

A. SUBJECT: Policy on Gene Transfer Research Trials

B. EFFECTIVE DATE: 1 January 2002

C. POLICY

This policy applies to experiments involving the deliberate transfer of recombinant DNA, (or DNA or RNA derived from recombinant DNA), into one or more human research participants at the University of Virginia.

Oversight of Gene Transfer Research Trials is regulated at the Federal level by the National Institutes of Health (NIH), Office of Biotechnology Activities (OBA)/Recombinant DNA Advisory Committee (RAC). All proposed study protocols must be submitted to the OBA in accordance with the “Guidelines for Research Involving Recombinant DNA Molecules”, Appendix M. (Please see procedure section for link to this Appendix)

Final approval of all Gene Transfer Research Trials at the University of Virginia is the responsibility of the Human Investigation Committee (HIC) and the Institutional Biosafety Committee (IBC).

The HIC will:

- Verify that the consent form meets all federal regulations according to 45CFR46 and 21CFR50
- Verify that all appropriate information as outlined in Appendix M of the RAC application is included in the protocol and consent form.
- Verify that all items as suggested by the IBC and RAC are included in the consent form.
- Verify that complete disclosure of any conflict of interest is noted in the consent form.
- Confirm that approval from all other required review committees or bodies have been obtained. A representative from each required committee or body may be present at the HIC meeting when final approval is given. If a representative is unable to attend, a written approval from them must be submitted for review at the meeting.
- Confirm all protocol procedures with Principal Investigator during the HIC meeting when final approval is given.
- Confirm that key personnel have completed the HIC Investigators Training Program.

The IBC will:

- Assess the scientific relevance of the protocol.
- Review the existing knowledge of the disease state and current therapy, route of administration, dose, and vector virulence. Additional ad hoc members may be appointed from within the institution on an as needed basis.
- Recommend information to be provided to family and other caretakers pertaining to potential risks and precautions to be stated in either a separate document or in the consent form.
- Recommend additional information the HIC may wish to have included in the consent form pertaining to potential risks to subjects.
- Assess risks to the environment and the necessity to inform medical care personnel, (e.g., nurses, technicians), of risks, precautions, and recommended health surveillance procedures.
- Confirm that key personnel have completed the appropriate biosafety training.

- Review the mandatory document entitled “Biosafety Manual and Standard Procedures for the Transfer of Recombinant DNA Molecules into Human Subjects.” to confirm that it accurately reflects the protocol.
- Perform initial and regularly scheduled inspections of clinical facilities where vector distribution, administration and potential subsequent viral shedding may occur to certify the implementation of appropriate work practices and physical controls.

Additional approvals will be required from the following committees or bodies:

UVA General Clinical Research Center (GCRC) Advisory Committee will:

- Review the document entitled “Biosafety Manual and Standard Procedures for the Transfer of Recombinant DNA Molecules Into Human Subjects” to confirm it accurately reflects the Protocol, Consent Form and Appendix M.
- Verify that all GCRC Advisory Committee personnel who will be working on this protocol have been trained.

UVA School of Medicine Clinical Trials Office (CTO) will:

- Review the Case Report Forms to verify they are clear, concise and accurate according to the Protocol, Consent Form and Appendix M.
- Verify that procedures are adequate to oversee management of data.
- Review the Monitoring Plan

Additional approval may be required by the UVA Cancer Center Protocol Review Committee if the protocol has an inclusion criterion stating the participants must have cancer and the protocol is NOT sponsored by the NIH, ACS, DOD, NSF or a Cancer Cooperative Group.

UVA Cancer Center Protocol Review Committee will:

- Review the scientific relevance of the study in cancer patients.
- Review the quality of the study design, including entry criteria, patient assessment and follow-up, toxicity assessment and dose modification criteria, and biostatistical analytical plan.
- Verify that the Protocol and Consent Form accurately reflects the study as outlined in Appendix M.

Please Note:

- The RAC requests that the HIC and IBC provide a “PRELIMINARY approval pending RAC Review” prior to the initial submission of the protocol to the RAC. The protocol must be reviewed by the full committee of the HIC and IBC prior to a preliminary approval status being given.
- No study participants may be enrolled until final approval is granted by the HIC and the PI has obtained an IND from the FDA.
- The mechanism for submittal and approval of study protocols is outlined in the Procedures section below.

Additional information regarding the review committees or bodies can be found on their web sites:

- RAC: <http://www.nih.gov/od/oba/>
- HIC: www.hsc.virginia.edu/HIC
- IBC: <http://keats.admin.virginia.edu/gene/home.html>
- Cancer Center Protocol Review Committee:
<http://www.med.virginia.edu/medcntr/cancer/ctprotocol.html>
- GCRC: <http://gcr.med.virginia.edu>

Pharmacy: <http://www.hsc.virginia.edu/pharmacy-services/>

- School of Medicine Clinical Trials Office: <http://hesweb1.med.virginia.edu/clintrials>

D. PROCEDURES

New Application

1. Submit an application to the HIC and the IBC using the UVA Gene Transfer Study HIC/IBC Application Form (see attached). Please refer to the application form to determine the number of copies to be submitted.
2. The application must include a completed Attachment M which can be found at <http://www4.od.nih.gov/oba/guidelines.html>. Attachment M is part of the RAC “Guidelines for Research Involving Recombinant DNA Molecules.” The RAC application requires information about the disease under study, vector being used, and nature of the proposal in addition to other items. The NIH review process is open to the public so proprietary information should be withheld.
3. When the Principal Investigator has received pending approval from the HIC and IBC, he/she should then submit the application to OBA for RAC review. If the RAC review indicates areas of concern (e.g., novel vectors, unresolved health concerns, or other potential problems) the protocol will be selected for public review. RAC currently estimates that this public review process will occur for about 10 % of the submissions.
4. Following RAC review, submit revised protocol and consent forms, along with a copy of the RAC review comments for full committee review. Submit the following number of copies:
 - HIC: 16 copies
 - IBC: 9 copies
 - Cancer Center Protocol Review Committee (if applicable): 16 copies
 - GCRC Advisory Committee: 1 paper copy of the protocol and consent, and 1 electronic copy of the protocol and consent
 - School of Medicine Clinical Trials Office: 3 copies
5. Final approval will be given by the HIC only after the HIC has received approval and all required documentation from all other committees or bodies.
6. Following HIC approval, submit application to FDA.
7. Participants may not be enrolled until final HIC approval is obtained and no “hold” notification from the FDA is received 30 days following the submission of the Investigational New Drug (IND) Application.

Adverse Event Reporting

ALL SERIOUS ADVERSE EVENTS (SAE) MUST BE REPORTED WITHIN 24 HOURS TO THE HIC, IBC, FDA AND THE OBA/RAC USING THE ATTACHED REPORTING FORM. PLEASE NOTE THAT ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED EVEN IF THE ADVERSE EVENT IS FELT TO BE UNRELATED OR EXPECTED.

A **Serious Adverse Event** is defined as:

"any expected or unexpected adverse event, related or unrelated to the intervention, occurring at any dose that results in any of the following outcomes; death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization also may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."

Monitoring of Protocol After Approval

HIC: Quarterly Status Report for first year, then every 6 months. A copy of the annual report and any other correspondence to the FDA/NIH regarding this protocol should be submitted with the Status Report.

IBC: A copy of the annual report to the FDA/NIH must be submitted concurrently to the IBC.

Cancer Center Protocol Review Committee: 6-month status reports summarizing enrollment data, changes to the protocol and unexpected toxicities.

GCRC Advisory Committee: Quality Improvement Monitoring Plan in place for each protocol.

Gene Transfer Oversight Committee: a group made up of at least one person each from GCRC Advisory Committee, HIC, IBC, CTO and the Cancer Center Protocol Review Committee will meet at least once a year to review this policy and related compliance issues.

School of Medicine Clinical Trials Office: Protocol compliance and periodic review of completion of Case Report Forms.

SIGNATURE _____

DATE _____

ATTACHMENTS:

1. HIC/IBC Gene Transfer Study Application Form
2. Serious Adverse Event Reporting Form for Gene Transfer Protocols