DARTMOUTH
ENVIRONMENTAL HEALTH & SAFETY
Biological Safety Program

Dartmouth Health
Institutional Biosafety Committee for Clinical Gene Transfer
Charter

Version: 4

The Dartmouth Health (DH) Institutional Biosafety Committee for Clinical Gene Transfer (IBC-CGT) is a formal committee of subject matter experts and community representatives who provide oversight of safe work practices for gene therapy-related clinical trials at Dartmouth-Hitchcock Medical Center (DHMC) in Lebanon, NH.

The DH IBC-CGT is administered by the Dartmouth College Biological Safety Officer (BSO) under contract with the Dartmouth College Office of Environmental Health & Safety (EHS).

I. PURPOSE

Institutions that receive support from the National Institutes of Health (NIH) for recombinant or synthetic nucleic acid research are required to establish and register an IBC with the NIH Office of Science Policy (OSP) in compliance with the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (*NIH Guidelines*). The establishment and operation of the Dartmouth Health IBC-CGT fulfills this requirement. The NIH requires all institutions receiving NIH research funds to have all human gene transfer research reviewed by an IBC (regardless of whether that research is directly supported by the NIH), as stipulated by the *NIH Guidelines*. IBC approval must be obtained from each institution at which recombinant or synthetic nucleic acid molecule material will be administered to human subjects. If such research is conducted without approval, the NIH has the authority to withdrawal research support from that study or institution.

The *NIH Guidelines* note that "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."

II. DEFINITIONS

A. Human gene transfer

Section III-C-1 of the *NIH Guidelines* defines human gene transfer as the deliberate transfer into human research participants of either:

i. Recombinant nucleic acid molecules, or DNA or RNA derived from recombinant nucleic acid molecules, or

ii. Synthetic nucleic acid molecules, or DNA or RNA derived from synthetic nucleic acid molecules, that meet any one of the following criteria:

- Contain more than 100 nucleotides; or
- Possess biological properties that enable integration into the genome (e.g., *cis* elements involved in integration, gene editing); or
- Have the potential to replicate in a cell; or
- Can be translated or transcribed.

B. Recombinant or Synthetic Nucleic Acid Molecules

In the context of the *NIH Guidelines*, recombinant and synthetic nucleic acids are defined as:

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

ii. nucleic acid molecules that are chemically or by other means synthesized or amplified, including those 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.

III. FUNCTION

Experiments involving the use of recombinant or synthetic nucleic acids can pose potential risk to study subjects, clinical research personnel, and the environment. The function of the IBC-CGT is to ensure that all aspects of HGT research are conducted in a safe manner according to established biosafety standards, principles, practices, and authorizations.

To serve this function, the IBC-CGT reviews:

i. the scientific principles and objectives of the clinical gene transfer protocol

ii. the clinical protocol, investigator's brochure, and pharmacy manual for concerns of the safety of personnel, the community, and the environment

iii. the Local Safety SOP developed by the BSO and Principal Investigator (PI)

The IBC-CGT has the authority to approve, require modifications in, or disapprove research activities that fall within its jurisdiction. New clinical gene transfer protocols and amendments to existing protocols are subject to review by the committee prior to activation.

IV. REVIEW OF CHARTER

This charter shall be reviewed and reassessed by the IBC-CGT at least every three years, or when relevant changes to the *NIH Guidelines* occur, and any proposed changes shall be submitted to the IBC-CGT for approval.

V. SUBCOMMITTEES

When needed, the IBC-CGT can form subcommittees for specific research oversight. These subcommittees will report to the IBC-CGT.

VI. BY-LAWS

A. Membership Organization

The Dartmouth IBC-CGT may contain no fewer than five members, with at least:

- A Chair
- The BSO
- A representative from the DH Human Research Protection Program
- Two community members who work or live in the Upper Valley area and who represent the interest of the surrounding community with respect to health and protection of the environment. These members will not be directly affiliated with Dartmouth Health (required by NIH)

Regular IBC-CGT membership will also include representatives from areas such as, but not limited to:

- Human research protocol review
- Clinical trials
- Basic and/or translational research
- Infectious disease and/or occupational medicine
- Pharmacy and/or pharmacology
- The Dartmouth Health basic research IBC

The IBC-CGT may use consulting experts or establish working groups of members or non-members to execute its responsibilities or acquire needed expertise for select tasks. Consultants or working group members may include, for example, persons knowledgeable in institutional commitments and policies, applicable law, standards of professional conduct and practice, community attitudes, the environment, or any scientific area where the IBC-CGT members do not have expertise. Consultants or working group members are not IBC voting members unless nominated and appointed as described below.

B. Procedure for Appointing Members

The Dartmouth College EHS Director formally appoints all IBC-CGT members. Department Chairs are consulted prior to membership invitation of faculty. Regular and ad-hoc members will be selected by the IBC-CGT Chair or BSO.

C. Terms of Membership

IBC membership is a minimum three-year period of service. Members may be appointed for subsequent three-year terms if they are willing to continue to serve. If a member does not attend three consecutive meetings, the IBC-CGT Chair may motion that a replacement be nominated.

D. Conflict of Interest Policy

No member of the IBC-CGT may be involved (except to provide information requested by the IBC-CGT) in the review or approval of a project in which he/she has been (or expects to be) engaged or in which he/she has a direct financial interest. IBC-CGT members are also asked to withdraw from decisions where, owing to their personal relationships, there might be either real or perceived conflicts of interest. Each member is expected to notify the IBC-CGT Chair in these circumstances and recuse him/herself when such proposals are being discussed and are up for a vote. In addition, if the IBC-CGT Chair is the principal investigator on a project, the Biosafety Officer and EHS Director will sign the approval letter or any resulting correspondence.

E. Quorum

Meetings will proceed with a majority (over 50%) of the current membership. All IBC-CGT members are voting members. Decisions such as approval of research projects or policies are approved when a majority of IBC-CGT members present vote for approval. In the event that the IBC-CGT Chair must be absent, he/she will request another committee member to serve as chair during the absence.

F. Meetings

The IBC-CGT will convene on an ad-hoc basis for initial consideration of clinical gene transfer protocols and modifications to those protocols, and at least annually for study updates and refresher training. A proposed agenda will be developed and distributed before the meeting by the BSO or his/her designee. Meeting minutes will be taken by the BSO or his/her designee to accurately reflect the topics of discussion. Meeting minutes will be reviewed, approved by the members, and maintained on file at EHS for at least five years. Principal Investigators are always welcome to present their work to the IBC-CGT and are encouraged to attend. When possible and consistent with protection of privacy and proprietary interests, IBC-CGT meetings will be made publicly accessible upon request.

G. Agenda, Minutes, Approval Letters, and Reports

The BSO, in collaboration with the IBC-CGT Chair, shall be responsible for establishing the agendas for meetings. An agenda, together with relevant materials, shall be sent to committee members at least 5 days in advance of the meeting. Minutes for all meetings shall be drafted by the BSO and emailed to all committee members within one week of a meeting. Because the IBC-CGT meets infrequently, members may vote to approve minutes via email to the BSO. This vote must be unanimous and no other topics may be voted on outside a meeting. Decision letters will be drafted by the BSO and co-signed by the Chair. Reports to institutional management and outside agencies will be drafted by the BSO in collaboration with the Chair.

DH shall make available to the public all IBC-CGT meeting minutes and any documents submitted to or received from funding agencies upon request in accordance with requirements of the *NIH Guidelines*. If public comments are made on IBC-CGT actions, the BSO shall forward both the public comments and the IBC-CGT's response to the 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).

The DH IBC-CGT shall follow the current policies of the Dartmouth College IBC relating to public attendance at meetings, public access to meeting minutes, and redaction of minutes.

H. Relationships to Other Committees

The IBC-CGT supports transparency between the IBC-CGT, basic research IBC, Human Research Protection Program, Office of Clinical Research, the Clinical Cancer Review Committee, and other groups involved in clinical research oversight. Overlap of membership between these committees will be prioritized in order maintain this collaborative oversight.

I. Confidentiality

IBC-CGT members are required to maintain confidential and/or proprietary information that they may have access to in connection with their role on the IBC strictly confidential, and to use it only for the purposes of carrying out their duties as IBC-CGT members.

VII. ROLES & RESPONSIBILITIES

A. Institution (in accordance with NIH Guidelines Section IV-B-1)

Dartmouth Health is ultimately responsible for the effectiveness of the IBC-CGT and may establish procedures that the IBC-CGT shall follow in its initial and continuing review and approval of applications, proposals, and activities. Specifically, Dartmouth Health's responsibilities include:

i. maintaining the IBC-CGT so that the committee meets the requirements and carries out the functions detailed in the *NIH Guidelines*;

ii. appointing the required expertise to the IBC-CGT, including a Biosafety Officer, an expert in human gene transfer studies, and experts in the handling of recombinant or synthetic nucleic acids, and community members;

iii. ensuring appropriate training for the IBC-CGT Chair and members, Biosafety Officer and other containment experts (when applicable), Principal Investigators, and laboratory or clinical staff regarding safety and implementation of the *NIH Guidelines*.

iv. ensuring that no human gene transfer experiment shall be initiated until Institutional Biosafety Committee approval has been obtained and all other applicable institutional and regulatory authorization(s) and approvals have been obtained. Institutional Biosafety Committee approval must be obtained from the clinical trial site.

B. Institutional Biosafety Committee (IBC) (in accordance with NIH Guidelines, Section IV-B-2)

IBC-CGT duties include:

i. review of all human gene transfer experiments for compliance with the *NIH Guidelines* as specified in Section III-C: Experiments Covered by the *NIH Guidelines*, and approving those research projects that are found to conform with the *NIH Guidelines*;

ii. assessment of the facilities, procedures, practices, and training and expertise of personnel involved in human gene transfer research to determine appropriate biocontainment levels required by the *NIH Guidelines* for the proposed research;

iii. notifying the Principal Investigator of the results of the IBC-CGT's review and approval;

iv. investigating and reporting any significant problems with or violations of the *NIH Guidelines* and any significant research-related accidents and illnesses to the appropriate institutional official and NIH OSP within 30 days. Reports shall be sent to the Office of Science Policy, National Institutes of Health, preferably by e-mail to: NIHGuidelines@od.nih.gov; additional contact information is also available here and on the OSP website(www.osp.od.nih.gov).

C. Biosafety Officer (BSO) (in accordance with NIH Guidelines Section IV-B-3)

The Biosafety Officer's duties include, but are not limited to:

i. submit an annual report to NIH/OBA that includes a roster of IBC-CGT members, indicating the Chair, contact person, Biosafety Officer, human gene therapy expert or ad hoc consultant (if applicable), other member roles, and biographical sketches of each member;

ii. report to the IBC-CGT any significant problems, violations of the *NIH Guidelines*, and any significant research-related accidents or illnesses or severe adverse events of which the BSO becomes aware;

iii. develop training materials for the IBC-CGT on the NIH Guidelines

iv. provide administrative support for IBC-CGT activities, including preparation of meeting agendas, minutes, and materials;

v. provide technical advice to Principal Investigators and the IBC-CGT on research safety procedures;

vi. follow-up on contingent approvals to ensure all contingencies are met and report to the IBC when contingencies have been met and final approval given.

D. Principal Investigator (in accordance with NIH Guidelines Section IV-B-7)

On behalf of Dartmouth Health, 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 local faculty member or clinician who has primary responsibility and accountability to direct the proper conduct of a scientific research project or program at DHMC. For IBC-CGT purposes, this is the individual listed as PI with the DH Institutional Review Board. 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, the PI shall:

i. not initiate or modify any human gene transfer research prior to review and approval by the IBC-CGT;

ii. submit the initial research protocol and any subsequent changes to the IBC-CGT for review and approval or disapproval and make an initial determination of the required levels of physical and biological containment in accordance with the *NIH Guidelines*;

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

iv. immediately report any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses to the Biosafety Officer, IBC-CGT, NIH/OSP, and other applicable authorities;

v. adhere to Dartmouth IBC-CGT 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. instruct and train laboratory/clinical staff in: (a) the practices and techniques required to ensure safety, (b) the procedures for dealing with accidents, and (c) the reasons and provisions for any precautionary medical practices advised or requested (e.g., vaccinations or serum collection);

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

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

VIII. IBC-CGT SUBMISSION AND APPROVAL PROCESS

The research review process by the IBC is conducted in a step-wise fashion, starting with the submission of research information by the PI.

A. IBC-CGT Submission

For full-committee reviews, the following materials must be submitted to the Biosafety Officer:

i. Correspondence Materials:
- Letter of scientific review/merit (e.g., Department Approval Letter, CCRC Approval Letter)
- Letter of IRB approval or date of expected IRB review
- Letter of assurance from the investigational/site pharmacy of ability to receive, house, and dispense study agent

ii. Protocols/Procedures/Manuals
- Completed Local Safety Standard Operating Procedure (SOP) template
- Clinical Protocol
- Signed Investigator Protocol Signature Page
- Investigator's Brochure (IB)
- Pharmacy and/or Laboratory Manual for study agent

iii. Documentation of completion of appropriate training requirements (e.g. BSL2, bloodborne pathogens training) for all study personnel and pharmacy personnel who will come into contact with study agent.

iv. For amendments to existing studies, only the modified materials need to be submitted.

B. IBC-CGT Review Process for New Studies

i. BSO Pre-Review: The BSO will review the submitted research materials and conduct a risk assessment based upon the information provided. Any questions/problems/concerns will be directed back to the PI for clarification. Once all aspects of the risk assessment have been satisfied, the research will be presented to the IBC-CGT for review by either the BSO or the PI. Or, if the BSO determines that the proposed study is not subject to or exempt from the *NIH Guidelines*, and the IBC-CGT Chair agrees, the research will not be reviewed by the IBC-CGT.

ii. IBC-CGT Review: The IBC will review the research information submitted and discuss the safety and regulatory aspects of the research project. Discussion topics include: the nature of experimentation, biohazards and use of other hazardous materials, containment, location, recombinant or synthetic nucleic acid aspects, training requirements, etc. All non-members, ad-hoc members, and members with conflicts of interest will leave the room prior to final discussion and voting. At the time of voting, the IBC-CGT will vote for one of the following:

- Approve: the study has scientific merit, necessary regulatory requirements have been met and there are no outstanding biological safety issues. The study is approved as submitted. The investigator is not required to change any aspect of the protocol or provide any additional documentation. A letter of approval is sent to the investigator with copies to CPHS/IRB.

- Conditionally Approve: the study has scientific merit; however, the committee may require clarification or minor modifications of the protocol relevant to its design, conduct or biosafety issues. The committee may also require additional regulatory documentation. The investigator's response will be reviewed by the Chair, BSO, and any other designated committee member(s). The reviewers may determine that all conditions of the committee have been adequately addressed, that the conditions have not been adequately addressed, or that the response should be reviewed by the full committee, in which case the committee will be convened to review the response.

- Deny: the concerns of the committee are substantive and that the magnitude and/or number of concerns are such that conditional approval is not appropriate. Full IBC-CGT review is required if the protocol is resubmitted.

- Table: a final decision has not been made and the IBC-CGT will revisit the review at a future time. This may be due to the need for further consideration or discussion, but generally not due to specific deficiencies which would otherwise result in conditional approval.

iii. Decision Letter Sent to PI: After the IBC-CGT makes a decision regarding the reviewed study, a decision letter will be sent to the PI co-signed by the Chair and BSO. Decision letters are sent for any approval, conditional approval, or denial of approval. A letter will also be furnished to the PI for projects deemed not subject to or exempt from the *NIH Guidelines*, which were not reviewed by full committee.

C. IBC-CGT Review of Amendments or Modifications to Existing Studies

Amendments to IBC-CGT approved research will be reviewed by the BSO and Chair to determine if any of the study changes are subject to the *NIH Guidelines* or otherwise increase the risks of using the study agent. If the *NIH Guidelines* apply or there are increased risks, the amendment will be brought

to full-committee review following the process for new studies outlines above. If the amendment is not subject to or exempt from the *NIH Guidelines* and does not increase the risks of using the study agent, the amendment will be administratively approved by the BSO and Chair and a decision letter provided to the PI.

D. Appeals

Principal Investigators may appeal IBC-CGT decisions in writing to the Chair, detailing the reasons for their objection(s) and proposing possible alternatives. The Chair, in consultation with the BSO, and other IBC-CGT members or advisors as needed, will determine if the appeal sufficiently justifies revisiting the decision with the full committee. If the appeal is denied, the reasons for the denial will be communicated in a letter to the PI and the decision will be final.

IX. RESOURCES

- *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*. National Institutes of Health Office of Science Policy, 89 FR 24016, 2024 April https://osp.od.nih.gov/biotechnology/nih-guidelines/