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

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1. The NIH and Human Gene Transfer Trials

1.1. What is human gene transfer research?

Human gene transfer is the process of transferring genetic material (DNA or RNA) into a person. At present, human gene transfer is experimental and is being studied to see whether it could treat certain health problems by compensating for defective genes, producing a potentially therapeutic substance, or triggering the immune system to fight disease. Human gene transfer may help improve genetic disorders, particularly those conditions that result from inborn errors in a single gene (for example, sickle cell anemia, hemophilia, and cystic fibrosis). It may also hold promise for diseases with more complex origins, like cancer and heart disease. Gene transfer is also being studied as a possible treatment for certain infectious diseases, such as AIDS. This type of experimentation is sometimes called "gene therapy" research.

1.1. Why are human gene transfer trials reviewed by the NIH?

Human gene transfer research raises scientific, medical, ethical, and social considerations worthy of special attention and public discussion. Some of these issues arise from the fact that the techniques being used are relatively new and their risks and benefits are not well characterized.

The NIH review process allows for an in-depth examination of the issues associated with this technology in a setting where public input and comment is encouraged. This open discussion has two important benefits. First, it disseminates this information to scientists who can then incorporate new scientific findings and ethical considerations into the design of trials they may be conducting or planning. The efficiency of the research system is improved by allowing scientists to build on a common foundation of new knowledge emanating from this ongoing process of analysis and assessment. Second, it creates enhanced public awareness and allows for a public voice in the review of the safety and ethics of gene transfer research. This helps assure the public that scientists are attending to these important matters and sustains confidence in the enterprise.

Finally, as the major funder of human gene transfer research and the basic science that underpins it, the NIH has an important responsibility for the appropriate stewardship of this area of scientific activity. This stewardship role is both an ethical obligation and a public mandate associated with the tax-derived research funds appropriated to the agency by Congress.

1.2. What characteristics distinguish the NIH review process from others that my protocol may have to undergo?

The NIH review process was established in response to public and scientific concern about the special ethical, scientific, and safety dimensions of gene transfer research. Thus, a salient and unique feature of the NIH review process is public discussion during meetings of the "Recombinant DNA Advisory Committee" or "RAC." The

RAC is composed of experts with diverse backgrounds, expertise, and points of view. The RAC is thereby constituted to provide full, in-depth review of the many dimensions of human gene transfer research.

Another special characteristic of the NIH process is open access to information, since materials submitted to the NIH, through OBA, are generally considered to be in the public domain and are made freely available. Much of this material is accessible electronically from OBA's Web site. Openness and public participation contribute toward a better scientific understanding of this field of research and provide the public a voice in deliberations about the various dimensions of gene transfer research.

1.3. What are the "*NIH Guidelines*" and how do they guide the process of NIH oversight of human gene transfer trials?

The *NIH Guidelines* set forth the principles for NIH and institutional oversight of recombinant DNA research, including human gene transfer trials. The *NIH Guidelines* were first published in 1976 as an outcome of a public process by which scientists developed standards to address the risks associated with recombinant DNA research. The *NIH Guidelines* articulate standards for investigators and institutions to follow to ensure the safe handling and containment of recombinant DNA and products derived therefrom. They outline requirements for institutional oversight, including IBCs, and describe the procedures of the RAC.

The *NIH Guidelines* are a dynamic document that changes with the science and knowledge of recombinant DNA research. In 1990, a new section to the *NIH Guidelines* was added, Appendix M, which describes points to consider in the design and submission of human gene transfer trials, including the standards and procedures to which investigators must adhere. Appendix M is described in greater detail below.

To facilitate navigation of the *NIH Guidelines*, the electronic version is fully indexed and hyperlinked to allow immediate access to any section, appendix, or referenced resource of particular interest.

2. The Recombinant DNA Advisory Committee

2.1. What is the Recombinant DNA Advisory Committee?

The Recombinant DNA Advisory Committee is a panel of up to 21 national experts in various fields of science, medicine, genetics, ethics, and patient perspectives that considers the current state of knowledge and technology regarding recombinant DNA research. A key role of the RAC is to advise the NIH Director and the NIH OBA, which is the NIH locus of oversight for recombinant DNA research. In this capacity, the RAC recommends changes to the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*), which outline responsible research practices in basic and clinical recombinant DNA research. Another important RAC function is to review research proposals involving human gene transfer research, or "gene therapy" as it is often called. All human gene transfer trials occurring at or sponsored by institutions receiving NIH funds for

recombinant DNA research must be submitted to OBA for review by the RAC.

2.2. I am an investigator whose projects are funded entirely by private industry. Must I submit my protocol to NIH for RAC review?

Even if your project is funded entirely by private sources, you must submit your protocol to the NIH if the sponsor of your research or the institution where you will conduct your project receives any NIH money for recombinant DNA research. Also, research involving the testing in humans of materials containing recombinant DNA developed with NIH funds must be reviewed by the RAC, if the institution that developed those materials sponsors or participates in those projects.

If the site and sponsor for your research are entirely privately funded, you may submit your protocol voluntarily. Following the *NIH Guidelines* helps assure yourself and others that you are conducting your research safely. Undergoing RAC review allows you to obtain feedback on the conduct and design of your protocol from a panel of experts that helps improve the science and safety of the study.

2.3. Are there any kinds of human gene transfer trials that are specifically exempted from the RAC review process?

Appendix M-VI-A of the *NIH Guidelines* exempts certain types of vaccine trials from the requirements for submission of the protocol to NIH OBA, RAC review, and subsequent reporting (Appendix M-I). Specifically, this exemption applies to "human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected." Trials with these characteristics do not have to be registered with NIH OBA or undergo RAC review, but can be submitted on a voluntary basis, particularly if the investigator believes that a trial presents scientific, safety, or ethical concerns that would benefit from RAC review and public discussion. Investigators that submit trials voluntarily will be expected to comply with all aspects of the protocol review and reporting requirements. OBA encourages investigators and institutional review bodies to contact us (oba@od.nih.gov) for assistance in determining whether this exemption applies to particular trials.

2.4. Are these vaccine trials also exempt from other requirements specified in the *NIH Guidelines*?

It is important to note that Appendix M-VI-A does <u>not</u> exempt these vaccine trials from other requirements specified in the *NIH Guidelines*, including biosafety review. Thus, vaccine trials, like other human gene transfer trials subject to the *NIH Guidelines*, must be reviewed and approved by an Institutional Biosafety Committee (IBC) before research participants can be enrolled. More information about IBCs can be found on the IBC page of OBA's Web site (http://www4.od.nih.gov/oba).

2.5. I am an investigator developing a protocol for a gene transfer clinical trial. What are the first things I need to do to prepare for a review of my trial by the RAC?

First, you should read Appendix M of the *NIH Guidelines*, which outlines points to consider in the design and conduct of these trials. It also includes details about submitting your protocol for review by the RAC.

As part of the packet of materials that you will send to the NIH, you will need to submit responses to Appendices M-II through M-V of the *NIH Guidelines*, which pose questions concerning the objective and rationale of the proposed research. These sections also explore how you will handle informed consent and privacy for research participants and their families. In addition to these responses, your packet should contain:

- A cover letter on institutional letterhead signed by you (and your colleagues) as the Principal Investigator(s). The letter should (1) acknowledge that the documentation submitted to NIH OBA complies with the requirements set forth in Appendix M-I-A, "Requirements for Protocol Submission"; (2) identify the IBC and IRB) at the proposed clinical trial site(s) responsible for local review and approval of the protocol; and (3) acknowledge that no research participant will be enrolled (see definition of enrollment in Section I-E-7 of the *NIH Guidelines*) until the RAC review process has been completed (see Appendix M-I-B, "RAC Review Requirements"), IBC approval (from the clinical trial site), IRB approval, and all applicable regulatory authorizations have been obtained;
- A scientific abstract;
- A non-technical abstract;
- The proposed clinical protocol, including tables, figures, and relevant manuscripts;
- The proposed informed consent document; and
- *Curriculum vitae* of the principal investigator(s).

3. Submitting your protocol

3.1. To whom do I send my protocol?

You may submit your completed Appendix M submission by mail, by overnight express, or by email.

By U.S. mail, send it to:

NIH Office of Biotechnology Activities
National Institutes of Health,
6705 Rockledge Drive, Suite 750, MSC 7985
Bethesda, Maryland 20892

By overnight express, send it to:

NIH Office of Biotechnology Activities
National Institutes of Health,
6705 Rockledge Drive, Suite 750
Bethesda, Maryland 20817
Telephone: 301-496-9838

By email, send it to: rosenthg@od.nih.gov

3.2. Should I submit the very same information that I send to the Food and Drug Administration (FDA)?

Investigators should submit all the material specified in Appendix M of the *NIH Guidelines*. This includes information that would not normally be part of an FDA investigational new drug application, since the scope and purpose of RAC review is different from that of the FDA. Furthermore, unlike FDA review, the RAC process is open to the public. Any member of the public may observe discussion of your protocol at a RAC meeting or request the materials that you submit to this office. This allows all interested parties to consider this field of research in all its dimensions. Because of this characteristic, in general, you should not submit trade secrets or confidential commercial information in your Appendix M submission to the NIH. If for some reason you find it necessary to include trade secrets or confidential commercial information in your submission, it should be clearly labeled as such. It is never acceptable to label the entirety of your Appendix M submission as confidential.

3.3. What happens to my protocol when OBA receives it?

NIH OBA will confirm receipt of your protocol within three working days. If it appears that any portion of the necessary submission is missing, OBA staff will contact you immediately to request those materials.

Once your submission is complete, it is sent to members of the RAC for an initial review. During the preliminary protocol review process, individual RAC members may request additional information or clarification about your submission and sometimes make specific comments or suggestions about the protocol design, informed consent document, or other matters. Any individual RAC comments of this nature are then conveyed to you. All such correspondence is part of the public record of this protocol, and is available to the investigators, sponsor, the IRB, and the IBC upon request.

As an outcome of this initial review, RAC members determine whether the protocol raises important scientific, safety, medical, ethical, or social issues that warrant in-depth discussion at the RAC's quarterly public meetings. Factors that may warrant public discussion include unique applications of gene transfer research, the use of new or otherwise salient vector or gene delivery systems, special clinical concerns, or important social or

ethical issues raised by the proposed research.

Within 15 working days of submitting all the information required under Appendix M, you will be notified of the outcome of this initial review process and whether your protocol has been selected for public RAC review. The in-depth, public review of a protocol occurs when (1) the OBA Director initiates that review following a recommendation for review by at least three RAC members or another federal agency; or (2) the NIH Director initiates that review.

4. Your Protocol and the Public RAC Meeting

4.1. What happens if my protocol is selected for public RAC review?

If your protocol has been selected for public review, and if you have completed your submission at least eight weeks before the next RAC meeting, your protocol will be reviewed at the next meeting. If the next RAC meeting is less than eight weeks away, public discussion of your protocol will be deferred until the following RAC meeting to allow sufficient time for the review process.

As the person responsible for the design and conduct of the trial, you will be asked to make a 15-20 minute presentation about your protocol at the RAC meeting. You are welcome to bring colleagues to the meeting to help with your presentation and to answer questions. Several RAC members assigned to conduct an in-depth review of your protocol will then make remarks and pose questions about its details. Other experts in the field (*ad hoc* reviewers) may be asked to provide a review of some key aspects of your protocol, as well. This face-to-face interaction greatly improves the quality of the discussion and permits immediate and in-depth exploration of issues that your protocol may raise.

4.2. What is the outcome of the RAC review?

The outcome of RAC review is a series of recommendations and advice from experts in the field. RAC review does not entail a formal approval of your proposed protocol. Investigators and sponsors should carefully consider these recommendations as part of optimizing the safe and ethical conduct of the trial. These recommendations will be captured in a summary letter prepared by OBA staff, which will be sent to you within 10 working days after completion of the RAC meeting. The summary letter also will be sent to the IRB and IBC reviewing your protocol, as well as the FDA.

4.3. What is the relationship of RAC review to review by the IRB, the IBC, and the FDA?

Unlike the RAC, these other entities will be reviewing your protocol as part of a formal approval process, either for conduct at your institution (in the case of local review bodies) or for authorizing your Investigational New Drug (IND) application (in the case of the FDA). A benefit of the RAC process is that it informs the

discussions that these other bodies will undertake in making certain determinations about your protocol.

RAC review occurs before final IBC approval in order to inform that committee of the RAC's recommendations before the IBC makes its final determination. Your IRB and the FDA may review your protocol before or after RAC review, but both will nonetheless be notified of the RAC recommendations.

5. After the RAC Meeting

5.1. When may I start enrolling patients in my protocol?

Under the *NIH Guidelines*, patient enrollment is considered to begin with the process of obtaining informed consent from prospective participants. This process cannot begin until: (1) the RAC review process has been completed; and (2) IBC and IRB approvals and FDA and all other applicable regulatory authorization(s) have been obtained.

For a clinical trial site that is added after the RAC review process, no research participant may be enrolled at the clinical trial site until the following documentation has been submitted to NIH OBA:

- IBC approval (from the clinical trial site);
- IRB approval;
- IRB-approved informed consent document;
- *Curriculum vitae* of the principal investigator(s) (no more than two pages in biographical sketch format); and
- NIH grant number(s) if applicable.

5.2. After I enroll my patients, am I finished with the RAC process and my interactions with OBA?

No. Within 20 working days of consenting the first research participant, you must submit the following documentation to NIH OBA:

- 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.

Investigators also have an ongoing responsibility to monitor the trial and to keep OBA, as well as IRBs, IBCs, the FDA, and any sponsoring NIH institutes or centers, informed of any adverse events on the trial. Serious adverse events that are unexpected and possibly associated with the gene transfer product should be submitted to OBA within 15 calendar days of sponsor notification, unless they are fatal or life threatening, in which case they should be reported within 7 calendar days. Investigators are encouraged to report serious adverse events electronically to NIH by using GeMCRIS.

In addition, investigators must file an annual report with OBA, providing specific information about the trials. The formats of these reports can be found in Appendix M-I-C-4 and M-I-C-3 of the *NIH Guidelines*, respectively. Investigators should also notify OBA of any additional sites that are conducting the trial, and submit for the new site:

- IBC approval (from the clinical trial site);
- IRB approval;
- The IRB-approved informed consent form;
- *Curriculum vitae* of the investigator(s); and
- NIH grant number(s), if applicable.