Ann & Robert H. Lurie
Children's Hospital of Chicago®

Stanley Manne Children's Research Institute
Institutional Biosafety Program

NIH Guidelines

The purpose of the National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules *(NIH Guidelines)* is to specify the practices for constructing and handling: (i) recombinant nucleic acid molecules, (ii) synthetic nucleic acid molecules, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, and (iii) cells, organisms, and viruses containing such molecules.

Recombinant and synthetic nucleic acid molecules are defined as:

1) molecules that a) are constructed by joining nucleic acid molecules and b) that can replicate in a living cell; or
2) 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
3) molecules that result from the replication of those described in 1 or 2 above.

The *NIH Guidelines* also cover risk assessment for various types of organisms that may be source, vector or host for recombinant and synthetic nucleic acid molecules including:

1) Pathogens

A pathogen or infectious agent is any agent associated with disease in healthy human adults. There are four Risk Groups (RGs) discussed in the *NIH Guidelines* which generally correlate with the Biosafety Levels (BSL) described in the CDC publication "*Biosafety in Microbiological and Biomedical Laboratories* (BMBL)." Agents in RG2/BSL2 or higher are considered human pathogens.

2) Biohazards

Biohazards are infectious agents or hazardous biological materials that present a risk or potential risk to the health of humans, animals, or the environment. The risk can be direct through infection or indirect through damage to the environment. Biohazardous materials include certain types of recombinant DNA; organisms and viruses infectious to humans, animals or plants (e.g. parasites, viruses, bacteria, fungi, prions, rickettsia); and biologically active agents (i.e. toxins, allergens, venoms) that may cause disease in other living organisms or cause significant impact to the environment or community.

Any nucleic acid molecule experiment, which according to the *NIH Guidelines* requires approval by NIH, must be submitted to NIH or to another Federal agency that has jurisdiction for review and approval. When experiments involve the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into human research participants (human gene transfer), no research participant shall be enrolled until the NIH has informed the investigator that the protocol registration process and Recombinant DNA Advisory Committee (RAC) review (if applicable) has been completed; Institutional Biosafety Committee (IBC) approval (from the clinical trial site) has been obtained; Institutional Review Board (IRB) approval has been obtained; and all applicable regulatory authorization(s) have been obtained.

Assessment of Human Gene Therapy Trials

In April 2016, the NIH streamlined the review process for human gene transfer protocols subject to the *NIH Guidelines*. RAC review of individual human gene transfer protocols will be performed only in exceptional cases that meet the following specified criteria:

1. An oversight body (e.g., Institutional Biosafety Committee (IBC) or Institutional Review Board (IRB)) determines that a human gene transfer protocol submitted to it for approval would significantly benefit from RAC review; AND

2. One or more of the criteria below are satisfied:

    a. The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk.

    b. The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value.

    c. The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate the protocol rigorously.

In consistency with this, the oversight bodies of the Institution (the IBC and IRB) will conduct independent assessments of proposed gene transfer protocols to determine if the criteria above are met and if a request for RAC review is warranted.

Once done, a single letter will be sent to the NIH/PI summarizing the assessments. If neither oversight body request RAC review, the letter will be signed by the Institutional Official (IO) or designee. If RAC review is being requested, the letter will be signed by the Chair(s) of the Committee(s) making the request.

Institutional Biosafety Committee

The *NIH Guidelines* are applicable to all recombinant and synthetic nucleic acid research that is conducted at or sponsored by an institution that receives any support for recombinant or nucleic acid research from NIH. All non-NIH funded projects involving recombinant or synthetic nucleic acid molecules conducted at or sponsored by an institution that receives NIH funds for projects involving such techniques must comply with the *NIH Guidelines*.

In compliance with the *NIH Guidelines*, Stanley Manne Children's Research Institute affiliated with Ann & Robert H. Lurie Children's Hospital of Chicago has established an Institutional Biosafety Committee (IBC) which is responsible for the local review and oversight of all research utilizing recombinant and synthetic nucleic acid molecules.

The *NIH Guidelines* detail safety practices and containment procedures for basic and clinical research involving recombinant and synthetic nucleic acid molecules, including the creation and use of organisms and viruses containing these molecules. The IBC considers a number of matters including containment levels, facilities, institutional procedures and practices, training and expertise of

personnel. The Manne Children's Research Institute is equipped for Biosafety Level 1 and 2 experiments (BSL1 & BSL2).

The *NIH Guidelines* are intended to assist the IBC and principal investigators in determining safeguards prior to conducting experiments involving recombinant DNA. It is the responsibility of the individual conducting such experiments to ensure that safe practices are followed by adhering to the *NIH Guidelines* and internal policies and procedures, with assistance from the IBC.

IBC Convening Authority and Composition

The Lurie Children's IBC shall include no fewer than five members selected to collectively have experience and expertise in recombinant and synthetic nucleic acid research, the capability to assess the safety of recombinant and synthetic nucleic acid molecules and infectious and biohazardous agents, and the ability to identify any potential risk to public health or the environment. At least two members represent the interest of the surrounding community with respect to health and protection of the environment and shall not be affiliated with Lurie Children's. At least one scientist with expertise in animal containment principles is required when research involves use of recombinant or synthetic nucleic acid molecules or biohazardous agents in animals. At least one plant expert is needed if research involves plants containing recombinant or synthetic nucleic acid molecules, plant-associated microorganisms, or plant-associated small animals are conducted. At least one member shall be a person from laboratory technical staff. At least one person with expertise in vector biology is needed to serve as member or consultant.

The Chief Research Officer appoints the Chair of the IBC. The Chair of the IBC, in consultation with Research Leadership, selects and appoints the Vice Chair and other committee members. Membership is renewable annually upon mutual agreement of the Chair and the committee member(s).

The Chair shall preside over the IBC meetings and act as liaison between the academic community and the IBC. The Vice Chair performs all the duties of the Chair in the Chair's absence and other such duties as may be assigned.

The Chair shall review all instances of noncompliance and present them to the IBC at a convened meeting for appropriate corrective action, which may include suspension of the registration for possession and/or use of recombinant or synthetic nucleic acid molecules or biohazardous materials. The Chair communicates with and works closely with the Institutional Official and the Director of the Office of Research Integrity and Compliance to evaluate complaints or findings of non-compliance.

To help prepare for their position on the committee, IBC members are required to complete introductory training conducted by the IBC Chair, which includes an overview of the *NIH Guidelines.*

The IBC is registered with the National Institutes of Health Office of Biotechnology Activities (OBA) and provides OBA with an updated list of IBC members annually, the role of each member, and the biosketch for each member. The OBA considers IBCs as key partners in efforts to ensure that institutions and their research personnel employ procedures and practices that conform to the *NIH Guidelines*. The expertise of IBC members, as well as their knowledge of applicable environmental health and safety practices, is critical to achieving this goal. More information is available at http://oba.od.nih.gov/.

IBC Meetings

The IBC typically meets monthly, but may meet more or less frequently as necessary to implement the *NIH Guidelines*. The IBC meeting dates may be found on the research institute website. The IBC Chair may call an emergency meeting of the IBC as necessary to address noncompliance or serious and/or unexpected events.

Prior to any regular meeting, each member shall be sent a copy of all the documents to be discussed at the meeting including, but not limited to IBC registration forms, modifications, inactivations, agenda and minutes, and other documents to be reviewed at the meeting.

Quorum needed to conduct business of the IBC shall consist of a simple majority of members (>50%). The approval or disapproval of registration or suspension of the registration for possession and/or use of recombinant or synthetic nucleic acid molecules or biohazardous agents due to non-compliance requires a majority vote of IBC members present and voting. All members of the IBC except ex-officio members shall have voting rights.

Per institutional policy, IBC members who have a conflict of interest in a project being discussed at the meeting (e.g., are acting as a research investigator, have financial interest in the project, etc.) shall not be present during the IBC's initial or continuing review deliberations and voting.

Minutes of IBC meetings shall include, but not be limited to, the following information:

- Attendance of members and guests;
- IBC actions taken on each registration reviewed and if the registration requires modifications for IBC approval;
- Notation of members who were not present during deliberations and voting on projects with which they have a conflict of interest.

The IBC retains all records for at least three (3) years after completion of the research/project.

IBC Responsibilities

- Review and approve, approve with modifications, table or disapprove Biosafety Registrations for research that involves recombinant and synthetic nucleic acid molecules, pathogens, and/or select agents including a full risk assessment, selection of proper containment and any required special provisions. Neither the Chief Research Officer nor any other institutional official may approve any protocol which the IBC has disapproved. However, the Chief Research Officer or his/her designee may disapprove any protocol which the IBC has approved. Such disapproval may not be appealed and is final.
- Conduct an independent assessment of the containment levels recommended by the PI, as well as those required by the *NIH Guidelines* for any proposed research involving recombinant and synthetic nucleic acid molecules – and – may lower or raise containment within what is allowed by the *NIH Guidelines* based on the risk assessment.
- Conduct an assessment of the facilities, procedures, practices, training and expertise of personnel involved in research with recombinant and synthetic nucleic acids and/or biohazardous agents.
- Where applicable, ensure that all required approvals under the *NIH Guidelines* have been obtained from NIH/OBA and RAC (when applicable) prior to initiation of recombinant and synthetic nucleic acid research.
- Review Amendments to previously approved registrations.
- Conduct a periodic review of protocols when a PI plans to continue activity described in the Biosafety Registration beyond the initial approval period. Notify investigators in writing of the results of the review and the IBC decisions.
- Adopt emergency plans for spill or exposure.

- Report any significant problems with or violations of the *NIH Guidelines* or any significant accidents or illnesses to the Institutional Official and NIH/OBA within 30 days. Significant violations or incidents may include items such as:
    - Breach of containment for recombinant and synthetic nucleic acid molecules such as escaped animals or microorganisms, or a spill, outside of containment (i.e.: Biological Safety Cabinet) that cannot be easily and quickly cleaned up by one person.
    - Any illness likely caused by exposure to recombinant and synthetic nucleic acid molecules and biohazards.
    - Willful violation of protocols or conduct of work without prior IBC approval.
- Review policies and procedures pertaining to recombinant and synthetic nucleic acid research and present such for final approval by the Chief Research Officer of the research institute.
- Record all IBC actions and meeting minutes which will be made available for public inspection upon request.
- Conduct periodic inspections of laboratories engaged in recombinant and synthetic nucleic acid research to ensure standards are followed.
- Ensure that all IBC members are adequately trained in state and federal regulations, and institutional policies and standard operating procedures necessary to reasonably evaluate Biosafety Registrations;
- Establish a subcommittee or ad hoc committee as necessary to carry out its overall responsibilities
- For human gene transfer experiments, where the Lurie Children's Hospital is the principal sponsoring institution (and not just a clinical trial site), the IBC is also responsible for ensuring that all aspects of Appendix M of the *NIH Guidelines* (requirements for human gene transfer experiments) have been addressed by the PI, the review process by the Recombinant DNA Advisory Committee (RAC) has been completed (if applicable), and projects are conducted in compliance with the Lurie Children's health surveillance, and data and adverse event reporting requirements.
- Section III of the *NIH Guidelines* covers the different types of recombinant and synthetic nucleic acid research and the levels of review required for each, ranging from exempt to full review by the IBC and RAC depending on the safety risk posed. At Lurie Children's, ALL recombinant and synthetic nucleic acid research must be reviewed by the IBC even if it is "exempt" to ensure the correct status.

Compliance Oversight and Reporting

The IBC has authority to address non-compliance with the Biosafety Registrations or the *NIH Guidelines* in consult with the Institutional Official and the Director of the Office of Research Integrity and Compliance.

The IBC shall take any actions, including suspending an activity or revoking approval of a Biosafety Registration, that are in the committee's judgment necessary, to ensure compliance with applicable

federal, state, or local policies, procedures, and regulations. The IBC may take appropriate action in instances where, in its judgment, personnel, property or the community may be endangered.

Non-compliance can result in the IBC taking one or more of the following actions:

- Suspending use of recombinant and synthetic nucleic acid molecules including pathogens and biohazardous materials used in nucleic acid research;
- Termination of the IBC Biosafety Registration;
- Confiscation of the biohazardous material;
- Destruction of the biohazardous material;
- Any other action necessary to protect the public and/or the Lurie Children's

In consultation with the Institutional Official (IO), the Chair or his/her designee has the authority to close any laboratory in which a required safety procedure is violated. Such action and the safety violations shall be reported immediately to the IBC and the Chief Research Officer of the research institute.

The IO shall ensure prompt filing of all required reports including, but not limited to, self-reporting to regulatory agencies regarding any noncompliance with laws and regulations. The IO does not have the authority to approve a program, project or activity denied by the IBC. The IO shall report any significant problems with or violations of the *NIH Guidelines* and any significant research-related accidents or illnesses related to recombinant and synthetic nucleic acid molecules to NIH/OBA within 30 days; unless a report has already been filed by the PI. Reports to NIH/OBA are sent to the following address:

Office of Biotechnology Activities
National Institutes of Health
6705 Rockledge Drive, Suite 750, MSC 7985
Bethesda, MD 20892-7985 (20817 for non-USPS mail)
Phone: 301-496-9838 Fax: 301-496-9839

Principal Investigator (PI) Responsibilities

- Submit a completed Biosafety Registration application for all activities involving recombinant and synthetic nucleic acid and biohazardous materials to the IBC for review and approval;
- Receive written approval of the Biosafety Registration from the IBC prior to acquiring or working with recombinant and synthetic nucleic acid molecules and/or and biohazardous materials;
- Keep Biosafety Registrations up-to-date by submitting modification requests and continuing reviews in a timely manner;
- Comply with all federal requirements and state requirements when conducting research involving biohazardous materials and with the *NIH Guidelines* when conducting research with recombinant and synthetic nucleic acid.
- Ensure all reporting requirements under the *NIH Guidelines* involving recombinant and synthetic nucleic acid molecules are fulfilled;
- Adhere to IBC approved emergency plans for handling accidental spills and personnel contamination;
- Report immediately any significant problems related to the use of biohazardous materials or any significant research-related accidents and illnesses to Northwestern Memorial Physician Group (NMPG) Corporate Health, the IBC and any other Institutional Committee that has reviewed and approved the research activity;
- Review applicable lab safety guidelines, procedures, and requirements related to the biohazardous materials involved in the research activity;
- Develop standard operating procedures incorporating biosafety procedures or a biosafety manual prepared specifically for the laboratory describing the potential biohazards and the precautions to be taken (e.g., hazards and risks, immunizations, personal protective equipment required, decontamination, storage and disposal, spill procedures).
- Train all project personnel in the safe handling of biohazardous material; at minimum, this means ensuring that all personnel have been informed of any potential health risks and have completed required training before accessing biohazardous material and providing initial training as necessary for procedural or policy changes;
- Limit access to laboratory personnel who are involved in the project, have been advised on the potential hazards and properly trained on use of protective clothing and other precautions to prevent exposures, and the exposure evaluation procedures.
- Supervise the safety performance of laboratory staff to ensure that the required safety practices and techniques are employed;
- Investigate and report any significant problems pertaining to the operating and implementation of containment practices and procedures in writing to the IO, IBC, NIH/OBA, and/or other appropriate regulatory authorities.
- Correct work errors and conditions that may result in the release of biohazardous materials;

- Ensure the integrity of the biological and physical containment (biosafety level);
- Ensure the security of biohazardous materials at all times.

Biosafety Registration Process

Principal Investigators intending to utilize recombinant and synthetic nucleic acid molecules, as described in the *NIH Guidelines*, are required to submit a Biosafety Registration Document to the IBC for review and approval. IBC approval of the Biosafety Registration is valid for five (5) years. At expiration, a new Biosafety Registration Document and Safety Protocol must be submitted to the IBC for review and approval to continue research involving recombinant and synthetic nucleic acid molecules and/or biohazardous agents.

The following are experiments covered by the *NIH Guidelines:*

There are six categories of experiments involving recombinant or synthetic nucleic acid molecules:

(i) those that require IBC approval, Recombinant DNA Advisory Committee (RAC) review, and NIH Director approval before initiation (see *NIH Guidelines* Section III-A)

(ii) those that require NIH Office of Science Policy (OSP) and IBC approval before initiation (see *NIH Guidelines* Section III-B.

(iii) those that require IBC and IRB approvals and RAC review before research participant enrollment (see *NIH Guidelines* Section III-C) *e.g. human gene transfer*.

(iv) those that require IBC approval before initiation (see *NIH Guidelines* Section III-D),

(v) those that require IBC notification simultaneous with initiation (see *NIH Guidelines* Section III-E) e.g. research involving transgenic rodents, and

(vi) those that are exempt from the *NIH Guidelines* (see *NIH Guidelines* Section III-F).

If an experiment falls into Section III-A, III-B, or III-C and one of the other Sections as well, the rules pertaining to Section III-A, III-B, III-C shall be followed. If an experiment falls into Section III-F alone, or into Section III-F and into Section III-D or III-E as well, the experiment is considered exempt from the NIH guidelines.

Amendments

If the PI wishes to make modifications to an approved Biosafety Registration Document, an amendment request must be submitted to the IBC for review and approval. Amendments include, but are not limited to, modification of biohazardous materials, changes in research procedures, or changes that change the risk of the project and/or the biosafety level.

Modifications to research conducted under Sections III-A, III-B, III-C, and III-D must be approved prior to implementing new procedures. The PI must submit an Amendment Request Form. The IBC may request the additional submission of a signed, dated revised Registration Document (revisions highlighted) when the amendment involves substantive changes to the construction, handling and/or use of recombinant or synthetic nucleic acids; or changes that modify the risk category or biosafety level of agents used in the study. The IBC must be notified of modifications under Section III-E at the time they are implemented.

Notification of modifications to exempt research conducted under Section III-F is not required.

The IBC Personnel Change Form must be submitted for modifications to approved registrations involving a change in personnel only. The Chair of the IBC, acting on behalf of the Committee, may review and approve amendments that do not require safety review. The IBC will be notified of these administratively approved amendments when they are reported during the next convened IBC meeting.

Inactivations

The IBC Coordinator will send out expiration reminder emails to the Principal Investigator prior to expiration. A final expiration notice will be sent on the date of expiration, informing the PI that all study activity must cease immediately until IBC approval has been obtained. If at that time the PI wishes to obtain IBC approval, a new Biosafety Registration Form and Safety Protocol must be submitted and reviewed by the convened committee. If the PI wishes to inactivate the protocol, an Inactivation form must be submitted.

The Chair of the IBC, acting on behalf of the Committee, may review and approve protocol Inactivations upon completion of appropriate form. The Chair of the IBC, acting on behalf of the Committee, may administratively inactivate protocols after the date of expiration with no response from the study team. The IBC will be notified of these administratively approved inactivations when they are reported during the next convened IBC meeting.