the experimental intervention probably bear some relationship to the dose level. Potential participants should be informed that any adverse reactions might be worse at higher doses.
- The potential for direct benefit, if any, may also vary with the dose level. Potential participants should be informed that any likelihood or amount of benefit might be different at different doses.

Other Study Designs: Many Phase III studies involve such features as randomization, inclusion of control groups, use of placebos, and blinding. All of these features should be explained simply and clearly in the consent form and process. Double-blind design explanations should include the information that the blind may be broken if necessary to protect the participant's health and welfare. IRBs and IBCs can provide guidance and sample language on blinding and randomization.

Procedures Language: In order to simplify consent forms, researchers are encouraged to consult resources like the Simplification Guide to Medical Terms that suggest replacements for terms that are difficult to understand and, thus, require explanation or substitution. In addition, dosage information should be as precise as possible; terms like low, medium, or high dose should be quantified in terms that are most informative to potential participants.

SAMPLE LANGUAGE

Sample 1 - Dose Escalation Design

We do not know the highest dose of the gene transfer agent that is safe. To find out we will give the gene transfer agent to [number] participants at one dose level. If that is safe we will raise the dose given to the next group of participants. The dose you will get will depend on how many participants get the agent before you and how they react. The investigator will tell you this information. This will help you think about possible harms and benefits. Since the gene transfer intervention is experimental, what is likely to happen at any dose is not known.

Sample 2 - Randomization to Experimental or Control Arm

It is not clear whether experimental gene transfer will be more effective than standard treatment. For this reason, you will be randomly assigned (like the flip of a coin) to one of two groups: the experimental group (gene transfer) or control group (standard treatment). You will have a 50% chance of being assigned to either group.

Appendix M-III-B-1-b

Alternatives

NIH GUIDELINES: "The Informed Consent document should indicate the availability of therapies and the possibility of other investigational interventions and approaches."

DISCUSSION

Potential participants should be informed of any available alternatives to participation in the current study, including other experimental interventions. This information is especially important for potential participants interested in participating in studies involving combinations of interventions of which gene transfer is only a part.

Disease-appropriate alternatives include:

- Standard treatments, procedures, drugs, and devices
- Experimental interventions, procedures, drugs, and devices available at the trial site and/or elsewhere. Many sources of information about clinical trials are available on the web (see the Tools & Background Materials box for examples of these

SAMPLE LANGUAGE

- Sample 1 - Standard Treatment Alternatives
- Sample 2 - Experimental Alternatives
- Sample 3 - Palliative Care Alternatives
- Sample 4 - Combination of Alternatives
- Sample 5 - Combination of Alternatives
- Sample 6 - Combination of Alternatives

TOOLS & BACKGROUND MATERIALS

- www.clinicaltrials.gov

websites). Investigators may wish to provide information about such websites so potential participants can learn about other research.

- Pain and symptom management, palliative and supportive care, counseling and other support services without further life-prolonging interventions. This formulation is preferable to the language of "no treatment" since it identifies other forms of care for potential participants with serious illness. It is especially important that potential participants who are dying receive information about alternatives involving palliative care.

There may be no alternatives that have been shown to have significant success in individuals with certain diseases or conditions. Researchers should discuss this situation with potential participants, as appropriate.

- AIDS Clinical Trial Information Service
- NCI Cancer Clinical Trials

MAIN POINTS

When available, potential participants should be given information about:

- **Alternative standard or experimental treatments, procedures, drugs, and devices**
- **Pain and symptoms management, palliative care, and support services**

In the consent process, investigators should recognize that some potential participants may consider themselves to have no real choice other than to participate in research. Investigators should take extra care in explaining and discussing alternatives with these potential participants. In contrast, very ill potential participants, whom investigators may be tempted to characterize as having no options, may view themselves as having a range of choices. Investigators should be sure to give these potential participants complete information about alternatives to participation.

SAMPLE LANGUAGE

Sample 1 - Standard Treatment Alternatives

Instead of being in this study, you may choose to have treatment with one or more standard chemotherapy drugs, alone or in combination. Some individuals have responded to standard treatments. The drugs used for your type of cancer include: [drug listing]. Or you may choose to have radiation treatment to control symptoms of your disease

Sample 2 - Experimental alternatives

It is not known whether any of the other experimental agents being studied are effective in your disease. If you decide not to be in this study, you can still join other studies, here or at other medical centers, if you wish.

Sample 3 - Palliative care alternatives

You may decline life-prolonging interventions for your disease. If you did, you would receive palliative care. This is supportive care that will not help you live longer, but will make you as comfortable as possible for as long as you live.

Sample 4 - Combination of alternatives

You do not have to participate in this study. You may want to be in a different study. You can choose not to participate in this study and continue to be cared for regularly here at [hospital]. You may choose at any time to stop being in this study and maintain all other aspects of your care by your doctors at [hospital]. [INCLUDE WHEN APPLICABLE: Getting the gene transfer in this study should not prevent future treatment with standard therapy. Getting the gene transfer in this study should not make you ineligible for participation in other studies either.]

Sample 5 - Combination of alternatives

You may choose not to participate in this study. If you choose not to, your decision will not affect your care at [study site]. Alternatives to being in this study include:

- *[list alternatives]*

You can receive these treatments during and after the study. Since this study will not directly treat your [disease], a decision not to participate will not affect your health.

Sample 6 - Randomization to Experimental or Control Arm

Standard treatment cannot cure your disease. You may be in other studies that may improve your quality of life and help you live longer even though they will not cure your cancer. A variety of research studies for your cancer are going on in medical centers around the world. The effectiveness of these approaches is unknown. [New treatment X] has recently shown longer survival in some patients. Other treatments may also be available. You can also decline further life-prolonging treatment for your disease, and receive palliative care to manage your symptoms. If you decide not to participate in this research study, we will discuss all appropriate treatments with you and help you decide what to do next.

Appendix M-III-B-1-c

Voluntary Participation

NIH GUIDELINES: "The subjects should be informed that participation in the study is voluntary and that failure to participate in the study or withdrawal of consent will not result in any penalty or loss of benefits to which the subjects are otherwise entitled."

SAMPLE LANGUAGE

- Sample 1
- Sample 2
- Sample 3

MAIN POINTS

Potential participants should be informed:

- **That they may decline to enroll**
- **That they may withdraw at any time**
- **About the implications of withdrawing**
- **That the investigator may terminate the participant's enrollment**

DISCUSSION

Deciding not to enroll: Investigators should inform potential participants that they may decline to participate in the study without risk of compromising present or future medical care and without suffering a penalty or loss of benefits to which they are otherwise entitled. Investigators may also emphasize that full participation is important for scientific reasons and that participants should enroll only if they are willing and able to complete the entire study.

Withdrawal: Participants have the right to withdraw from the study at any time, including during follow-up. The implications and consequences of withdrawal (from the intervention only or from the entire study) should be discussed as part of the consent process. Potential issues to consider include:

- Irreversible course of action: Whenever applicable, potential participants should be informed that, in the event that they withdraw after receiving the experimental intervention, the intervention cannot be undone. If early withdrawal could pose any special risks of harm to participants or others, they should be described.
- Request for follow-up: If follow-up is necessary or highly desirable for health and safety purposes, participants should be encouraged (but not required) to return for needed follow-up in the event that they withdraw from the study.
- Risks to close contacts: If early withdrawal could pose risks to third parties, for example, transmission of vector to close contacts if the participant withdraws during a period of viral shedding, participants should be strongly urged to comply with any necessary precautions to minimize the risks.
- Data and stored specimens: Potential participants should be informed about what will happen to data and specimens, if any, already collected from them should they withdraw from the study. Investigators should inform potential participants about their rights to withdraw data and specimens.

Investigators may emphasize that withdrawal may deprive the research of important data, and they may request (but not require) that participants who do not want to complete a full course of the experimental intervention or long-term follow-up nonetheless remain in the study and complete all study visits.

Study Discontinuation: Potential participants should be informed that the investigator or the study sponsor may terminate their participation in the study at any time without their consent if it is believed to be in their best interest, if they do not comply with study requirements, or if the study is discontinued. The investigator should explain the reason for terminating participants' involvement in the study and what arrangements will be made for continued care.

SAMPLE LANGUAGE

Sample 1

You do not have to be in this study. You can say no. If you join the study, you can leave it at any time. If you choose not to participate, there will be no penalties, and no bad effects on any benefits or medical care that you are entitled to get from this hospital or from your health care providers. If you leave the study, please tell the investigator or research coordinator. Then we will ask you to come back to the clinic for a final assessment and discussion of future treatment options.

Sample 2

Being in this study is completely voluntary. You may withdraw at any time without penalty, without loss of benefits to which you are entitled, and without affecting the medical care you get at our hospital. However, once you receive the gene transfer, there may be some effects that cannot be reversed.

Sample 3

The investigators may stop your participation at any time. This could be because you have had an unexpected reaction or because the whole study has been stopped.

Appendix M-III-B-1-d

Potential Benefits

NIH GUIDELINES: "The subjects should be provided with an accurate description of the possible benefits, if any, of participating in the proposed study. For studies that are not reasonably expected to provide a therapeutic benefit to subjects, the Informed Consent document should clearly state that no direct clinical benefit to subjects is expected to occur as a result of participation in the study, although knowledge may be gained that may benefit others."

DISCUSSION

Because of the experimental nature of gene transfer research, it is important for investigators to emphasize to potential participants the speculative nature of the potential benefits from the gene transfer intervention. To this end, the benefits section of the consent form should be labeled as Potential Benefits or presented as a question, such as *Are there any possible benefits from this study?*

Generic benefits discussions are commonly found in gene transfer research consent forms, but they should be avoided. Simple potential benefit statements, such as "You may or may not benefit from being in this study," or "Personal benefit cannot be predicted or guaranteed," do not provide sufficient meaningful information for potential participants in gene transfer research, particularly in early-phase studies. Such statements should be avoided whenever it is possible to provide more specific information about the nature and likelihood of potential benefits, if any, and their limitations, as described in the text of Appendix M-III-B-1-d and throughout this guidance section.

Vague statements like "Getting the gene transfer in this study may or may not improve your health, reduce your symptoms, or make you feel better" should also be replaced by appropriate discussion of specific disease aspects, since the meaning of "reduce symptoms", "improve health", and "feel better" may be interpreted differently by different potential

SAMPLE LANGUAGE

- Sample 1 - Societal Benefit
- Sample 2 - phase I
- Sample 3 - phase I
- Sample 4 - phase I
- Sample 5 - phase I
- Sample 6 - phase II
- Sample 7 - phase II
- Sample 8 - phase III1
- Sample 9 - phase III2
- Sample 10 - phase III3
- Sample 11- Surrogate Endpoints2

TOOLS & BACKGROUND MATERIALS

- King N, et. al. Consent Forms and the Therapeutic Misconception. IRB Ethics and Human Research 2005

MAIN POINTS

- **Investigators should be cautious in how potential benefits are conveyed to avoid unrealistic expectations of clinical improvement, i.e., therapeutic misconception.**
- **Descriptions of potential benefits depend on the study phase.**
- **Concepts such as benefits to society and surrogate endpoints must be clearly communicated to potential**

Detailed discussion of potential benefits may assist potential participants in understanding the differences between receiving medical treatment and participating in research. An explicit statement of differences between treatment and research may also be helpful. In addition, investigators should distinguish between the ultimate goal of the line of research, the endpoints of the current study, and potential benefits to participants from the gene transfer. Without careful differentiation, the consent form could inappropriately convey the impression that the long-term goal of curing disease with gene transfer is identical to the potential benefit offered in a Phase I trial.

Societal Benefit: Many gene transfer consent forms fail to mention benefit to society. However, potential participants should always be informed that early phase studies are designed for scientific purposes and that those who participate in these studies may extend benefit to future patients by helping to advance scientific and medical knowledge. The investigator should distinguish between these benefits to society and potential benefits, if any, to participants.

Reducing Therapeutic Misconception: Characterizing an experimental study as treatment may be misleading to potential participants because it incorrectly implies that the experimental intervention is in fact a treatment -- or at least that it would not be tried unless there was some realistic expectation of its success for that potential participant. However, in a research context, benefits may not be anticipated with such confidence. This is especially true in early-phase trials, in new fields like gene transfer research, and when participants are seriously ill. Correcting inappropriate "treatment" language may help not only participants but also study personnel and oversight bodies avoid developing unrealistic expectations of clinical improvement from the gene transfer intervention.

Some examples of misleading language are:

- *Your doctor is recommending this experimental treatment.*
- *Your doctor feels that treatment on this study will give you at least as good a chance as you might expect from other therapies.*

Examples of misleading terms that may imply medical benefit include therapy, treatment, and patient. These terms should be replaced with terms such as gene transfer or gene transfer agent, and research participant, respectively.

Describing Potential Benefit for Different Phases and Designs: What is known about the potential benefits, if any, of a gene transfer intervention in a given study depend on the design and phase of the study and available evidence. Potential benefits discussions should be phase-specific. For combined Phase I/II studies, it is important to distinguish between the potential benefits of each phase.

Investigators should consider how to present information about prior experience and its limitations in the consent form so as to best inform potential participants. Previous experiences related to benefits in animal studies, and possibly even in vitro experience, may be relevant when the meaning and limitations of the findings are carefully described. Previous human experience is usually relevant, but should nonetheless be described carefully and its limitations addressed.

Uncertainty about the likelihood of the occurrence of direct personal benefit from the gene transfer intervention should always be mentioned. Especially in Phase I and II trials, it is appropriate to say that the primary purpose of the study is to produce benefits to society - that is, contributions to scientific knowledge and medical progress, and perhaps benefits to future patients.

- *Phase I Study:* Phase I trials involve the greatest uncertainty about the possibility of personal benefits, since existing data are limited. This uncertainty, and the early stage of the research, should be pointed out in the consent form. When presenting animal data, a general statement that humans and animals may respond very differently would be appropriate. The mere hope that the intervention will be therapeutic is not sufficient justification for suggesting the possibility of direct personal benefit. Depending on the specifics of the study, including existing data, study design, and power, it may be appropriate to state that direct personal benefit is unlikely, or that there will be none.
- *Phase II Study:* The possibility of direct personal benefits from the intervention may be somewhat better defined in Phase II studies. The consent form may include descriptions of suggestions of direct personal benefit that were discovered in Phase I. It should be acknowledged that the extent of experience is still limited; it is certainly still inappropriate to encourage the expectation of personal benefit.
- *Phase III Study:* The possible personal benefit statement for a Phase III trial should reflect the findings of the

earlier phases. It should also acknowledge the results with a greater number of enrolled participants may be very different from those found in earlier phase trials.

Surrogate Endpoints: In gene transfer research, investigators most often seek to measure surrogate endpoints. However, these surrogate endpoints may not directly relate to any benefits that participants may clinically experience. Surrogate endpoints should not be described as benefits to participants unless there is a well-established, direct link to a clear health benefit. The challenge of discussing potential benefits lies in explaining the relationship, or lack thereof, between what the investigators seek to measure and what participants might experience. Whenever appropriate, investigators are encouraged to discuss explicitly and specifically the nature and extent of clear clinical benefits that potential participants may be expecting, in order to explain what expectations are reasonable and why, and what expectations are not reasonable and why.

SAMPLE LANGUAGE

Sample 1 - Societal Benefit

This study is meant to answer scientific questions about gene transfer for your disease. The results may give investigators information to use in future research, even if the gene transfer does not work. Some people find potential societal benefits like these a good reason to participate in this study. Please consider whether you think that as well.

Sample 2 - Phase I

The gene transfer you get in this study is not likely to change the natural course of your disease. This study is not meant to be a treatment for your disease. Instead, the investigators hope that the information learned from this study can benefit patients with [condition] in the future.

Sample 3 - Phase I

The purpose of this study is to test the safety of this gene transfer and to see if we can successfully put the gene into cells of people with [condition]. Treating your disease is not the purpose of this study. It is very unlikely that getting the gene transfer in this study will improve your health or [specific symptoms].

Sample 4 - Phase I

This study is not intended to benefit you directly. Investigators simply want an understanding of gene transfer for [condition]. Information about the amount of DNA needed and the effects of the gene transfer agent will be critical for further studies in the future. Getting the gene transfer in this study will not improve your health or [specific symptoms].

Sample 5 - Phase I

The reason for doing this study is to test the safety of different doses of gene transfer given to participants with [condition]. Although there is some evidence that the gene transfer injections could help [achieve surrogate endpoint] in some participants, we do not know if that will happen to you. Even if it does, the good effect would probably be small and not last long. However, it is very unlikely that this will happen. Benefit to you is not the goal of this study. Instead, we want to see if the study injections are safe. We also want to provide a foundation for future studies of these injections. We hope to benefit future patients with [condition].

Sample 6 - Phase II

Earlier studies support the safety of the gene transfer, but it is far too early to say whether it will help you at all. Even if it does, it is far too soon to know how much it may help and how long any benefit might last.

Sample 7 - Phase II

This is a Phase II study. It is the first systematic attempt to find out if this gene transfer will help individuals like you.

You should not enroll in this study with any expectation that you will personally benefit.

Sample 8 - Phase III

Earlier research shows that this intervention may help individuals like you. However, we are not sure there will be any helpful effects. If there are any, we do not know how great those effects might be, or how long they might last. You should keep this uncertainty in mind as you decide whether you want to participate in this research.

Sample 9 - Phase III

This is a Phase III trial. It is an attempt to identify the extent and duration of benefit of this intervention. Any hope you have of gaining a meaningful personal benefit should be just a hope and not an expectation.

Sample 10 - Phase III

We cannot predict if you will gain any personal benefit from getting this gene transfer. Earlier studies show that the experimental gene transfer agent may shrink some tumors. This could decrease cancer-associated symptoms or prolong life for a time. However, the gene transfer may have no good effects on your disease at all. If your disease becomes worse, or if the side effects from the gene transfer become too great, or if there is any other reason to think that participation in this research is not in your best interest, we will stop your participation so that you can be treated with standard therapy.

Sample 11 - Surrogate Endpoints

In this study we are measuring [surrogate endpoint-SE]. We hope that a change in this measure will have [beneficial clinical effect] on this disease. But because this study is short, we do not know if changes in [SE] will change how participants in this study feel. We also do not know if [SE] will last for longer than a short time. It is also possible that for participants whose disease is very severe, a beneficial effect might not be felt very much or at all.

Appendix M-III-B-1-e

Possible Risks, Discomforts, and Side Effects

NIH GUIDELINES: "There should be clear itemization in the Informed Consent document of types of adverse experiences, their relative severity, and their expected frequencies. For consistency, the following definitions are suggested: side effects that are listed as mild should be ones which do not require a therapeutic intervention; moderate side effects require an intervention; and severe side effects are potentially fatal or life-threatening, disabling, or require prolonged hospitalization. If verbal descriptors (e.g. 'rare,' 'uncommon,' or 'frequent') are used to express quantitative information regarding risk, these terms should be explained. The Informed Consent document should provide information regarding the approximate number of people who have previously received the genetic material under study. It is necessary to warn potential subjects that, for genetic materials previously used in relatively few or no humans, unforeseen risks are possible, including ones that could be severe. The Informed Consent document should indicate any possible adverse medical consequences that may occur if the subjects withdraw from the study once the study has started."

DISCUSSION

Gene transfer is a deliberate intervention with potential risk. Potential participants should be given information about all reasonably foreseeable

SAMPLE LANGUAGE

- Sample 1 - Risks Associated with Study Agent
- Sample 2 - Risk of Cancer Caused by Gene Transfer
- Problematic Sample 1

TOOLS & BACKGROUND MATERIALS

- Kimmelman J. Recent developments in gene transfer: risk and ethics. British Medical Journal 2005

MAIN POINTS

- Potential participants should be given detailed information about all reasonably foreseeable risks of harm, discomforts, and potential side effects.
- Potential participants should be told that there might also be unknown harms that could occur.
- Descriptions of risks of harm should be phase-specific.

risks of harm, discomforts, and potential side effects associated with the procedures and agent as outlined in the study. Such information should include the seriousness, likelihood of occurrence, timing (short- or long-term), and reversibility of the possible harm.

- **A distinction should be made between risks of harm from procedures and risks of harm from agents.**

Bulleted lists of clearly defined items with a brief explanation of what the risk or side effect may entail may be helpful way to present the risks of harm in the consent form.

Since some risks of harm cannot be known with certainty, it is always helpful to discuss what is uncertain and unknown.

Differences in Risk of Harm for Phase I, II, III Studies: The available evidence about risks of harm and potential discomforts of a gene transfer intervention differ according to the phase of the study. Risk discussions should be phase-specific. For combined phase I/II studies, it is especially important to distinguish (preferably in separate consent forms) between the risks for harm of each phase.

- *Phase I Study:* Phase I trials involve the greatest uncertainty about risks of harm, since existing evidence is limited to animal or laboratory studies or to results of the gene transfer intervention in a separate disease. All the expected and remote risks of harm that may foreseeably be associated with participation in the study should be listed and explained.

  Previous experiences with the same or similar vector, or even a different transgene, should be included in the risks section, particularly in phase I studies. Experience with animal studies may be relevant, as well as other human experience, and possibly even in vitro experience, when the meaning and limitations of the findings are carefully described. A general statement that humans and animals respond very differently, and a statement about the relationship between the dose levels used in animals and humans would be appropriate. Uncertainty about the likelihood of the occurrence of most risks of harm from the gene transfer intervention at this early stage of research should be acknowledged.
- *Phase II Study:* The risks of harm from the intervention are better defined for a Phase II study. The consent form should include descriptions of risks of harm that were discovered in Phase I, such as reactions to the maximum-tolerated dose. It should be acknowledged that the extent of experience is still limited and that unanticipated harms may develop.
- *Phase III Study:* The risk statement of a Phase III trial should reflect the results of earlier trials. It should also acknowledge that with a greater number of enrolled participants, less-common side effects are likely to be recognized at this stage.

Types of Risks: It may also be important to distinguish risks of procedures from risks of harm from investigational agents:

- *Risks associated with the study procedures:* If the study includes non-research procedures as well as study procedures, the risks of harm from medical procedures that are not being conducted for research purposes are better addressed in a treatment consent form separate from the consent form for the gene transfer experiment. If it is essential to include risks of harm from medical procedures that are not being conducted for research purposes in the research consent form, such risk statements should be distinguished from the risks of harm from the research procedures, and the latter should remain the primary focus of the risk section.
- *Risks of harm associated with the study agent:* Potential participants should be informed of the specific risks of harm from the vector and transgene used in the given study. The following risks of harm from gene transfer should be included whenever appropriate:
  - The added vector and/or gene could create changes in cells that could lead to cancer
  - The added vector and/or gene could create permanent changes in cells that could be passed on to children conceived and born during or after study participation
  - The added vector and gene could go to unexpected cells or tissues in the body
  - The added vector could become able to reproduce itself, and the added vector and gene could be passed on to close contacts like an infection

SAMPLE LANGUAGE

Sample 1 - Risks Associated with a Study Agent

The vector, which carries the gene into your cells, is considered harmless in humans. However, it is possible that the virus could grow and/or make the cells cancerous. There is a risk that the vector may enter the normal tissue surrounding the tumor, or other sites in the body. Another risk is that the vector might stay in your body and cause cancer or other diseases. Your immune system is expected to reject (kill) the vector in [time amount]. Thus, the vector should not be able to survive and grow in your body. The risk of causing a new cancer is probably very small. Although some vectors have caused cancers, no cancers have yet been found in any of the experiments in which genes have been transferred into monkeys and humans using this vector.

Sample 2 - Risk of Cancer Caused by Gene Transfer

Researchers have wondered whether a transferred gene might sometimes land in a place in a cell where it can cause harm. This happened to two children in another study. After getting the gene transfer, they developed leukemia (a type of blood cell cancer). A group of experts looked at all the test results. They found that gene transfer caused the leukemia by making some cells grow out of control. The children appear to be responding to treatment of the leukemia, but their long-term health is unknown at this time.

There is a risk of unknown size of your child developing cancer, such as leukemia, should you volunteer your child to enter into this experimental study. This is a serious risk because cancers of the blood can lead to death.

PROBLEMATIC LANGUAGE

Problematic Sample 1

[Gene transfer agent] may cause pain at the injection site. It may also cause some heart toxicity. Patients may also have shortness of breath and/or allergic reactions, including hives, skin rash, difficulty breathing, and/or fever. There may be damage to the liver and kidneys. These reactions could result in death. Having a tumor biopsy may cause air in the chest and/or bleeding to occur. Air in the chest is treated with the insertion of a small tube. A bronchoscopic biopsy (sample of very tiny piece of the mucosa inside the lung) may cause coughing up of blood. This is usually temporary. Severe bleeding requiring emergency treatment such as intubation and thoracotomy could also occur. This clinical research study may involve risks to the participants that are unknown at this time.

Comments: The risks of harm would be clearer if they were ranked according to likelihood and severity. Risks of harm particular to the gene transfer should be included. Also, medical terms like "intubation" and "thoracotomy" need to be described in lay terms.

Appendix M-III-B-1-f

Costs

NIH GUIDELINES: "The subjects should be provided with specific information about any financial costs associated with their participation in the protocol and in the long-term follow-up to the protocol that are not covered by the investigators or the institution involved. Subjects should be provided an explanation about the extent to which they will be responsible for any costs for medical treatment required as a result of research-related injury."

DISCUSSION

The investigator should make clear to potential participants who will bear financial responsibility for various aspects of the trial. In every intervention study, it is likely that:

- Study sponsors may pay for some interventions, tests, and procedures

SAMPLE LANGUAGE

- Sample 1
- Problematic Sample 1

MAIN POINTS

- **Investigators should clearly indicate what costs, if any:**
  - **Will be paid by the study sponsors**
  - **Are expected to be covered by health insurance**
  - **The participant will be responsible for**
- **Costs to consider include:**
  - **Research-related costs**

- The participant's health insurance, when available, may pay for some interventions, tests, and procedures
- Participants will be expected to pay for some costs covered neither by the study nor by health insurance, such as transportation and lodging costs

- Standard care
- Research-related injury
- Long-term follow-up

Participant Costs: Costs associated with participation in the study and long-term follow-up that will be the responsibility of the participant should be enumerated. Such costs may include:

- Research-related costs, i.e. out-of-pocket participant costs for experimental components not paid by the sponsor nor reimbursed by health insurance
- Standard care, i.e., out-of-pocket participant costs for tests, procedures, and interventions that would be necessary even if not participating in the study. Such costs are often reimbursed by health insurance, but some potential participants may be uninsured or underinsured. (Discussion of financial costs associated with standard interventions is only necessary in circumstances where the non-research and the research procedures cannot be separated into two consent forms.)
- Treatment of adverse events related to study participation, both during and after study participation.

Bulleted lists of the costs that will be incurred may be helpful to potential participants, including:

- You or your insurance carrier WILL be charged for
- You or your insurance carrier WILL NOT be charged for

Research-Related Injury: Institutions and sponsors are not required to compensate or provide free treatment to participants for research-related injuries. However, institutions and sponsors may adopt individual policies regarding compensation and provision of treatment for research-related injuries. Investigators should consult with their sponsors, Institutional Review Board and Institutional Biosafety Committee for their policy and model language. Investigators should provide information about the study's policy on research-related injuries, including whom to contact if a research-related injury should occur, regardless of whether compensation or treatment will be provided.

Financial Counseling: An increasing number of institutions make financial counseling available to potential research participants. Such counseling can help determine what is likely to be covered by the participant's health insurance and can help identify sources of supplemental support, such as uncompensated care funds, special arrangements and discounts from institutions and sponsors, subsidization for travel and living expenses for participants and families, and the like. Financial information and counseling may be particularly helpful for gene transfer trial participants. Although insurance coverage for participation in clinical trials has broadened considerably in recent years, coverage for early-phase trials, like most gene transfer, is far from certain because of the low likelihood of direct benefit from the experimental intervention. The investigator should provide information about financial counseling available to potential study participants.

SAMPLE LANGUAGE

Sample 1

The following items will not be charged to you or to your insurance company:

1. *[Gene transfer agent]*
2. *Hospitalization for the first day you receive the gene transfer intervention*
3. *Laboratory evaluations for research purposes [list]*
4. *Tumor biopsies for research purposes*

Health care costs not related to this study are billed to your health insurance company. Because this is a research study, insurance companies or government health care programs may not pay for the experimental interventions, research-related tests, or treatment of research-related injuries. You must pay all charges related to the medical care you receive for treatment of your disease except for those listed above. This includes charges your insurance company refuses to pay because of the connection with an experimental procedure. You will not be paid for being in this study.

PROBLEMATIC LANGUAGE

Sample 1

There will be no costs to you for any research-related laboratory tests, investigator's time, or the [gene transfer agent]. You or your insurance company will be billed for tests and treatments that are considered standard care. Medical treatment for physical injuries directly resulting from research procedures that are not covered by your insurance will be provided free of charge at [study site] by the [study sponsor].

Comments: Although this sample language is common, it is insufficiently helpful. It does not allow potential participants to reasonably foresee the costs they will be expected to pay as a result of their participation in the study, since these are merely described as "standard care".

Appendix M-III-B-2-a

Reproductive Considerations

NIH GUIDELINES: "To avoid the possibility that any of the reagents employed in the gene transfer research could cause harm to a fetus/child, subjects should be given information concerning possible risks and the need for contraception by males and females during the active phase of the study. The period of time for the use of contraception should be specified. The inclusion of pregnant or lactating women should be addressed."

DISCUSSION

Some vectors used in gene transfer experiments have the capacity to integrate and alter the germ line. When data are inadequate to rule out the possibility of inadvertent germline alteration, non-sterile participants should be informed that the biological consequences of this procedure are not known and, therefore, unborn children, children who are breast-feeding, and mothers could be harmed.

Discussion of the risk of reproductive harm should always be study-specific. Study-specific factors include, but are not limited to, frequency of pregnancy testing and the possibility of inadvertent germline effects, which could be teratogenic.

Reproductive considerations may be unique to one gender or may need to be discussed differently for men and women. It may be worthwhile to have separate sections in the consent form for issues especially pertinent to men or to women.

SAMPLE LANGUAGE

- Sample 1 - Men and Women
- Sample 2 - Men and Women
- Sample 3 - Men and Women
- Sample 4 - Men and Women
- Sample 5 - Men Only
- Sample 6 - Men Only
- Sample 7 - Women Only

TOOLS & BACKGROUND MATERIALS

- FDA Guidance on Participation of Women of Childbearing Potential in Clinical Studies
- OHRP Guidance on Participation of Women in Research

MAIN POINTS

- **Potential participants should be informed of the risk of germline alteration and ways to minimize this risk.**

Avoiding Risk of Reproductive Harm: To avoid the possibility of causing harm or abnormalities to an unborn child, participants and their sexual partners should be encouraged to practice abstinence for an appropriate length of time or, at minimum, to use certain methods of contraception. The short- and long-term advantages and disadvantages of each method should be explained. In some studies, it may be advisable for investigators to discuss sperm and ova banking, which may involve an additional cost to the participant.

The risk of horizontal transmission of the vector-transgene combination to sexual partners should be addressed separately in the consent form. Here, too, the advantages and disadvantages of typical contraceptive methods should be discussed.

Under some circumstances, pregnant or nursing women may not be eligible to participate in gene transfer trials that

pose risks of reproductive harm. When such exclusions are justified, investigators should inform potential participants that they will be tested to rule out pregnancy. In some gene transfer studies, women who are breast-feeding may not be eligible for participation or may be asked to stop breast-feeding during and for a specified period after the study completion.

In addition to discussing possible reproductive harms relevant to both sexes, investigators should also discuss with potential participants what will happen if a study participant or the partner of a participant becomes pregnant. This should include information about reporting pregnancies to the investigators, so that risks of harm may be individually assessed and counseling may be offered. It may also include requests for long-term monitoring of offspring.

SAMPLE LANGUAGE

Sample 1 - Men and Women

Risks of harm from this study include the possibility that the genes in some of your sperm (men) or eggs (women) may be permanently changed. Some of these changes could lead to miscarriage or birth defects in your future children. Other changes may have no apparent effects but could still be passed on to future generations. The likelihood of such outcomes is currently unknown.

Sample 2 - Men and Women

It is not known if DNA injected into your muscles can become part of the DNA of your reproductive cells (eggs or sperm). If this happens, it may cause fetal death or birth defects in future pregnancies of participants and their partners. It is also unknown whether or not the gene transfer vector will be present in body fluids (semen, vaginal secretions) and, if so, whether it will be transmitted to a sexual partner.

Sample 3 - Men and Women

You should not be in this study if you are planning a pregnancy soon. The risk of transmission of the gene transfer vector to a sexual partner or an embryo or fetus is unknown. It is possible that harmful side effects could occur to both the mother and unborn or breast-feeding children. You should not become pregnant during the study. The risks of harm from the gene transfer vector to an unborn or newborn child are unknown. If you become pregnant while in this study, you must tell your investigator at once. If you can give birth or father a child, you must use an adequate form of birth control. If you are able to become pregnant, you must have a negative pregnancy test within [time] before you get the first dose of the gene transfer. You may not take part in this study if you are pregnant or a nursing mother.

Sample 4 - Men and Women

You should not become pregnant or father a child while taking part in this study. Women who are pregnant or breast- feeding may not be in this study. If you are a female who can have children, you will take a pregnancy test and the results will be given to you. You must confirm that you do not plan to become pregnant while on this study. If you are capable of giving birth or fathering a child, you must use an acceptable form of birth control. For women, contraception should go on for [time period] after the last dose of the [gene transfer agent] to ensure that it has completely cleared from your body. For men, contraception should go on for [time period] after the last dose of the [gene transfer agent] to make sure that all sperm in the body during the trial have been replaced. If you or your partner becomes pregnant, or you suspect that you or your partner is pregnant while in this study, notify the investigator at once.

Sample 5 - Men Only

There is no information on whether the vector and gene can be transferred to sperm cells. Thus, the risk of gene transfer to germline cells (sperm cells) is unknown. Transfer of gene to germline cells could cause serious birth defects or fetal death. It could also lead to unknown health problems (such as cancer) in the child. If you may want to have children in the future, we recommend that you bank sperm before beginning the study, so that you have sperm available that has no DNA from the vector and gene. The investigators will provide you with information on sperm banking at [study site] or at your home institution. In addition to sperm banking, fertile men are encouraged to use barrier birth control devices (i.e., condoms). The investigators will notify you when it is safe to stop barrier methods of birth control.

Sample 6 - Men Only

One risk of this study is that [gene transfer agent] could have harmful effects on an unborn child. We do not know if the gene transfer you will get can become part of normal reproductive cells. If it can, it could cause harm to fetuses conceived after the gene transfer. These harms could include birth defects or death of the fetus, or of the child after birth. If you can father a child you should use precautions to prevent any sexual partner from becoming pregnant during this study.

Also, we do not know if the [gene transfer agent] may be present in body fluids. If it is, it could be transmitted to sexual partners. Condoms are essential for preventing transmission to a sexual partner.

Sample 7 - Randomization to Experimental or Control Arm

One risk of this study is that the [gene transfer agent] could have harmful effects on an unborn child. We do not know if the gene transfer you will get can become part of normal reproductive cells. If it can, it could case harm to fetuses conceived after the gene transfer. These harms could include birth defects or death of the fetus, or of the child after birth. If you are capable getting pregnant, you should use precautions to prevent becoming pregnant during this study.

If you become pregnant during the study or suspect that you may be pregnant, you should tell the investigator immediately. You also should not breastfeed during the study.

Also, we do not know if the [gene transfer agent] may be present in body fluids. If it is, it could be transmitted to sexual partners. Condoms are essential for preventing transmission to a sexual partner.

Appendix M-III-B-2-b

Long-term Follow-up

SAMPLE LANGUAGE

- Sample 1 - Long-term Follow-up
- Sample 2 - Long-term Follow-up
- Sample 3 - Significant Findings

MAIN POINTS

- Long-term follow-up should be explained to potential participants.
- Researchers should make efforts to keep track of participant whereabouts to facilitate long-term follow-up.
- If new, significant findings are generated, investigators should:
  - Report significant findings to past, current, and future participants
  - Re-contact current participants and remind them that they can withdraw at any time
  - Modify the consent form for potential participants

NIH GUIDELINES: "To permit evaluation of long-term safety and efficacy of gene transfer, the prospective participants should be asked to agree to long-term follow-up that extends beyond the active phase of the study. The informed consent document should include a list of persons who can be contacted in the event that questions arise during the follow-up period. The investigator should request that subjects continue to provide a current address and telephone number.

The subjects should be informed that any significant findings resulting from the study will be made known in a timely manner to them and/or their parent or guardian including new information about the experimental procedure, the harms and benefits experienced by other individuals involved in the study, and any long-term effects that have been observed."

DISCUSSION

Long-term Follow-up: Because gene transfer is innovative and its long-term risks are not well understood, it is important to try to obtain long-term toxicity data on participants and to provide to participants any new significant clinical information that might affect their future care.

Investigators need to inform prospective participants that they will be expected to participate in long-term follow-up that extends beyond the active phase of the study. Investigators should explain the rationale for long-term follow-up and describe the specific follow-up activities planned, including

the desire to collect information about new cancers, blood disorders, autoimmune diseases, and neurologic disorders. Long-term follow-up may be viewed by participants as a benefit, a burden, or both. Potential participants need to understand what long-term follow-up activities will occur, how long follow-up will continue, and what, if any, procedures they will be asked to undergo.

Both the design and extent of long-term follow-up and its discussion in the consent form and process should always be tailored to the specific study design and vector used.

Although participants have the right to withdraw from research, they should be encouraged (but not required) to provide follow-up information even if they do not complete the gene transfer administration. Additional discussion about participants who withdraw from the study can be found in the Voluntariness section.

Facilitating Long-term Contact: To make long-term follow-up possible, participants should be asked to provide a current address and telephone number to the research staff, as well as the names and addresses of their current primary care provider and someone whom the research staff can contact to locate them. They should also be encouraged to contact the research staff when their contact information changes. Investigators may want to consider other ways to maintain current contact information, such as holiday cards or a newsletter, and inform participants of such efforts to maintain contact at the time of consent. The need to retain contact information for long-term follow-up raises privacy and confidentiality concerns, which are addressed in the Privacy section of this guidance.

Government Requirements: Gene transfer studies are subject to oversight by other Federal agencies, such as the Food and Drug Administration, which may have specific requirements for the duration of long-term follow-up. Investigators should know the current FDA policy regarding long-term follow-up, and the impact of these requirements on the participant should be discussed.

Significant Findings: If significant information is generated during or after the study that may be pertinent to a potential participant's decision to enroll or a current participant's continued involvement in a study, the investigator should consult the Institutional Review Board to determine whether the new findings are significant enough to:

- Revise the consent form;
- Inform already enrolled participants about the new information; and
- Initiate a re-consent process in which current participants are informed that they can refuse further gene transfer interventions in the study because of the new findings.

SAMPLE LANGUAGE

Sample 1 - Long-term Follow-up

Long-term follow-up in gene transfer research allows for the collection of important information on the long-term safety and effects of the gene transfer intervention used in this study. The long-term follow-up planned for this study will occur [frequency] for [length of time]. It includes [study-specific information, as available; e.g., drawing a small amount of blood once a year; completing a health history questionnaire every year; having a biopsy of the injection site every five years; etc.]. The investigators will try to make it easier for you to participate in long-term follow-up by [study-specific information as available, e.g., using mail and telephone to collect some information; arranging with your local doctor to collect blood or biopsy specimens and send them to investigators; etc.].

Sample 2 - Long-term Follow-up

At the end of the experimental phase of the study you will be asked to participate in the long-term follow-up phase for the rest of your life. Once a year you will be asked to have your blood drawn (~[amount]) and answer questions about your general health and medical condition. The investigators may ask you to report any recent hospitalizations, new medications, or the development of conditions or illness that were not present when you enrolled in the study and may request that physical exams and/or laboratory tests be performed if necessary. We will also ask you to participate in the long-term follow-up phase if you leave the study early.

Sample 3 - Significant Findings

We will give you any new information we learn during this study that might affect your willingness to stay in the study. This includes new information about the procedures used, the [gene transfer intervention], or side effects other participants in the study may have had.

Appendix M-III-B-2-c

Request for Autopsy

NIH GUIDELINES: "To obtain vital information about the safety and efficacy of gene transfer, subjects should be informed that at the time of death, no matter what the cause, permission for an autopsy will be requested of their families. Subjects should be asked to advise their families of the request and of its scientific and medical importance."

DISCUSSION

The autopsy request is one aspect of long-term follow up that is unique to gene transfer. Autopsies can yield important information that may enable a better understanding about the long-term effects of gene transfer intervention at the time of death.

Potential participants should be informed that at the time of their death, regardless of cause, an autopsy will be requested. The investigator should explain that they are not being asked at this time to consent to autopsy nor is it required for study participation. However, participants should be encouraged to express their wishes about an autopsy to their families so that families are prepared to take those wishes into account at the time of the participant's death.

SAMPLE LANGUAGE

- Sample 1
- Sample 2
- Sample 3

MAIN POINTS

- **Participants should be informed that an autopsy will be requested upon their death.**
- **Investigators should explain that a participant's expression of autopsy wishes is:**
  - **Not a consent to autopsy**
  - **Not required for study participation**
- **Participants should express their wishes about an autopsy to their families and encourage the families to take their wishes into account.**

When possible and appropriate, investigators may wish to further specify the nature and extent of postmortem testing that is likely to be of greatest interest for a particular study or whether a "partial autopsy" would be of value. If such a limited postmortem examination would be of scientific value, granting permission for specific testing only may be a desirable option for some participants and, at the time of the participant's death, for their families.

SAMPLE LANGUAGE

Sample 1

When you die, no matter what the cause, investigators will ask your family if they can do an autopsy. An autopsy will help the investigators learn more about the safety and efficacy of gene transfer. Please advise your family about your wishes regarding autopsy.

Sample 2

Because you are a study participant, investigators will ask your family for permission to do an autopsy when you die, even though this may be years after the study. This may help investigators learn about the effects of gene transfer. By signing this consent form, you are not forcing your family to agree to this. You should talk about this request with your family and advise them of your wishes.

Sample 3

Your investigator will ask your family for permission to perform an autopsy when you die, no matter what the cause. The evaluation of your organs after your death is a very valuable method to learn more about the good and bad effects of gene transfer. A "partial autopsy," in which needles are used to take samples of specific organs, may also be helpful. This type of autopsy does not require surgical incisions. You should talk about the possibility of autopsy with your family and health provider, and advise them of your wishes. The investigator may be able to tell you or your family what kind of autopsy information will be most helpful for this study. The study sponsor will pay all costs of the autopsy.

Appendix M-III-B-2-d

Interest of the Media and Others

NIH GUIDELINES: "To alert subjects that others may have an interest in the innovative character of the protocol and in the status of the treated subjects, the subjects should be informed of the following:

- **That the institution and investigators will make efforts to provide protection from the media in an effort to protect the participants' privacy, and**
- **That representatives of applicable Federal agencies (e.g., the National Institutes of Health and the Food and Drug Administration), representatives of collaborating institutions, vector suppliers, etc., will have access to the subjects' medical records."**

SAMPLE LANGUAGE

- Sample 1
- Sample 2
- Sample 3

TOOLS & BACKGROUND MATERIALS

- Health Insurance Portability and Accountability Act (HIPAA)
- Privacy Rule
- National Standards to Protect the Privacy of Personal Health Information in Research

MAIN POINTS

- Every effort should be made to protect participants' privacy and maintain confidentiality.
- Potential participants should be told:
  - Who will have access their personal information and research results
  - That, in spite of efforts to protect participants' identity, potentially identifiable data may become publicly known.

Appendix M-IV

Privacy and Confidentiality

NIH GUIDELINES: "Indicate what measures will be taken to protect the privacy of subjects and their families as well as maintain the confidentiality of research data. These measures should help protect the confidentiality of information that could directly or indirectly identify study participants.

Appendix M-IV-A. What provisions will be made to honor the wishes of individual human subjects (and the parents or guardians of pediatric or mentally handicapped subjects) as to whether, when, or how the identity of a subject is publicly disclosed.

Appendix M-IV-B. What provisions will be made to maintain the confidentiality of research data, at least in cases where data could be linked to individual subjects?"

DISCUSSION

Privacy and Confidentiality: Protection of participants' privacy and the confidentiality of research data are issues that investigators and institutional review boards (IRBs) and institutional biosafety committees (IBCs) routinely consider. Gene transfer research presents special challenges to privacy and confidentiality protections. These issues should be handled according to basic ethical principles as well as extant law (e.g., Health Insurance Portability and Affordability Act of 1996). Many IRBs and IBCs provide guidance about confidentiality protections that may be adapted to address the implications of participation in gene transfer research.

In particular, investigators should address potential participants' concerns about protection of their identities against undesired intrusions by the media and others (privacy) and about limiting access to study information that might identify them (confidentiality).

Maintaining Contact Information: Long-term follow-up of gene transfer research participants and the desire for autopsy information may require keeping basic contact information for participants as well as preserving links between names, contact information, and study results for many years. The consent form should alert potential participants that long-term follow-up will require the investigator to keep contact information, sometimes for long periods.

Stored Data and Specimens: Sometimes data or specimens collected as part of the gene transfer study may be stored for use in other research. In such cases, the investigator should:

- Explain how participant information and specimens will be secured in order to protect against inadvertent or unauthorized disclosure.
- Employ a separate consent form and procedure for research with stored specimens.

IRBs and IBCs can provide guidance for investigators about the uses of stored specimens, including model consent language.

Reporting Requirements: While every effort should be made to keep confidential any information that identifies the participant, certain groups or individuals may inspect and/or copy participant research records for quality assurance and data analysis. The potential participant should be informed that information obtained in connection with the study may be disclosed to:

- Local hospitals or treatment centers
- Staff or agents of the study sponsor
- U.S. Food and Drug Administration
- National Institutes of Health (NIH)
- Governmental agencies in other countries where the study drug may be considered for approval
- IRB and IBC

Public Discussion: An additional concern arises in gene transfer studies with regard to the privacy of participants after an adverse event. Gene transfer safety information must be reported to the NIH Office of Biotechnology Activities. These reporting requirements have been developed to keep gene transfer research as safe as possible for all research participants. Potential participants should be told before they enter a gene transfer study that adverse events and other safety information derived from their research experience could be discussed at a public session of the NIH Recombinant DNA Advisory Committee. Although individually identifiable information is not released or discussed at these meetings, they often draw public and media attention.

Media Interest: Because of the high degree of public interest in gene transfer research, the local or national media may seek information on or interviews with study participants. Investigators must be sensitive to the needs and interests of participants, both when public interest arises from positive information and when it arises from adverse events. Potential participants should be informed that every effort will be made to keep personal information confidential, but it is unwise to imply that the media will never discover or report the identity of individuals. Moreover, sometimes research participants may choose to permit disclosure of their identities, and even to participate in media coverage. Therefore, investigators should discuss the circumstances in which information would be provided to the media. The investigator should also acknowledge that sometimes disclosure of only a small amount of information might lead to the identification of the participant.

Publication of Research Data: Research results are often published in medical literature or used for teaching purposes. Potential participants should be informed that a publication will not individually identify them and that any potentially identifying information, including family pedigrees, photographs, and audiotapes or videotapes, will be used only with their explicit permission.

SAMPLE LANGUAGE

Sample 1

We will try to keep your identity and other information collected in this study confidential. There may be some exceptions when the law requires disclosure. Representatives of [study site], and/or the Food and Drug Administration, and/or the National Institutes of Health, or other regulatory agencies outside [study site] may ask to review the data collected from this study. These groups can have access to your name and medical records.

It is possible that the media may want to find out about you because you took part in this study. We will take every precaution to protect your privacy and that of your family. We will also maintain the confidentiality of the research data. To lower the chance that your identity will be made public, all requests for information will be directed to the [study site] Public Relations Office. Despite these efforts, reporters may try to find out who you are without the approval of the [study site]. If the media succeed, they might ask to interview you and your privacy may be invaded. Every effort will be made to protect your privacy but it may not be possible to do so.

Sample 2

If you become part of this study, investigators and their assistants can look at your medical records as necessary for the purposes of this study. The U.S. Department of Health and Human Services, employees of the study sponsor, the sponsor's monitor, contractors, and auditors, may do so as well.

The media may be interested in this study. You can talk to reporters about being in the study if you want to. The investigators will not talk about the results of the study until study information has been published in a scientific journal. Investigators will not give away your identity to news reporters at any time.

Sample 3

Because this study involves gene transfer, safety information must be reported to the Recombinant DNA Advisory Committee of the National Institutes of Health. This information is available to the public. However, no information by which participants can be identified will be reported with the safety information.

The media (TV, newspapers, radio, Internet, etc.) may also want to know about this study. We will try our best to protect your privacy. However, because we have to share safety information, it is always possible that the media could find out who has been in the study.

Additional Resources

MAIN POINTS

- Articles
- Bibliographies
- Books
- Brochures
- Glossaries
- Government Guidelines and Regulations

In addition to the resources within this guidance, the following resource materials may be valuable. Some of these materials are specific to human gene transfer research. Others deal with informed consent and other research ethics issues that are particularly salient in these trials (e.g., therapeutic misconception).

These materials were selected because they provide additional information on the topics discussed in the guidance that may assist investigators, institutional review boards, and institutional biosafety committees in developing consent forms or aiding the consent process for gene transfer. Materials that report the results of empirical research without providing such assistance have not been included. This list is not exhaustive and will be periodically updated.

Articles

Annas G. Reforming informed consent to genetic research. JAMA 2001. 286:2326-28.

The author asserts that current human subjects research protections are in need of reform. Changes should focus on using informed consent as an educational process. Issues are raised that relate specifically to educating potential study participants about genetic research.

Appelbaum PS, et al. False hopes and best data: consent to research and the therapeutic misconception. Hastings Center Report 1987. 17(2): 20-24.

This publication offers ethical commentary regarding the authors' research on therapeutic misconception. The authors suggest ways to improve the informed consent process, including the use of a trained, neutral educator to guide the consent process. This third party would focus discussion on information regarding the subject's personal care, dispel the therapeutic misconception, and better explain the purposes of the study, randomization, and use of placebos.

Beecher HK. Ethics and clinical research. The New England Journal of Medicine 1966. 274(24): 1354-1360.

The author discusses the ethics of experiments that do not confer direct benefit on participants themselves. Several case studies are analyzed with respect to shared difficulties with informed consent. Suggestions are made which may help researchers provide a more thorough and effective consent process.

Bosk CL. Obtaining voluntary consent for research in desperately ill patients. Medical Care 2002. 40(9): V-64-V-68.

The author considers informed consent for study participants who are desperately ill and for whom a clinical trial may falsely offer a "last hope." To protect this vulnerable population from coercion, a decision to participate in a clinical trial must be based on a careful weighing of risks and benefits.

Brody BA. Making informed consent meaningful. IRB: A Review of Human Subjects Research 2001. 23(5): 1-5.

The author asserts that informed consent must strike a compromise between promoting moral values and ensuring risk management. This can be accomplished by using the informed consent process to encourage autonomous decision-making. A study participant's intentionality, voluntariness, and understanding are essential to this approach.

Burger IM and Wilfond BS. Limitations of informed consent for in utero gene transfer research: implications for investigators and institutional review boards. Human Gene Therapy 2000. 11(7): 1057-63.

The authors suggest that, given the rapid pace of research in this area, human protocols for in utero gene transfer research may be seriously considered in the foreseeable future. Federal guidelines for fetal research rely on minimizing risk and informed consent to protect the "rights and welfare" of both the fetus and pregnant woman. However, in utero gene transfer research poses special challenges to informed consent. An expectant parents' comprehension of, and voluntariness for participation in, research may be easily undermined, leaving the fetus unprotected from undue research risks. To compensate for this limitation, a greater emphasis should be placed on the benefit/harm assessment.

Churchill, LR, et al. Assessing benefits in clinical research: why diversity in benefit assessment can be risky. IRB: Ethics and Human Research 2003. 25(3): 1-8.

An empirical study that explores the kinds of potential benefits IRBs look for when reviewing a study and how they prioritize particular benefits. The authors conclude that there is a great deal of heterogeneity in how IRBs consider benefits in research and that standards and common tools for assessment would be helpful in defining and clarifying the critical assessment elements.

Churchill, LR, et al. Genetic research as therapy: Implications of 'gene therapy' for informed consent. Journal of Law, Medicine and Ethics 1998. 26(1): 38-47.

After the release of the Belmont Report, the volume of information disclosed to potential study participants increased substantially. To make sure this information is conveyed thoroughly, researchers should approach this task with a commitment to open communication and collaborative decision-making.

Daugherty C, et al. A feasibility study of informed consent and medical decision-making: Employing an interactive patient choice design in phase I trials. Presented at the 1996 Annual Meeting of the American Society of Clinical Oncology 1996.

A report on a study in which participants chose from a range of predetermined dose levels after extensive information regarding risks and potential toxicities of drugs was provided. Participants were then surveyed after giving consent. Results show that allowing participants to choose their dosage level is feasible and does not interfere with the overall informed consent process. Authors assert it may even provide participants with an additional sense of control, empowerment or self-worth, and could facilitate rapid dose escalation n some Phase I studies.

Daugherty C, et al. Perceptions of cancer patients and their physicians involved in phase I trials. Journal of Clinical Oncology 1995. 13(5): 1062-1072.

A study revealed that most patients who participate in Phase I trials are strongly motivated by the hope of therapeutic benefit. Accordingly, only a minority of participants appears to have an adequate understanding of the purpose of Phase I trials as dose-escalation/dose-determination studies. The implications of these results are

discussed.

Daugherty CK. Informed consent, the cancer patient, and phase I clinical trials. In: Angelos P, Ed. Ethical Issues in Cancer Patient Care. Norwell, MA: Kluwer Academic, 1999, pp. 77-89.

The meaning and historical development of informed consent are analyzed from the standpoint of Phase I clinical trials for cancer. The author reviews empirical studies of informed consent in these Phase I trials, and calls for further research on the intricacies of communication between investigators and research participants.

Daugherty CK. Impact of therapeutic research on informed consent and the ethics of clinical trials: a medical oncology perspective. Journal of Clinical Oncology 1999. 17(5): 1601-17.

Ethical issues associated with informed consent are reviewed on the basis of personal experience and reviews of current research. The ethical underpinnings of informed consent are discussed and the inadequacies of some informed consent documents are highlighted. Suggestions for future research are made which may help investigators and study participants maximize the educational value of informed consent.

Dettweiler U and Simon P. Points to consider for ethics committees in human gene therapy trials. Bioethics 2001. 15(5-6): 491-50.

The authors discuss the possibility that the current system for informed consent places a researcher's need for impartiality in direct conflict with his or her fiduciary obligation to a sick patient. The roles of the FDA and the NIH in resolving these conflicts are discussed, as is the importance of adverse event reporting.

Glass KC, et al. Structuring the review of human genetics protocols, part III: gene therapy studies. IRB 1999. 21(2): 1-9.

This article proposes a framework for reviewing human gene therapy protocols for clinical trials. The author provides a description of gene transfer techniques along with a checklist of issues commonly faced by IRBs. Major points of controversy regarding gene therapy are discussed as well, including national and local review, risks to society and individuals, and the ethical quandaries raised by the prospect of germ line intervention.

King NM. Defining and describing benefit approximately in clinical trials. Journal of Law, Medicine and Ethics 2000. 28(4): 332-343.

To avoid the therapeutic misconception, researchers and IRBs should make sure that study participants who enroll based on potential benefits stand a reasonable chance of obtaining them. Throughout this process, researchers and IRBs must carefully distinguish between the different types of benefit and, in doing so, must discuss the nature of the potential benefit, its potential magnitude and the likelihood that it will occur, while acknowledging any uncertainty.

King NM. Rewriting the "points to consider": The ethical impact of guidance document language. Human Gene Therapy 1999. 10(1): 133-9.

Investigators preparing to engage in human gene transfer research must use the NIH guidance document, "The Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into the Genome of One or More Human Subjects," written by the Recombinant DNA Advisory Committee, to prepare for the submission of a research protocol. Several corrections in the terminology (like using "gene transfer" instead of "gene therapy" and "subject" instead of "patient") employed by this guidance document could help to avoid misconceptions about gene transfer research and clarify both the promise and the limits of the research enterprise for investigators and subjects.

Ledley FD, et al. The challenge of follow-up for clinical trials of somatic gene therapy. Human Gene Therapy 1999. 3(6): 657-63.

This article emphasizes the importance of follow up for participants in gene transfer trials. Each investigator is responsible for ensuring that participants receive proper long-term follow-up. This is especially important for gene transfer, a cutting edge technology for which public support is often tenuous. Also, the merits of a system for participant tracking are evaluated.

Levine RJ. Clinical trials and physicians as double agents. Yale Journal of Biology and Medicine 1992. 65: 65-74.

This article explores what happens when a physician assumes the role of researcher. In these cases, a physician's fiduciary duty to individual patients competes with a new obligation to contribute to generalizable knowledge. When conflict arises, individual IRBs can choose to introduce a third party to educate the potential study participant regarding possible risks and the expectation of benefit.

Levinsky NG. Nonfinancial conflicts of interest in research. New England Journal of Medicine 2002. 347: 759-61.

The author suggests that nonfinancial conflicts of interest are intrinsic to human subjects research. Institutions must emphasize proper behavior. IRBs should conduct widespread audits of ongoing research so that conflicts are exposed before they become problematic.

Lind SE. Innovative medical therapies: Between practice and research. Clinical Research 1988. 36: 546-551.

A look at some of the questions raised by minor modifications in medical practice. Focusing on the example of a change in the administration of chemotherapy for ovarian cancer, the author considers whether such innovations should be considered research and whether they should undergo review by an IRB.

Morin K, et al. Managing conflicts of interest in the conduct of clinical trials. JAMA 2002. 287: 78-84.

This source suggests that physicians receive training in both research techniques and ethics in before they assume the role of investigator. Furthermore, when a potential participant is also the physician's patient, the physician should enlist a third party to assist in the informed consent process. Also, any financial compensation must be commensurate with the tasks performed by the physician-investigator and disclosed to the public.

NIH Recombinant DNA Advisory Committee. Assessment of adenoviral vector safety and toxicity: report of the National Institute of Health Recombinant DNA Advisory Committee. Human Gene Therapy 2002. 13(1): 3-13.

This source focuses on the gene transfer community's response to the death of Jesse Gelsinger. Particular areas of focus include adverse event reporting and information sharing as means of increasing the safety of vector use.

Sorscher EJ, et al. Informed consent to participate in a research study - gene therapy for cystic fibrosis using cationic liposome mediated gene transfer: a phase I trial of safety and efficacy in the nasal airway. Human Gene Therapy 1994. 5(10): 1271-7.

The authors provide an example of an informed consent document used in a gene transfer trial for cystic fibrosis. It may be of more general interest as a model, since the document covers the major topics raised by Appendix M for all gene transfer studies, such as the purpose of the study, procedures, follow-up, risks and discomforts, benefits, confidentiality, alternatives, and the right to withdraw from the study.

Bibliographies

Human Gene Therapy, Scope Note 24. National Reference Center for Bioethics Literature, The Joseph and Rose Kennedy Institute of Ethics, Georgetown University, Washington, DC.

Issued by the Kennedy Institute of Ethics, this web site compiles gene transfer bibliographies on topics ranging from general information to philosophical and religious perspectives. "Quick Bib" search engine provides the most recent literature on this topic.

Sugarman J, et al. Empirical research on informed consent: An annotated bibliography. Hastings Center Report 1999. 29(1):S1-42.

Some of the most recent articles about informed consent in clinical studies are referenced.

Books

Berg JW, et al. Informed Consent: Legal Theory and Clinical Practice. Oxford University Press, 2001.

An overview of informed consent, emphasizing the practical issues facing both physicians and investigators. The historical and ethical underpinnings of informed consent are discussed, along with the challenges faced when applying current legal theory in the clinical setting.

Brody BA. The Ethics of Biomedical Research: An International Perspective. Oxford University Press, 1998.

This book analyzes the major issues of research ethics, including human subjects research protections, via a review of official policies from throughout the world.

Faden RR and Beauchamp TL with King NMP. History and Theory of Informed Consent. Oxford University Press, 1990.

Current ways of thinking about informed consent are explained from a historical perspective. Philosophical and legal frameworks are used to explore informed consent as it pertains to clinical medicine, federal policy and research involving human subjects. Autonomy is considered the foundation of current informed consent theory.

Fletcher JC. The Evolution of the Ethics of Informed Consent. In: Research Ethics. New York: Alan R. Liss, Inc., 1983, pp. 187-228.

This book addresses the philosophical, historical, and societal touchstones of informed consent. It begins with the biological and social basis for altruism (which is at the core of human concern for ethics and others), applies those concepts to the notion of consent in the practice of medicine, reviews the abominable practices of Nazi physicians at Nuremberg and the outcome of the Nuremberg trials, and closes with the more recent development of Public Health Service policy.

Getz K and Borfitz D. Informed Consent: The Consumer's Guide to the Risks and Benefits of Volunteering for Clinical Trials.

This guidebook provides the information that may help potential participants and their advocates make well-informed decisions about participating in clinical trials. Participants' rights and reasonable expectations are illustrated. Special focus is attributed to various ways participants can seek recourse if an adverse event occurs.

Katz J. Experimentation with Human Beings: The Authority of the Investigator, Subject, Professions and the State in the Human Experimentation Process. New York: Russell Sage Foundation, 1972.

This publication explores the rights and responsibilities of the various participants in clinical research. The roles of investigators, subjects, medical professionals and the state are portrayed through a case-based analysis of legal precedent.

Levine, RJ. Ethics and Regulation of Clinical Research. 2nd ed. Baltimore: Urban and Schwarzenberg, 1988.

This resource presents an overview of the medical, ethical and regulatory underpinnings of clinical research. Fundamental concepts like balancing harms and benefits are discussed, along with proper methods for selecting participants and protecting their privacy. The responsibilities of IRBs are illuminated through a case study based on Yale-New Haven Medical Center.

Veatch RM. The Patient as Partner: A Theory of Human Experimentation Ethics. Bloomington: Indiana University Press, 1987.

A review of the general ethics of experimentation and the federal regulations governing research with human subjects. Ethical dilemmas in research design and recruitment are examined, along with potential ethical problems inherent in investigations involving particular risks or patient populations. The author calls for participants to be regarded as partners in research who are well informed regarding purposes, methods, and alternatives.

Brochures

Office of Biotechnology Activities, Deciding Whether to Participate in Gene Transfer Research.

The National Institute of Health Office of Biotechnology Activities compiled this brochure as a way to educate potential study participants' about what gene transfer is and how it is performed. It also includes a list of questions potential participants may want to ask when deciding whether or not to enroll in a gene transfer clinical trial.

Chew AJ and Butler R. What You Should Know About Enrolling in a Gene Therapy Trial. National Hemophilia Foundation.

Assembled by the National Hemophilia Foundation, this brochure discusses both positive and negative aspects of enrolling in gene transfer trials. The need for potential study participants to gather a significant amount of information prior to making their decisions is stressed.

National Cancer Institute, A Guide to Understanding Informed Consent.

A guide to understanding the process of informed consent through which potential study participants can learn about possible risks and benefits as well as their rights and responsibilities. Contains some sample forms and templates.

ECRI, Should I Enter a Clinical Trial? A Patient Reference Guide for Adults with Serious or Life-Threatening Illness.

This patient reference guide, published by the American Association of Health Plans, highlights key issues for adult patients who are thinking about enrolling in a clinical trial.

Centers for Disease Control and Prevention, Taking Part in Research Studies: What Questions Should I Ask?

This pamphlet provides important questions that potential study participants should ask before participating in a clinical trial.

Glossaries

Glossary and Acronyms. NIH Office of Rare Diseases.

This site provides a glossary pertinent to rare diseases and conditions that was compiled by the NIH Office of Rare Diseases. It also provides links to other sources of information about clinical trials more generally.

Simplification Guide to Medical Terms. University of Michigan Medical School Institutional Review Board.

The University of Michigan IRB compiled definitions of scientific terms that frequently appear in informed consent documents but may be unfamiliar to potential study participants. In addition to helping potential study participants, this is a useful tool for researchers and IRB members as they write and evaluate informed consent documents.

Talking Glossary of Genetic Terms. National Human Genome Research Institute.

The National Human Genome Research Institute (NHGRI) created this database to help potential study participants better understand the terms and concepts used in genetic research. One click on the term of interest reveals information ranging from term's pronunciation, audio information, images and additional links to related terms.

Government Guidelines and Regulations

Department of Health and Human Services: Protection of Human Subjects. Code of Federal Regulations, 45 CFR 46.

Subpart A provides the basic federal policy for the protection of human subjects. Subparts B, C, and D, respectively, set forth additional protection for research, development and related activities involving fetuses, pregnant women,

and in vitro fertilization; research involving prisoners; and research involving children.

Food and Drug Administration: Protection of Human Subjects. Code of Federal Regulations, 21 CFR Parts 50 and 56.

Part 50 sets forth the Food and Drug Administration's requirements for informed consent, while Part 56 outlines the agency's provisions for IRBs. Though largely similar, the FDA regulations differ in several key respects from the "Common Rule" (45 CFR Part 46) adopted by other agencies and administered by the Department of Health and Human Services. For research falling under the purview of both HHS and FDA, the requirements of both sets of regulations must be met.

Food and Drug Administration: Information Sheets on Guidance for Institutional Review Boards and Clinical Investigators.

This document represents the FDA's current guidance on protection of human subjects involved in clinical research. While this document is not intended create or confer any rights and does not operate to bind the FDA or the public, it is meant to serve as an aid to IRBs as in effectively protecting human research subjects.

International Conference on Harmonisation, Harmonised Tripartite Guideline

- **General Considerations for Clinical Trials**
- **Guideline for Good Clinical Practice**

This document recommends ways to attain higher levels of harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonization is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.

Office of Human Research Protections: 1993 IRB Guidebook.

IRBs confront many complex issues. Familiarizing oneself with the pertinent regulations is a challenge, and understanding the concepts involved, how they relate to human subject research, and how they should be applied can be equally difficult. This document offers an explanation of the legal and ethical constructs that form the basis for human subjects research regulations which researchers and IRB members may find helpful.