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 Guidelines), April 2016 or latest edition, and in the Code of Federal Regulations, 21 CFR, Part 312 (FDA Points to Consider).

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 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
   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:
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

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.

The Yale Biological Safety Committee reviews all human gene transfer protocols for conformity with Appendix M of the NIH Guidelines. Appendix M can be accessed at the following web site:

NIH Guidelines Appendix M (Human Gene Transfer):
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 or latest edition. To obtain a copy of the NIH Guidelines, access the NIH OSP web site or contact the Biosafety Office at (203)785-3550.

Link to the latest Edition of the NIH Guidelines at the NIH Office of Science Policy web site:
https://osp.od.nih.gov/biotechnology/nih-guidelines/

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
- A copy of your HIC clinical protocol (your IND Submission)
- A copy of the HIC approved Informed Consent Document (provide a draft if not approved yet)
- Patient Education Materials
- Sponsor’s Study Protocol
- Principal Investigator’s Brochure
- Pharmacy Brochure or Standard Operating Procedures for this study drug
- Nursing Manual or Infection Control Plan for trial at YNHH
- Sponsor training materials for clinical staff
- 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 or study drug (if applicable)
- 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 (if applicable)

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: https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.html#_Toc446948348

Yale Biological Safety Committee Human Gene Transfer Registration Form
**Protocol Profile**

<table>
<thead>
<tr>
<th>Principal Investigator</th>
<th>Sponsor:</th>
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**Title of Protocol**

<table>
<thead>
<tr>
<th>FDA IND #:</th>
<th>Sponsor Protocol #:</th>
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<tr>
<td>Yale HIC#:</td>
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**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:**

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.
<table>
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<th>Question</th>
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<tr>
<td>Describe the dosing regimen for the recombinant molecule and other study drugs (please include</td>
</tr>
<tr>
<td>starting dose, maximum allowable dose, and the study administration schedule).</td>
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<tr>
<td>How many cycles are allowed for study subjects:</td>
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<tr>
<td>Provide any history of use of the recombinant molecule in other studies (include the total number</td>
</tr>
<tr>
<td>of subjects, and numbers of Adverse Events and Serious Adverse Events)</td>
</tr>
<tr>
<td>Please provide the proposed study location (where the drug will be administered)?</td>
</tr>
<tr>
<td>Has the Principal Investigator confirmed participation by a suitable number of healthcare</td>
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<td>workers to participate in all required aspects of the study?</td>
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<tr>
<td>Will the YNHH Pharmacy been involved?</td>
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<tr>
<td>Have Pharmacy personnel confirmed their participation in the study?</td>
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<tr>
<td>Please provide the date the study presentation was provided by the sponsor to the potential</td>
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<tr>
<td>study participants at YNHH:</td>
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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 Yale Biological Safety Committee:

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.

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.

**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, 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 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.
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.
Updated Process for Review of Human Gene Transfer Protocols
Yale Biological Safety Committee
Human Gene Transfer Subcommittee
January 2018

Human Gene Transfer protocols or those protocols that involve the use of recombinant or synthetic nucleic acid molecules (or molecules derived from them) in clinical subjects require review and approval by the host clinical site’s Institutional Biosafety Committee (IBC). The Yale University Biological Safety Committee serves as the Yale University IBC.

In order to support the Committee’s responsibilities for human gene transfer protocols, the Human Gene Transfer (HGT) Subcommittee was established. The composition of the HGT Subcommittee was selected to have a core group of experts in some of the more likely diseases, treatments and vectors or delivery vehicles that would likely be utilized in HGT clinical trials. The HGT Subcommittee’s membership also includes experts in infection prevention, pharmacy, health and safety, and clinical trials. Membership fluctuates to include recruitment of protocol specific expertise as applicable for a comprehensive review of each HGT trial. Currently, there are 22 members who serve as the foundational core of the Yale Human Gene Transfer Subcommittee. The HGT Subcommittee is currently chaired by Professor Diane Krause. Current membership includes representatives from:

- Yale University
  - Lab Medicine
  - Infectious Diseases
  - Microbial Pathogenesis
  - Immunobiology
  - Environmental Health and Safety Biosafety
  - Employee Health
  - Human Research Protection Program
- Yale New Haven Hospital or Yale New Haven Health (YNHH)
  - Infection Prevention
  - Infectious Diseases
  - Clinical Virology
  - YNHH Pharmacy
  - Smilow Pharmacy
  - Occupational Health and Safety
- Other members as applicable
  - HGT or IBC members can recommend additional experts from Yale, YNHH or outside the institution to participate on a specific protocol

A modified review process for HGT protocols was introduced in January 2018. This change was made due to concerns that the original review process is excessively long, requires a significant amount of time for each member, and more importantly, the current review process is incapable of reviewing multiple protocols simultaneously. In the last 4 years, the HGT Subcommittee has seen a significant increase in the numbers of protocols reviewed than in the previous time period. The number of inquiries regarding the registration process for HGT protocols has also increased.
The steps for the new HGT protocol review process involve the following:

- **Receipt by Yale EHS of a sufficient amount of the required documentation to conduct a comprehensive preliminary review of the HGT project.**
  - The determination of sufficient documentation to start the review is made by the HGT Subcommittee Chair.
  - The initiation of the preliminary does not eliminate the need for all required documentation for the review of an HGT project as outlined in Appendix F of the Yale Biological Safety Committee manual. All required documents must be received by Yale EHS for the Yale Biological Safety Committee prior to issuing an approval letter for the project.

- If the HGT Subcommittee Chair identifies that sufficient documentation exists for the initiation of a preliminary review, a preliminary review subcommittee is established.
  - The preliminary review subcommittee is assembled from the current HGT Subcommittee membership and any other individuals at Yale, YNHH or outside the institution that the HGT Subcommittee Chair believes would be helpful for the review.
    - The Biosafety Officer notifies the members of the subcommittee, confirms their ability to participate in the preliminary review, and notifies the HGT Subcommittee Chair that the members have been confirmed.

- The HGT Protocol documents identified by the HGT Subcommittee Chair are submitted to the assembled preliminary review subcommittee.
  - The preliminary review subcommittee must include the following individuals:
    - The HGT Subcommittee Chair
    - A representative from YNHH Infection Control/Hospital Epidemiology
    - An EHS Biosafety Officer
    - Subject matter experts with knowledge of the disease, delivery methods and/or likely risks to study subjects.

- The HGT preliminary review subcommittee will conduct a thorough review of the submitted HGT Protocol.
  - This will include the development of questions for the Principal Investigator and Sponsor.
  - This may include a teleconference call with presentation by the Principal Investigator and Sponsor to provide an overview of the protocol and to answer questions generated by the preliminary review.

- The HGT Subcommittee Chair and the preliminary review subcommittee will make one of the following recommendations upon the completion of their initial review.
  - Recommendation for a full meeting and full review of the Human Gene Transfer Subcommittee.
    - This process will involve:
      - Submission of the HGT protocol documents to all HGT Subcommittee members.
      - Identification of a meeting time for the HGT Subcommittee Meeting to include:
- Presentation by the PI and Sponsor
- Response verbally and in writing to the HGT Subcommittee questions
- Documentation of the HGT Subcommittee review for distribution to the Yale Biological Safety Committee members.
- Recommendation to Yale Biological Safety Committee that they consider approval or disapproval of the HGT protocol.
- Identification of the HGT Subcommittee member(s) who will present the results of the HGT Subcommittee review to the Yale Biological Safety Committee at their next meeting.

- Recommendation to waive the need for a full HGT Subcommittee meeting with a direct recommendation to the full Yale Biological Safety Committee for approval of the HGT Protocol.
  - This process will involve:
    - Documentation of the HGT preliminary review subcommittee review for distribution to the Yale Biological Safety Committee members and HGT Subcommittee.
    - Notification to the Yale Biological Safety Committee leadership and to the members of the full HGT Subcommittee of the results of the HGT preliminary review subcommittee.
    - Submission of the HGT protocol documents to the Yale Biological Safety Committee and to HGT Subcommittee members.
    - Identification of the HGT Subcommittee member(s) who will make a presentation regarding the HGT protocol review at the next scheduled Yale Biological Safety Committee meeting.

- Presentation of the HGT protocol to the Yale Biological Safety Committee
  - This may include the presentation of a site-specific protocol information sheet developed by the YNHH Infection Control/Hospital Epidemiology Office that outlines risks to patients, workers and other notes relevant for the protocol.
- If approved, the development of an HGT approval letter that will include the requirement of an YNHH start-up meeting involving all relevant groups as determined by the YNHH Infection Control/Hospital Epidemiology Office and the research team conducting the HGT protocol.
- EHS Biosafety is responsible for the documentation of the review process for the HGT protocol on behalf of the Yale Biological Safety Committee.
On August 16, 2018, the NIH issued a proposal for public comment on the streamlining of gene therapy oversight. The proposal can be found at: https://osp.od.nih.gov/biotechnology/nih-guidelines/. Comments will be accepted until October 16, 2018, and can be made at: https://osp.od.nih.gov/comment-form-nih-guidelines/.

As part of the proposal and effective immediately per an NIH Director’s statement and Guide notice, during this comment period, the NIH OSP will not:

- accept new human gene transfer protocols for the protocol registration process under the NIH Guidelines
- convene the Recombinant DNA Advisory Committee (RAC) to review individual human gene transfer protocols
- accept annual reports, safety reports, amendments or other documentation for any previously registered human gene transfer protocols under the NIH Guidelines (Appendix M-I-C-1).

The roles and responsibilities of Institutional Biosafety Committees (IBCs) at the local level will continue as described in the NIH Guidelines. These trials remain subject to FDA and other clinical trial regulations, and only after FDA, IBC, and other relevant approvals are in place can these protocols proceed. During this time, IBCs and Institutional Review Boards (IRBs) will not be required to submit documentation to the NIH assessing whether a particular protocol meets the criteria for RAC review.

Specifically, the NIH seeks to streamline the oversight of human gene transfer clinical research protocols (i.e. gene therapy research) and reduce duplicative reporting requirements already captured within the existing regulatory framework. As part of the proposal, NIH would remove the protocol submission, review, and reporting requirements under Appendix M of the NIH Guidelines and modify the roles and responsibilities of the Recombinant DNA Advisory Committee (RAC).

For more information about the importance of these proposed changes, please visit the following links.

- New England Journal of Medicine Perspective article authored by NIH Director Dr. Francis Collins and FDA Commissioner, Dr. Scott Gottlieb
- NIH Director’s Statement
- Under the Poliscope blog by Dr. Carrie D. Wolinetz, Acting NIH Chief of Staff and Associate Director for Science Policy
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 requiring the use of standard precautions, BSL-2 containment and safe sharps work practices.

The protocol also has 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.

- Documentation of a start-up discussion of this protocol with representatives from YNHH that may include: nursing for the staff involved in the project, YNHH Occupational Health and Safety, YNHH Epidemiology and Infection Control, YNHH and/or Smilow Pharmacy, the research study team, and a patient advocate representative. Please contact Dr. Richard Martinello, Medical Director, Hospital Epidemiology and Infection Control at 203-688-4634 for the specific groups required to attend the start-up meeting for your protocol.

You cannot begin the protocol until this start-up meeting is documented with YNHH Hospital Epidemiology and Infection Control.

- 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.

- Verification 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.

- 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.
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) HIC Protocol #:

2) Title of Protocol:

3) Principal Investigator:

4) Verification that the protocol is still active.

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

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

7) 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.

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

9) 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.

10) Have you received an annual report from the Sponsor? Can you forward a copy to us as well for the Principal Investigator’s file?