

Guidance: Regulatory Requirements Human Gene Transfer Research

Human gene transfer is an experimental procedure of recombinant DNA technology. Clinical research with genetic material poses many safety and methodologic challenges not shared by other forms of human investigation. As a result, there are a number of regulatory requirements that must be satisfied before any human studies involving gene transfer can be initiated. To ensure management and minimization of significant risks, IRBs, Institutional Biosafety Committees (IBC) and federal agencies are responsible for overseeing such trials. Presented below are guidelines to assist the clinical investigator in initiating a gene therapy study. The Office of Research Compliance and Assurance will confirm that a protocol is approved by all of the necessary review committees before the first patient is enrolled.

REGULATORY REQUIREMENTS

Clinical protocols that involve the administration of recombinant DNA products into human subjects must be approved by the following reviewing bodies:

FEDERAL REQUIREMENTS:

- 1) Food and Drug Administration (FDA) <http://www.fda.gov/cber/>

The pharmaceutical sponsor or the principal investigator must file an Investigational New Drug (IND) application with the Center for Biologics Evaluation and Research (CBER) for each new investigational agent intended for human study. The format and requirements of the IND are provided in Title 21 of the Code of Federal Regulations. The IND must include extensive documentation regarding methods of production and preclinical testing.

The FDA has published a document entitled “Guidance for Human Somatic Cell Therapy and Gene Therapy” <http://www.fda.gov/cber/gdlns/somgene.txt>, which provides guidelines and recommendations relating to the clinical use of gene products.

- 2) NIH-Office of Biotechnology Activities (OBA) /Recombinant DNA Advisory Committee (RAC) <http://www.nih.gov/od/orda/toc.htm>

Applications must be in accordance with the “Guidelines for Research Involving Recombinant DNA Molecules”, Appendix M <http://www.nih.gov/od/orda/apndxm.htm>. This application requires information about the disease under study, vector being used, nature of the proposal in addition to other items. Appendix M is titled, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Research Participants*, and is outlined that must be completed prior to review by the NIH RAC. The NIH review process is open to the public so proprietary information should be withheld. Gene transfer trials that are funded by NIH or that take place at an institution receiving NIH funds must adhere to the

guidelines issued by OBA. Submission of human gene transfer protocols to NIH must be in the format outlined in Appendix L-1-A of the NIH rDNA guidelines. This allows each submission to be registered with the NIH and provides the public with a current list of ongoing trials that involve gene transfer. After receiving the proposed research, the NIH/OBA will determine whether the trial warrants full review by the RAC. The initial RAC review takes place within 15 days of receipt with the following outcomes:

- experiment does not present characteristics that warrant further review/discussion and is therefore exempt from public RAC review
- the experiment presents characteristics that warrant public RAC review and discussion

The investigator will receive a letter from the NIH/OBA indicating the outcome of the review. As stated in Appendix L-1-B-1, research subjects may not be enrolled until all of the following requirements are met:

1. RAC review process is completed
2. IBC approval obtained
3. IRB approval obtained
4. All applicable regulatory authorizations have been obtained (i.e., IND application filed with the FDA)

Other reporting requirements:

Serious and unexpected adverse events experienced by subjects enrolled in gene therapy trials must be reported to the IRB, IBC, OBA and other federal agencies, if applicable.

Approval must be obtained from the IRB and IBC before submission to the NIH, Office of Biotechnology Activities.

LOCAL REQUIREMENTS:

- 1) Institutional Biosafety Committee (IBC)

<http://www.southalabama.edu/com/research/biosafety/index.shtml>

The mission of the IBC is to ensure that biologic agents, including genetic material, are being handled using appropriate safe techniques and that risk of transmission to others is minimal. Section III-C of the NIH requires both IRB and IBC approval and RAC review before research participation.

Safety Concerns

The following questions should adequately be addressed:

Vector information:

- 1) Is a vector being used?
- 2) Source of the vector?
- 3) What type of vector?
- 4) Biosafety level/containment?
- 5) Replication competent?
- 6) Risk of viral shedding? Where (what body fluid) is virus shed?

DNA product administration:

- 1) Where will the DNA product be stored?
- 2) Where will the DNA product be prepared?
- 3) How will the DNA product be transported from the place of storage?
- 3) Where will the DNA product be administered?

Patient factors:

- 1) Where will the patient be treated?
- 2) Will patients be isolated, what type of isolation, for what duration?
- 3) How and where will patient specimens be obtained, transported, stored?

2) Institutional Review Committee (IRB)

<http://www.southalabama.edu/com/research/humansubjects/index.shtml>

Gene transfer research concepts are often difficult for potential participants to understand. Thus, the Office of Biotechnology Activities (OBA) has developed guidance on the issue of informed consent in gene transfer studies

(http://www4.od.nih.gov/oba/rac/ic/pdfs/temp_pdf.pdf). The guidance focuses on the issues of conflict of interest, comprehension, time of consent, and assent. The guidance can be used as a resource for Investigators in developing an informed consent document for a gene transfer protocol by discussing each topic that should be covered. For more information on this topic, Investigators should visit: <http://www4.od.nih.gov/oba/RDNA.htm>.

Consent Form Requirements

Due to the novelty of the procedures that are used in gene transfer protocols, the potentially irreversible consequences of the procedures performed, and the fact that many of the potential risks remain undefined, the consent form for gene transfer protocols must include the following information in addition to the requirements prescribed in 45 CFR 46.116 and 21 CFR 50.25.

Please note that a separate consent form should be used if the 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).

Purpose: The purpose and procedures associated with the gene transfer component of the research should be explained to study participants in 6th to 8th grade language.

Risks: The types, relative severity, and expected frequencies of potential adverse events should be stated in the consent form.

The consent form should state the approximate number of people who have previously received the genetic material under study. The consent form should warn potential participants that unforeseen and severe risks are possible for research involving genetic materials previously used in relatively few or no humans. The consent form should also state any potential adverse medical consequences that may occur if the participant withdraws from the study.

Reproductive Considerations: To avoid the possibility that any of the reagents employed in the gene transfer research could cause harm to a fetus/child, the consent form should include 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 and the inclusion of pregnant or lactating women should be addressed.

Benefits: For studies that are not reasonably expected to provide a therapeutic benefit to participants, the consent form should clearly state that no direct clinical benefit to participants is expected . . . although knowledge may be gained that may benefit others.

Alternatives: The consent form should indicate the availability of therapies and the possibility of other investigational interventions and approaches.

Long Term Follow-Up: To permit evaluation of long-term safety and efficacy of gene transfer, the prospective participants should be informed that they are expected to participate in long-term follow-up that extends beyond the active phase of the study. The consent form should include a list of persons who can be contacted in the event that questions arise during the follow-up period. The PI should require that participants continue to provide a current address and telephone number.

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

AFTER INSTITUTIONAL IRB AND IBC APPROVAL:

- 1) Obtain committee approval letters
- 2) Verification of local oversight and approval must be submitted to the NIH, Office of Biotechnology Activities
- 3) OBA registers all human gene therapy experiments and maintains a database of registered/approved experiments
- 4) Within 20 days from enrolling the first participant, investigator/sponsor must submit to NIH/OBA: a) copy of informed consent; b) copy of protocol; c) copy of IRB and IBC approval letters; d) FDA IND number; e) date of trial initiation;