Human Gene Therapy (HGT): Clinical Trials with Recombinant DNA

National Institutes of Health (NIH) Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules is the definitive reference for rDNA research in the United States. As NIH grantee, it is required for UCI to follow the NIH gene transfer clinical trial (Human Gene Therapy - HGT) guidelines.

The following information will help UCI investigators to comply with NIH Guidelines. Although the information below is extensive, PIs should not consider this a complete list of all requirements. It is the principal investigator's responsibility to ensure ALL regulations and requirements are met.

Submission Process
Consider how you want to sequence the various reviews and approvals. Normally, it is advisable to start with the RAC* review and then follow with Food & Drug Administration, Institutional Biosafety Committee, and finally the Institutional Review Board.

For example:
UCI's IBC will not approve a study without the RAC’s recommendations, and the IRB will not approve a study involving rDNA without IBC approval. Submission procedures depend on if the clinical trial study will be initiated at UC Irvine, or if UCI will be an additional site for a trial initiated elsewhere.

* Recombinant DNA Advisory Committee, or RAC, reviews protocol, scientific and safety related dimensions of the gene transfer intervention, and issues pertinent to the informed consent.

If initiated at UCI, the submission process is:
- E-mail NIH required documents to the Biosafety officer at shedayat@uci.edu for review prior to submittal to the NIH Office of Biotechnology Activities (OBA).
- After EH&S Biosafety approval, submit required documents to NIH/OBA.
- Following responses from NIH regarding public RAC review:
  - If public review is NOT warranted: complete and submit an IBC application for IBC approval. (See Section 3 for details)
  - If public review IS warranted: after public review and completion of necessary documentation in response to RAC’s comments, complete and submit an IBC application for IBC approval. (See Section 3 for details)

If initiated elsewhere:
- Complete and submit an IBC application for IBC approval. After IBC and IRB approvals are granted, send additional clinical site package to NIH. (Please contact your sponsor for this requirement)
- After enrollment of the first trial participant at UCI, do the following:
  - Work with the sponsor to ensure that the 20-day initiation report is sent to the NIH.
  - Notify UCI IBC within 20 working days of first enrollment.
  - Prepare the initial protocol for submission to UCI IBC

Submitting UCI IBC application
The protocol must be approved by RAC to be reviewed by UCI IBC

Follow these steps to prepare and submit the initial protocol to UCI’s IBC:
1. Assemble the documents included in the HGT Checklist: Provide link to the checklist here
   Complete the HGT checklist and upload it as supporting documents with your IBC application in iMedRIS. All documents included in the HGT checklist must be uploaded as additional documents. If any documents are not available, clarify on the checklist why the documents are not available.
2. Cover letter on UC Irvine letterhead signed by the PI that:
   Acknowledges the documentation submitted to the NIH/OBA complies with requirements in Appendix M-1-A of the NIH Recombinant DNA Guidelines
   Identifies the UCI Institutional Biosafety Committee and UCI Institutional Review Board as the proposed clinical trial site that will be responsible for local review and approval of the protocol
   Acknowledges that no research participant will be enrolled until the NIH RAC review process has been completed.
3. Submit an IBC application for IBC approval.
Every clinical trial protocol involving gene transfer must have IBC-approval before work can begin.
Submission dates: IBC applications are reviewed at the IBC's monthly meeting. See the 2016 dates on

Follow these steps to create and submit an IBC application:
Create an IBC application on iMedRIS: https://www.ehs.uci.edu/programs/biosafety/ibc/index.html

Follow instructions on How to Add a New Study: https://www.ehs.uci.edu/programs/biosafety/ibc/PIHowtoAddNewStudy.pdf

- Section 1: Enter the title of your study and abbreviated title
- Section 2: Enter the Department associated with the study
- Section 3: Assign key personnel, additional investigators, research support staff and study contact. The IBC will contact the PI and the study contact regarding all communications related to the study.
- Section 4: Provide information as required
- Section 5: Include the training and Occupational Health requirements. All personnel storing/processing/handling the agent require training. If there are any personnel who do not fall under these category and do not require the training, please identify them in section 5.1 and explain why.
- Section 6: Include the locations that fall under UCIMC and UCI in this section. If outside locations, not under the jurisdiction of UCIMC and UCI are used, do not include them in this section. Those locations and their uses must be included in section 14.2.
- Section 7: Include the PPE required by personnel.
- Section 8: Provide information as required
- Section 9: Include all locations where the material will be shipped from or shipped to. This will include the location where the agent is coming from and also the location where the agent or any materials collected from human subjects will be shipped to.
- Section 10, 11, 12 and 13: Provide information as required
- Section 14: Include information on
  o Why is this study being conducted? Describe the background and rationale of the study.
  o What are the other options for the research participants and why this therapy is used instead of the currently available therapies, if any are available?
  o What is expected from this study?
- Section 14.2
  o Describe the agent being used and how this agent will act on its target.
  o What kind of preparation is required for this agent? Will this agent come as ready to dose, or the agent will have to be prepared at UCI/UCIMC. How will the agent be stored and prepared for patient use?
  o How will the material be transported from the GMP facility to the preparation site?
  o How will the material be transported from the preparation site (pharmacy or equivalent) to the patient delivery site?
  o How will the agent be delivered onto the patient?
  o Will any fluids/tissue/organs be collected from the participants after delivery of the agent?
  o What kind of analysis will be done on the collected materials? How will the analysis be done? Who will carry out the analytical procedures?
- Section 14.3
  o In this section, include the health risks, to the patient, personnel providing treatment and family members of the patients, associated with the agent. What are the preventive measures employed to isolate/reduce these risks or any exposures to the agent. Include information on what kind of treatment is required if personnel/ family members are exposed to this agent.
  o In this section, include the potential of the agent to cause tumor formation.
  o In this section include the health risks to immunocompromised individuals including pregnant women and human embryo or fetus. The immunocompromised individual can be a personnel who might be involved in providing the treatment or any family members.
- Section 14.4: Provide information as required
- Section 15: Check NIH guidelines III-C-1 and any other applicable guidelines.
- Section 16, 17, 18, 19, 20 and 21: Provide information as required
**EH&S Biosafety staff will:**
Carry out a walkthrough of the location included in Section 6 of the IBC application
Attend the site initiation visit

**Post-approval reporting requirements**

**Delegation if applicable**
Delegation of NIH reporting responsibility (optional): Principal investigators may delegate to another party, such as a corporate sponsor, the reporting functions set forth in Appendix M, with written notification to the NIH/OBA of the delegation and of the name(s), address, and telephone and fax numbers of the contact. The PI is responsible for ensuring that the reporting requirements are fulfilled and will be held accountable for any reporting lapses. Attach a copy of the delegation letter in the IBC application.

**Enrollment of first trial participant**

**If the clinical trial is initiated at UCI:**
Within 20 business days after enrollment of the first trial participant, submit the following documentation to the NIH/OBA (see the “Contacts” section below for NIH/OBA reporting methods) and to UCI’s IBC via e-mail at ibc@uci.edu
Copies of the:
- Informed consent document approved by the Institutional Review Board (IRB)
- Clinical protocol approved by the IBC and IRB
- Final IBC approval letter from the clinical trial site
- Final IRB approval letter
- A brief written report that includes the following information:
  - How the investigator(s) responded to each of the RAC’s recommendations on the protocol (if applicable)
  - Any modifications to the protocol required by FDA
  - Applicable NIH grant number(s)
  - FDA Investigational New Drug Application (IND) number
  - Initiation date of the trial

**If the clinical trial is initiated elsewhere and UCI is additional clinical trial sites:**
Notify the NIH/OBA that UCI is an additional trial site BEFORE the first trial participant is enrolled by submitting the following documentation:
- IBC approval letter from the clinical trial site
- IRB approval letter
- IRB-approved informed consent document
- Curriculum vitae of the PI(s) (no more than 2 pages in biographical sketch format)
- NIH grant number(s) if applicable
- After enrollment of the first trial participant at UCI, confirm with the sponsor that the 20-day initiation report has been sent.

**Annual Report to the NIH and UCI’s IBC**
Within 60 days after the 1 year anniversary of the date on which the investigational new drug (IND) application went into effect, and after each subsequent anniversary until the trial is completed, the PI (or delegate) must submit an annual report to the NIH/OBA and IBC.

Note: If your trial is exempt from Appendix M (see Appendix M-VI-A), the NIH annual report is not required. UCI’s IBC, however, requires an annual report without exception. In the case of exempt protocols, the most current summary update submitted to the IRB may be submitted to the IBC to fulfill the annual report requirement.
How to Submit the Annual Report

NIH/OBA
Submit the report (for non-exempt protocols) separately to the NIH/OBA. See the “Contacts” section below for NIH/OBA reporting methods. Please note that failure to submit the annual report to the NIH by the due date will require EH&S Biosafety to send a notification of non-compliance to NIH.

UCI’s IBC
Submit the Annual report that was submitted to NIH to UCI’s IBC at ibc@uci.edu
The IBC approval expires in 3 years but is subject to annual verification.

Safety reports as required
A written report clearly labeled “Safety Report” must be submitted to the NIH/OBA and the UCI IBC in the following instances:
Any serious adverse event (SAE) that is both unexpected and associated with the use of the gene transfer product (i.e., there is reasonable possibility that the event may have been caused by the use of the product; investigators should not await definitive proof of association before reporting such events).
Any SAE that is fatal or life-threatening, that is unexpected, and associated with the use of the gene transfer product must be reported to the NIH/OBA as soon as possible, but not later than 7 calendar days after the sponsor’s initial receipt of the information (i.e., at the same time the event must be reported to the FDA).
SAEs that are unexpected and associated with the use of the gene transfer product, but are not fatal or life-threatening, must be reported to the NIH/OBA as soon as possible, but not later than 15 calendar days after the sponsor’s initial receipt of the information (i.e., at the same time the event must be reported to the FDA).
Any finding from tests in laboratory animals that suggests a significant risk for human research participants including reports of mutagenicity, teratogenicity, or carcinogenicity must be reported as soon as possible, but not later than 15 calendar days after the sponsor’s initial receipt of the information (i.e., at the same time the event must be reported to the FDA).

The SAE report must include (but is not limited to):
- Date of the event
- Designation of the report as an initial report or a follow-up report, identification of all safety reports previously filed for the clinical protocol concerning a similar adverse event, and an analysis of the significance of the adverse event in light of previous similar reports
- Clinical site
- Principal investigator
- NIH protocol number
- FDA’s Investigational New Drug (IND) application number
- Vector type (i.e., adenovirus)
- Vector subtype (i.e., type 5, relevant deletions)
- Gene delivery method (i.e., in vivo, ex vivo transduction)
- Route of administration (i.e., intratumoral, intravenous)
- Dosing schedule
- A complete description of the event
- Relevant clinical observations
- Relevant clinical history
- Relevant tests that were or are planned to be conducted
- Date of any treatment of the event
- Suspected cause of the event

Note: SAE Reports from clinical studies as delineated in Appendix M-I-C-4 must be submitted in a narrative format.

How to Report
NIH/OBA - Submit safety reports using the recommended Adverse Event Reporting Template (PDF) available on NIH/OBA’s web site, the FDA MedWatch forms, or other means provided that all of the above elements are specifically included.
UCI’s IBC - Report serious adverse events to UCI’s IBC
There are 3 mechanisms for reporting information to the NIH/OBA:

<table>
<thead>
<tr>
<th>Mail</th>
<th>E-mail</th>
<th>Fax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office of Biotechnology Activities National Institutes of Health, MSC 7985 6705 Rockledge Drive, Suite 750 Bethesda, Maryland 20892-7985</td>
<td><a href="mailto:oba@od.nih.gov">oba@od.nih.gov</a></td>
<td>(301) 496-9839</td>
</tr>
</tbody>
</table>

**Making changes to your protocol**

Significant changes to an approved protocol may require an amendment or a new IBC application. All changes cannot be addressed here. Consult IBC, before making changes to an approved IBC application.

Typical occasions when an amendment or a new IBC application are required are listed below.

- Serious adverse event (SAE) reporting (see Section 9 for details)
- Changes in location
- Title changes that do not change study parameters
- Changes to the investigational drug (at a minimum this requires an amendment, but might it require a new IBC application)
- New IBC application’s may be required for the following (contact IBC):
  - Changes to the investigational drug
  - Changes in the study population
  - Changes in administration of the investigational drug
  - New phase (i.e., going from phase 1 to phase 2)
  - Changes to the IRB number

**References**

- NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules
- Investigator Responsibilities Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (PDF)
- UCSD Clinical trials with rDNA: Instructions for Submission to the IBC