Office of Research Services
Serving the NIH Community

The NIH Institutional Biosafety Committee (IBC) and the Review of Clinical Protocols submitted through the Electronic Registration System (ERS)

Richard G. Baumann, Ph.D.
NIH BSO
Division of Safety
13 Center Drive; Room 3W-65
Off:(301) 496-1987
baumannrg@nih.gov
nihbso@mail.nih.gov

Also with IBC Chair Harry Malech, M.D.

NIH National Institutes of Health
Office of Management

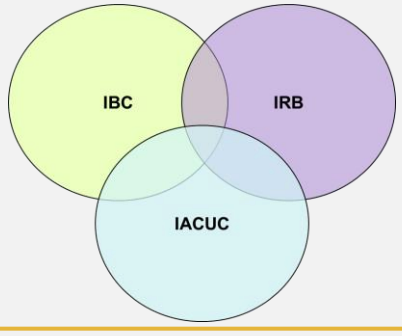
1

Office of Research Services
Serving the NIH Community

The Institutional Biosafety Committee (IBC)

IBC Responsibilities according to the Office of Scientific Policy (OSP):

- **Receive NIH Funding- must follow *NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules***
- **Formalizes review by an Institutional Biosafety Committee (IBC)**
- **what must IBCs review?**
  - **All research involving recombinant or synthetic nucleic acid molecules for conformity with the *NIH Guidelines***
  - **Potential risk to environment and public health**
    - **Containment levels per *NIH Guidelines***
    - **Adequacy of facilities, SOPs, PI and lab personnel training**
    - **Institutional and investigator compliance with the *Guidelines***



- **In basic and preclinical research, IBCs have authority to:**
  - **Lower containment levels for certain experiments**
  - **Set containment levels for certain experiments involving animals**
  - **Periodically review institutional compliance with *NIH Guidelines***
  - **Adopt emergency plans covering spills, contamination, other accidents**

NIH National Institutes of Health
Office of Management

2

Office of Research Services
Serving the NIH Community

For rDNA registration : Clinical Trials involving 'human gene transfer'

The '*NIH Guidelines*'

Section III-A & B – Requires NIH Director and IBC approval, other regulatory review (OSP) PRIOR to initiation:
Major actions; deliberate transfer of a drug resistance trait to microorganisms not known to acquire the trait naturally if such could compromise the use of the drug to control disease, or cloning of toxin genes with low LD50

Section III-C – Requires IBC and IRB review PRIOR to research participant enrollment:
Experiments Involving the transfer of recombinant DNA or RNA derived from rDNA, into one or more human research participants

Section III-D - Require registration & IBC approval PRIOR to initiation:
- "Other" experiments at NIH not being discussed today – Majority of all rDNA research at NIH

"*NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT OR SYNTHETIC NUCLEIC ACID MOLECULES*" (NIH GUIDELINES) APRIL 2019

NIH National Institutes of Health
Office of Management

3

Office of Research Services
Serving the NIH Community

Other Research Categories under Section III-D and III-E

Section III-D - Require registration & IBC approval PRIOR to initiation:
1. Using Risk Group 2, 3, or 4 agents as host-vector systems.
2. DNA from Risk Group 2, 3 or 4 agents is cloned into nonpathogenic prok or lower euk host vector systems.
3. Use of Infectious DNA or RNA Viruses or Defective DNA/RNA Viruses w/Helper in vitro
4. Experiments in whole animals.
5. Experiments involving whole plants.
6. Experiments involving more than 10 liters of culture.
7. Experiments involving human infl. strains H2N2, 1918 H1N1, and/or HPAI H5N1.

Section III-E - Require IBC notice by registration simultaneous with initiation:
1. Formation of rDNA molecules containing <2/3 of the genome of any eukaryotic virus.
2. Experiments involving whole plants.
3. Generation of transgenic rodents requiring BSL-1 containment.

NIH National Institutes of Health
Office of Management

4

Office of Research Services
Serving the NIH Community

NIH Guidelines: Institutional Responsibilities

The Institution shall:

- Establish and implement policies for the safe conduct of research subject to the *NIH Guidelines*
- Establish an Institutional Biosafety Committee
- Assist and ensure compliance with the *NIH Guidelines* by investigators
- Ensure appropriate training for IBC members and staff, PIs, laboratory staff
- Determine necessity for health surveillance of personnel (OMS)
- Report any significant accidents, incidents or violations to NIH OSP within 30 days (or immediately as required)

NIH National Institutes of Health
Office of Management

5

Office of Research Services
Serving the NIH Community

NIH Guidelines : PI Responsibilities

The Principal Investigator shall (among other things):

- Will not initiate research subject to the *NIH Guidelines* which requires IBC approval until approval is granted
- Be adequately trained in good microbiological techniques
- Adhere to IBC stipulations and emergency plans for spills and personnel contamination (ECP)
- Report any significant problems or violations to NIH OSP within 30 days or immediately as required. (These are reported to Division of Safety, who reports to OSP)

NIH National Institutes of Health
Office of Management

6

Office of Research Services
Serving the NIH Community

IBC Roles and Responsibilities: Membership

- **Recommended members (no fewer than 5):**
  - Collective experience in rDNA technology
  - Community representation (2, unaffiliated with the NIH)
  - Expertise in biosafety, physical containment
  - Expertise in animal or plant experimentation (as applicable)
  - Expertise in clinical research (Section III-C work)
  - BSO for large scale, High/ Maximum containment work, Gene drives
  - Knowledge of institutional policies, applicable law
  - 1 member representing the laboratory technical staff

NIH National Institutes of Health
Office of Management

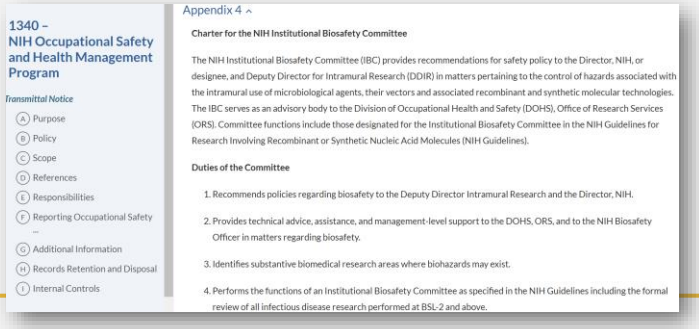
- IBCs are encouraged to open their meetings to the public
- IBCs will make their minutes available to the public on request (FOIA) and these will be posted for the public after 6/2/2025

7

Office of Research Services
Serving the NIH Community

IBC Roles and Responsibilities defined in IBC Charter

- Described under Section lV-B-2 of the *NIH Guidelines*.
- Membership and Procedures
- Functions as a Committee (rDNA review)
- *NIH IBCs- responsible for all high and maximum containment research review
- IBC has a written charter describing its duties, meetings, and membership which is part of NIH Manual Chapter #1340: Occ. Safety and Health Management Program



1340 – NIH Occupational Safety and Health Management Program

Transmittal Notice

- A Purpose
- B Policy
- C Scope
- D References
- E Responsibilities
- F Reporting Occupational Safety ...
- G Additional Information
- H Records Retention and Disposal
- I Internal Controls

Appendix 4

Charter for the NIH Institutional Biosafety Committee

The NIH Institutional Biosafety Committee (IBC) provides recommendations for safety policy to the Director, NIH, or designee, and Deputy Director for Intramural Research (DDIR) in matters pertaining to the control of hazards associated with the intramural use of microbiological agents, their vectors and associated recombinant and synthetic molecular technologies. The IBC serves as an advisory body to the Division of Occupational Health and Safety (DOHS), Office of Research Services (ORS). Committee functions include those designated for the Institutional Biosafety Committee in the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines).

Duties of the Committee

1. Recommends policies regarding biosafety to the Deputy Director Intramural Research and the Director, NIH.
2. Provides technical advice, assistance, and management-level support to the DOHS, ORS, and to the NIH Biosafety Officer in matters regarding biosafety.
3. Identifies substantive biomedical research areas where biohazards may exist.
4. Performs the functions of an Institutional Biosafety Committee as specified in the NIH Guidelines including the formal review of all infectious disease research performed at BSL-2 and above.

NIH National Institutes of Health
Office of Management

https://policymanual.nih.gov/1340

8

Office of Research Services
Serving the NIH Community

Clinical Trial Review: IBC Functions

- Reviewing rDNA research (such as that associated with Clinical Trial products being used)
- Notifying PI of the timing, results of IBC review and approval stipulations (Division of Safety)
- Lowering containment levels for certain experiments (applies more to non-clinical work)
- Periodically reviewing rDNA research
  - Substantive changes that may impact risk should be submitted as amendments
  - Annual reviews occur every year for all biological registrations (these are not IBC reviewed)

    For clinical Trials- submit Annual Reviews/ Continuing Reviews/ SAEs via the Amendment process
  - Expiration period plan in ERS - 7-years, looking to streamline renewals * -stay tuned!
- Adopting emergency plans covering spills and accidents with rDNA (Exposure Control Plan)
- Reporting violations of the Guidelines and any rDNA research accidents or illnesses to OSP (DOHS biosafety staff)

NIH National Institutes of Health
Office of Management

9

Office of Research Services
Serving the NIH Community

Determining Appropriate Biosafety Levels

Performing Biological Risk Assessment

Agent Hazards:

- Assess risk of biological agent, taking into account (in addition to risk-group):
  - virulence
  - severity of disease & availability of effective treatments
  - infectious dose & route(s) of transmission
  - environmental stability
  - concentration
  - availability of information
- How may these be altered by genetic manipulation or the introduction of antibiotic resistance?

Review all proposed procedures and determine appropriate Biosafety Level (BSL)

NIH National Institutes of Health
Office of Management

10

Office of Research Services
Serving the NIH Community

Specific IBC Functions

- Review Registration Forms via ERS portal- Set BSL levels
- **Review 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**
- Review all registrations for DURC // PEPP effective May 2025: DURC and PEPP
- Review all BSL-3 and BSL-4 research activities
- Review pathogen inactivation validation studies and protocols for RG-3 and RG-4 agents
- IBCs may NOT approve experiments involving rDNA not specifically covered by the NIH Guidelines until NIH/OSP establishes containment requirements (reason for referencing Guideline Sections)
- Adequacy of facilities, staff, training (with Safety Personnel)

NIH National Institutes of Health
Office of Management

11

Office of Research Services
Serving the NIH Community

Section III-C

- **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 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 introduction of stable genetic modifications into the genome (e.g., cis elements involved in integration, gene editing); or

c) Have the potential to replicate in a cell; or

d) Can be translated or transcribed.

Research cannot be initiated until Institutional Biosafety Committee and all other applicable institutional and regulatory authorization(s) and approvals have been obtained.

NIH National Institutes of Health
Office of Management

12

Office of Research Services
Serving the NIH Community

Section III-C

Something to know! – Be careful in interpreting this wording in this section:

"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".

The Policy of the **NIH IBC** regarding such clinical trials- asks that you check with the BSO**!**

IBC Policy:

Per the NIH guidelines, all Expanded Access Protocols (EAPs, that are FDA authorized*, and single patient only) do not require IBC review. However, for some protocols or products, the NIH IBC may still elect to review the study to reduce risk for the NIH. For any new product used in an expanded access protocol at the NIH that has not previously been reviewed by the NIH IBC, consult with the Biological Safety Officer for the NIH Bethesda IBC at (NIHBSO@nih.gov) to determine if IBC review of this product will be required prior to submission of the study to the NIH IRB.

NIH National Institutes of Health
Office of Management

13

Office of Research Services
Serving the NIH Community

ERS: Electronic Registration System

DOHS ERS Electronic Registration System

- **https://ers.ors.nih.gov/** , https://nih.sharepoint.com/sites/ORS-ORF-HealthandSafetyApplicationResources
- Stand-alone biosafety registration platform by Division of Safety (DS)
  - ERS replaces the previous 'PI-Dashboard', encourages Project-based Registrations
- IBC Meeting cadence: Monthly- 1st Wednesday each month (Jan/July- 2nd Wed), no August meeting
- Deadline is 2 Weeks Prior to Meeting date!
- **Human Gene Transfer studies** - still separate and uniquely identified in ERS, **always take priority**
  - IBC review is required BEFORE IRB review
  - FDA review need not occur before IBC, best time is after the Scientific Review
  - PI asked to present at meeting 5-8min slide presentation, answer questions from IBC

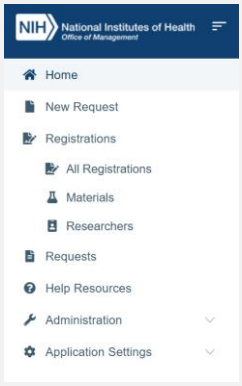
NIH National Institutes of Health
Office of Management

14

Office of Research Services
Serving the NIH Community

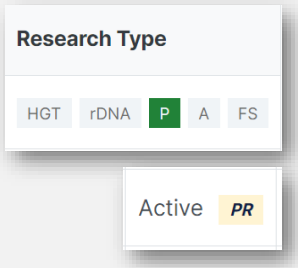
ERS Navigation

	RD-18-IX-18	Copy of original test reg with…	HGT rDNA P A FS	BC	Active	ORS	Richard Baumann	09/05/2025	12/21/2028



View all previous registration summaries and review history

- HGT = human gene transfer
- rDNA = recombinant DNA
- P = Pathogen (and/or Toxin)
- A = Animal and/ or arthropod
- FS = Field Study
- PR = Pending (Annual) Review
- [N] = Number of amendments



NIH National Institutes of Health
Office of Management

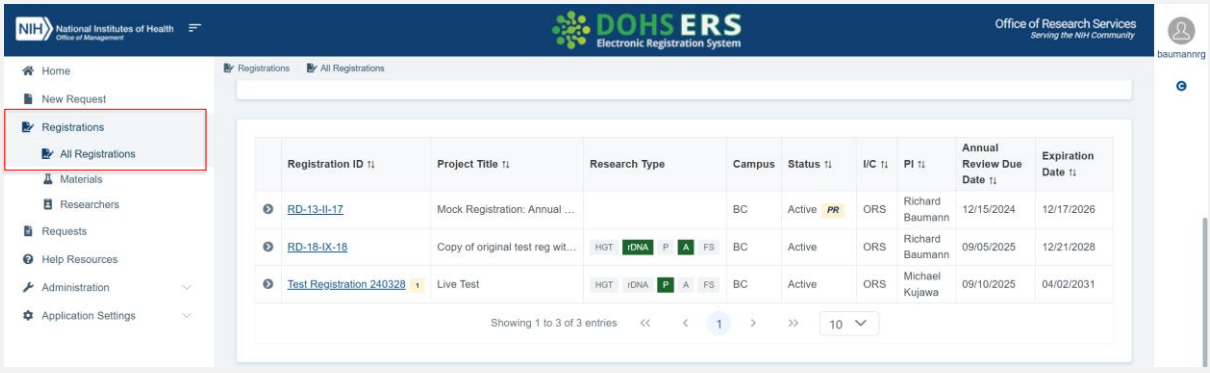
DOHS ERS
Electronic Registration System

15

Office of Research Services
Serving the NIH Community

Project-based Framework

DOHS ERS
Electronic Registration System



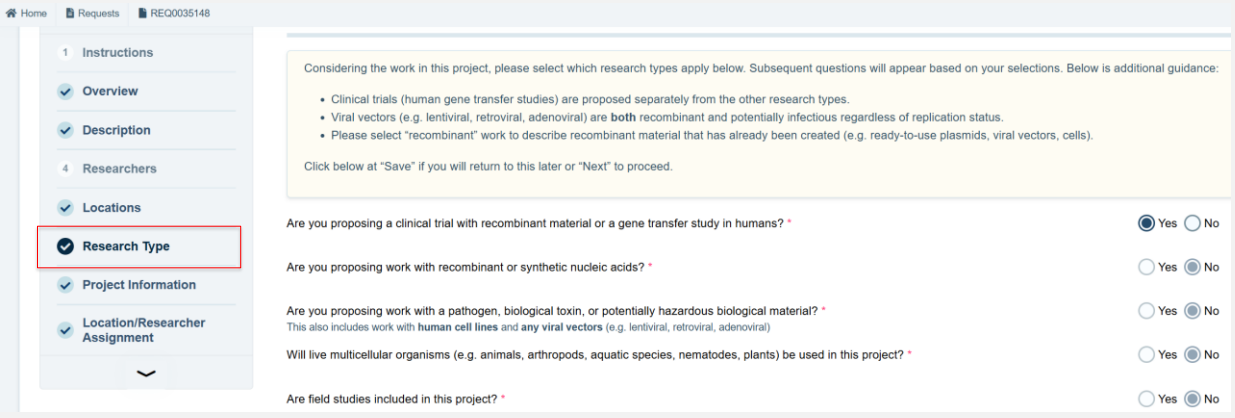
NIH National Institutes of Health
Office of Management

16

Office of Research Services
Serving the NIH Community

Research Registration: Type Selection

DOHS ERS Electronic Registration System



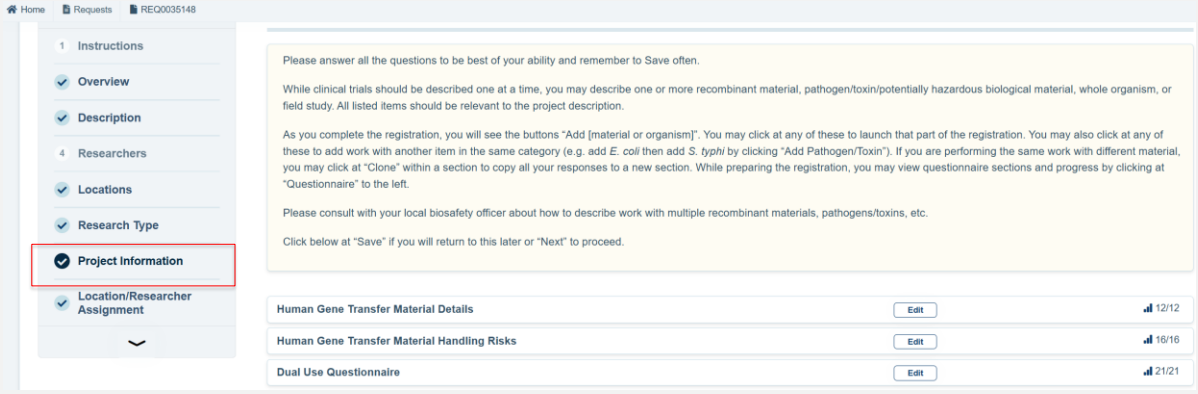
NIH National Institutes of Health
Office of Management

17

Office of Research Services
Serving the NIH Community

Clinical Trial Submission/ Gene Transfer

DOHS ERS Electronic Registration System



NIH National Institutes of Health
Office of Management

18

Office of Research Services
Serving the NIH Community

Clinical Trial Submission/ Gene Transfer

DOHS ERS Electronic Registration System

Human Gene Transfer - Material Details

- Describe the structure and composition of any recombinant or synthetic nucleic acid materials (e.g. viral vectors, plasmids) used in the therapeutic product or for manufacture of the therapeutic product.
- Please further describe the nature of the recombinant microbes or vectors, DNA or RNA vectors, or modified cells be administered directly to participants.
- What protein(s) and/or recombinant product are being expressed in the trial participants?
- What is the biological origin of the sequences that will be modified or expressed?
- If needed, please further describe the biological origin of the recombinant material.
- What is the replication status of the recombinant microbe or vector?
- Please further describe how the recombinant microbe or vector is made replication-incompetent, attenuated, or inactivated.
- Describe the method(s) (e.g. transduction) for generating the recombinant cell therapeutic.
- Indicate how the recombinant molecule(s) or cell therapeutic(s) is obtained.

NIH National Institutes of Health
Office of Management

19

Office of Research Services
Serving the NIH Community

Clinical Trial Submission/ Gene Transfer

DOHS ERS Electronic Registration System

Human Gene Transfer - Material Handling Risks

- What risks for integration or expression are there for participants?
- Please describe precautions in place to prevent transmission.
- What personal protective equipment will be worn during preparation and administration of the therapeutic product? (Select, and Please also use the comment feature to explain)
- How will the product be prepared for administration (Select)?
- How will the product be safely transferred to the administration area (Select)?
- How will the product be administered (Select)?
- Is there any possibility that live/replication-competent microbes or vectors could be spread from the recipient to close contacts? (If so, please explain preventative measures in comments)?
- Please describe any potential exposure risks for handling or administering the therapeutic product and how these are mitigated?
- Please describe how personnel are educated about potential exposure risks?

NIH National Institutes of Health
Office of Management

20

Office of Research Services
Serving the NIH Community

Clinical Trial Submission/ Gene Transfer

DOHS ERS Electronic Registration System

Human Gene Transfer - Material Handling Risks

- Please describe response and reporting procedure(s) that will be followed in the event of a spill of the therapeutic product, including disinfectants?
- Has this vector been used previously in human gene transfer or therapy products?
- Indicate supporting documents that are uploaded.
- Select phase of study. (Select one option)

  Phase I / Phase II / Phase III / Phase IV
- What is your realistic expected or desired IBC approval date based on the schedule of IBC meetings and your expectation for IRB review and approval processing and timing? (comment as necessary)
- Which NIH Guidelines section(s) best applies to the proposed research?
- III-C

NIH National Institutes of Health
Office of Management

21

Office of Research Services
Serving the NIH Community

Electronic Registration System (ERS)

https://ers.ors.nih.gov/

Questions?

Richard G. Baumann, Ph.D., SM (NRCM)
NIH BSO
Off:(301) 496-1987
baumannrg@nih.gov
nihbso@mail.nih.gov

NIH National Institutes of Health
Office of Management

22

Office of Research Services
Serving the NIH Community

The following slides present

background and useful information

NIH National Institutes of Health
Office of Management

23

Office of Research Services
Serving the NIH Community

IBC Policy: Registration of ANY research work with human and NHP cell lines

Work with ANY human cell lines or human or NHP materials requires registration…

- Register work with all human cell lines- material type "*human blood and body fluids*"
- work with human or 'old world' NHP cells, blood and tissues samples, also iPS cells
- Testing performed on human cell lines is a snapshot in time, and these materials are frequently grown and shared
- Per the OSHA BBP Standard- Impossible to declare any cell line 'free' from all human pathogens
- Single registration covers all cell lines and procedures: Personnel are consulted, trained and aware

  - consultation with Occupational Medical Services (possible need for HepB vaccination if warranted)
  - training required by law under OSHA : *Basic Laboratory Safety Training* and *BBP training* annually.
  - ensures awareness of any potential risks associated with the proposed work (aerosolization, etc.)

NIH National Institutes of Health
Office of Management

24

NIH Institutional Biosafety Committee (IBC) Review of Clinical Protocols

Harry L. Malech, MD

Chair, NIH Institutional Biosafety Committee

Chief, Genetic Immunotherapy Section

Deputy Chief, Laboratory of Clinical Immunology and Microbiology

National Institute of Allergy and Infectious Diseases, NIH

Some Background: My Experience as a PI or AI with IBC Review of Our Lab's Clinical Gene Therapy Protocols

Currently Approved Gene Therapy Clinical Protocols from GIS, LCIM, NIAID

1. 11-I-0007 "**Lentiviral Gene Transfer** for Treatment of Children Older Than 2 Years of Age with **X-Linked Severe Combined Immunodeficiency**" Suk See De Ravin, PI

2. 22-I-0001 "NADPH Oxidase Correction in **mRNA transfected Granulocyte**-enriched Cells in **Chronic Granulomatous Disease** (CGD)" Suk See De Ravin, PI

3. 000186-I "Part B- Phase I/II, Non-randomized, Single center study, Open-label Study of G1XCGD (**Lentiviral Vector** Transduced CD34+ Cells) in Patients with **X-Linked Chronic Granulomatous Disease**" Elizabeth Kang, PI

4. 001562-I "A Phase I/II, Non-Randomized, Open-Label Study of pCCLCHIM-p47 (**Lentiviral Vector** Transduced CD34+ Cells) in Patients with **p47 Autosomal Recessive Chronic Granulomatous Disease** (AR-CGD" Elizabeth Kang, PI

5. 001580-I "Phase 1/2 Trial of **Base Editing** for Mutation Repair in Hematopoietic Stem & Progenitor Cells for **X-linked Chronic Granulomatous Disease**" Suk See De Ravin, PI

6. 002199-I "A Phase 1/2 Study Evaluating Gene Therapy by Transplantation of Autologous CD34+ Stem Cells Modified Ex Vivo Using **Prime Editing** (PM359) in Participants with Autosomal Recessive Chronic Granulomatous Disease due to **Mutations in the NCF1 Gene**" Harry Malech, PI

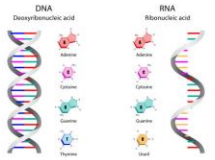
7. 002273-I "Phase 1/2 **Base-Edited** Hematopoietic Stem/Progenitor Cell **X-Linked Severe Combined Immunodeficiency** Gene Therapy" Suk See De Ravin, PI

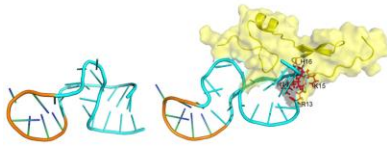
8. 002385-I "**Base editing** hematopoietic stem cell and BE T cell gene therapy for **CD40L-HyperIgM syndrome**-Single Patient Study" Suk See De Ravin, PI

Does Your Clinical Protocol Require IBC Review?

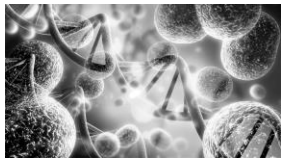
IBC Review Required:

1. The clinical protocol study treatment is a recombinant DNA or RNA, including Antisense Oligonucleotides (ASOs) or RNA aptamer that is not FDA approved, or is being used to study treatment of an unapproved indication or at an unapproved dosing or timetable.

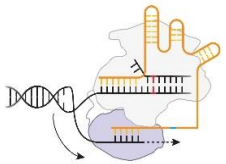




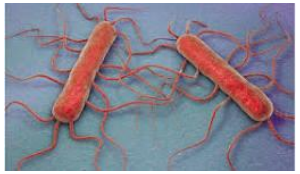
2. The clinical treatment is a genetically modified cell (autologous or allogeneic human; animal cell; yeast or other eukaryote; or prokaryote).

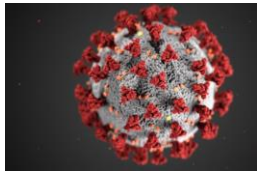


3. The clinical treatment is designed to alter the genome of a human subject in a target organ or tissue (example is gene editing materials such as a CRISPR system delivered in vivo via virus or lipid nanoparticles).



4. The clinical treatment uses a live potential pathogen, even if it is attenuated (example is attenuated listeria used as part of a cancer vaccine); exceptions may apply when an FDA approved live vaccine strain is used even if not for the approved indication (ask your Safety Office).





Does Your Clinical Protocol Require IBC Review?

EXCEPTION: If it is an **FDA approved treatment** being administered for the **approved indication** and at the **approved dosing and timetable**, then IBC review may not be required. If in doubt, ask your Safety Officer for advice.

Hypothetical examples:

1. Commercially available FDA approved CD19-CAR T cell therapy for B cell lymphoma, where the protocol is using the approved therapy to treat an approved indication at the approved dosing and timetable, but the study is focused on assaying the mechanisms and timing of tumor killing by collecting serial biopsies and/or blood samples.

2. Commercially available FDA approved mRNA vaccine for COVID, where the protocol is using the approved therapy to immunize a subset of the approved target population (such as patients post chemotherapy for cancer treatment, who may have impaired immune response), at the approved dosing and timetable, but the study is focused on assaying the immune response to the immunization.

EXCEPTION: If it is an **FDA approved treatment** used to treat a single patient ‘off label’ it may not require IBC review. Again, ask your Safety Officer.

How Does the IBC Review of a Clinical Protocol Overlap or Differ with Respect to Issues Assessed by the IRB, FDA or a DSMB?

OVERLAP:

1. Assessing the composition of the treatment product including some pre-clinical measures of efficacy and safety for the patient;

2. Any prior experience in the clinic with this or similar product;

3. What is the patient being informed (in the consent document) about the risks and safety of the product;

How Does the IBC Review of a Clinical Protocol Overlap or Differ in Focus with Respect to Issues Assessed by the IRB, FDA or a DSMB?

IBC FOCUS:

1. The sourcing (and validation/approval of the manufacturer sourcing of recombinant materials including virus vectors); Note that there is an NIH Vendor Qualification Committee that documents the qualification of a source of gene therapy vector (as a product example); your product may also require review by the Risk Assessment Review Committee and the Sterile Products for Human Administration (SPHA) Committee; Contact Virginia Guptill, PhD, Chief, Office of Research Support and Compliance, NIH CC if you have questions about whether your product requires review by these other committees.

2. Safety testing of any recombinant components, including those used in any manufacture process;

3. Provide plasmid and/or vector maps as appropriate (full sequence information is not needed for IBC review but the FDA normally requires this);

4. Provide a safety plan for handling infectious vector and assessment of risks to NIH personnel (in pharmacy, floor nurses, others handling potentially infectious agents);

5. If only the NIH CC DTM Center for Cellular Engineering will be receiving and handling, and only a non-infectious modified human cell product will be issued to the patient floor by CCE then this should be noted, and few additional details are required about handling in CCE;

How Does the IBC Review of a Clinical Protocol Overlap or Differ in Focus with Respect to Issues Assessed by the IRB, FDA or a DSMB?

IBC FOCUS:

6. If the patient is to receive any infectious product treatment where there is any risk of shedding or passage to staff, family or the public then this should be noted and a risk management plan should be proposed to determine when the patient is not at risk of shedding and how staff, family and the public would be protected during the potential shedding/infectious period (e.g. listeria or certain recombinant vaccinias and other live vaccines);

7. Assessing the composition of the treatment product including some pre-clinical measures of efficacy and safety for the patient;

8. Any prior experience in the clinic with this or similar product;

9. What is the patient being informed (in the consent document) about the risks and safety of the product, not just for the patient but for the patient's family and the public;

Thank you for your attention.

Questions?