IBC REVIEW & APPROVAL PROCESS FOR USC CLINICAL TRIALS

CONTENTS

1.0 PURPOSE and SCOPE

The Office of Environmental Health & Safety in collaboration with the Clinical Investigation Support Office (CISO) at USC has created this document as a guide to explain the stepwise processes involved with review of Institutional Biosafety Committee (IBC) protocols involving Human Gene Transfer clinical trials.

Human Gene Transfer (HGT) refers to a subset of research involving the transfer of synthetic/recombinant DNA, or DNA/RNA derived from recombinant/synthetic DNA, into human subjects. These types of research are usually designated as clinical trials and are sometimes referred to as “Gene Therapy”.

The *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH Guidelines) sets forth the requirements regarding oversight and regulation on the conduct of Human Gene Transfer to ensure the safe handling and containment of recombinant DNA (Note: Although titled “Guidelines”, they are requirements since USC receives NIH grant funding). Specifically, the NIH Guidelines states the following regarding Human Gene Transfer Clinical Trials in Section 3C (III-C).

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 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.

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

The deliberate transfer of recombinant or synthetic nucleic acids into one human research participant, conducted under an FDA-regulated individual patient expanded access 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.

USC researchers that will conduct Human Gene Transfer (HGT) clinical trials must first obtain USC IBC approval or concurrent approval from both USC IBC and an external IBC chosen by USC as an additional reviewer. Once approval is granted, participants may then be enrolled in the HGT clinical study.

Purpose

This clinical trial IBC protocol review manual will serve as a resource for Sponsors, Principal Investigators (PIs), and regulatory specialists at the Clinical Investigation Support Office (CISO) when the need arises to review IBC protocols involving HGT clinical trials. Having this reference guide during various stages of the HGT clinical trial approval process will assist different stakeholders in getting the approval of the HGT IBC protocols in a timely manner.

Scope

This document pertains to all HGT clinical trial sponsors, PIs selected by the sponsors to conduct the specific HGT clinical trials at USC, and regulatory specialists from CISO who assist administratively with the HGT clinical trials. Specifically, this document is intended for new and ongoing clinical trials at USC including but not limited to University Park Campus (UPC) and Health Sciences Campus (HSC).

2.0 REGULATORY REQUIREMENTS

Federal

- FDA Regulations: Good Clinical Practice and Clinical Trials
- OSHA Blood Borne Pathogen - 29 CFR 1910.1030

NIH

- Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines), 2019

State

CCR Title 8 General Industry Safety Orders

- Protection of Human Subjects in Medical Experimentation Act - California Health and Safety Code Sections 24170 - 24179.5
- §5193. Bloodborne Pathogens
- §5199. Aerosol Transmissible Diseases
- California Health and Safety Code Sections 117600 – 118360

USC

- Responsible Conduct of Research
- Research Compliance
- Conflict of Interest
- Personal Protective Equipment Standard

3.0 ACRONYMS/ABBREVIATIONS/DEFINITIONS

BUA	Biological Use Authorization
CDC	Centers for Disease Control Prevention
CISO	Clinical Investigation Support Office
EH&S	Environmental Health and Safety
FDA	Food and Drug Administration
HGT	Human Gene Transfer
HIPAA	Health Insurance Portability and Accountability
HSC	Health Sciences Campus
IBC	Institutional Biosafety Committee
IND	Investigational New Drug
IRB	Institutional Review Board
iStar	A web-based application routing and tracking system for: • Institutional Review Board (USC, CHLA, Los Angeles General Medical Center) • Institutional Animal Care and Use Committee (USC) • Institutional Biosafety Committee (USC & CHLA) • Radiation Safety Committee (USC)
NIH	National Institutes of Health
RSOC	Research Safety Oversight Committee
UPC	University Park Campus

4.0 ROLES AND RESPONSIBILITIES

Research Safety Oversight Committee (RSOC)
The RSOC is convened to provide high level oversight of all aspects of health and safety related to research at USC. The RSOC specifically facilitates communication between other specialized safety committees: Institutional Biosafety Committee (IBC), Institutional Animal Care and Use Committee (IACUC), Radiation Safety Committee (RSC), Campus-Wide Chemical Safety Committee (CCSC), and additional stakeholders.

Institutional Biosafety Committee (IBC)
The IBC is responsible for reviewing projects in which biohazards are used (including work with recombinant and synthetic DNA), ensuring that research is conducted safely, and assessing and minimizing risks.

IBC has the responsibility to:

- Review and approve research including clinical trial protocols involving recombinant and synthetic DNA material prior to the initiation of the study.
- Provide recommendations to mitigate potential health and safety risks when working with biohazardous materials including recombinant and synthetic DNA material.
- Provide recommendations for appropriate training sessions and any required medical surveillance for study personnel who prepare and administer the study agent and their staff to follow.

IBC has the authority to:

- Disapprove all proposals that do not meet NIH guidelines and federal CDC regulations regarding work with recombinant and synthetic DNA material and other pertinent USC policy requirements.

Institutional Review Board (IRB)
FDA regulations stipulate the requirement of an Institutional Review Board (IRB) in institutions that engage in human subjects research. An IRB is formally designated and is tasked with review and monitoring of biomedical research involving human subjects.

The IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. The IRB is an integral part of an institution's oversight committees, and it serves an important role in the protection of the rights and welfare of human research subjects.

Through advance and periodic review, an IRB assures that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures).

Sponsor
The Sponsor (usually a pharmaceutical company e.g., Pfizer, Amgen) develops an experimental drug and utilizes clinical trials throughout the world to test its safety and efficacy. The Sponsor then seeks approval from the FDA to market the drug.

Principal Investigator (PI)
The person(s) in charge of a clinical trial. At USC, this is usually a Medical Doctor affiliated with USC Keck Hospitals at the clinical trial site that the sponsor has chosen to oversee their specific clinical trial.

The Clinical Investigations Support Office (CISO)
CISO serves as a centralized unit to: (a) oversee the clinical research infrastructure and (b) assist investigators in their conduct of clinical trials and translational research projects.
The regulatory specialists that work at CISO are responsible for the administrative aspects of each clinical trials including HGT studies. They also serve as the liaison between the drug sponsor and USC administration and pharmacy personnel involved with the clinical trial.

External IBC Vendors (CBS or WCG)
Some sponsors may request an external IBC to expedite review of their clinical trial protocol rather than pursue approval through USC's IBC Committee. An external IBC (similar to the USC IBC) will comprehensively evaluate the biosafety risks to staff and study personnel handling study agents containing biological agents (e.g., Lentiviral mediated CAR-T cell modification etc.) and make recommendations accordingly.

Environmental Health & Safety (EH&S)
The Biosafety Officer (BSO) and Biosafety staff from the Office of Environmental Health and Safety (EH&S) assist CISO and clinical trial coordinators with obtaining the necessary IBC approval for specific clinical trials as needed. They also coordinate with sponsors and external IBC vendors during the approval process.

For clinical trials with internal IBC reviews, a Biosafety Specialist will conduct an initial review of the clinical trial protocol. As part of the review process, the specialists will perform an annual site risk assessment of the preparation and administration locations where the investigational drug/recombinant DNA combination will be handled.

For clinical trials occurring at USC where the sponsor requests to conduct an externally administered IBC (e.g., WCG, Clinical Biosafety), the CISO will facilitate collaboration between USC Biosafety staff and the administrators of the externally administered IBC. The administrators may have additional requests regarding the clinical trial, for example, pictures and site maps of the drug preparation and drug handling locations (e.g., patient rooms, clinical pharmacy) and information regarding waste disposal. The EH&S Biosafety staff will assist external IBC administrators to ensure that specific clinical trials are approved in a timely manner. Additionally, the EH&S Biosafety Officer and one of the Biosafety staff members will attend the IBC to address any questions that the IBC members may have.

NOTE: Sponsors requesting the services of an externally administered IBC for their clinical trials still require approval internally by USC IBC before those clinical trials can commence.

5.0 USC INTERNAL IBC PROTOCOL REVIEW AND APPROVAL

The roles and responsibilities for Human Gene Transfer (HGT) protocol review by USC EH&S Biosafety, USC IBC, CISO specialists, and external IBC vendors are described below.

Pre-Review

EH&S Biosafety

1. USC CISO contacts EH&S Biosafety when clinical trials possessing recombinant/synthetic DNA needs USC IBC approval.
2. EH&S Biosafety conducts a pre-review of the protocol and request changes prior to the USC IBC meeting.
3. If necessary, EH&S Biosafety conducts a biosafety inspection of the clinical sites where the experimental drug is handled.
4. EH&S Biosafety conducts an annual site risk assessment to vet all safety features for the clinical trial.

CISO

1. CISO assists the PI in submitting the BUA via iStar for review and approval.
2. CISO provides all required documentation requested by the USC IBC.
3. CISO coordinates with pharmacy and administration stakeholders to facilitate a site visit inspection of drug preparation and administration areas.

Review

EH&S Biosafety

1. EH&S Biosafety assigns the HGT BUA to the upcoming USC IBC meeting. An ad hoc meeting may be conducted to discuss any major comments and to bring up any specific stipulations.
2. The stipulations regarding the HGT clinical trial BUA are forwarded to the USC IBC to be reviewed at the upcoming committee meeting.

CISO

Principal Investigator and CISO specialists are invited to participate at the ad hoc meeting (if applicable) and the USC IBC meeting where the clinical trial is reviewed.

Post Review

EH&S Biosafety

1. EH&S Biosafety follows up on stipulations and recommendations based on the USC IBC review.
2. IBC approval is provided after all stipulations have been addressed by the PI with assistance from the CISO office.

CISO

CISO assists the PI in providing any protocol related information to EH&S Biosafety to address the stipulations.

Annual Follow-Up

EH&S Biosafety

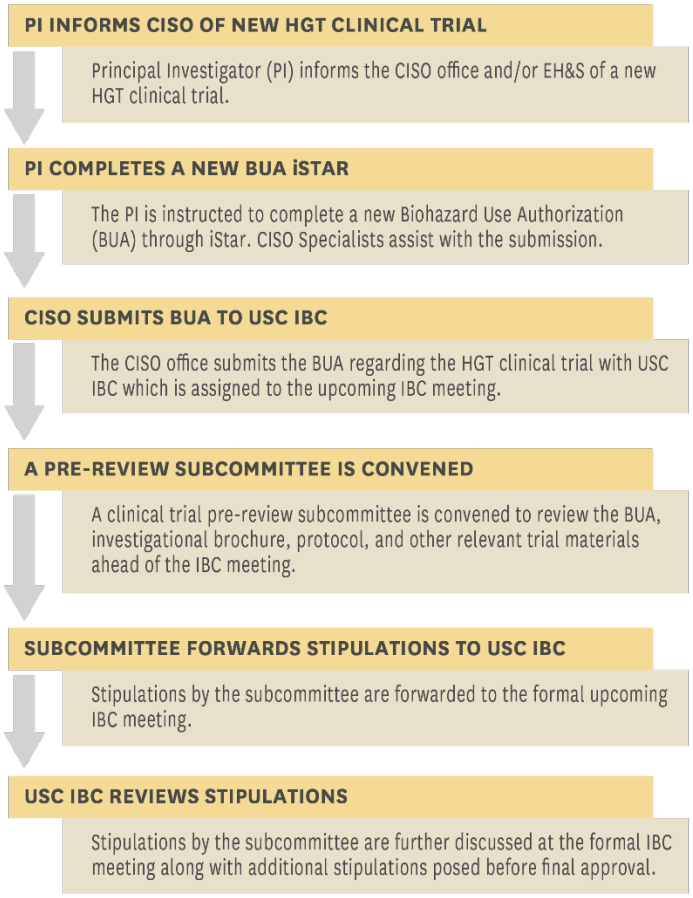
1. EH&S Biosafety reviews and assigns the BUA to the USC IBC for annual approval.
2. USC IBC will review the clinical trial for any updates and will approve it as necessary.

CISO

1. PI submits the clinical trial for renewal on an annual basis via iStar.
2. During the annual review, CISO provides updates on the protocol [e.g., Enrollment, Serious Adverse Events (SAE), etc.

See **Clinical Trial Flow Chart – Internal IBC Review Process** on next page.

Clinical Trial Flow Chart – Internal IBC Review Process



6.0 USC EXTERNAL IBC PROTOCOL REVIEW AND APPROVAL

The roles and responsibilities for Human Gene Transfer (HGT) protocol review by USC-approved external IBC services vendor are described below.

Pre-Review

The clinical trial sponsor requests external IBC review for the clinical trial. The external IBC vendor contacts CISO and EH&S Biosafety to gather the necessary materials to conduct the external IBC.

EH&S Biosafety

1. EH&S Biosafety acts as the liaison to obtain any necessary materials requested by the external IBC vendor e.g., pictures and site maps of the drug preparation and drug handling locations (patient rooms, clinical pharmacy) and information regarding waste disposal.
2. EH&S Biosafety verifies pertinent training records of the study personnel (Blood Borne Pathogens, Shipping of Biological Materials) and provides records to vendor.
3. If applicable, EH&S Biosafety conducts a risk assessment of the preparation and administration areas and provides the report to external IBC services vendor.

4. EH&S Biosafety requests representative personnel from drug preparation and drug handling locations (patient rooms, clinical pharmacy locations) to attend the meeting to address any specific questions regarding the sites and the procedures carried out in them.
5. EH&S Biosafety requests CISO office to submit an internal BUA through iStar to register the pending external IBC review of the HGT clinical trial with the USC IBC.

CISO

1. CISO provides EH&S Biosafety with contact details of the external IBC vendor.
2. CISO assists EH&S Biosafety in scheduling site visits for risk assessments of preparation and administration areas.
3. CISO submits an internal Biohazard Use Authorization (BUA) with USC IBC through iStar for internal approval.

Review

EH&S Biosafety

1. EH&S Biosafety participates in the externally-administered IBC meeting to provide an assessment of the locations that EH&S Biosafety may have visited as part of a risk assessment.
2. EH&S Biosafety requires CISO and the PI in charge of the clinical trial to submit an internal Biohazard Use Authorization (BUA) regarding the HGT clinical trial with USC IBC so that USC IBC is aware of the external IBC proceedings.
3. The internal USC BUA may have the option to expedite approval by the USC IBC. The USC internal IBC approval is required prior to the commencement of the clinical trials.

CISO

Personnel representing drug preparation and drug handling locations attend the meeting to address any questions that the external IBC reviewers may have regarding the specific procedures during the clinical trial.

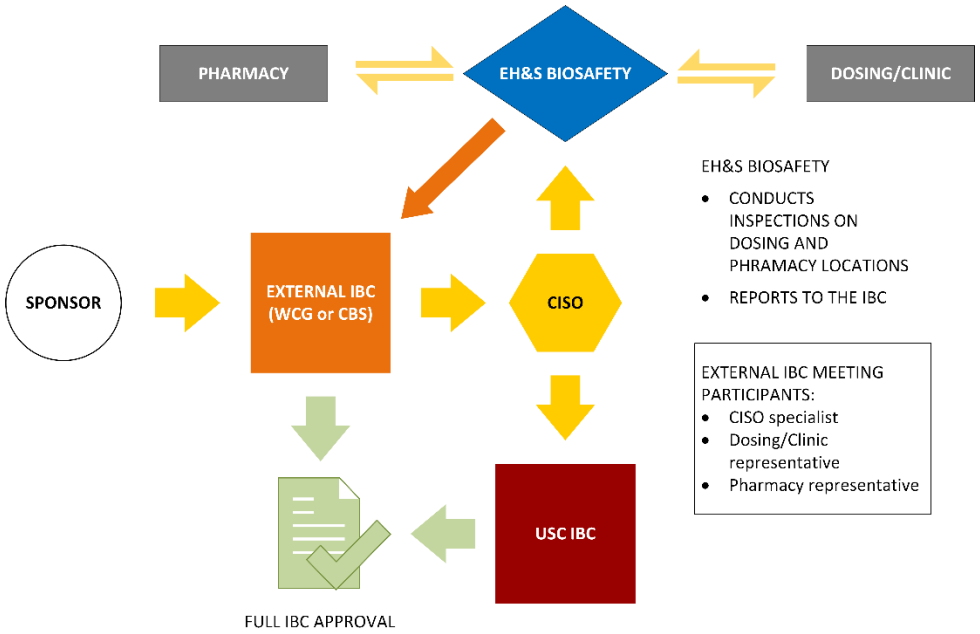


Figure 1 Who's Who in IBC Reviews

Post Review

EH&S Biosafety

1. EH&S Biosafety follows up on stipulations and recommendations based on the external IBC review.
2. EH&S Biosafety provides documentation for verification to external IBC services vendor to address the stipulations and recommendations made during the external IBC review.

CISO

1. CISO assists EH&S Biosafety in obtaining any necessary information regarding the clinical trial to address stipulations/recommendations that were brought up during the meeting.
2. CISO is required to inform the external IBC vendor if any changes are made to the clinical trial (e.g., changes made by the investigator, institution, and/or study sponsor). Additionally, CISO is required to inform any incidents that may have occurred during the year (e.g., enrollment, Serious Adverse Events (SAE)).

Annual Follow-Up

EH&S Biosafety

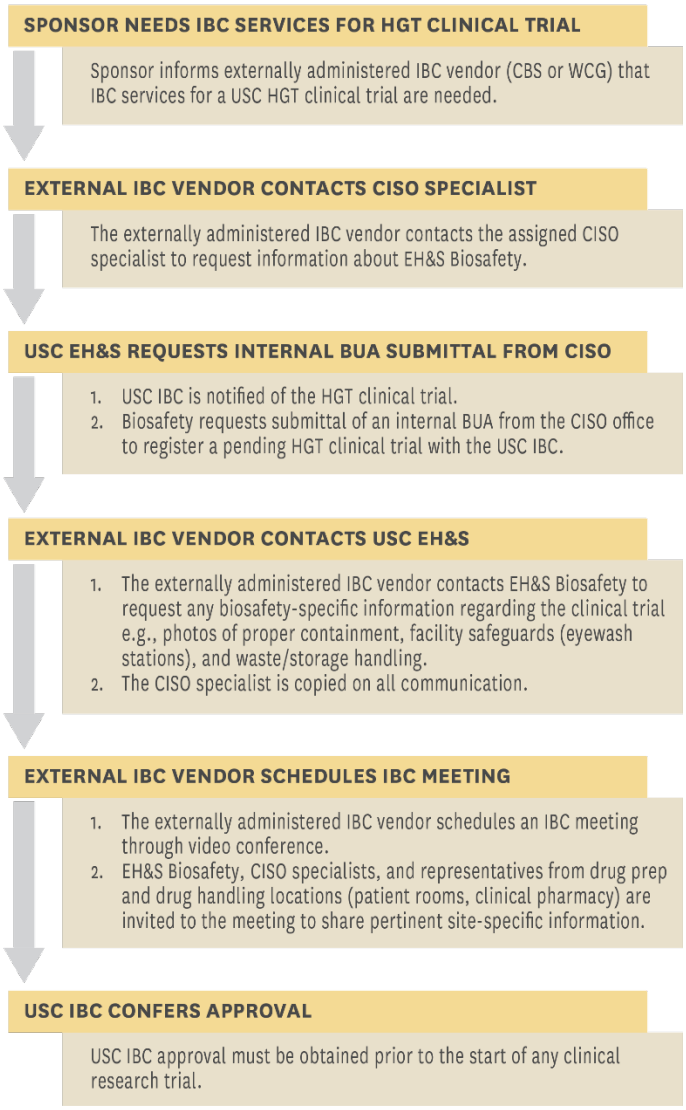
1. EH&S Biosafety participates in the annual external IBC review meeting regarding the specific clinical trials administered by the external IBC vendor. In these meetings, USC IBC will provide any feedback to external IBC committee members as requested.
2. The internal IBC BUA on file will also be reviewed and approved concurrently.

CISO

- CISO provides updates on the clinical trial protocol (e.g., enrollment, Serious Adverse Events (SAE)) as requested by the external IBC vendor.

See **Clinical Trial Flow Chart – External IBC Review Process** below.

Clinical Trial Flow Chart – External IBC Review Process



7.0 TRANSFER EXTERNALLY ADMINISTERED IBC INFORMATION TO AN INTERNAL USC BUA

The following outline offers guidance on transferring externally administered IBC information into an internal USC BUA.

Section 1.3:

Ensure all individuals who are not listed as “administrative only” have completed BBP training and that there is at least one individual who has successfully completed the BHS (shipping) training. Exception is made for the Principal Investigator and Co-Investigator(s).

Section 2.1:

- Objective – *what is the aim of the study?*
  Provide a brief overview of the study which includes:
  - The name of the study agent
  - Method of administration
  - Frequency of administration
  - Process for following-up with patient.

  In your explanation, clearly define any acronyms and define scientific terms to be understood by the lay person. This section should also clearly state the overarching objective of the study.

  Example:
  The purpose of this study is to evaluate the efficacy and safety of [***insert study drug and/or study drug plus chemotherapy agent***] as [***intended effect***] for patients with [***explain pre-disposed condition***].

  In this study, patients who have [***explain pre-disposed condition***] will have their tumor removed surgically (tumor resection). [***Insert study drug and/or study drug plus chemotherapy agent***] is a personalized cancer vaccine that will be developed to match the genetic make-up of each patient by using their removed tumor sample and blood samples, and then given to patients 6 times, once a week for 6 weeks. [***Insert study drug and/or study drug plus chemotherapy agent***] is a therapy made from a human antibody that helps boost immune cells, which have anti-tumor activity, and will be given once on Day 1 of Week 3 to patients. [***Insert study drug and/or study drug plus chemotherapy agent***] is a combination of drugs that is approved by the FDA to treat patients with [***explain pre-disposed***] condition and will be given to patients in 14-day cycles for up to 12 times. All of these will be given to patients through their [***method of administration***].

  Some patients will receive [***insert study drug and/or study drug plus chemotherapy agent***] and some patients will receive [***insert study drug and/or study drug plus chemotherapy agent***] only, to understand if [***insert study drug and/or study drug plus chemotherapy agent***] help [***intended effect***].

  After treatment, patients will be followed for [*explain follow-up and duration for which they should expect to receive the study drug*].

Section 2.2:

- Study breakdown – *describe the various parts of the study.*
  Example: Part 1 of the study will first evaluate the safety of various dose levels of [*insert study drug*] alone or with [***chemotherapeutic/other gene therapy product***] supplementation. Part 2 will enroll and treat up to an additional 12 subjects to validate the safety and tolerability of the selected dose level and dose schedule.
- Study Population – *this should be copied and pasted from the "Objective"*
  Example: Patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL) and follicular lymphoma (FL)

- Study Length – *how long is the study from start to finish?*
  Example: 23 months from initial administration of the study drug to end of study
- Study Endpoints – *when will patients have shown a "complete response?"*
  Example: 23 months post treatment, or until response/progression of disease occurs
- Description of Investigational Product (IP) – *information on IP should be taken directly from the investigator's brochure.*
  Example: The investigational drug product, [***insert name of study drug***], is an allogeneic cell therapy product consisting of [***insert technical description related to the gene map and design of the product***].
- Method for administration of IP – *how will the IP be administered to patients?*
  Example: Intravenous, Intramuscular, Nasally, etc.
- Plans for the Follow-up – *how often will patients be returning for treatment regimen?*
  Example: Participants will be followed per the protocol, monthly for 3 months, then every 3 months until 23 months post treatment (end of study), or until complete response or progression of disease occurs.
- *Maximum Concentration and Volume of the Study Drug: this would be in reference to the amount to be primed prior to administering to patient at the dosing location. This information should be in line with the Investigational Brochure.*
  Example: The starting dose (for dose escalation) of [***Insert Study Drug***] will be $3.4E^{+6}$ TU/kg given IV over 15 minutes on Day 1, 3 and 8 every 4 weeks. The maximum tolerated dose (MTD) will be determined following dose escalation, for dose expansion.

Section 2.3:
Check the appropriate laboratory containment level. This would be at BSL-2 at a minimum since the protocol usually involves the collection of human biofluids, tissues, and/or materials. This is in addition to the administration of the IP which could be derived from a viral vector which again necessitates the need to be working under BSL-2 conditions.

Section 2.4:
This is for manipulations done at the pharmacy and when the study drug is administered. All boxes should be checked as all are applicable.

Section 2.5:
All boxes should be checked except for the following:
"For animal injections, the animal must be mechanically restrained or anesthetized. Hand-restrain shall not be used without justification."

Section 2.6:
All boxes should be checked.

Section 2.7:
All boxes should be checked.

Section 2.8:
Check the box for Standard Method.

Section 2.9:
Check the box for Standard Method.

Section 2.10:
Please check the following at a minimum: “solid waste”, “sharps waste.” There may potentially be “pathological waste” if human tissues are collected and/or the collection of any other human materials.

Section 2.11:
Please check all boxes in case of spill inside or outside of BSC.

Section 2.12:
Please check the box for “Standard Procedure” for Exposure Procedure.

Sections 3-6:
If a viral vector is used for the IP, the host, vector, genetic insert information can usually be found in the Investigations Brochure (IB). Additionally, you may also contact the sponsor for the necessary information as well.

Section 7:
Please check III-C-1 as this is the NIH Guideline directly related to the deliberate administration of recombinant/synthetic nucleic acids to human subjects.

Section 10:
Please list all human materials collected from the study patients as applicable. This includes biofluids, tissues, primary cells, etc.

Section 14:
Please identify the preparation and dosing locations for the Study Drug.

Section 15.2
- Link to related internal IRB protocol.

Section 15.5
- Include the following:
  - Informed Consent
  - Investigator's Brochure
  - Investigator/Pharmacy Protocol/Manual
  - CV of the PI

8.0 TRAINING AND DOCUMENTATION

The Principal Investigator must ensure that his/her research group is trained in the application of this SOP by the principal investigator himself/herself or designee. Each user will enter his/her name, physical or electronic signature, and date below once he/she has read and understands the content of this SOP. The Principal Investigator will maintain this document (electronic or hard copy) in his/her files or central repository and will make it available upon request by EH&S during periodic or impromptu inspections. Each user will have access to a copy of the signed document.

NOTE: Users are subject to all applicable safety trainings including the General Lab Safety Course, annual laboratory safety training refresher, etc.

Name	Signature	Date

9.0 SOP REVIEW/REVISION

Date revised: 04/01/2024