Appendix F  Human Gene Transfer Clinical Trials

The following guide has been prepared to assist Principal Investigators and their supporting groups with the registration and review process for clinical research studies that involve the use of recombinant or synthetic nucleic acid molecules in human subjects. Although the guide provides assistance with the submission and registration process and ongoing requirements after initiation of a human gene transfer protocol at Yale, it may not cover every question that may arise. Please contact the EHS Office (203) 785-3550 and ask to speak to the Biosafety Office or the Safety Advisor assigned to your research or clinical area if you have any questions.

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**Introduction**

Proposed clinical trials involving human gene transfer require registration and approval from both campus and federal agencies before initiation. Human gene transfer is the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human subjects. The NIH formal definition of Human Gene Transfer is provided in the next paragraph. This document outlines the Yale University Biological Safety Committee requirements for human gene transfer protocols. Additional 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 Definition of Human Gene Transfer Research
Section III–C–1. Experiments Involving the Deliberate Transfer of Recombinant or Synthetic Nucleic Acid Molecules, or DNA or RNA Derived from Recombinant or Synthetic Nucleic Acid Molecules, into One or More Human Research Participants Human gene transfer is the deliberate transfer into human research participants of either:

1. Recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or
2. Synthetic nucleic acid molecules, or
3. DNA or RNA derived from synthetic nucleic acid molecules that meet any one of the following criteria:
   a. Contain more than 100 nucleotides; or
   b. Possess biological properties that enable integration into the genome (e.g., cis elements involved in integration); or
   c. Have the potential to replicate in a cell; or
   d. Can be translated or transcribed

On Campus Registrations and Approvals:
It is recommended that HGT registrations or notifications are pursued in the following order:

A. Notification to YNHH Hospital Epidemiology and YNHH Occupational Health of the request to conduct a HGT protocol at the YNHH.
   a. It is preferred that the Principal Investigator invite the Sponsor to YNHH to provide a presentation on the description of the proposed project for representatives of these two groups AND representatives from all groups who may participate in the project, especially if any hazards are involved. This would include the pharmacists who will handle and prepare the study drug for administration, the physicians and nurses who will have to deliver the study drug, and any other healthcare workers who will work with study subjects.
      i. It is imperative that the Principal Investigator or Department confirm that there are sufficient personnel willing to participate in the protocol prior to registration with the following campus groups.
      ii. Verification that personnel will participate on the project is required prior to the initiation of review of the protocol by the Yale Biological Safety Committee.

B. Registration with the Yale Biological Safety Committee and the Committee’s Human Gene Transfer Subcommittee
C. Registration with the Yale Human Research Protection Program Human Investigation Committee

Contact information for each of these groups is provided below.

A. Yale New Haven Hospital  (203) 688-4634 (YNHH Hospital Epidemiology)
                                 (203) 688-4242 (YNHH Occupational Health – York St)
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 (203) 688-4634. All personnel who handle potential hazards at YNHH must also notify the YNHH Occupational Health Office at (203) 688-4242 for additional health and safety information. This includes physicians, nurses, pharmacists and others who may handle the study drug or study subjects when potential hazards are involved. 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.

B. Yale Biological Safety Committee (IBC) (203) 785-3550 (through Biosafety Representatives)
   http://ehs.yale.edu/biosafety-committee
   http://provost.yale.edu/committees

C. Yale Human Research Protection Program (IRB) (203) 785-4688
   (Human Investigation Committee)
   http://www.yale.edu/hrpp/
   http://www.yale.edu/hrpp/forms-templates/biomedical.html

HRPP Contact Information:
25 Science Park, 3rd Floor
150 Munson Street
PO Box 208327
New Haven, CT 06520-8327
Phone: (203) 785-4688
Fax: (203) 785-2847
hrpp@yale.edu

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.

Federal Registration and Approval:
NIH Office of Science Policy (301) 496-9838
NIH Guidelines Appendix M (Human Gene Transfer):

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=528ebe054b8cf1dc958289ee9fc1f972&rgn=div5&view=text&node=21:5.0.1.1.3&idno=21

Appendix M-I of the NIH Guidelines includes the submission requirements and addresses for both the NIH Office of Science Policy and the 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 University

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), April 2016. To obtain a copy of the NIH Guidelines, access the NIH OSP web site or contact the Biosafety Office at (203)785-3550. Send a copy of your completed Appendix M, along with the additional documents detailed below to:

The Yale Biological Safety Committee  
C/O Biosafety Office  
Yale Office of Environmental Health & Safety  
135 College Street, Suite 100  /New Haven, CT 06510  
Contact person: Biosafety Officer, (203) 785-3550

Yale Biological Safety Committee Submission Requirements for the Review of Human Gene Transfer Protocols

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

- The Yale Biological Safety Committee Human Gene Transfer Registration Form (Protocol Profile)

- Scientific abstract

- Non-technical abstract

- Your responses to Appendix M-I

- Your response to Adverse Event reporting requirements detailed in Appendix M-II

- A copy of your HIC clinical protocol (your IND Submission)

- A copy of the HIC approved Informed Consent Document

- Sponsor’s Protocol

- Principal Investigator’s Brochure

- 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](http://oba.od.nih.gov/rdna/nih_guidelines_new.htm)
Yale Biological Safety Committee Human Gene Transfer Registration Form  
(Protocol Profile)

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**Title of Protocol**

**FDA IND #:**  
**Sponsor Protocol #:**  
**NIH OBA/OSP #:**

**Targeted Disease or Clinical Aim of Project:**

**Description of the Vector or Recombinant Molecule:**

Certificate of Analysis for adventitious agents and replication competency (if applicable) must be provided for each lot of study drug used at Yale.

**Other Clinical Trial Sites approved for the project:**

**Other sites proposed for the study?**

**Total number of subjects enrolled to date:**

□ YES  □ NO  
Has the determination of need for NIH Recombinant DNA Advisor Committee review been made by the initial site for this study?

If Yes to the above question, was RAC review required?

If Yes, please attach the results of the RAC review for the Committee and any comments from the NIH OBA or OSP provided to the Sponsor, Principal Investigator or initial trial site.

What supporting safety data (cell culture, animal model, etc.) was utilized to move forward with research involving human subjects? Please provide safety data for the recombinant
molecule and other study drugs involved.

Describe the dosing regimen for the recombinant molecule and other study drugs (please include starting dose, maximum allowable dose, and the study administration schedule).

How many cycles are allowed for study subjects:

Provide any history of use of the recombinant molecule in other studies (include the total number of subjects, and numbers of Adverse Events and Serious Adverse Events)

Please provide the proposed study location (where the drug will be administered)?

Has the Principal Investigator confirmed participation by a suitable number of healthcare workers to participate in all required aspects of the study?

Will the YNHH Pharmacy been involved?

Have Pharmacy personnel confirmed their participation in the study?

Please provide the date the study presentation was provided by the sponsor to the potential study participants at YNHH:
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, 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 OSP, 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 OSP reporting form can be downloaded from their website at http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment/hgt

Updated Appendix M-1-A. Requirements for Protocol Submission (New Appendix M-I):

The following documentation must be submitted according to institutional policy, to the appropriate oversight bodies and subsequently in electronic form to the NIH OSP:

1. A scientific abstract.

2. The proposed clinical protocol, including tables, figures, and any relevant publications.

3. Summary of preclinical studies conducted in support of the proposed clinical trial or reference to the specific section of the protocol providing this information.

4. A description of the product:
   
   a. Describe the derivation of the delivery vector system including the source (e.g., viral, bacterial, or plasmid vector); and modifications (e.g., deletions to attenuate or self-inactivate, encapsulation in any synthetic complex, changes to tropisms, etc.). Please reference any previous clinical experience with this vector or similar vectors.

   b. Describe the genetic content of the transgene or nucleic acid delivered including the species source of the sequence and whether any modifications have been made (e.g. mutations, deletions, and truncations). What are the regulatory elements contained in the construct?

   c. Describe any other material to be used in preparation of the agent (vector and transgene) that will be administered to the human research subject (e.g., helper virus, packaging cell line, carrier particles).

   d. Describe the methods for replication competent virus testing, if applicable.

   e. Describe the intended ex vivo or in vivo target cells and transduction efficiency.
f. Describe the gene transfer agent delivery method.

5. The proposed informed consent document.

6. Specifically for submission to the NIH OSP, the PI shall provide additional documentation from oversight bodies regarding their assessment of whether RAC review is warranted. In the event that review is requested, the documentation shall include a justification that the protocol characteristics (see Section III–C–1) that would warrant RAC public review have been met.

**Note:** Any application submitted shall not contain any document that is designated as 'confidential' in its entirety. In the event that a sponsor determines that a portion of a specific document should be considered as proprietary or trade secret, each portion of the document should be clearly identified as such. In the event that a specific portion of the submission does contain information that a sponsor considers to be proprietary or trade secret, the submission to the NIH OSP must contain a letter from the sponsor that: (1) Clearly indicates what select portions of the application contain information considered as proprietary or trade secret, (2) provides an adequate and convincing justification as to the reason that this information is considered to be proprietary or trade secret. The justification must be able to demonstrate with specificity how release of that information will reveal a trade secret or will result in substantial competitive harm. Appendix M–I–B, RAC Review Requirements is proposed to be amended to change the process and timing of initial and RAC review. Currently, investigators are informed within 15 working days whether or not the protocol requires public RAC review. Public discussion of selected protocols then occurs at the next quarterly RAC meeting, which occurs, at a minimum of, eight weeks after receipt of a complete protocol submission. Under the proposal, individual RAC members will no longer make a recommendation regarding whether a protocol should be selected for review at a public meeting.

**For a clinical trial site that is added after completion of the NIH protocol registration process,** no research participant shall be enrolled (see definition of enrollment in Section I–E–7) at the clinical trial site until the following documentation has been submitted to the NIH OSP:

1. IBC approval (from the clinical trial site);
2. IRB approval;
3. IRB-approved informed consent document; and
4. NIH grant number(s) if applicable.
PATHWAY FOR HUMAN GENE TRANSFER PROTOCOLS AT YALE UNIVERSITY:

1. If the protocol will be conducted at YNHH and involves hazards, the Principal Investigator must notify YNHH Hospital Epidemiology/Infection Prevention and YNHH Occupational Health for additional review and information.

2. The Sponsor conducts an introductory meeting with the Principal Investigator and all possible healthcare workers, including pharmacy staff, who may participate in the project. The presentation covers the rational for the project and any hazards involved for the subjects and healthcare workers.

3. The Principal Investigator verifies that there is sufficient staffing after the Sponsor’s presentation to participate in all required aspects of the study.

4. Principal Investigator submits the required documentation listed above (pp 5 – 9) to the Yale Biological Safety Committee.

5. The EHS Biosafety Office verifies that all documentation has been received and submits the completed protocol members of the Yale Biological Safety Committee’s Human Gene Transfer Subcommittee.

6. If needed, an HGT Subcommittee meeting is scheduled with the Principal Investigator and technical representatives from the Sponsor who are familiar with the recombinant molecules utilized in the protocol. Sponsor representatives generally participate by teleconference at the live HGT meeting. HGT Subcommittee meetings are scheduled as needed and meeting dates are coordinated with HGT Subcommittee members and representatives from the Principal Investigators research team.

7. The HGT Subcommittee and the Principal Investigator must also confirm that the initial trial site has determined if review by the NIH RAC is recommended or not. (If Yale University is the initial site, this determination must be made and submitted to the NIH Office of Science Policy if NIH RAC review is warranted).

8. The HGT Subcommittee will provide its recommendation on the protocol to the Yale Biological Safety Committee.

9. The Yale Biological Safety Committee will review the recommendations from the HGT Subcommittee and will vote on the protocol. Yale Biological Safety Committee meetings are normally held monthly on the third Thursday of each month.

10. The results of the Yale Biological Safety Committee review are submitted to the Yale Human Investigation Committee. If approved, the Principal Investigator will receive an approval letter for the protocol from the Yale Biological Safety Committee.

11. Principal Investigator submits a registration for conducting research involving human subjects to the Yale Human Investigation Committee.

12. The Yale Human Investigation Committee will complete its review of the project. If approved, the Principal Investigator will receive an approval letter from the Human Investigation Committee.
April 2016 Changes to the NIH Guidelines for Human Gene Transfer Experiments

The NIH Office of Science Policy has made changes to Appendix M of the NIH Guidelines, which address the review and management of human gene transfer protocols. The major change involves the process for determining if a human gene transfer research protocol requires review by the NIH Recombinant DNA Advisory Committee (RAC). The initial determination for RAC review will now be made by the initial clinical site where a human gene transfer research protocol is conducted. (Additional research sites added to the protocol at a later date must ensure that this determination was made by the initial site). A summary of the major changes to the NIH Guidelines are provided below.

- Transfer of the responsibility for making the initial request for the review of a human gene transfer protocol by the NIH Recombinant DNA Advisory Committee (RAC) to a host or local oversight body, such as an Institutional Biosafety Committee (IBC) or an Institutional Review Board (IRB), instead of the NIH Office of Science and Policy;

- Update of Section M-I-A Requirements for Protocol Submission to simplify and consolidate the responses provided by the Principal Investigator and clarify what constitutes a trade secret; and

- The deletion of Appendices M-II, M-III, M-IV and M-V (with the exception of Section M-III-B-2-b Long Term Follow up). Long Term Follow up will be updated with information from the FDA on this topic. Long Term Follow up will be the subject of the new Section M-II.

NIH Criteria for Requesting RAC Review by an oversight body:

If an oversight body determines that:

(1) A protocol submission would significantly benefit from public RAC review and discussion AND

(2) that one or more of the following NIH RAC review criteria are met:
   (i) The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk; or

   (ii) the protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value; or

   (iii) the proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for local and federal regulatory bodies to evaluate the protocol rigorously.
March 2013 Changes to the NIH Guidelines (Addressing Synthetic Biology)

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.

The NIH Guidelines were 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” 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.

Standard Approval Letter Language from the Yale Biological Safety Committee for HGT Protocols

The application was approved at Biosafety Level 2 containment (Standard and Universal Precautions) and sharps precautions for inoculating patients with the study drug, with the following additional requirements:

- Authorization from the Yale Human Investigation Committee (HIC). Please send the Yale IBC a copy of your Yale HIC approval letter for your IBC protocol file.
- The Principal Investigator must ensure compliance with all applicable reporting requirements as specified in Appendix M-I-C of the NIH Guidelines for Research Involving Recombinant DNA Molecules. Appendix M-I-C-2 specifies reporting requirements for additional clinical trial sites; Appendix M-I-C-3 details annual report requirements; Appendix M-I-C-4 specifies safety reporting requirements; and Appendix M-I-C-5 outlines confidentiality elements. A complete copy of Appendix M-I-C is attached to this approval letter.
- Any serious event that is both unexpected and associated with the use of the gene transfer product (i.e. there is reasonable possibility that the event may have been caused by the use of the product) must be reported to the Yale HIC within 48 hours.
• A copy of the Certificate of Analysis (CoA) for each lot of vector used to transform autologous cells of patients enrolled in the trial at Yale University must be filed with the Principal Investigator prior to patient enrollment in the trial.
• A copy of the FDA IND authorization for the trial at Yale must be on file with the Yale IBC prior to the enrollment of patients in the trial at the University.
• A copy of the latest version of your FDA-authorized protocol. If relevant, please describe any substantive differences between your current protocol and the protocol registered with the Yale IBC and the NIH Office of Biotechnology Activities.
• A copy of the annual report to the FDA and the HIC must also be submitted to the Yale IBC for the protocol file.
• Your protocol will expire on the one-year anniversary of the HIC Committee review date as reflected in the HIC approval letter. The protocol must be re-approved by the HIC annually.

Should you wish to add personnel to your project, change the scope or location of your work, you must notify the Biosafety Office. It is the responsibility of the Principal Investigator to train new personnel before they begin work.

Current Reporting Requirements for HGT Protocols in the NIH Guidelines

Reporting Requirements of the NIH Guidelines for Research Involving Recombinant DNA Molecules (Appendix M-I-C)

Appendix M-I-C-1. Initiation of the Clinical Investigation

No later than 20 working days after enrollment (see definition of enrollment in Section I-E-7) of the first research participant in a human gene transfer experiment, the Principal Investigator(s) shall submit the following documentation to NIH OSP: (1) a copy of the informed consent document approved by the Institutional Review Board (IRB); (2) a copy of the protocol approved by the Institutional Biosafety Committee (IBC) and IRB; (3) a copy of the final IBC approval from the clinical trial site; (4) a copy of the final IRB approval; (5) a brief written report that includes the following information: (a) how the investigator(s) responded to each of the RAC’s recommendations on the protocol (if applicable); and (b) any modifications to the protocol as required by FDA; (6) applicable NIH grant number(s); (7) the FDA Investigational New Drug Application (IND) number; and (8) the date of the initiation of the trial. The purpose of requesting the FDA IND number is for facilitating interagency collaboration in the Federal oversight of human gene transfer research.

Appendix M-I-C-2. Additional Clinical Trial Sites

No research participant shall be enrolled (see definition of enrollment in Section I-E-7) at a clinical trial site until the following documentation has been submitted to NIH OSP: (1) Institutional Biosafety Committee approval (from the clinical trial site); (2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; (4) curriculum vitae of the principal investigator(s) (no more than two pages in biographical sketch format); and (5) NIH grant number(s) if applicable.

Appendix M-I-C-3. Annual Reports

Within 60 days after the one-year anniversary of the date on which the investigational new drug (IND) application went into effect, and after each subsequent anniversary until the trial is
completed, the Principal Investigator (or delegate) shall submit the information set forth in (a), (b), and (c). When multiple studies are conducted under the single IND, the Principal Investigator (or delegate) may choose to submit a single annual report covering all studies, provided that each study is identified by its OBA protocol number.

(a) Clinical Trial Information. A brief summary of the status of each trial in progress and each trial completed during the previous year. The summary is required to include the following information for each trial: (1) the title and purpose of the trial; (2) clinical site; (3) the Principal Investigator; (4) clinical protocol identifiers, including the NIH OSP protocol number, NIH grant number(s) (if applicable), and the FDA IND application number; (5) participant population (such as disease indication and general age group, e.g., adult or pediatric); (6) the total number of participants planned for inclusion in the trial; the number entered into the trial to date; the number

whose participation in the trial was completed; and the number who dropped out of the trial with a brief description of the reasons; (7) the status of the trial, e.g., open to accrual of subjects, closed but data collection ongoing, or fully completed, and (8) if the trial has been completed, a brief description of any study results.

(b) Progress Report and Data Analysis. Information obtained during the previous year’s clinical and non-clinical investigations, including: (1) a narrative or tabular summary showing the most frequent and most serious adverse experiences by body system; (2) a summary of all serious adverse events submitted during the past year; (3) a summary of serious adverse events that were expected or considered to have causes not associated with the use of the gene transfer product such as disease progression or concurrent medications; (4) if any deaths have occurred, the number of participants who died during participation in the investigation and causes of death; and (5) a brief description of any information obtained that is pertinent to an understanding of the gene transfer product’s actions, including, for example, information about dose-response, information from controlled trials, and information about bioavailability.

(c) A copy of the updated clinical protocol including a technical and non-technical abstract.

**Appendix M-I-C-4. Safety Reporting**

Principal Investigators must submit, in accordance with this section, Appendix M-I-C-4-a and Appendix M-I-C-4-b, a written report on: (1) any serious adverse event that is both unexpected and associated with the use of the gene transfer product (i.e., there is reasonable possibility that the event may have been caused by the use of the product; investigators should not await definitive proof of association before reporting such events); and (2) any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity. The report must be clearly labeled as a “Safety Report” and must be submitted to the NIH Office of Biotechnology Activities (NIH OSP) and to the local Institutional Biosafety Committee within the timeframes set forth in Appendix M-I-C-4-b.

Principal Investigators should adhere to any other serious adverse event reporting requirements in accordance with federal regulations, state laws, and local institutional policies and procedures, as applicable.

Principal Investigators may delegate to another party, such as a corporate sponsor, the reporting functions set forth in Appendix M, with written notification to the NIH OSP of the delegation and of the name(s), address, telephone and fax numbers of the contact(s). The Principal Investigator is responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses.
The three alternative mechanisms for reporting serious adverse events to the NIH OSP are: by e-mail to oba@od.nih.gov; by fax to 301-496-9839; or by mail to the Office of Biotechnology Activities, National Institutes of Health, MSC 7985, 6705 Rockledge Drive, Suite 750, Bethesda, Maryland 20892-7985.

**Appendix M-I-C-4-a. Safety Reporting: Content and Format**

The serious adverse event report must include, but need not be limited to: (1) the date of the event; (2) designation of the report as an initial report or a follow-up report, identification of all safety reports previously filed for the clinical protocol concerning a similar adverse event, and an analysis of the significance of the adverse event in light of previous similar reports; (3) clinical site; (4) the Principal Investigator; (5) NIH Protocol number; (6) FDA’s Investigational New Drug (IND) Application number; (7) vector type, e.g., adenovirus; (8) vector subtype, e.g., type 5, relevant deletions; (9) gene delivery method, e.g., *in vivo*, *ex vivo* transduction; (10) route of administration, e.g., intratumoral, intravenous; (11) dosing schedule; (12) a complete description of the event; (13) relevant clinical observations; (14) relevant clinical history; (15) relevant tests that were or are planned to be conducted; (16) date of any treatment of the event; and (17) the suspected cause of the event. These items may be reported by using the recommended Adverse Event Reporting Template available on NIH OSP’s web site at: [http://www4.od.nih.gov/oba/rac/documents1.htm](http://www4.od.nih.gov/oba/rac/documents1.htm), the FDA MedWatch forms, or other means provided that all of the above elements are specifically included.

Reports from laboratory animal studies as delineated in Appendix M-I-C-4 must be submitted in a narrative format.

**Appendix M-I-C-4-b. Safety Reporting: Time frames for Expedited Reports**

Any serious adverse event that is fatal or life-threatening, that is unexpected, and associated with the use of the gene transfer product must be reported to the NIH OSP as soon as possible, but not later than 7 calendar days after the sponsor’s initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

Serious adverse events that are unexpected and associated with the use of the gene transfer product, but are not fatal or life-threatening, must be reported to the NIH OSP as soon as possible, but not later than 15 calendar days after the sponsor’s initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

Changes in this schedule are permitted only where, under the FDA IND regulations [21 CFR 312(c)(3)], changes in this reporting schedule have been approved by the FDA and are reflected in the protocol.

If, after further evaluation, an adverse event initially considered not to be associated with the use of the gene transfer product is subsequently determined to be associated, then the event must be reported to the NIH OSP within 15 days of the determination.

Relevant additional clinical and laboratory data may become available following the initial serious adverse event report. Any follow-up information relevant to a serious adverse event must be reported within 15 calendar days of the sponsor’s receipt of the information. If a serious adverse event occurs after the end of a clinical trial and is determined to be associated with the use of the gene transfer product, that event shall be reported to the NIH OSP within 15 calendar days of the determination.
Any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity must be reported as soon as possible, but not later than 15 calendar days after the sponsor’s initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

**Appendix M-I-C-5. Confidentiality**

Data submitted in accordance with Appendix M-I-C that are claimed to be confidential commercial or trade secret information must be clearly labeled as such. Prior to making its determination about the confidentiality of data labeled confidential commercial or trade secret, the NIH will contact the Principal Investigator or delegate to ascertain the basis for the claim and subsequently will notify the Principal Investigator or delegate of its final determination regarding the claim.

If NIH determines that the data so labeled are confidential commercial or trade secret and that their public disclosure would promote an understanding of key scientific or safety issues, the NIH will seek agreement from the appropriate party to release such data. Public discussion of scientific and safety issues raised by data submitted in accordance with Appendix M-I-C is vital to informing both investigators and human subjects about the safety of gene transfer research.

To protect the privacy of participants in gene transfer research, any serious adverse event or annual reports submitted to NIH OSP must not contain any information that would identify the human research participants.

**Annual Reporting Requirements for Principal Investigators with Active Human Gene Transfer Protocols**

By the one year anniversary of the approval date of a HGT Protocol, Principal Investigators must provide the Yale EHS Biosafety Office with an annual report that includes the following information.

1) Verification that the protocol is still active.

2) The date of the last Yale Human Investigation Committee authorization (annual HIC authorization is required for the continuation of an HGT Protocol).

3) For protocols that have been activated, a report that includes the number of subjects enrolled since the protocol has been initiated.

   a) This report must also include a summary of all adverse and serious adverse events reported for each enrolled patient in the last year identified by your team, another institution or the Sponsor.

   b) You may also provide the EHS Biosafety Office with an annual report from the Sponsor that includes this information.

4) Verification that each batch of the study drug shipped to Yale for use has been tested for adventitious agents and if applicable replication competent vectors.
Template for Reporting Adverse Events
In Human Gene Transfer Trials

This template is intended to facilitate the reporting of adverse events in human gene transfer trials. You may download this as a Word document and the fields will expand according to the amount of text entered. Use of this template is not required and other formats (e.g., AdEERS reports, MedWatch forms) may be acceptable provided that they include all the information specified in M-I-C-4-a of the NIH Guidelines for Research Involving Recombinant DNA Molecules.  

A reporting tool that investigators (and those who report on their behalf) may find particularly convenient is the Genetic Modification Clinical Research Information System (GeMCRIS). GeMCRIS provides a Web-based reporting format that enables investigators to prepare and submit information on serious adverse events electronically to the NIH Office of Biotechnology Activities. The GeMCRIS template includes all the data elements required by Appendix M-I-C-4-a and includes features, such as drop-down lists, that can greatly facilitate data entry. More information on submitting adverse event reports through GeMCRIS can be obtained at:  
http://www.gemcris.od.nih.gov/Contents/GC_HOME.asp

Submitting reports to the NIH Office of Biotechnology Activities alone does NOT fulfill the reporting requirements of other agencies. However, other agencies may accept submission of a duplicate copy of this completed template or a GeMCRIS report, which can be printed and provided in hard copy to other entities to which adverse events must be reported.

Completed reports may be sent via U.S. mail, courier service, e-mail, or facsimile to:

NIH Office of Biotechnology Activities  
6705 Rockledge Drive, Suite 750  
Bethesda, Maryland 20892-7985  
(For all non-USPS deliveries use Zip Code 20817)  
Telephone 301-496-9838  
Fax 301-496-9839

E-mail address for Reporting Adverse Events: GeMCRIS@od.nih.gov


General E-mail queries: oba-osp@od.nih.gov

**PROTOCOL AND EVENT TYPE**

<table>
<thead>
<tr>
<th>NIH/OBA RAC Protocol Number</th>
<th>FDA IND Number</th>
</tr>
</thead>
</table>

Date this report completed:

<table>
<thead>
<tr>
<th>Seriousness of the AE (choose one)</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Life-threatening</td>
</tr>
<tr>
<td></td>
<td>Initial or prolonged hospitalization</td>
</tr>
<tr>
<td></td>
<td>Disability</td>
</tr>
<tr>
<td></td>
<td>Congenital anomaly</td>
</tr>
<tr>
<td></td>
<td>Required intervention to prevent permanent impairment/damage</td>
</tr>
<tr>
<td></td>
<td>Other medically important condition</td>
</tr>
<tr>
<td></td>
<td>Non-serious</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity of Event</th>
<th>Minimal</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Life-Threatening</td>
<td>Fatal</td>
<td></td>
</tr>
</tbody>
</table>

Was this event expected in terms of its severity? Yes No

Was this event expected in terms of its specificity? Yes No

Relationship of Event to gene transfer product

<table>
<thead>
<tr>
<th>Attribution of AE</th>
<th>Concomitant medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Product</td>
</tr>
<tr>
<td></td>
<td>Intervention</td>
</tr>
<tr>
<td></td>
<td>Underlying disease</td>
</tr>
<tr>
<td></td>
<td>Route of administration</td>
</tr>
<tr>
<td></td>
<td>Other suspected cause (describe)</td>
</tr>
</tbody>
</table>

Type of Report

<table>
<thead>
<tr>
<th>PI Name</th>
</tr>
</thead>
</table>

Name of Clinical Trial Site/Organization

<table>
<thead>
<tr>
<th>PI Telephone Number</th>
</tr>
</thead>
</table>

| PI E-mail Address |
| **Reporter Name** |  |
| **Reporter Telephone number** |  |
| **Reporter E-mail address** |  |
| **Research Participant’s study identification number** |  |
| **Research Participant’s gender** |  |
| **Research Participant’s date of birth** |  |
| **Research Participant’s date of death** |  |
| **Research Participant’s weight in kgs** |  |
| **Research Participant’s height in cms** |  |
| **Which Arm/Cohort/treatment group was the subject assigned to?** |  |
| **Was subject dosed?** | Yes | No | Information Not Available |
| **What study agent was received:** | IND agent | Placebo | Blinded Study Agent |
| **Were there any Protocol Deviations/Violations/Exceptions for this participant?** | Yes: ________________________________  
______________________________  
______________________________  
No |

**DETAILED ADVERSE EVENT INFORMATION**

| **Adverse Event Date** |  |
| **Description of Event** |  |
| **Relevant tests (e.g. x-rays) and results** |  |
| **Treatment (s) of Adverse Event (Include medications used to treat this event.)** |  |
| **Name of Concomitant Medications** |  |
## (Do not include medications used to treat this event.)

<table>
<thead>
<tr>
<th>Pre-existing conditions/ relevant clinical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>(if this is an oncology trial, please designate primary disease, e.g. ovarian cancer)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date(s) of treatment(s) of the adverse event</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was autopsy performed?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Date of autopsy</th>
<th>_____________ or Not Applicable _____</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcome of the event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered/resolved</td>
</tr>
<tr>
<td>Recovering/resolving</td>
</tr>
<tr>
<td>Not recovered/not resolved</td>
</tr>
<tr>
<td>Recovered/resolved with sequelae</td>
</tr>
<tr>
<td>Fatal</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Documentation accompanying the report</th>
</tr>
</thead>
<tbody>
<tr>
<td>(e.g., H&amp; P, Progress Notes, Discharge Summary, Lab or Autopsy Reports, Other, etc.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Description of any “other” documentation</th>
</tr>
</thead>
</table>

## PRODUCT AND DOSING INFORMATION

<table>
<thead>
<tr>
<th>Name of gene transfer product</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Vector type (e.g. adenovirus)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Vector Sub-Type (E.G. Type 5, also include relevant deletions)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Lot number</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Was the agent manufactured at an NGVL?</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Route of administration</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Site of administration</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Did subject receive the dose specified in the protocol?</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>If not, what dose was given?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Date of first exposure to study agent?</td>
</tr>
<tr>
<td>Date of most recent exposure to study agent?</td>
</tr>
<tr>
<td>Total dose received prior to this event?</td>
</tr>
<tr>
<td>Total dose quantity administered to subject to date</td>
</tr>
<tr>
<td>Unit of measure for a single dose</td>
</tr>
<tr>
<td>Dose quantity in a single administration</td>
</tr>
<tr>
<td>If courses used, how many were given prior to this event?</td>
</tr>
<tr>
<td>How many doses on the last course were given?</td>
</tr>
<tr>
<td>Was the administration of this product stopped because of this adverse event?</td>
</tr>
<tr>
<td>Name of other treatment(s) (medications, radiation, surgery) received by research participant as required by the protocol</td>
</tr>
</tbody>
</table>
NIH Frequently Asked Questions About the Registration and Review Process for Human Gene Transfer Protocols

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules
(NIH Guidelines)

Frequently Asked Questions about the Registration and Review Process for Human Gene Transfer Protocols

What is the process for initiating review of individual human gene transfer protocols by the NIH Recombinant DNA Advisory Committee (RAC)?

In April 2016, the NIH streamlined the review process for human gene transfer protocols subject to the NIH Guidelines. RAC review of individual human gene transfer protocols will be performed only in exceptional cases that meet the following specified criteria (criteria listed in both items 1 and 2 must be met):

1. An oversight body (e.g., Institutional Biosafety Committee or Institutional Review Board) determines that a human gene transfer protocol submitted to it for approval would significantly benefit from RAC review; and
2. One or more of the criteria below are satisfied:
   a. The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk.
   b. The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.
   c. The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate the protocol rigorously.

Does the NIH need to concur that both criteria listed above are met in order for RAC review to proceed?

The NIH must concur that both criteria listed in items 1 and 2 above are met in order to initiate RAC review. If one or more oversight bodies requests RAC review but the NIH does not concur that both criteria are met, then the NIH will inform, within 10 working days, the requesting and other oversight bodies involved in the process that RAC review is not warranted. The modifications to the Guidelines, as posted in the Federal Register on March 22, 2016 (81 FR 15318), will be further revised to clearly articulate that both criteria must be met.

As a note, even if a protocol does not meet the criteria listed above, the NIH Director, in consultation (if needed) with appropriate regulatory authorities (e.g., the Office for Human Research Protections, the Food and Drug Administration), can select a protocol for review that may present significant scientific, societal, or ethical concerns.

Who can request RAC review?

The chair of an oversight body (e.g., Institutional Biosafety Committee or Institutional Review Board) or an institutionally authorized representative may submit a request for RAC review by sending the request to the NIH as part of the submission materials provided by the principal investigator. Requests for RAC review must originate from oversight bodies involved in the initial site(s) review, and must include the rationale for why the protocol satisfies both criteria for initiating RAC review.

NIH
National Institutes of Health
Office of Science Policy

Web: http://osp.od.nih.gov
Address: 6705 Rockledge Dr #750, Bethesda, MD 20817
Phone: (301) 496-9838
The NIH will review the request and notify the institution as to whether it concurs with its assessment within 10 working days. Oversight bodies reviewing protocols at sites added after the initial registration process has been completed may not request RAC review.

**Will oversight bodies have to change the way they review human gene transfer protocols?**

It is expected that Institutional Biosafety Committees and Institutional Review Boards will continue to review protocols in the same manner they always have. In cases where an oversight body feels additional expertise is required, they are encouraged to augment the committee with appropriate ad hoc members. NIH can also assist oversight bodies upon request by providing them with publicly available information, including data from its Genetic Modification Clinical Research Information System (GeMCRIS®): https://www.gemcris.od.nih.gov/.

**Do all human gene transfer protocols still need to be registered with the NIH?**

As previously, all human gene transfer protocols subject to the NIH Guidelines must be registered with the NIH.

**Have the submission requirements for the human gene transfer protocol registration process changed?**

The information required to be submitted by investigators is listed in Appendix M-I-A. As part of the submission, the principal investigator will be required to include written assessments from the oversight bodies (e.g., Institutional Biosafety Committees and Institutional Review Boards) involved in the review of the protocol at the initial trial site(s) as to whether further review by the RAC is warranted.

**When is an Institutional Biosafety Committee permitted to approve a human gene transfer protocol?**

The Institutional Biosafety Committee is permitted to approve the protocol upon confirmation from the NIH that the protocol registration process is complete. In the event that RAC review is requested and the NIH concurs, the protocol registration process cannot be completed until the RAC review has taken place.

**When may an investigator start enrolling participants in a human gene transfer protocol?**

Under the NIH Guidelines, participant enrollment begins with the process of obtaining informed consent from prospective participants. For an initial clinical trial site(s), enrollment cannot begin until: (1) All documentation described in Appendix M-I-A has been submitted, and the NIH has informed the investigator that the protocol registration process/RAC review (if applicable) has been completed; and (2) Institutional Biosafety Committee approval as well as all applicable regulatory authorization(s) have been obtained. All documentation described in Appendix M-I-C-1 of the NIH Guidelines must then be provided no later than 30 days after enrollment of the first participant.

For a clinical trial site that is added after the completion of the NIH protocol registration process, no research participant shall be enrolled at the clinical trial site until IBC approval and IRB approval from that site have been obtained. Within 30 days of enrollment at a clinical trial site, the following documentation shall be submitted to NIH: (1) Institutional Biosafety Committee approval (from the clinical trial site); (2) Institutional Review Board approval; (3) Institutional Review Board-approved informed consent document; and (4) NIH grant number(s) if applicable.

**Are investigators still required to submit follow-up information to the NIH after the human gene transfer protocol registration process is complete?**

Principal investigators remain responsible for submitting appropriate and timely follow-up data including protocol amendments, serious adverse events, and annual reports with cumulative safety data for all protocols subject to the NIH Guidelines. Safety information such as adverse events occurring on human gene transfer trials and annual reports may be reported directly to NIH using GeMCRIS® (https://www.gemcris.od.nih.gov/) or via email at NIH.protocols@mail.nih.gov.
Is information regarding human gene transfer protocols submitted to NIH confidential?

Documents submitted to NIH should not contain information considered confidential, and a document such as a clinical protocol cannot be classified as "confidential" in its entirety. Should a submitter choose to provide information that is considered to be trade secret, commercial confidential, or financial in nature, it is incumbent on the submitter to clearly identify those portions of the document and to justify with specificity how the release of that information could cause financial or competitive harm. All records submitted to NIH, including human gene transfer clinical trial information, are subject to the Freedom of Information Act (FOIA – 5 U.S.C. 552) and the Department of Health and Human Services FOIA regulations (45 CFR part 5).

Where can individuals obtain more information about the requirements for human gene transfer protocol registration and review under the NIH Guidelines?

For more information about the registration and review process for human gene transfer trials under the NIH Guidelines, please email OSP at NIHGuidelines@od.nih.gov or call 301-496-9838.
Frequently Asked Questions about the Vaccine Exemption in the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

(NIH Guidelines)

Are there any clinical trials involving the administration of recombinant or synthetic nucleic acid molecules to human research participants that are specifically exempted from the NIH human gene transfer protocol registration process and subsequent reporting requirements?

Yes. Appendix M-III-A of the NIH Guidelines exempts certain types of vaccine trials from the requirements for submission of the protocol to the NIH Office of Science Policy (OSP) and subsequent reporting (Appendix M-I of the NIH Guidelines). Specifically, this exemption applies to clinical studies involving the administration of recombinant or synthetic nucleic acid molecules 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 OSP or adhere to reporting requirements under Appendix M-I of the NIH Guidelines; they do, however, require Institutional Biosafety Committee (IBC) review and approval. These trials can be submitted to NIH OSP on a voluntary basis. Investigators who submit trials voluntarily will be expected to comply with all aspects of the protocol review and reporting requirements. Investigators and institutional oversight bodies are encouraged to contact NIH OSP by email at HGTprotocols@mail.nih.gov for assistance in determining whether this exemption applies to a specific trial.

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

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 exemption.

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 interleukin-2. Such trials are also not exempt under Appendix M-III-A since the recombinant DNA encoding the cytokine is not of microbial origin.

Are clinical trials that fulfill all of the criteria as outlined in Appendix M-III-A exempt from all other requirements specified in the NIH Guidelines?

No. Vaccine trials that meet the exemption criteria set forth in Appendix M-III-A of the NIH Guidelines are exempt only from the requirements of Appendix M-I (Requirements for Protocol Submission, Review and Reporting – Human Gene Transfer Experiments) and are expected to follow all other requirements of the NIH Guidelines. This includes having the vaccine trial reviewed and approved by an IBC before research participants are enrolled.