Human Gene Transfer/Recombinant DNA Research

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Regulatory Requirements

IMPORTANT NOTE: The UCSF IRB is in the process of updating this guidance to comply with recently revised NIH guidelines. Some of the information below is outdated. For example, RAC review is no longer required for each study. Please contact us [1] for more information and review the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules [2] and NIH Review Process for Human Gene Transfer Trials [3].

Human gene transfer research is defined by federal regulations as "any deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA (technology), into human research participants." Special provisions are necessary for conducting human gene transfer research at UCSF. PIs must complete a process of multiple reviews and approvals at both federal and local/institutional levels.

Applications to the following groups are required:

- FDA ? Food and Drug Administration
- IBC ? Biological Safety Committee at UCSF
- IRB at UCSF
- RAC ? Recombinant DNA Advisory Committee (NIH) in some cases

These NIH guidelines apply to any research to be conducted at or sponsored by an institution receiving support for recombinant DNA research from NIH. Thus, they apply to all UCSF PIs involved in such research.

**Applications at the Federal Level**

**FDA Review:** The study sponsor or investigator-sponsor will need to submit an Investigational New Drug (IND) application to the FDA (see UCSF guidance on Investigational New Drugs and Biologics [5]). The IND number will be required for final IRB approval.

**RAC Review:** The NIH Guidelines, Appendix M [4], outlines the scope of acceptable gene transfer proposals, as well as specific review requirements and procedures of the Recombinant DNA Advisory Committee (RAC) [6] within the NIH Office of Biotechnology Activities (OBA). RAC [6] is a federal advisory committee that provides recommendations to the NIH Director related to basic and clinical research involving recombinant or synthetic nucleic acid molecules.

*RAC review must precede local/institutional review.* Any recommendations resulting from the RAC review must be included in the applications to the UCSF IBC and IRB.

The initial RAC review process will include a determination as to whether the study presents characteristics that warrant public RAC review and discussion. RAC may decide that the protocol does not need further in-depth review at a public meeting. However, FDA and local review will still be needed.


Also, submit the following documentation to NIH OBA within 20 working days of consenting the first research participant.

- A copy of the informed consent document approved by the IRB;
- A copy of the protocol approved by the IBC and IRB;
- A copy of the final IBC approval from the clinical trial site;
- A copy of the final IRB approval;
- A brief written report that includes the following information: (1) how the investigator(s) responded to each of the RAC?s recommendations on the protocol (if applicable); and (2) any modifications to the protocol as required by FDA;
- Applicable NIH grant number(s);
- The FDA IND number; and
- The date of the initiation of the trial.

See the FAQs [9] for up-to-date information.

**Who is responsible for the RAC/OBA submission?**

**UCSF investigator-initiated study**

For an investigator-initiated study (e.g., production of vectors for human application is
performed by the UCSF investigator), the UCSF PI is responsible for the submission of the relevant information on the proposed human gene transfer research to OBA.

**Sponsor-initiated study**

For a sponsor-initiated study (e.g., the production of vectors for human application is not performed by the UCSF investigator), the sponsor must complete the RAC submission process and provide the UCSF PI with the required Appendix M [4] information for the UCSF IBC and IRB reviews.

**Applications at UCSF**

After the study sponsor or investigator-sponsor has sought initial RAC review and IND approval from the FDA, the UCSF PI must apply for institutional review of the gene transfer research.

**IBC Review:** The PI will need to obtain a Biological Use Authorization (BUA) [10].

**IRB Review:** The PI must also obtain approval from the IRB. In the "Other Approvals and Registrations" section of the IRB Application, indicate that the study involves human gene transfer. Attach the following as Other Study Documents:

- NIH Appendix M-II: Description of Proposal
- RAC correspondence, recommendations and review letter

Applications may be submitted simultaneously to the IBC and IRB for parallel review.

**Coordination of Approvals**

**IRB, IBC and RAC:** Provide a copy of final RAC review letter to the IRB and IBC with the initial application. The IRB will not review the study without this letter. Provide a copy of IRB and IBC approvals to OBA, as described above.

**IRB and IBC:** The IRB and IBC will coordinate resolution of any concerns raised by either committee before issuing final authorization and approval. A link will be maintained between the approved IRB Application and the BUA for the life of the study.

**IRB and FDA:** The IRB must receive the IND approval number (obtained from the FDA) before final IRB approval is issued.

**Reporting Adverse Events**

Should an adverse event occur within a gene transfer study, submissions may be required to the following groups:

**IRB and IBC**

The UCSF PI must consult and follow policies and procedures for reporting adverse events to the IRB [11] and the IBC [10].

**OBA**

PIs at all sites must report qualifying serious adverse events to the OBA according to the
guidance provided in Appendix M-I-C-3 and M-I-C-4 of the NIH Guidelines [4]. PIs may delegate this task to another party (e.g., the sponsor), provided a letter of delegation signed by the PI is on file with the OBA. In either case, any OBA reports concerning UCSF-enrolled participants should also be submitted to the IRB and IBC.

FDA

If the study IND is held by a UCSF investigator (investigator-sponsor), the PI must also report qualifying SAEs directly to the FDA (see 21 CFR 312.32 [12]). If the study IND is held by an outside sponsor (sponsor-initiated), this responsibility falls to the sponsor.