

## 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 information about the submission and registration process and ongoing requirements after initiation of a human gene transfer protocol at Yale, it may not address every question that may arise. If you have any questions, please call the EHS Office at (203) 785-3550 and ask to speak to the Biosafety Office or the Safety Advisor assigned to your research or clinical area.

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## **Introduction**

Proposed clinical trials involving human gene transfer (HGT) require registration with, and approval from, both campus and federal agencies before initiation. HGT is the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human subjects. The National Institutes of Health (NIH) formal definition of HGT is provided in the next paragraph. This document outlines the Yale University Biological Safety Committee (Committee) requirements for HGT protocols. Additional federal requirements (NIH and United States Food and Drug Administration) for these experiments are described in Section III-C of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH Guidelines), April 2019, and in the Code of Federal Regulations, 21 CFR, Part 312 (FDA Points to Consider).

## **NIH Definition of Human Gene Transfer Research (HGT) and Exemptions**

### **NIH Definition of Human Gene Transfer Research (HGT)**

*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

### **Expanded Access Exemption**

The deliberate transfer of recombinant or synthetic nucleic acids into one human research participant, conducted under a Food and Drug Administration (FDA) regulated individual patient expanded access Investigational New Drug (IND) or protocol, including for emergency use, is not research subject to the NIH Guidelines and thus does not need to be submitted to an IBC for review and approval. These protocols still require registration with the Yale Human Investigation Committee.

### **Treatment Exemption**

If the use of recombinant or synthetic nucleic acid molecules is for “treatment”, such as used in an emergency IND, review by the Yale Biological Safety Committee would not be required. Only protocols involving recombinant or synthetic nucleic acid molecules in human subjects classified

as “research” require Committee review and authorization prior to initiation. These protocols still require registration with the Yale Human Investigation Committee.

### **On Campus Registrations and Approvals**

It is recommended that HGT registrations or notifications are pursued in the following order:

- A. Notification to Yale New Haven Hospital (YNHH) Hospital Epidemiology and YNHH Occupational Health of the request to conduct a HGT protocol at the YNHH.

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 is a sufficient number of personnel from the groups above (pharmacists, nurses, doctors, and other health care providers) 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

**General registrations must be received by the Biological Safety Committee by the 1<sup>st</sup> Thursday of each month, to have an opportunity to be reviewed by the Committee at the monthly meeting on the 3<sup>rd</sup> Thursday of each month.**

**As these protocols are usually more complex than a standard recombinant DNA project that does not involve human subjects, the “best” day to submit a Human Gene Transfer Protocol is on the 3<sup>rd</sup> Thursday of the month. This will guarantee the “longest” time in between monthly Committee meetings to allow sufficient time for review.**

C. Registration with the Yale Human Research Protection Program Human Investigation Committee

Contact information for each of these groups is provided below.

**Yale New Haven Hospital**

YNHH Infection Prevention (203) 688-4634

YNHH Occupational Health – York St (203) 688-4242

**Note: Human Gene Transfer (HGT) at Yale New Haven Hospital**

To determine if your proposed HGT research may require review and clearance from the YNHH Infection Prevention Department, please contact the Medical Director, Infection Prevention, at (203) 688-4634. All personnel who handle potential hazards at YNHH must notify the YNHH Occupational Health Office at (203) 688-4242 to receive additional health and safety information related to the project. 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 HGT experiments planned within YNHH.**

***Once your HGT Protocol is approved by the***

***Yale HIC and the Yale IBC:***

***The Yale IBC approval letter will require a “start-up meeting” with YNHH. It is advisable that you contact YNHH immediately after receiving all approvals to set up this meeting.***

Please don't hesitate to contact Biosafety at (203) 785-3550 if you have any questions.

**Yale Biological Safety Committee (IBC)**

(203) 785-3550 (through Biosafety Representatives)

<http://ehs.yale.edu/biosafety-committee>

<http://provost.yale.edu/committees>

**Yale Human Research Protection Program (IRB): Human Investigation Committee**

(203) 785-4688

<http://www.yale.edu/hrpp/>

<http://www.yale.edu/hrpp/forms-templates/biomedical.html>

**HRPP Contact Information:**

25 Science Park, 3<sup>rd</sup> Floor  
150 Munson Street  
PO Box 208327  
New Haven, CT 06520-8327  
Phone: (203) 785-4688  
Fax: (203) 785-2847  
[hrpp@yale.edu](mailto: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 (203) 785-4688 for information on their requirements.

**Federal Registration and Approval**

As of August 2018, registration with the NIH for recombinant and synthetic nucleic acids research involving human subjects is no longer required. However, projects with recombinant and synthetic nucleic acids research involving human subjects must be registered with and approved by the FDA.

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.

## **Application for Human Gene Transfer (HGT) Clinical Trials at Yale University**

To initiate the review of a proposed HGT clinical trial, please follow the instructions on pages 9 – 12 of this document. Please forward your documents to the Yale Biological Safety Committee at the address below. You may also submit your required documents electronically to [ehs@yale.edu](mailto:ehs@yale.edu).

The Yale Biological Safety Committee meets on the 3<sup>rd</sup> Thursday of each month.

The deadline for the receipt of recombinant DNA and HGT protocols is the 1<sup>st</sup> Thursday of each month.

As HGT protocols are usually more complex than non-clinical recombinant DNA protocols, it is highly recommended that they are submitted well before the Committee meeting date. **THE IDEAL DATE FOR THE SUBMISSION OF AN HGT PROTOCOL IS THE 3<sup>RD</sup> THURSDAY OF THE MONTH. This will provide at least 30 days for the review of the protocol by the Human Gene Transfer Subcommittee for the Yale Biological Safety Committee.**

The latest edition of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH Guidelines) was published in April 2019. To obtain a copy of the NIH Guidelines, access the NIH Office of Science Policy (OSP) web site at the URL shown below or contact the Biosafety Office at (203)785-3550.

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

NIH OSP web site:

<https://osp.od.nih.gov/biotechnology/biosafety-and-recombinant-dna-activities/>

## **Yale Biological Safety Committee Submission Requirements for the Review of Human Gene Transfer (HGT) Protocols**

For initial review by the HGT Subcommittee of the Yale Biological Safety Committee the following are required:

- Yale EHS IBC HGT Registration Form ('Protocol Profile') [included on pages 9 - 12]
- Sponsor's Protocol (or Clinical Study Protocol)
- Investigator's Brochure (or Principal Investigator's Brochure)

Only complete protocols will be sent to Yale Biological Safety Committee members for review. Specifically, we'll need:

- The Yale Biological Safety Committee HGT Registration Form ('Protocol Profile')
- Scientific abstract (as provided in the (Principal) Investigator's brochure)
- Non-technical abstract (as provided in the informed consent document)
- A copy of the HIC Informed Consent Document (a draft is acceptable for Yale Biological Safety Committee review process)
- Sponsor's Protocol (Clinical Study Protocol)
- Principal Investigator's (Investigator's) Brochure
- Sponsor's Pharmacy Manual (and if available Sponsor's Nursing Manual)
- Curricula vitae (2 pages) for each key professional in biographical sketch format (The Principal Investigator and 2 to 3 other lead personnel is sufficient)
- The proposed location for vector production and description of the Good Manufacturing or Good Clinical Practices that will be utilized to prepare the research material (study drug)
- A copy of the Certificate of Analysis (CoA) for sterility for each lot of study drug made at Yale or sent to the University for this experiment (this may be submitted after Yale Biological Safety Committee review but will be needed prior to administration of the study drug to the first patient).

**Yale EHS IBC Human Gene Transfer (HGT) Registration Form ('Protocol Profile')**

*If this information is already detailed in one of your existing documents, please provide the document title and page number(s) in the applicable spaces below*

Principal Investigator	Sponsor: Manufacturer (of product):
Title of Protocol	
FDA IND #: Yale HIC#:	Sponsor Protocol #:
Targeted Disease or Clinical Aim of Project:	
Summary of preclinical studies conducted in support of the proposed clinical trial or reference to the specific section of the protocol providing this information.	
Product description	
Derivation of the delivery vector system including the source (e.g., viral, bacterial, plasmid), associated modifications (i.e., deletions to attenuate or self-inactivate, encapsulation in any synthetic complex, changes to tropisms), and previous clinical experience with the system	



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, truncations)

Any other material to be used in preparation of the agent (vector and transgene) to be administered to research participants (e.g., helper virus, packaging cell line, carrier particles)?

Intended *ex vivo* or *in vivo* target cells and transduction efficiency

Gene transfer agent delivery method

Methods for replication-competent virus testing

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:

Please outline the procedures that will be followed in the event of a spill of the investigational agent:

Please outline the procedures that will be followed in the event of a staff member's exposure to the investigational agent:

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:

**Note:** Any application submitted shall not contain any document that is designated as 'confidential' in its entirety. If a determination has been made that a specific portion of a document should be considered proprietary or trade secret, each specific portion shall be clearly identified as such. If a specific portion of the submission is identified to be proprietary or trade secret, the submission to the Yale IBC must contain a letter that: (1) clearly indicates what select portions of the application contain information considered as proprietary or trade secret, and (2) provides justification as to why this information is 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.

## **Pathway for human gene transfer (HGT) 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 rationale 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 (pages 7 - 12) to the Yale Biological Safety Committee.
5. The EHS Biosafety Office verifies that all documentation has been received and submits the complete protocol to members of the Yale Biological Safety Committee's HGT 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 Investigator's research team.
7. The chair of the HGT Subcommittee, or designee, will provide the recommendation of the HGT Subcommittee on the protocol to the Yale Biological Safety Committee.
8. 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 usually held monthly on the third Thursday of the month.
9. The results of the Yale Biological Safety Committee review are communicated to the Principal Investigator and the Yale Human Investigation Committee. If approved, the Principal Investigator will receive an approval letter for the protocol from the Yale Biological Safety Committee.
10. Principal Investigator submits a registration for conducting research involving human subjects to the Yale Human Investigation Committee.
11. 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.
12. For protocols being conducted at the Yale New Haven Hospital: Once the Principal Investigator receives approvals from both Committees (the Biological Safety Committee and the Human Investigation Committee), the Principal investigator must contact the Yale New Haven Hospital Infection Control Committee to set up a protocol review meeting prior to the initiation of the protocol.

## **Adverse Events and Reporting Requirements**

### **Unintended Consequences Among Staff**

If a clinical study team member experiences an exposure, injury, or infection related to their participation in the study, this must be reported to both the Yale Biological Safety Committee and the Yale Human Investigation Committee. Each Committee has subsequent reporting requirements to their respective federal agencies (NIH Office of Science Policy and the FDA).

### **Adverse Events Experienced by Study Subjects**

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 the sponsor. Any **Serious Adverse Events (SAE's)** must be reported by telephone (to who?) 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, and the FDA 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 number, 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.

## April 2019 Yale and NIH Points to Consider for the IBC Review of Human Gene Transfer Protocols

The following documentation must be submitted to the Yale Institutional Biological Safety Committee to initiate the review of an HGT protocol.

- A scientific abstract as provided in (Principal) Investigator's Brochure
- The proposed clinical protocol, including tables, figures, and any relevant publications

Ensure that the information described in the bulleted list below is included in the materials submitted to the Committee. The information may be described in the Clinical Study Protocol or the Investigator's Brochure. If not, please provide the information in a separate document.

- Summary of preclinical studies conducted in support of the proposed clinical trial or reference to the specific section of the protocol providing this information.
- Product description, for instance:
  - Derivation of the delivery vector system including the source (e.g., viral, bacterial, plasmid), associated modifications (i.e., deletions to attenuate or self-inactivate, encapsulation in any synthetic complex, changes to tropisms), and previous clinical experience with the system
  - 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, truncations)
  - Any other material to be used in preparation of the agent (vector and transgene) to be administered to research participants (e.g., helper virus, packaging cell line, carrier particles)
  - Methods for replication-competent virus testing
  - Intended *ex vivo* or *in vivo* target cells and transduction efficiency
  - Gene transfer agent delivery method

**Note:** Any application submitted shall not contain any document that is designated as 'confidential' in its entirety. If a determination has been made that a specific portion of a document should be considered proprietary or trade secret, each specific portion shall be clearly identified as such. If a specific portion of the submission is identified to be proprietary or trade secret, the submission to the Yale IBC must contain a letter that: (1) clearly indicates what select portions of the application contain information considered as proprietary or trade secret, and (2) provides justification as to why this information is 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.

## **April 2019 Amendment of the *NIH Guidelines* - NIH Office of Science Policy**

This section provides many of the frequently asked questions (FAQs) related to human gene transfer from the NIH Office of Science Policy web site. Additional FAQs are available on the NIH Office of Science Policy web site at <https://osp.od.nih.gov/biotechnology/faqs-on-the-nih-guidelines-research-synthetic-nucleic-acid-molecules/>.

### **What specific changes have been made to the *NIH Guidelines* regarding human gene transfer (HGT) protocol submission and reporting requirements to NIH's Office of Science Policy (OSP)?**

Under the *NIH Guidelines*, individual HGT protocol submission and reporting to NIH/OSP are no longer required. Specifically, NIH/OSP will not: accept or register new HGT protocols; convene the Recombinant DNA Advisory Committee (RAC) to review individual HGT protocols; accept annual reports, safety reports, amendments or other documentation for any HGT protocols previously registered under the *NIH Guidelines* (formerly, Appendix MI-C).

### **What changes have been made to the *NIH Guidelines* regarding the roles and responsibilities of relevant entities?**

It is important to note that while NIH is streamlining individual human gene transfer (HGT) protocol reporting requirements, robust oversight over HGT research will continue through both Federal and local oversight bodies. The roles and responsibilities of investigators, institutions, and oversight bodies involved in HGT research remain the same, except: The roles of Institutional Biosafety Committees in reviewing HGT research have been modified to be consistent with the review of other research covered by the *NIH Guidelines*.

Principal Investigators (PIs) will no longer be responsible for ensuring requirements for protocol submission, review, and reporting for HGT protocols to NIH's Office of Science Policy are addressed, since these responsibilities have been eliminated. All other roles and responsibilities for PIs will remain the same.

Because the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC) will now focus on advising the NIH Director on scientific, safety, and ethical issues associated with emerging biotechnologies (which is not necessarily limited to recombinant or synthetic nucleic acid molecule research), non-historical references to the Recombinant DNA Advisory Committee will be removed from the *NIH Guidelines*. The roles and responsibilities will be delineated in the charter, as is typical for such committees.

### **Is human gene transfer (HGT) research still covered under the *NIH Guidelines*? What is required before a Principal Investigator or sponsor can initiate HGT research and begin enrollment/recruitment/accrual?**

Yes. When conducted by an entity subject to the *NIH Guidelines* (see Section I-C), HGT research (see Section III-C) is still covered, as protocols must still be reviewed and approved by Institutional Biosafety Committees to assess biosafety considerations at the clinical trial site. In addition, all other applicable institutional and regulatory authorization(s) and approvals must be obtained before any research with human participants can be initiated.



**If human gene transfer (HGT) protocols are no longer registered with NIH's Office of Science Policy (OSP), will sites conducting only HGT research still need to register their Institutional Biosafety Committees (IBCs) with NIH/OSP?**

Yes. All entities conducting research subject to the *NIH Guidelines*, including HGT research, must have an appropriately constituted IBC registered with NIH/OSP. For additional information on registering an IBC, see Section IV-B-2 of the *NIH Guidelines* and on the NIH/OSP website: <https://osp.od.nih.gov/biotechnology/faqs-on-ibc-administration/>.

**Is human gene transfer research conducted under Food and Drug Administration (FDA)-regulated individual patient expanded access Investigational New Drug (IND) applications subject to the *NIH Guidelines*?**

No. The deliberate transfer of recombinant or synthetic nucleic acids into one human research participant, conducted under an FDA-regulated individual patient expanded access IND or protocol, including for emergency use, is not research subject to the *NIH Guidelines* and thus, does not need to be submitted to an Institutional Biosafety Committee for review and approval. Specific guidance regarding FDA requirements is provided at:

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expanded-access-investigational-drugs-treatment-use-questions-and-answers>

**Will Institutional Biosafety Committees (IBCs) be required to change their review processes? What aspects of human gene transfer (HGT) research should IBCs focus on?**

The focus of the IBC review of HGT research should be equivalent to their review of the biosafety aspects of other covered research, e.g.:

- required containment levels
- potential for shedding
- safety and training of laboratory/technical personnel involved in the clinical protocol details of the facilities
- adequacy and maintenance of safety equipment that may be used in support of the clinical protocol
- safety procedures and practices when working with the product and during administration to a protocol participant
- reporting of biosafety accidents and incidents occurring during conduct of the protocol
- approving emergency response plans for accidental spills and personnel contamination

As with other research reviewed by IBCs, IBCs should determine what information they require to complete their biosafety review of HGT protocols.

IBC oversight may conclude after the last participant is administered the final dose of product. However, IBCs may choose to establish other end points for oversight, based on their biosafety assessment of the proposed research.

Other aspects of HGT research, such as review of informed consent, are under the purview of the Food and Drug Administration and Institutional Review Boards.

**Should biosafety incidents occurring during the conduct of human gene transfer (HGT) research still be reported to NIH’s Office of Science Policy (OSP)?**

Yes. The *NIH Guidelines* require that “...any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses” be reported to NIH. Reports of incidents can be emailed to [NIHGuidelines@od.nih.gov](mailto:NIHGuidelines@od.nih.gov). Relevant incidents would include spills and accidents that result in overt exposures to organisms containing recombinant or synthetic nucleic acid molecules in the laboratory, rather than serious adverse events that may occur in the conduct of HGT research. Additional information on incident reporting and a reporting template are available on the NIH/OSP website at <https://osp.od.nih.gov/biotechnology/nih-guidelines/>.

### **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 (HGT) 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 Human Gene Transfer (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:

The protocol also has the following additional requirements:

- IRB Approval Letter. Please send the Yale IBC a copy of the current IRB Approval Letter for your IBC protocol file.
- Documentation of a start-up discussion of this protocol with representatives from YNHH that may include: nursing 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 using the product) must be reported to the IRB of Record within 48 hours.
- A copy of the FDA IND authorization email accepting the initiation of the trial at Yale must be on file with the Yale IBC prior to the enrollment of patients in the trial. 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 approved by the FDA.
- A copy of the annual report to the FDA and the IRB must also be submitted to the Yale IBC for the protocol file.

The Yale IBC approval of your protocol will expire on the expiration date of the IRB protocol as reflected in the IRB approval letter. The IBC re-approval is contingent on the re-approval by the IRB of record. The protocol must be re-approved by the IRB of record at least 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 (HGT) 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.