INSTITUTIONAL BIOSAFETY COMMITTEE FOR CLINICAL GENE TRANSFER (IBC-CGT) CHARTER

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I. PURPOSE

The Dartmouth College Institutional Biosafety Committee for Clinical Gene Transfer (IBC-CGT) is a formal Institutional Biosafety Committee (IBC) consisting of subject matter experts and overlapping members with the Dartmouth IBC for Basic Research, the Committee for the Protection of Human Subjects (CPHS, the Institutional Review Board (IRB)), and the Dartmouth-Hitchcock Health Human Research Protection Program (D-HH HRPP, IRB).

The purpose of the IBC-CGT is to review human gene transfer (HGT) studies as defined by the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines, 2019)* conducted at Dartmouth College, Geisel School of Medicine at Dartmouth, Mary Hitchcock Hospital, and Dartmouth-Hitchcock Clinic, including the Norris Cotton Cancer Center and the Department of Veterans Affairs Research Service, on the Hanover and Lebanon, NH and White River Junction, VT campuses. Collectively, these locations will be referred to as "Dartmouth" herein.

II. REGULATORY BACKGROUND

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.* The establishment of the Dartmouth IBC-CGT complies with this federal regulation. The NIH requires all institutions receiving research funds to have all HGT research reviewed by an IBC (regardless of whether that research is directly supported by the NIH). Institutional Biosafety Committee 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.

III. DEFINITIONS

Human gene transfer (HGT) 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 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.

IV. 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. This committee works closely with the Committee for Protection of Human Subjects (CPHS), the IRB at Dartmouth, as well as the Office of Clinical Research. Approvals are reported to the IRB.

To serve this function, the IBC-CGT reviews:

1) the scientific principles and objectives of the clinical gene transfer protocol
2) the clinical protocol, investigator's brochure, and pharmacy manual for concerns of the safety of personnel, the community, and the environment
3) the Local Safety SOP

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

V. REVIEW OF CHARTER

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

VI. BY-LAWS

A. Membership Organization

The Dartmouth IBC-CGT may contain no fewer than five members. Standing memberships on the IBC-CGT include the IBC Chair, the Biological Safety Officer (BSO), a representative from the IRBs and two community/non-affiliated members. Based on the purview of this committee, regular IBC-CGT membership will additionally include representatives from the following areas of expertise:

- Human research protocol review
- Clinical trials
- Basic and/or translational research
- Infectious disease
- Pharmacy, pharmacology
- Overlap members with the Dartmouth IBC for Basic Research

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 Biosafety Officer formally appoints all IBC 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 Biosafety Officer.

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 the IBC Chair will sign the approval letter or any resulting correspondence.

E. Quorum

Meetings will proceed with no less than five members present and must contain at least the IBC-CGT Chair, BSO, and a representative from CPHS. 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. A proposed agenda will be developed and distributed before the meeting by the Biosafety Officer (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 Environmental Health & Safety (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 publically accessible upon request.

G. Agenda, Minutes, Approval Letters, and Reports

The Biosafety Officer (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 approved by committee members at the following meeting. Approval letters will be drafted by the BSO and co-signed by the Chair. Reports to the Vice Provost for Research and federal agencies will be drafted by the BSO in collaboration with the Chair.

Dartmouth 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*.

The IBC *Public Attendance at IBC Meetings, Public Access to IBC Minutes, and IBC Minutes Redaction Policy* shall be followed.

H. Relationships to Other Committees

IBC-CGT supports transparency between the IBC for Basic Research, IBC-CGT, the Committee for the Protection of Human Subjects (CPHS, the Dartmouth Institutional Review Board (IRB)), the Office of Clinical Research, and the Clinical Cancer Review Committee (CCRC). Overlap of membership between these committees will be prioritized in order maintain this collaborative oversight.

VII. ROLES & RESPONSIBILITIES

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

Dartmouth 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. Institutional responsibilities will fall under the auspices of the Vice Provost for Research. Specifically, Dartmouth 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

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 laboratory 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)

The Dartmouth IBC-CGT reports to the Vice Provost of Research. IBC responsibilities under the *NIH Guidelines* are outlined in the *IBC Charter*.

The committee's responsibilities 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 HGT 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;

v. reporting any significant problems, violations of the NIH Guidelines, or any significant research-related accidents and illnesses to NIH OSP within thirty 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 are outlined in the Dartmouth IBC for Basic Research *Charter*. Duties and responsibilities on the IBC-CGT additionally include:

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 and 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.

D. Principal Investigator (in accordance with 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 clincal 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 Dartmouth 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 principal investigator (PI).

A. IBC-CGT Submission

The following materials must be included in the protocol submission and must be emailed to the Biosafety Officer:

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

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

c. Documentation of completion of appropriate training requirements (e.g. BSL2, blood borne pathogen training) for all study personnel and pharmacy personnel who will come into contact with study agent.

B. IBC Approval Process

All submitted documents will be distributed to committee members for their review prior to the committee meeting. Two reviewers to be appointed by the chair will review

submitted information and present their findings orally to the committee. The principal investigator or his/her representative will be invited to the meeting for the purpose of briefly presenting his/her protocol and to answer questions.

C. Voting Procedures

All non-members, including ad-hoc members, will leave the room prior to final discussion and voting. Any committee members who are principal or co-investigators on the study protocol under discussion will leave the room prior to final discussion and voting. Any committee members with an actual or perceived conflict of interest will leave the room prior to voting. Those leaving the room will be recorded in the meeting minutes. Voting results will be reported to the IBC. Letters of correspondence regarding the committee's decisions will be presented to the investigator and the D-HH HRPP or CPHS, as appropriate, with signatures of approval from the IBC-CGT chair and the Biosafety Officer.

Previously approved protocols submitting an amendment will be referred to the IBC-CGT for review by the CCRC and/or D-HH HRPP/CPHS dependent upon the amendment's impact on the safety and health of personnel, community, and environment.

D. Vote Categories

At the time of voting, committee members may vote in one of the following categories:

1. Approved

This vote means that 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.

2. Conditionally Approved

This vote means that 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. A letter describing the committee's conditions for approval will be sent to the investigator with a copy to the CPHS. The investigator's response will be reviewed by the committee chair or a designated committee member(s). This review will not be performed by a committee member who is an investigator on the study or who has actual or perceived conflict of interest. The reviewer may determine that all conditions of the committee have been adequately addressed, in which case a letter of approval will be sent as described above; that the conditions have not been adequately addressed, in which case a letter will be sent to the investigator describing the remaining conditions; or that the response should be reviewed by the full committee, in which case the committee will be convened to review the response.

3. Not Approved

This vote means that the concerns of the committee are substantive and that the magnitude and/or number of concerns are such that conditional approval is not appropriate. A letter describing the concerns is sent to the investigator with copies to CPHS/IRB. Full IBC-CGT review is required if the protocol is resubmitted.

4. **Voting Rules**
   In order for a study to receive "approval", "conditional approval" or "not approved" status it must obtain such a vote from the majority of the committee quorum.

5. **Appeal Procedures**
   Principal investigators may appeal committee's decisions in writing to the Chair of the IBC-CGT. If the decision regarding the appeal is unsatisfactory to the investigator, a second appeal may be made to the Chair of the IBC.

IX. RESOURCES

Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules (NIH Guidelines), Federal Register (April 2019).