Appendix F  Human Gene Transfer Clinical Trials

Proposed clinical trials involving human gene transfer require registration and approval from both campus and federal agencies before initiation. NIH defines human gene transfer as the “the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human subjects.” The Yale University Institutional Biological Safety Committee requirements for human gene therapy protocols are detailed below. Federal requirements (NIH and FDA) for these experiments are described in significant detail in Appendix M of the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines), March 2013, and in the Code of Federal Regulations, 21 CFR, Part 312 (FDA Points to Consider).

On Campus Registrations and Approvals:

Yale Human Research Protection Program (IRB)  785-4688
hrpp@yale.edu

Yale Biological Safety Committee (IBC)  785-3550 (through Biosafety Representatives)
http://www.yale.edu/ehs/ibc.htm
http://provost.yale.edu/committees

Yale New Haven Hospital    688-4634 (YNHH Hospital Epidemiology)

Federal Registration and Approval:

NIH Office of Biotechnology Activities (301) 496-9838
NIH Guidelines Appendix M (Human Gene Therapy):

FDA Center for Biologics Evaluation and Research:
http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/default.htm

21 CFR Part 312:
http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=528ebe054b8cf1dc958289ee9f6f1f972&rgn=div5&view=text&node=21:5.0.1.1.3&d&idno=21

Note: Approval from the Yale IRB and IBC are required prior to submission to the YNHH Subcommittee on Safe Handling of Gene Transfer Products, or the FDA. In accordance with the update in the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines), Appendix M, Yale University’s IRB and IBC cannot approve a HGT protocol until it has been reviewed by the NIH Recombinant DNA Advisory Committee. Upon notification from the NIH Office of Biotechnology Activities that the RAC has completed its review, the IRB and IBC will be eligible to complete their respective reviews and approve if warranted. The Yale Biological Safety Committee Human Gene Therapy Subcommittee is the primary review arm for the Yale Biological Safety Committee for protocols involving human gene transfer.

Appendix M-I of the NIH Guidelines includes the submission requirements and addresses for both the NIH Office of Biotechnology Activities and FDA Center for Biologics Evaluation and Research. A copy of the 21 CFR, Part 312 detailing the FDA IND Content and Format requirements can be downloaded directly from the FDA web address listed above.

Application for Human Gene Transfer Clinical Trials at Yale

To initiate the review of a proposed human gene transfer clinical trial, please submit a description of your protocol in the format described in Appendix M of the NIH Guidelines for Research Involving...
Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines), March 2013. To obtain a copy of the NIH Guidelines, access the NIH OBA web site or contact the Biosafety Office at 785-3550. Send a copy of your completed Appendix M to:

The Yale Biological Safety Committee  
C/O Biosafety Office  
Yale Office of Environmental Health & Safety  
135 College Street, 1st Floor  
New Haven, CT 06510  
Contact person: Biosafety Officer, 785-3550

Only complete protocols will be sent to Committee members for review. Specifically, we’ll need:

- Scientific abstract
- Non-technical abstract
- Your responses to Appendix M-II through M-V
- Your response to Adverse Event reporting requirements detailed in Appendix M-VII
- A copy of your HIC clinical protocol (your IND Submission)
- A copy of the HIC approved Informed Consent Document
- Curricula vitae (2 pages) for each key professional in biographical sketch format
- The proposed location for vector production and description of the Good Manufacturing or Good Clinical Practices that will be utilized to prepare the vector
- A copy of the Certificate of Analysis (CoA) for sterility for each lot of vector made at Yale or sent to the University for this experiment

Additional responsibilities of the Principal Investigator conducting a rDNA experiment are detailed in Section IV-B-7, Roles and Responsibilities of the NIH Guidelines. The full set of PI responsibilities can be accessed at: http://oba.od.nih.gov/rdna/nih_guidelines_new.htm

Adverse Events

All adverse events must be reported in an annual data summary that is prepared for the Yale HIC, the Yale Biological Safety Committee Human Gene Therapy Subcommittee, the FDA, the NIH Office of Biotechnology Activities, and your sponsor. Any Serious Adverse Events (SAE’s) must be reported by telephone within 24 hours followed by a written report within 10 days. This report must be on file with the Yale HIC, the Human Gene Therapy Subcommittee, the NIH OBA, the FDA, and NIH Office for Protection from Research Risks if applicable within 15 days. Please note that SAE’s must be reported whether related to the protocol or not. SAE’s shall not be designated as confidential, either in whole or in part, and the SAE reports shall be stripped of patient identifiers, such as name, address, contact information, social security numbers, and date of birth. If the SAE occurs after the trial and deemed related to the HGT trial, it must be reported within 15 days of the date of determination.

The NIH OBA reporting form can be downloaded from their website at http://oba.od.nih.gov/oba/rac/Adverse_Event_Template.doc.

Yale University Human Research Protection Program (HRPP)

The Yale HRPP must approve all experiments involving human subjects prior to initiation. Please contact the HRPP at 785-4688 for information on their requirements.

Human Gene Transfer at Yale New Haven Hospital

To determine if your proposed Human Gene Transfer research may require review and clearance from the YNHH Hospital Epidemiologist or Infection Control Department, please contact them at 688-4634. Notifications should be made well in advance of the proposed start date to initiate review of any human gene transfer experiments planned within YNHH.
Please don’t hesitate to contact Biosafety at 785-3550 if you have any questions.

**Information regarding the 2013 Update to the NIH Guidelines (adding Synthetic Nucleic Acid Molecules)**  
(Excerpts from the NIH OBA FAQ on the new Changes to the Guidelines)

**IMPACT on Human Gene Transfer Experiments:**

In March 2013, the NIH Guidelines will have a new title, the “NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. Even with a new title, the document is still referenced as the “NIH Guidelines.” The change was made to keep pace with rapid technological advancements in synthetic biology.

**Specific Changes to the NIH Guidelines**

Expanded to include new language to address nucleic acid molecules created solely by synthetic means, and will include:

- Recombinant nucleic acid molecules;
- Synthetic nucleic acid molecules, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules; and
- Cells, organisms and viruses containing such molecules.

The phrase “recombinant or synthetic nucleic acid molecules” has replaced the term “recombinant DNA molecules” throughout the text of the NIH Guidelines.

**Updated definition for recombinant and synthetic nucleic acid molecules:**

(i) Molecules that a) are constructed by joining nucleic acid molecules and b) can replicate in a living cell (i.e. recombinant nucleic acids);

(ii) Nucleic acid molecules that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules (i.e. synthetic nucleic acids); or

(iii) Molecules that result from the replication of those described in (i) or (ii) above.

**HGT Synthetic Nucleic Acid Experiments that are covered by the Guidelines:**

Human gene transfer experiments with synthetic nucleic acid molecules if any of the following criteria are met: The synthetic nucleic acid molecules:

- Contains more than 100 nucleotides; or
- Possess biological properties that enable integration into the genome (e.g. cis elements involved in integration); or
- Have the potential to replicate in a cell; or
- Can be translated or transcribed.
NIH Guidelines Vaccine Exemption

Frequently Asked Questions About the Vaccine Exemption in the NIH Guidelines for Research Involving Recombinant DNA Molecules

Q. Are there any clinical trials involving the administration of recombinant DNA that are specifically exempted from the RAC review process?

A. Yes. Appendix M-VI-A of the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines) exempts certain types of vaccine trials from the requirements for submission of the protocol to NIH OBA, RAC review, and subsequent reporting (Appendix M-I). Specifically, this exemption applies to clinical studies involving the administration of recombinant DNA in which "induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected." Trials fulfilling all three criteria do not have to be registered with NIH OBA, undergo RAC review, or adhere to clinical trial reporting requirements under Appendix M-I of the NIH Guidelines. These trials can be submitted on a voluntary basis, particularly if the investigator believes that a clinical trial involving the administration of recombinant DNA presents scientific, safety, or ethical issues that would benefit from RAC review and public discussion. Investigators who submit trials voluntarily will be expected to comply with all aspects of the protocol review and reporting requirements. OBA encourages investigators and institutional review bodies to contact us (oba@od.nih.gov) for assistance in determining whether this exemption applies to their specific trial.

Q. Do all clinical studies that involve the generation of an immune response to a microbial immunogen fall under the vaccine exemption?

A. No. This is just one of the three criteria that must be met for a trial to be exempted. The vaccine exemption was intended to streamline the development of new vaccines against infectious diseases. Some studies that involve generating an immune response to a microbial immunogen are targeting viruses that cause cancer. If the principal goal of the study is to treat a precancerous or cancerous lesion, the study does not fall under this section.

In addition, some human studies involve the administration of a microbial immunogen in combination with recombinant DNA that encodes for a cytokine or other immune stimulant, for example recombinant IL2, granulocyte macrophage-colony stimulating factor (GM-CSF), or IL12. Such trials
NIH Review Process for Human Gene Transfer Trials

Frequently Asked Questions (FAQs) about the NIH Review Process for Human Gene Transfer Trials

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1. The NIH and Human Gene Transfer Trials

1.1. What is human gene transfer research?

Human gene transfer is the process of transferring genetic material (DNA or RNA) into a person. At present, human gene transfer is experimental and is being studied to see whether it could treat certain health problems by compensating for defective genes, producing a potentially therapeutic substance, or triggering the immune system to fight disease. Human gene transfer may help improve genetic disorders, particularly those conditions that result from inborn errors in a single gene (for example, sickle cell anemia, hemophilia, and cystic fibrosis). It may also hold promise for diseases with more complex origins, like cancer and heart disease. Gene transfer is also being studied as a possible treatment for certain infectious diseases, such as AIDS. This type of experimentation is sometimes called “gene therapy” research.

1.1. Why are human gene transfer trials reviewed by the NIH?

Human gene transfer research raises scientific, medical, ethical, and social considerations worthy of special attention and public discussion. Some of these issues arise from the fact that the techniques being used are relatively new and their risks and benefits are not well characterized.

The NIH review process allows for an in-depth examination of the issues associated with this technology in a setting where public input and comment is encouraged. This open discussion has two important benefits. First, it disseminates this information to scientists who can then incorporate new scientific findings and ethical considerations into the design of trials they may be conducting or planning. The efficiency of the research system is improved by allowing scientists to build on a common foundation of new knowledge emanating from this ongoing process of analysis and assessment. Second, it creates enhanced public awareness and allows for a public voice in the review of the safety and ethics of gene transfer research. This helps ensure the public that scientists are attending to these important matters and sustains confidence in the enterprise.

Finally, as the major funder of human gene transfer research and the basic science that underpins it, the NIH has an important responsibility for the appropriate stewardship of this area of scientific activity. This stewardship role is both an ethical obligation and a public mandate associated with the tax-derived research funds appropriated to the agency by Congress.

1.2. What characteristics distinguish the NIH review process from others that my protocol may have to undergo?

The NIH review process was established in response to public and scientific concern about the special ethical, scientific, and safety dimensions of gene transfer research. Thus, a salient and unique feature of the NIH review process is public discussion during meetings of the “Recombinant DNA Advisory Committee” or “RAC.” The
RAC is composed of experts with diverse backgrounds, expertise, and points of view. The RAC is thereby constituted to provide full, in-depth review of the many dimensions of human gene transfer research.

Another special characteristic of the NIH process is open access to information. Since materials submitted to the NIH through OBA are generally considered to be in the public domain and are made freely available. Much of this material is accessible electronically from OBA’s Web site. Opinions and public participation contribute toward a better scientific understanding of this field of research and provide the public a voice in deliberations about the various dimensions of gene transfer research.

1.3. What are the "NIH Guidelines" and how do they guide the process of NIH oversight of human gene transfer trials?

The NIH Guidelines set forth the principles for NIH and institutional oversight of recombinant DNA research, including human gene transfer trials. The NIH Guidelines were first published in 1976 as an outcome of a public process by which scientists developed standards to address the risks associated with recombinant DNA research. The NIH Guidelines articulate standards for investigators and institutions to follow to ensure the safe handling and containment of recombinant DNA and products derived therefrom. They outline requirements for institutional oversight, including IBCs, and describe the procedures of the RAC.

The NIH Guidelines are a dynamic document that changes with the science and knowledge of recombinant DNA research. In 1990, a new section to the NIH Guidelines was added, Appendix M, which describes points to consider in the design and submission of human gene transfer trials, including the standards and procedures to which investigators must adhere. Appendix M is described in greater detail below.

To facilitate navigation of the NIH Guidelines, the electronic version is fully indexed and hyperlinked to allow immediate access to any section, appendix, or referenced resource of particular interest.

2. The Recombinant DNA Advisory Committee

2.1. What is the Recombinant DNA Advisory Committee?

The Recombinant DNA Advisory Committee is a panel of up to 21 national experts in various fields of science, medicine, genetics, ethics, and patient perspectives that considers the current state of knowledge and technology regarding recombinant DNA research. A key role of the RAC is to advise the NIH Director and the NIH OBA, which is the NIH office of oversight for recombinant DNA research. In this capacity, the RAC recommends changes to the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines), which outline responsible research practices in basic and clinical recombinant DNA research. Another important RAC function is to review research proposals involving human gene transfer research, or “gene therapy” as it is often called. All human gene transfer trials occurring at or sponsored by institutions receiving NIH funds for
recombinant DNA research must be submitted to OBA for review by the RAC.

2.2. I am an investigator whose projects are funded entirely by private industry. Must I submit my protocol to NIH for RAC review?

Even if your project is funded entirely by private sources, you must submit your protocol to the NIH if the sponsor of your research or the institution where you will conduct your project receives any NIH money for recombinant DNA research. Also, research involving the testing in humans of materials containing recombinant DNA developed with NIH funds must be reviewed by the RAC, if the institution that developed those materials sponsors or participates in those projects.

If the site and sponsor for your research are entirely privately funded, you may submit your protocol voluntarily. Following the *NIH Guidelines* helps assure yourself and others that you are conducting your research safely. Undergoing RAC review allows you to obtain feedback on the conduct and design of your protocol from a panel of experts that helps improve the science and safety of the study.

2.3. Are there any kinds of human gene transfer trials that are specifically exempted from the RAC review process?

Appendix M-VI-A of the *NIH Guidelines* exempts certain types of vaccine trials from the requirements for submission of the protocol to NIH OBA, RAC review, and subsequent reporting (Appendix M-I). Specifically, this exemption applies to "human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected." Trials with these characteristics do not have to be registered with NIH OBA or undergo RAC review, but can be submitted on a voluntary basis, particularly if the investigator believes that a trial presents scientific, safety, or ethical concerns that would benefit from RAC review and public discussion. Investigators that submit trials voluntarily will be expected to comply with all aspects of the protocol review and reporting requirements. ODA encourages investigators and institutional review bodies to contact us (obs@od.nih.gov) for assistance in determining whether this exemption applies to particular trials.

2.4. Are these vaccine trials also exempt from other requirements specified in the *NIH Guidelines*?

It is important to note that Appendix M-VI-A does not exempt these vaccine trials from other requirements specified in the *NIH Guidelines*, including biosafety review. Thus, vaccine trials, like other human gene transfer trials subject to the *NIH Guidelines*, must be reviewed and approved by an Institutional Biosafety Committee (IBC) before research participants can be enrolled. More information about IBCs can be found on the IBC page of OBA’s Web site (http://www4.od.nih.gov/obs).
2.5. I am an investigator developing a protocol for a gene transfer clinical trial. What are the first things I need to do to prepare for a review of my trial by the RAC?

First, you should read Appendix M of the NIH Guidelines, which outlines points to consider in the design and conduct of these trials. It also includes details about submitting your protocol for review by the RAC.

As part of the packet of materials that you will send to the NIH, you will need to submit responses to Appendices M-II through M-V of the NIH Guidelines, which pose questions concerning the objective and rationale of the proposed research. These sections also explore how you will handle informed consent and privacy for research participants and their families. In addition to these responses, your packet should contain:

- A cover letter on institutional letterhead signed by you (and your colleagues) as the Principal Investigator(s). The letter should (1) acknowledge that the documentation submitted to NIH OBA complies with the requirements set forth in Appendix M-I-A, "Requirements for Protocol Submission"; (2) identify the IBC and IRB at the proposed clinical trial site(s) responsible for local review and approval of the protocol; and (3) acknowledge that no research participant will be enrolled (see definition of enrollment in Section I-E-7 of the NIH Guidelines) until the RAC review process has been completed (see Appendix M-I-B, "RAC Review Requirements"). IBC approval (from the clinical trial site), IRB approval, and all applicable regulatory authorizations have been obtained;
  - A scientific abstract;
  - A non-technical abstract;
  - The proposed clinical protocol, including tables, figures, and relevant manuscripts;
  - The proposed informed consent document, and
  - Curriculum vitae of the principal investigator(s).

3. Submitting your protocol

3.1. To whom do I send my protocol?

You may submit your completed Appendix M submission by mail, by overnight express, or by email.

By U.S. mail, send it to:

NIH Office of Biotechnology Activities
National Institutes of Health,
6705 Rockledge Drive, Suite 750, MSC 7985
Bethesda, Maryland 20892
By overnight express, send it to:

NIH Office of Biotechnology Activities
National Institutes of Health,
6765 Rockledge Drive, Suite 710
Bethesda, Maryland 20817
Telephone: 301-496-9838

By email, send it to: rosentlb@od.nih.gov

3.2. Should I submit the very same information that I send to the Food and Drug Administration (FDA)?

Investigators should submit all the material specified in Appendix M of the NIH Guidelines. This includes information that would not normally be part of an FDA investigational new drug application, since the scope and purpose of RAC review is different from that of the FDA. Furthermore, unlike FDA review, the RAC process is open to the public. Any member of the public may observe discussion of your protocol at a RAC meeting or request the materials that you submit to this office. This allows all interested parties to consider this field of research in all its dimensions. Because of this characteristic, in general, you should not submit trade secret or confidential commercial information in your Appendix M submission to the NIH. If for some reason you find it necessary to include trade secrets or confidential commercial information in your submission, it should be clearly labeled as such. It is never acceptable to label the entirety of your Appendix M submission as confidential.

3.3. What happens to my protocol when OBA receives it?

NIH OBA will confirm receipt of your protocol within three working days. If it appears that any portion of the necessary submission is missing, OBA staff will contact you immediately to request those materials.

Once your submission is complete, it is sent to members of the RAC for an initial review. During the preliminary protocol review process, individual RAC members may request additional information or clarification about your submission and sometimes make specific comments or suggestions about the protocol design, informed consent document, or other matters. Any individual RAC comments of this nature are then conveyed to you. All such correspondence is part of the public record of this protocol, and is available to the investigators, sponsor, the IRB, and the IEC upon request.

As an outcome of this initial review, RAC members determine whether the protocol raises important scientific, safety, medical, ethical, or social issues that warrant in-depth discussion at the RAC’s quarterly public meetings. Factors that may warrant public discussion include unique applications of gene transfer research, the use of new or otherwise salient vector or gene delivery systems, special clinical concerns, or important social or
Within 15 working days of submitting all the information required under Appendix M, you will be notified of the outcome of this initial review process and whether your protocol has been selected for public RAC review. The in-depth, public review of a protocol occurs when (1) the OBA Director initiates that review following a recommendation for review by at least three RAC members or another federal agency, or (2) the NIH Director initiates that review.

4. Your Protocol and the Public RAC Meeting

4.1. What happens if my protocol is selected for public RAC review?

If your protocol has been selected for public review, and if you have completed your submission at least eight weeks before the next RAC meeting, your protocol will be reviewed at the next meeting. If the next RAC meeting is less than eight weeks away, public discussion of your protocol will be deferred until the following RAC meeting to allow sufficient time for the review process.

As the person responsible for the design and conduct of the trial, you will be asked to make a 15-20 minute presentation about your protocol at the RAC meeting. You are welcome to bring colleagues to the meeting to help with your presentation and to answer questions. Several RAC members assigned to conduct an in-depth review of your protocol will then make remarks and pose questions about its details. Other experts in the field (ad hoc reviewers) may be asked to provide a review of some key aspects of your protocol, as well. This face-to-face interaction greatly improves the quality of the discussion and permits immediate and in-depth exploration of issues that your protocol may raise.

4.2. What is the outcome of the RAC review?

The outcome of RAC review is a series of recommendations and advice from experts in the field. RAC review does not entail a formal approval of your proposed protocol. Investigators and sponsors should carefully consider these recommendations as part of optimizing the safe and ethical conduct of the trial. These recommendations will be captured in a summary letter prepared by OBA staff, which will be sent to you within 10 working days after completion of the RAC meeting. The summary letter will also be sent to the IRB and IBC reviewing your protocol, as well as the FDA.

4.3. What is the relationship of RAC review to review by the IRB, the IBC, and the FDA?

Unlike the RAC, these other entities will be reviewing your protocol as part of a formal approval process, either for conduct at your institution (in the case of local review bodies) or for authorizing your Investigational New Drug (IND) application (in the case of the FDA). A benefit of the RAC process is that it informs the
5. After the RAC Meeting

5.1. When may I start enrolling patients in my protocol?

Under the NIH Guidelines, patient enrollment is considered to begin with the process of obtaining informed consent from prospective participants. This process cannot begin until: (1) the RAC review process has been completed; and (2) IBC and IRB approvals and FDA and all other applicable regulatory authorizations(s) have been obtained.

For a clinical trial site that is added after the RAC review process, no research participant may be enrolled at the clinical trial site until the following documentation has been submitted to NIH OBA:

- IBC approval (from the clinical trial site);
- IRB approval;
- IRB-approved informed consent document;
- Curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format); and
- NIH grant number(s) of applicable

5.2. After I enroll my patients, am I finished with the RAC process and my interactions with OBA?

No. Within 20 working days of consenting the first research participant, you must submit the following documentation to NIH OBA:

- A copy of the informed consent document approved by the IRR;
- A copy of the protocol approved by the IBC and IRB;
- A copy of the final IBC approval from the clinical trial site;
- A copy of the final IRB approval;
- A brief written report that includes the following information: (1) how the investigator(s) responded to each of the RAC’s recommendations on the protocol (if applicable); and (2) any modifications to the protocol as required by FDA;
- Applicable NIH grant number(s);
- The FDA IND number, and
- The date of the initiation of the trial.
Investigators also have an ongoing responsibility to monitor the trial and to keep OBA, as well as IRBs, IBCs, the FDA, and any sponsoring NIH institutes or centers, informed of any adverse events on the trial. Serious adverse events that are unexpected and possibly associated with the gene transfer product should be submitted to OBA within 15 calendar days of sponsor notification, unless they are fatal or life threatening, in which case they should be reported within 7 calendar days. Investigators are encouraged to report serious adverse events electronically to NIH by using GeMCRIS.

In addition, investigators must file an annual report with OBA, providing specific information about the trials. The formats of these reports can be found in Appendix M-I-C-4 and M-I-C-3 of the NIH Guidelines, respectively. Investigators should also notify OBA of any additional sites that are conducting the trial, and submit for the new site:

- IBC approval (from the clinical trial site);
- IRB approval;
- The IRB-approved informed consent form;
- Curriculum vitae of the investigator(s); and
- NIH grant number(s), if applicable.