I. PURPOSE
The purpose of this SOP is to provide guidance to Principal Investigators (PIs) of human gene transfer (HGT) studies on federally and institutionally mandated reporting requirements. Reports should be submitted to the National Institutes of Health Office of Biotechnologies (NIH/OBA) and to the Dartmouth Biosafety Officer on behalf of the Dartmouth Institutional Biosafety Committee for Clinical Gene Transfer (IBC-CGT).

II. REGULATORY BACKGROUND
Institutions that receive support from the National Institutes of Health (NIH) for recombinant or synthetic nucleic acid research are required to comply with the NIH Guidelines for Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines). The NIH requires that all HGT research (regardless of whether that research is directly supported by the NIH) at NIH funded institutions is reviewed by the NIH Recombinant DNA Advisory Committee (RAC) and is reviewed and approved by the Institutional Biosafety Committee (IBC) before enrollment. If such research is conducted without approval, the NIH has the authority to withdrawal research support from that study or institution. The NIH Guidelines outlines specific safety reporting requirements, as summarized below.

III. PRINCIPAL INVESTIGATOR RESPONSIBILITIES (NIH Guidelines Section IV-B-7)
On behalf of Dartmouth, the Principal Investigator is responsible for full compliance with the NIH Guidelines in the conduct of recombinant or synthetic nucleic acid molecule research.

Definition: The Principal Investigator (PI) designation is given to a Dartmouth faculty member who has primary responsibility and accountability to direct the proper conduct of a scientific research project or program. If the research is conducted by a team of researchers at a research site, the Principal Investigator is the leader responsible for that team whose name appears as Principal Investigator on the Grant Application or Award. With regard to the IBC-CGT, the PI has overall responsibility of laboratory and/or clinical personnel working under the requirements of the NIH Guidelines.

Responsibilities: To comply with the NIH Guidelines and adhere to the institutional requirements of the Dartmouth IBC-CGT, the PI shall:

i. not initiate or modify any human gene transfer research prior to review and approval by the Dartmouth IBC-CGT;
ii. submit the initial research protocol and any subsequent changes to the IBC-CGT for review and approval in accordance with the \textit{NIH Guidelines};

iii. remain in communication with the IBC-CGT throughout the conduct of the project;

iv. immediately report any adverse events, significant problems, violations of the \textit{NIH Guidelines}, or any significant research-related accidents and illnesses to the Biosafety Officer, IBC-CGT, NIH/OBA, and other applicable authorities;

v. adhere to Dartmouth approved emergency plans for handling accidental spills and personnel contamination;

vi. comply with national and international shipping requirements for infectious agents and recombinant or synthetic nucleic acid molecules;

vii. supervise and correct the safety performance of the laboratory/clinical staff to ensure that the required safety practices and techniques are employed;

viii. ensure the integrity of the physical containment (e.g., biological safety cabinets) and the biological containment (e.g., purity and genotypic and phenotypic characteristics).

IV. REPORTING PROCEDURES

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

No later than \textit{20 working days} after enrollment of the first research participant in a human gene transfer experiment, the Principal Investigator(s) shall submit the following documentation to NIH OBA:

i. copy of the informed consent document approved by the Dartmouth IRB

ii. copy of the protocol approved by the Dartmouth IBC-CGT and IRB

iii. copy of the final Dartmouth IBC-CGT approval

iv. copy of the final Dartmouth IRB approval

v. 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

vi. applicable NIH grant number(s)

vii. the FDA Investigational New Drug Application (IND) number. The purpose of requesting the FDA IND number is for facilitating interagency collaboration in the Federal oversight of human gene transfer research.

viii. the date of the initiation of the trial

B. Additional Clinical Trial Sites (Appendix M-I-C-2)

If a Principal Investigator is leading a study for which Dartmouth is an additional clinical trial site and RAC review was already executed for the first trial site, then the Dartmouth PI must submit the following documentation to NIH OBA \textit{PRIOR} to enrollment:

i. Dartmouth IBC-CGT approval

ii. Dartmouth IRB approval

iii. IRB-approved informed consent document
iv. curriculum vitae of the Principal Investigator(s) (no more than two pages in biographical sketch format)

v. NIH grant number(s) if applicable.

These reports should be sent in paper or electronic form to: Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), 301-496-9838, 301-496-9839 (fax), E-mail: rosenthg@od.nih.gov. NIH OBA will confirm receipt within three working days after receiving the submission.

After receipt, the NIH will create a study profile in GeMCRIS http://osp.od.nih.gov/office-biotechnology-activities/biomedical-technology-assessment/hgt/gemcris. GeMCRIS is used as an electronic record for human gene transfer studies. Annual and safety reports should be uploaded into GeMCRIS.

C. Annual Reports (Appendix M-I-C-3)

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 (i), (ii), and (iii) to the IBC-CGT and to the NIH/OBA. 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. Reports submitted to the NIH/OBA may be uploaded directly to GeMCRIS and reports submitted the Dartmouth IBC-CGT may be sent to the Biosafety Officer.

i. 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:

a. the title and purpose of the trial
b. clinical site
c. Principal Investigator
d. clinical protocol identifiers, including the NIH OBA protocol number, NIH grant number(s) (if applicable), and the FDA IND application number
e. participant population (such as disease indication and general age group, e.g., adult or pediatric)
f. 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
g. the status of the trial, e.g., open to accrual of subjects, closed but data collection ongoing, or fully completed, and
h. if the trial has been completed, a brief description of any study results.

ii. Progress Report and Data Analysis. Information obtained during the previous year's clinical and non-clinical investigations, including:

a. a narrative or tabular summary showing the most frequent and most serious adverse experiences by body system
b. a summary of all serious adverse events submitted during the past year
c. 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
d. if any deaths have occurred, the number of participants who died during participation in the investigation and causes of death, and
e. 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.

iii. A copy of the updated clinical protocol including a technical and non-technical abstract.

D. Safety Reporting Requirements

1. Where to submit: Serious adverse events are to be reported to NIH/OBA: 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. PIs may also upload reports directly to GeMCRIS.

2. Definitions

A. Serious Adverse Event (SAE):
The NIH Guidelines define a “serious adverse event” as:
“any event occurring at any dose that results in any of the following outcomes: death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization also may be considered a serious adverse event when, upon the basis of appropriate medical judgment, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition” (Section I-E-8).

B. Adverse Event (AE):
The NIH Guidelines defines an “adverse event” as being “associated with the use of a gene transfer product” when there is a reasonable possibility that the event may have been caused by the use of that product” (Section I-E-9).

C. Unexpected Serious Adverse Event:
The NIH Guidelines defines an “unexpected serious adverse event” as “any serious adverse event for which the specificity or severity is not consistent with the risk information available in the current investigator’s brochure” (Section I-E-10).

3. Safety Reporting: Background (NIH Guidelines Appendix M-I-C-4)
Principal Investigators must submit 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 OBA) and to the local Institutional Biosafety Committee (IBC-SCGT) within the timeframes set forth in this Section.

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 OBA of the delegation and of the name(s), address, telephone and fax numbers of the contact(s). Even if the duty has been delegated, the Principal Investigator is responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses.

4. Safety Reporting: Content and Format (NIH Guidelines Appendix M-I-C-4a)
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
17. the suspected cause of the event
These items may be reported by using the recommended Adverse Event Reporting Template available on NIH OBA’s web site at: http://oba.od.nih.gov/rdna/adverse_event_oba.html, 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.

5. Safety Reporting: Time Frames for Expedited Reports (NIH Guidelines Appendix M-I-C-4b)

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 IBC-SCGT and NIH OBA 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 IBC-SCGT and NIH OBA 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 IBC-SCGT and NIH OBA 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 IBC-SCGT and NIH OBA 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).

V. RESOURCES