Guidance for Conducting Human Gene Transfer Research at UK

Overview:

Human gene transfer (HGT) research is defined by federal regulations as "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."

HGT research poses many scientific, medical, ethical, social, safety and methodological challenges not shared by other forms of human research. As such, a number of regulatory requirements must be satisfied before the initiation of any human research involving gene transfer. Principal Investigators (PIs) must navigate a complex process of multiple reviews and approvals at both federal and institutional levels. This help guide serves to assist PIs in initiating a human gene transfer protocol.

Institutional Requirements:

- **Institutional Biosafety Committee (IBC)**

  The IBC is responsible for reviewing recombinant DNA and biohazardous research conducted at or sponsored by the institution, regardless of funding source or location of research for compliance with the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* and other appropriate guidelines and University policies, to assess the safety of the research and identify any potential risk to public health of the environment.

  You must submit your study to the IBC for review via UK's online registration software. For more information regarding the online submission process, visit http://ehs.uky.edu/docs/pdf/bio_ibc_registration_0001.pdf In addition to completing the online protocol registration process, you must also submit the following:

  - Investigator's Brochure (sponsor)
  - Study Protocol (sponsor)
  - Pharmacy SOP for gene therapy
  - Any sponsor training materials for clinical staff
  - Patient education materials
  - Approval letter from departmental Medical Review Board (if applicable)
  - Infection Control plan for trial at UK
  - Informed Consent Form

A full description of the product must be included in the Summary Statement of the IBC registration form which includes:

- The derivation of the delivery vector system including the source (e.g., viral, bacterial, or plasmid vector); and modifications (e.g., deletions to attenuate or self-inactivate, encapsulation in any synthetic complex, changes to tropisms, etc.). Please reference any previous clinical experience with this vector or similar vectors.
- The genetic content of the transgene or nucleic acid delivered including the species source of the sequence and whether any modifications have been made (e.g. mutations, deletions, and truncations). What are the regulatory elements contained in the construct?
- Description of any other material to be used in preparation of the agent (vector and transgene) that will be administered to the human research subject (e.g., helper virus, packaging cell line, carrier particles).
- Methods for replication-competent virus testing, if applicable.
- The intended *ex vivo* or *in vivo* target cells and transduction efficiency.
- The gene transfer agent delivery method.

For protocols not requiring RAC review, the IBC will issue provisional approval. A memo indicating such will be sent to the PI. The "provisional approval" memo must be submitted to the IRB as part of the IRB application materials. **Please note** HGT protocols must be reviewed by the IBC and granted provisional approval prior to IRB submission. Once IRB approval is obtained, a copy of the IRB approved consent form, patient training materials, and IRB approval letter must be submitted to the Biological Safety Department before final approval is granted.

For Phase I trials with University of Kentucky as an initial trial site:

For protocols the IBC assesses RAC review is warranted:

If the University of Kentucky will be an initial trial site, studies that meet any of the following criteria will generally require RAC review.

1. the protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience.
2. the protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value
3. the proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known

If the IBC determines that RAC review is necessary, the Principal Investigator (usually in conjunction with the Study Sponsor) must submit materials to the NIH Office of Science Policy for registration and review. The RAC will make a decision to either register the product without further review or will send the protocol to the RAC for full review and public discussion. Materials must be submitted to the OSP 8 weeks before the next regularly scheduled RAC meeting.

Final IBC approval will be granted after the RAC process is complete and the PI/Sponsor has addressed all written comments from the RAC.

For Phase I protocols the IBC assesses RAC review is not necessary:

Before final approval may be granted the PI will register the UK IBC and UK IRB reviewed study to the NIH OSP. Registration materials will include the local IBC's and IRB's assessments of whether public RAC review is warranted. This documentation must be submitted no less than 10 working days prior to the anticipated date of enrollment of the first patient. The response from NIH stating the OSP registration is complete must be submitted to the IBC before final approval will be issued.

- **Institutional Review Board (IRB)** http://www.research.uky.edu/ori/

The IRB is a federally mandated committee responsible for review of research studies involving human subjects. Its purpose is to ensure that proper safeguards are in place to protect human subjects enrolled in research studies.

PIs must submit a Medical IRB Full Review Application available online (http://www.research.uky.edu/ori/MedicalFullReviewApplication.htm). There are seven sections to the IRB application. Depending on the nature of the research, some sections will apply while others will not. The PI must review each section to determine applicability to the research and include the appropriate forms in the IRB application submission.

The concepts of HGT research are often difficult for potential participants to understand. As such, NIH/OBA has developed guidance on the issue of informed consent in gene transfer studies (Annotated Compendium of NIH Resources on Informed Consent). This additional guidance is not part of the NIH Guidelines, or an amendment to Appendix M, but rather should be used by PIs as a resource in developing an informed consent document for a HGT protocol.

Prior to submission of IRB application material to the IRB for review, the protocol must be reviewed by the IBC and granted provisional approval.

The Medical IRB meets approximately six times per month. There is no deadline for submission of applications. Protocols are assigned on a "first come, first served" basis, and will be placed on the next available agenda.

Full reviews require that the PI attend the meeting at which the application is reviewed. A review date is assigned to the protocol at the time of submission. The PI must notify the Office of Research Integrity (859-257-9428) if he/she is not available on the assigned review date.

Federal Requirements:

- **Food and Drug Administration (FDA)** http://www.fda.gov/cber/

The Center for Biologics Evaluation and Research (CBER) regulates human gene therapy products (products that introduce genetic material into the body to replace faulty or missing genetic material) based upon the Public Health Service Act and the Federal Food Drug and Cosmetic Act. It is the responsibility of the pharmaceutical sponsor or principal investigator to file an Investigational New Drug (IND) application for each new investigational agent intended for human study in accordance with 21 CFR 312.

The FDA has published the "Guidance for Human Somatic Cell Therapy and Gene Therapy", containing guidelines and recommendations regarding the clinical use of gene products.

- **NIH-OBA / Recombinant DNA Advisory Committee (RAC)**
  https://osp.od.nih.gov/biotechnology/recombinant-dna-advisory-committee/

  The Recombinant DNA Advisory Committee (RAC) of the NIH-Office of Biotechnology Activities (OBA) is responsible for the review of research protocols involving the deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into human subjects (human gene transfer), funded by NIH or that take place at an institution receiving NIH funds. Human gene transfer protocols must be submitted to NIH as described in Appendix M, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Research Participants,* of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*. The process outlined in Appendix M must be completed prior to review by the NIH RAC. The NIH review process is open to the public so proprietary information should be withheld. Upon receipt of the complete human gene transfer protocol, it is sent to RAC members for an initial review. During this preliminary protocol review period, RAC members may request additional information or clarification regarding your submission and sometimes may make specific comments/suggestions regarding protocol design, informed consent document, etc. At the end of the preliminary review process, RAC members will determine if the protocol raises important scientific, safety, medical, ethical or social issues that warrant an in-depth public review.

  The outcome of public RAC review is a series of recommendations and advice from experts in the field. It does not entail a formal approval of the proposed protocol. The recommendations will be captured in a summary letter prepared by OBA and sent within ten (10) working days of completion of the RAC meeting. The summary letter will also be sent to the IRB and IBC reviewing your protocol, in addition to the FDA.

  See "Frequently Asked Questions about the NIH Review Process for Human Gene Transfer Trials" for guidelines and recommendations regarding the submission of human gene transfer protocols to NIH RAC for review.

After trial begins…

Please note - The FDA and NIH share reporting deadlines. The University of Kentucky IBC and IRB share reporting deadlines.

	Annual Reporting	Amendments	Adverse Events
FDA	In accordance with 21 CFR 312.33, submit within 60 days of the anniversary date the IND went into effect.	Submit to FDA in accordance with 21 CFR 312.30.	Submit in accordance with 21 CFR 312.32.
NIH/OBA	In accordance with Appendix M-I-C-3 of the NIH Guidelines, submit within 60 days of the anniversary date the IND went into effect.	No Submission Required.	Submit in accordance with Appendix M-I-C-4 of the NIH Guidelines to NIH using GeMCRIS.

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	Annual Reporting	**Amendments**	**Adverse Events**
IBC	Complete the IBC Annual Renewal form online http://topaz.uky.edu.	IBC approval is required for all amendments prior to implementation. Submit to IBC an amendment form online http://topaz.uky.edu.	Submit a UK Internal Prompt Reporting Form via email to bnels3@uky.edu. For more information, see the UK Policy on Prompt Reporting.
IRB	Complete the IRB Continuation Review report and return to the Office of Research Integrity http://www.research.uky.edu/ori/human/IRBReviewTypes.htm#CR.	Submit a Modification Request Form and include short summary letter sign by PI.	Submit a UK Internal Prompt Reporting Form to the Office of Research Integrity, 315 Kinkead Hall, 0057. For more information, see the UK Policy on Prompt Reporting

Additional Resources:

http://www.fda.gov/cber/

Guidance for Human Somatic Cell Therapy and Gene Therapy

https://osp.od.nih.gov/biotechnology/biosafety-and-recombinant-dna-activities/l

NIH Guidelines for Research Involving Recombinant DNA Molecules

Frequently Asked Questions about the NIH Review Process for Human Gene Transfer Trials

http://ehs.uky.edu/biosafety/

http://www.research.uky.edu/ori/