Gene Transfer Protocols Studies Guidance

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Guidance on gene transfer studies

All studies involving the deliberate transfer of DNA, or DNA or RNA derived from recombinant DNA (human gene transfer) are subject to special submission, review, and reporting requirements at both the Federal and UW levels. The overview of regulatory processes provided here summarizes NIH [insert the following hyperlink: http://oba.od.nih.gov/oba/ibc/FAQs/FAQs%20about%20the%20NIH%20Review%20Process%20for%20Human%20Gene%20Transfer%20Trials.pdf] and FDA [add hyperlink: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm] guidance on human gene transfer research. A complete copy of NIH guidance.

Regulatory Oversight and Institutional Review Requirements

All human gene transfer studies must be submitted in the following order to:

1. National Institutes of Health (NIH) Office of Biotechnology Activities (OBA)
2. Food and Drug Administration (FDA)
3. UW-Madison Institutional Biological Safety Committee (IBC)
4. UW-Madison Health Sciences Institutional Review Board (HS IRB)

University of Wisconsin Hospital and Clinics Research Safety Committee (RSC) review and approval is also required. Review by the RSC can be prior to or simultaneous with the IRB or IBC review.

No subjects may be enrolled in gene transfer protocols until the NIH OBA review process has been completed, IBC and HS IRB approval have been obtained, and any other applicable regulatory authorization(s) have been secured. The HS IRB will only review applications for gene transfer studies when all other required reviews and approvals are completed.

Federal Regulatory Oversight Requirements

NIH Review

For investigator-initiated studies, the Principal Investigator (PI) is responsible for submitting the required documents (see Appendix M-I-A of the NIH guidelines) to the NIH OBA. For sponsor-initiated studies, the sponsor must complete the submission process and provide the UW investigator with all information required for IBC and HS IRB review. In multi-center studies, the NIH OBA review process is the responsibility of the PI for the entire study.
After the documents are submitted, the NIH OBA will then provide a summary and copy of the submission to members of the Recombinant DNA Advisory Committee (RAC). As part of its initial review, RAC members assess whether the proposed study warrants public review and discussion at the RAC’s quarterly meetings open to the public. Investigators or sponsors will be notified within 15 days of submission to OBA whether their study has been selected for public RAC review. After the RAC has completed its review process (including a public discussion, if necessary) a letter summarizing its comments and recommendations will be sent to the sponsor or PI, the HS-IRB and IBC, the FDA, and appropriate DHHS offices. The RAC does not issue a formal approval for proposed studies; rather, its comments and recommendations are used to inform other review processes at the federal and local levels.

FDA Requirements

The FDA is responsible for the review and approval of gene therapy products as Investigational New Drugs (INDs). The study sponsor or PI for investigator-initiated studies will need to submit an IND application to the FDA. The IND number will be required for final HS-IRB approval. FDA guidelines for INDs and gene therapy studies.

Institutional Oversight and Review Requirements

Following the required federal regulatory reviews, investigators must have their proposed gene transfer studies reviewed and approved by the UW-Madison IBC and the HS IRB and the UW Hospital and Clinics RSC. Human gene transfer studies cannot begin without IBC and HS IRB approval.

IBC Review

To apply for IBC review, investigators should contact the Office for Biological Safety. All gene transfer studies must be reviewed and approved by the IBC prior to submission to the HS IRB.

HS IRB Review

In addition to general submission requirements, the HS IRB will withhold final approval of gene transfer studies until receipt of documentation of successful NIH OBA review and an IND number from the FDA. A copy of the materials submitted to NIH OBA also should be submitted to the HS IRB.

UWHC RSC Review

The purpose of the UWHC RSC is to establish a process by which clinical (human) research protocols possessing potential health hazards are identified, reviewed and approved before entrance into the University of Wisconsin Hospital and Clinics health system network. The RSC reviews research protocols involving drugs, agents, devices and/or procedures and possessing potential health hazards before said research could begin at UWHC. This committee focuses on research protocols possessing safety concerns that are not adequately covered by existing biohazardous or cytotoxic policies and/or where safety policies exist but the research location, route of administration or employees involved require changes from routine operating procedures. To arrange for RSC review, contact the committee at 608-263-4856.

Consent Form Requirements
Due to the novelty of the procedures that are used in gene transfer studies, the potentially irreversible consequences of the procedures performed, and the fact that many of the potential risks remain undefined, great care must be taken when preparing the consent form. In addition to the requirements prescribed in 45 CFR 46.116 and 21 CFR 50.25, investigators also should address the issues outlined below.

Reproductive Considerations: To avoid the possibility that any of the reagents employed in the gene transfer research could cause harm to a fetus or child, the consent form should include information concerning possible risks and the need for contraception by males and females during the active phase of the study. The period of time for the use of contraception should be specified and the inclusion of pregnant or lactating women should be addressed.

Long Term Follow-Up: To permit evaluation of long-term safety and efficacy of gene transfer, the prospective subjects should be informed about whether they are expected to participate in long-term follow-up and for what duration. The consent form should include a list of persons who can be contacted in the event that questions arise during the follow-up period. The PI should require that subjects continue to provide a current address and telephone number.

Request for Autopsy: To obtain information about the safety and efficacy of gene transfer, subjects should be informed if an autopsy is planned that at the time of death, no matter what the cause, and that permission for an autopsy will be requested of their families. Subjects should be asked to advise their families of the request and of its scientific and medical importance.

Adverse Event Reporting Monitoring

Requirements for reporting adverse events for protocols involving gene transfer are similar to those for non-gene transfer protocols. However, because of the nature of these research studies, additional robust adverse event monitoring plan oversight is required. A formal data monitoring committee is expected beyond phase I. In the case of phase I studies, the data safety and monitoring plan should include review by an independent expert at appropriate timepoints. The following exceptions apply to gene transfer protocols:

- All adverse events for any protocol involving gene transfer that are serious and unexpected, regardless of their suspected relationship (or lack thereof) to the study intervention or whether a formal DSMB or DMC exists for that study, must be reported to the IRB within 10 business days of the investigator becoming aware of the events.
- All deaths of subjects participating in gene transfer protocols must be reported to the IRB regardless of the length of time after the last treatment was administered. Deaths must be reported within 10 business days of the investigator becoming aware of the events.