National Institutes of Health

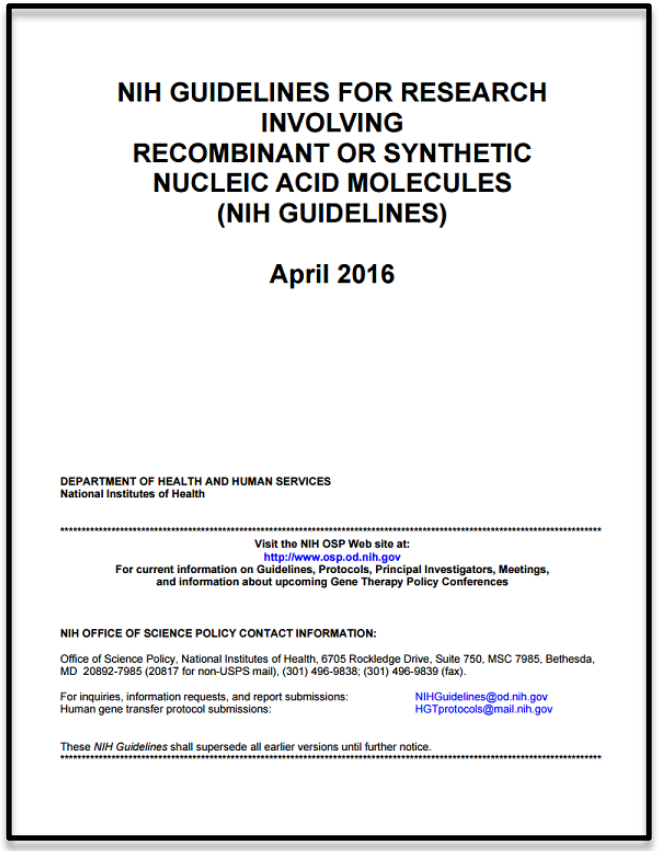
Office of Science Policy

An Overview of the Amended Human Gene Transfer Protocol Registration and Review Process

Kathryn Harris, PhD, RBP
Senior Outreach and Education Specialist

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

- Apply to basic and clinical recombinant or synthetic nucleic acid molecule research conducted at institutions that receive any NIH funding for such work
- Specify safety practices for the construction and handling of recombinant and synthetic nucleic acid molecules and organisms containing such molecules
- Term and condition of NIH funding



NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT OR SYNTHETIC NUCLEIC ACID MOLECULES (NIH GUIDELINES)

April 2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Visit the NIH OSP Web site at:
http://www.osp.od.nih.gov
For current information on Guidelines, Protocols, Principal Investigators, Meetings, and information about upcoming Gene Therapy Policy Conferences

NIH OFFICE OF SCIENCE POLICY CONTACT INFORMATION:

Office of Science Policy, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), (301) 496-9838; (301) 496-9839 (fax).

For inquiries, information requests, and report submissions: NIHGuidelines@od.nih.gov
Human gene transfer protocol submissions: HGTprotocols@mail.nih.gov

These *NIH Guidelines* shall supersede all earlier versions until further notice.

What is Human Gene Transfer?

- **Human Gene Transfer (HGT) is the "deliberate transfer of recombinant or synthetic nucleic acid molecules or DNA or RNA derived from recombinant or synthetic nucleic acid molecules into human subjects …"**
  - **to compensate for defective genes**
  - **to produce a potentially therapeutic substance**
  - **to trigger the immune system to fight disease**

NIH Oversight of HGT Research

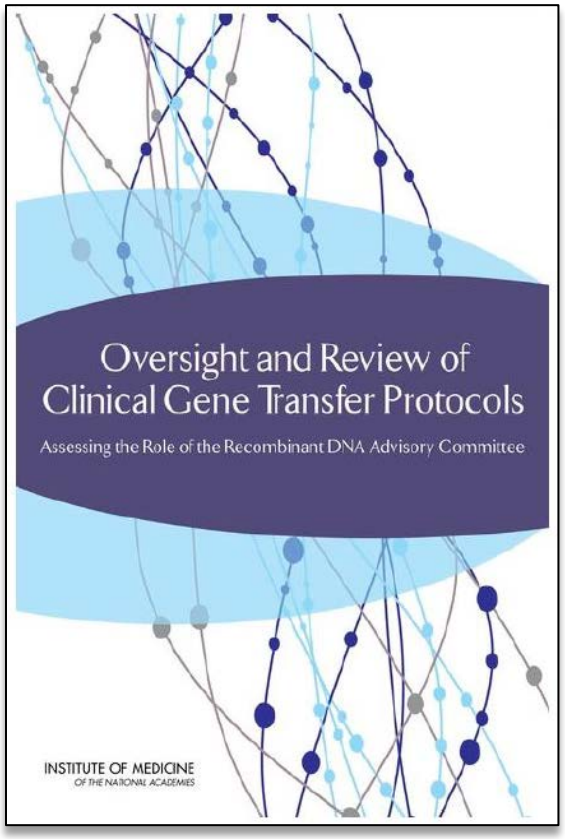
- **Ethical, safety and scientific concerns associated with:**
  - **Vertical Transmission (genome modification of participant)**
  - **Horizontal transmission (to close contacts of participant)**

NIH Guidelines: Appendix M

- **Requirements for Information Submission to NIH**
  - **Protocol**
  - **Responses to questions about the scientific and safety-related dimensions of the gene transfer intervention**
  - **Issues pertinent to the informed consent process**
- **Safety and Annual Reporting Requirements**
- **Recombinant DNA Advisory Committee (RAC) Review Process**

Institute of Medicine Study

- **NIH requested an independent review and assessment to:**
  - **Determine if HGT research raises issues of concern that warrant extra oversight by the RAC of individual protocols**
  - **Recommend criteria to guide when the RAC should review HGT research**



IOM Committee Recommendations

“The RAC has successfully provided oversight over a complex technology for nearly 40 years, providing a valuable service to NIH, the scientific community, and the public”

- **Restrict review of individual HGT protocols to exceptional cases that meet specific criteria**
- **Consider integrating oversight for HGT and other applications of emerging technologies**

NIH Accepts IOM Report

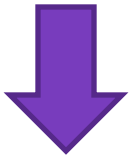
- **Implementation steps:**
  - **Proposed amendments to the NIH Guidelines published in the Federal Register for public comment**
  - **Final action notice published in the Federal Register with response to public comment**
  - **Changes in effect April 27, 2016**

April 2016 Amendments to the *NIH Guidelines*

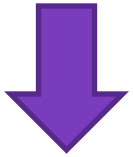
- Criteria for selecting HGT protocols for in-depth review and public discussion by the RAC
- Process by which HGT protocols are reviewed and registered with NIH
- Streamlining the NIH HGT protocol submission requirements under Appendix M-I-A of the *NIH Guidelines*

HGT Protocol Review and Submission Process

The Principal Investigator (PI) submits the protocol to the institutional oversight bodies (e.g., IBC, IRB)



Based on specific criteria, the oversight bodies at the initial trial site(s) review and determine whether RAC review is warranted



PI submits protocol documentation to NIH OSP, including a communication from all oversight bodies indicating whether RAC review is requested

Criteria for Selecting HGT Protocols for RAC Review

1. An oversight body (IBC or IRB) determines that a human gene transfer protocol submitted to it for approval would significantly benefit from RAC review, and…

Criteria for Selecting HGT Protocols for RAC Review

2. One or more of the criteria below are satisfied:

   a. The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk
   b. The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value
   c. The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies to evaluate the protocol rigorously

Protocol Review and Submission Process
Role of NIH OSP

- NIH determines whether the protocol satisfies the review criteria (both 1 and 2) and informs the PI within 10 working days

Protocol Review and Submission Process Role of NIH OSP

- If oversight bodies do NOT request RAC review
  - Registration process will be complete and IBC may approve protocol
  - However, the NIH Director may select the protocol for in-depth review and public discussion at a RAC meeting

Protocol Review and Submission Process Role of NIH OSP

- If one or more oversight bodies request RAC review
  - If NIH concurs, the protocol is selected for in-depth review and public discussion at a RAC meeting
  - If NIH does not concur, NIH informs PI and oversight bodies. The registration process is then complete and the IBC may approve the protocol

RAC Review

- No change to the process for in-depth RAC review and public discussion of selected HGT protocols
- If selected for RAC review, protocols submitted at least eight weeks in advance will be reviewed at the next quarterly RAC meeting
- Following the RAC meeting, OSP will send a letter with the RAC's comments and recommendations to the PI and oversight bodies

Dissemination of RAC Recommendations

RAC

PI

IRB & IBC

NIH IC
FDA
OHRP

Sponsor

OSP Web Site

Timing of Federal and Local Protocol Review Processes

- Final IBC approval cannot occur until the protocol registration is completed
- IRB review and approval can occur at any time
- FDA review and authorization of IND application can occur at any time

Streamlined Protocol Submission Requirements

- Appendix M reduced to require only information needed to:
  - Determine RAC review eligibility
  - Support the Genetic Modification Clinical Research Information System (GeMCRIS), which facilitates safety reporting and provides access to information about HGT protocols registered with NIH

Reporting Requirements

- No major changes
- Submission requirements remain for:
  - Initiation of clinical investigation
  - Additional clinical trial sites
  - Annual reports
  - Safety reporting

Post-Enrollment Reporting (Appendix M-I-C)

- **Within 30 days** of enrollment of the first participant, the PI must submit documentation to NIH OSP including:

- Response to RAC recommendations (if applicable)
- Copy of final protocol
- Copy of final IRB-approved informed consent
- Copy of IBC approval
- Copy of IRB approval

Additional Clinical Trial Sites (M-I-C-2)

- For clinical trial sites that are added after the completion of the NIH protocol registration process, no research participant shall be enrolled until IBC and IRB approval have been obtained

- Within 30 days of enrollment the following documentation must be submitted to NIH OSP: IBC approval, IRB approval, IRB approved informed consent document, and NIH grant number(s) if applicable

Post-Enrollment Reporting (Appendix M-I-C)

- **Subsequently, the PI must submit:**
  - **Protocol amendments**
  - **Serious adverse event reports**
    - **Within 15 days if possibly associated, unexpected**
    - **Within 7 days if fatal or life threatening**

Post-Enrollment Reporting (Appendix M-I-C)

- **PI must also submit:**
  - **Annual reports**
    - **Due within 60 days after the one-year anniversary date of IND authorization and yearly until trial is completed**
    - **Reports must include:**
      - **Summary of status of each trial in progress**
      - **Summary of all SAEs**
      - **Additional information pertinent to understanding gene transfer product**

Post-Enrollment Reporting (Appendix M-I-C)

- Delegation of reporting
  - Only after submission of a signed letter to NIH OSP
  - Task, but not responsibility, may be delegated

Benefits of New Process

- Streamlining review
  - Oversight bodies already approved more than 80% of HGT protocols not selected for in-depth RAC review
  - Reduction in required paperwork
- RAC can focus on novel HGT trials that would benefit from their expertise

HGT Protocol Submissions to NIH OSP

- **For protocol submissions, reports, and questions related to HGT protocol submission and review, please email:**

HGTprotocols@mail.nih.gov

National Biosafety Month

- Launched in 2014 to encourage institutional awareness of and commitment to biosafety policies, practices, and procedures
- Encourage institutions to undertake activities to strengthen their biosafety programs, if needed, and to recommit to a culture of responsibility

National Biosafety Month

Evaluation

- **Engage in self- and peer-evaluation of institutional governance structures for the oversight of biosafety using internally developed metrics and tools such as the OSP Institutional Biosafety Committee Self-Assessment Tool. Frequent review and assessment of biosafety oversight programs is key to maintaining their effectiveness**

Updated IBC Self-Assessment Tool

National Biosafety Month

Collaboration

- **Share best practices, procedures, strategies and solutions for enhancing biosafety programs with other institutions**

National Biosafety Month

Commitment

- **Ensure appropriate resources are devoted to biosafety and biosecurity oversight and compliance activities at the institution. Institutions should commit to providing adequate support (material and staffing, etc.) to ensure that all operational elements of the biosafety program (inspections, trainings, safety equipment maintenance, etc.) have the necessary resources and can function optimally**

National Biosafety Month

Spread the word!

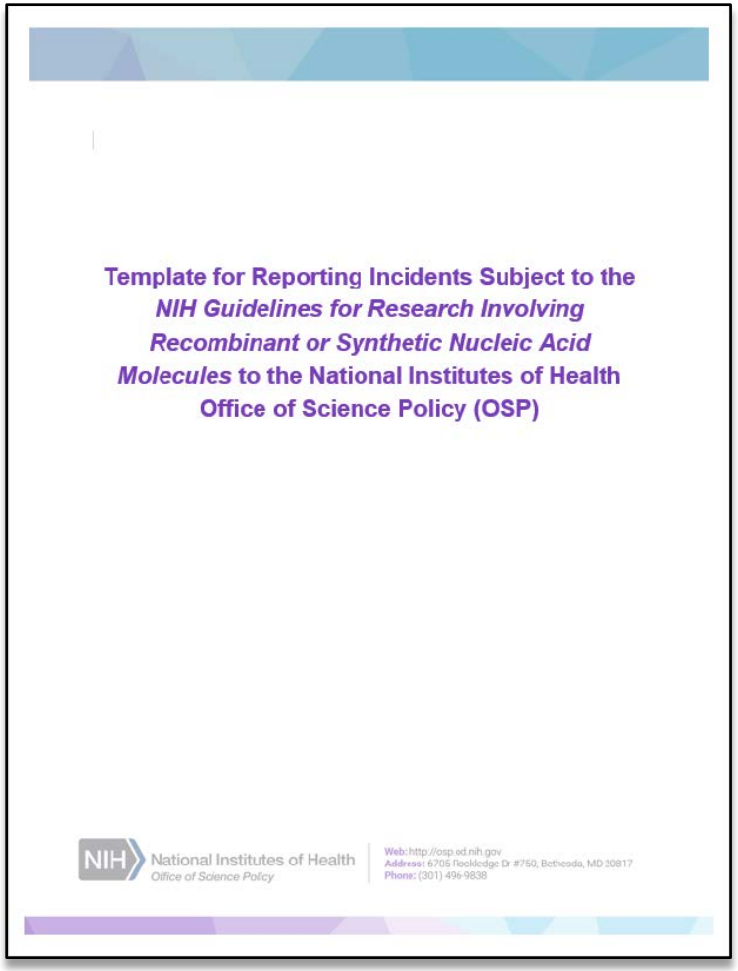
- **Use National Biosafety Month as an opportunity to talk to investigators and research administrators about the importance of biosafety. Answer questions, raise awareness, and seek their input on ways to strengthen your institutional biosafety program**

#Biosafety Month

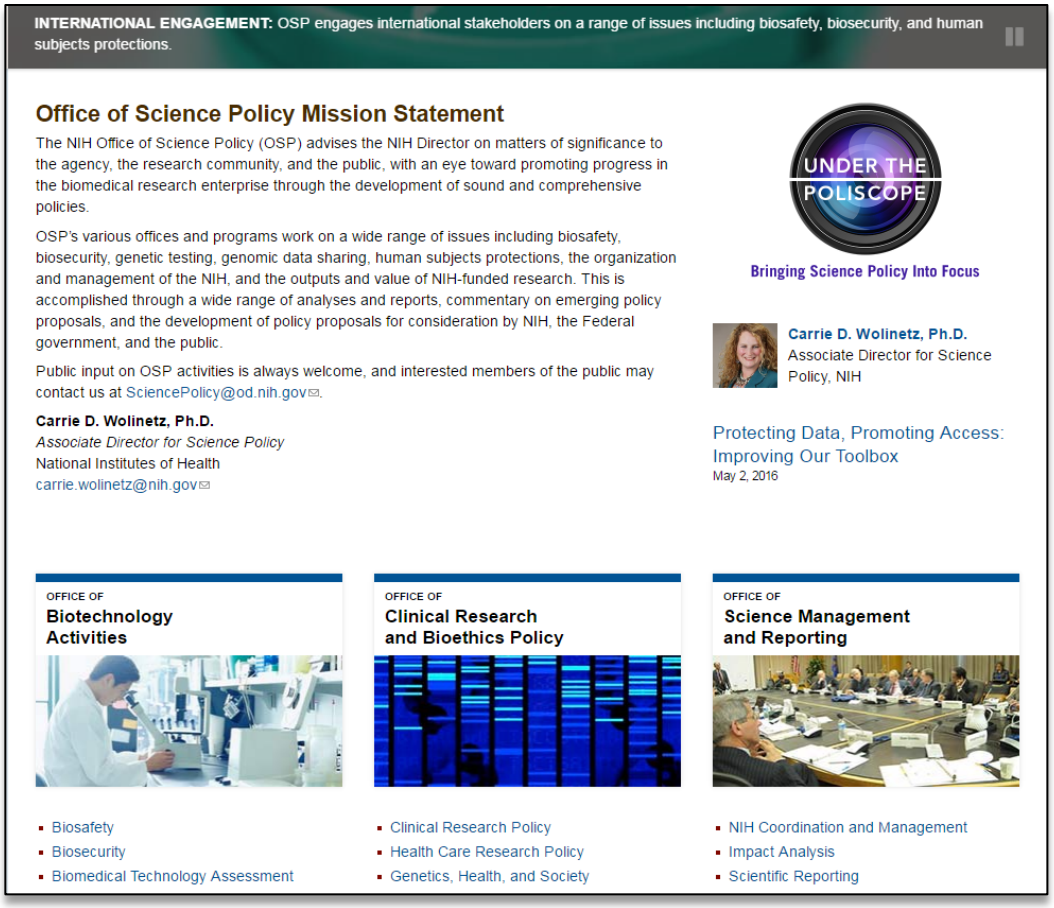
- Follow on Twitter

@CWolinetzNIH

New Incident Reporting Template



NIH OSP Web Site



http://osp.od.nih.gov

For Queries
Please Contact Us!

NIH Office of Science Policy
Suite 750
6705 Rockledge Drive,
Bethesda, MD 20892-7985

Phone (301) 496-9838
Fax (301) 496-9839

Additional Resources

Email:

For general inquiries:

SciencePolicy@od.nih.gov

For general questions related to the *NIH Guidelines*:

NIHGuidelines@od.nih.gov

Additional Resources

- **Subscribe to the OSP listserv**

  Send an email to:

  listserv@list.nih.gov

  In the body of the message type:

  Subscribe OSP_News

Additional Resources

Bringing Science Policy Into Focus

Learn more about the Office of Science Policy from our blog "Under the Poliscope"

http://osp.od.nih.gov/under-the-poliscope

Questions