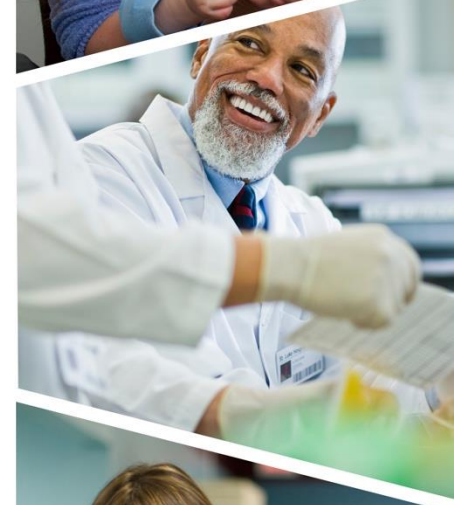


Streamlining RAC Review under the *NIH Guidelines*

Jessica Tucker, Ph.D.

Director, Division of Biosafety, Biosecurity and Emerging
Biotechnology Policy
Office of Science Policy, NIH



NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

- Applies to basic and clinical recombinant or synthetic nucleic acid research performed at or sponsored by an institution that receives any NIH funding for such research
- Safe practices for the constructing and handling of recombinant or 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) 496-9836; (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.

FEDERAL REGISTER NOTICES

Effective June 24, 1994, Published in Federal Register, July 5, 1994 (59 FR 34472)
Amendment Effective July 26, 1994, Federal Register, August 5, 1994 (59 FR 40170)
Amendment Effective April 17, 1995, Federal Register, April 27, 1995 (60 FR 20726)
Amendment Effective December 14, 1995, Federal Register, January 19, 1996 (61 FR 1482)
Amendment Effective March 1, 1996, Federal Register, March 12, 1996 (61 FR 10004)
Amendment Effective January 23, 1997, Federal Register, January 31, 1997 (62 FR 4782)
Amendment Effective September 30, 1997, Federal Register, October 14, 1997 (62 FR 53335)
Amendment Effective October 20, 1997, Federal Register, October 29, 1997 (62 FR 56196)
Amendment Effective October 22, 1997, Federal Register, October 31, 1997 (62 FR 59032)
Amendment Effective February 4, 1998, Federal Register, February 17, 1998 (63 FR 8052)
Amendment Effective April 30, 1998, Federal Register, May 11, 1998 (63 FR 26018)
Amendment Effective April 29, 1999, Federal Register, May 11, 1999 (64 FR 25361)

Recombinant DNA Advisory Committee (RAC) Roles

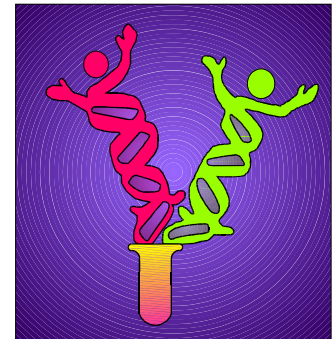
National advisory body established in 1974



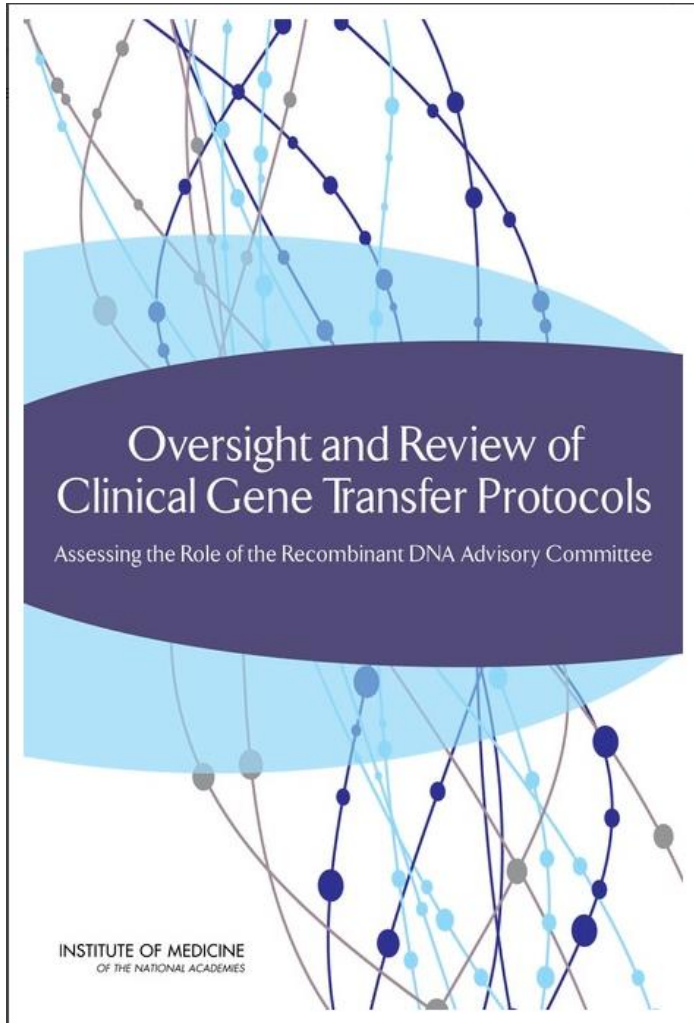
- Provides a public forum for policy development through the discussion of biosafety, clinical and ethical issues that arise from such research
- Provides advice and recommendations to the NIH Director on all aspects of basic or clinical recombinant or synthetic nucleic acid research
- Proposes changes to the *NIH Guidelines* as needed

RAC and Gene Transfer

- 1988-1994: The NIH Director approved each gene transfer protocol after receiving a recommendation from the RAC
- 1997-2016: RAC reviews protocols that involve novel scientific, safety, clinical, social, legal, or ethical issues and develops recommendations to improve the trial design
- Today RAC's role continues to evolve



Institute Of Medicine Study



- NIH requested an independent review and assessment to
 - ➔ • “Determine if gene transfer research raises issues of concern that warrant extra oversight by the RAC of individual clinical trial protocols involving gene transfer techniques”
 - ➔ • “Recommend criteria to guide when the RAC should review this research”

IOM Committee Recommendations

- Restrict individual gene transfer protocol reviews to exceptional cases that meet specified criteria
- Consider integrating oversight for gene transfer and other applications of emerging technologies

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

NIH Accepts Report

- NIH Director accepted IOM recommendation:

“Given the progress in the field, I am confident that the existing regulatory authorities can effectively review most gene transfer protocols and that a streamlined process will reduce duplication and delays in getting gene transfer trials initiated. Issues of concern that may arise in exceptional cases can still be addressed by consulting the expertise of the RAC.”

NIH Implementation Steps

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

Amendments to the *NIH Guidelines* effective April 27, 2016

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

Protocol Review and Submission Process

Roles of PI and Oversight Bodies

The Principal Investigator (PI) is responsible for submitting the protocol to the oversight bodies (e.g., IBC, IRB)



Based on the criteria, the oversight bodies at the initial site review and determine whether RAC review is warranted



PI submits to OSP protocol documentation including a written assessment from all oversight bodies regarding whether RAC review is requested

Criteria for Selecting Protocols for RAC Review

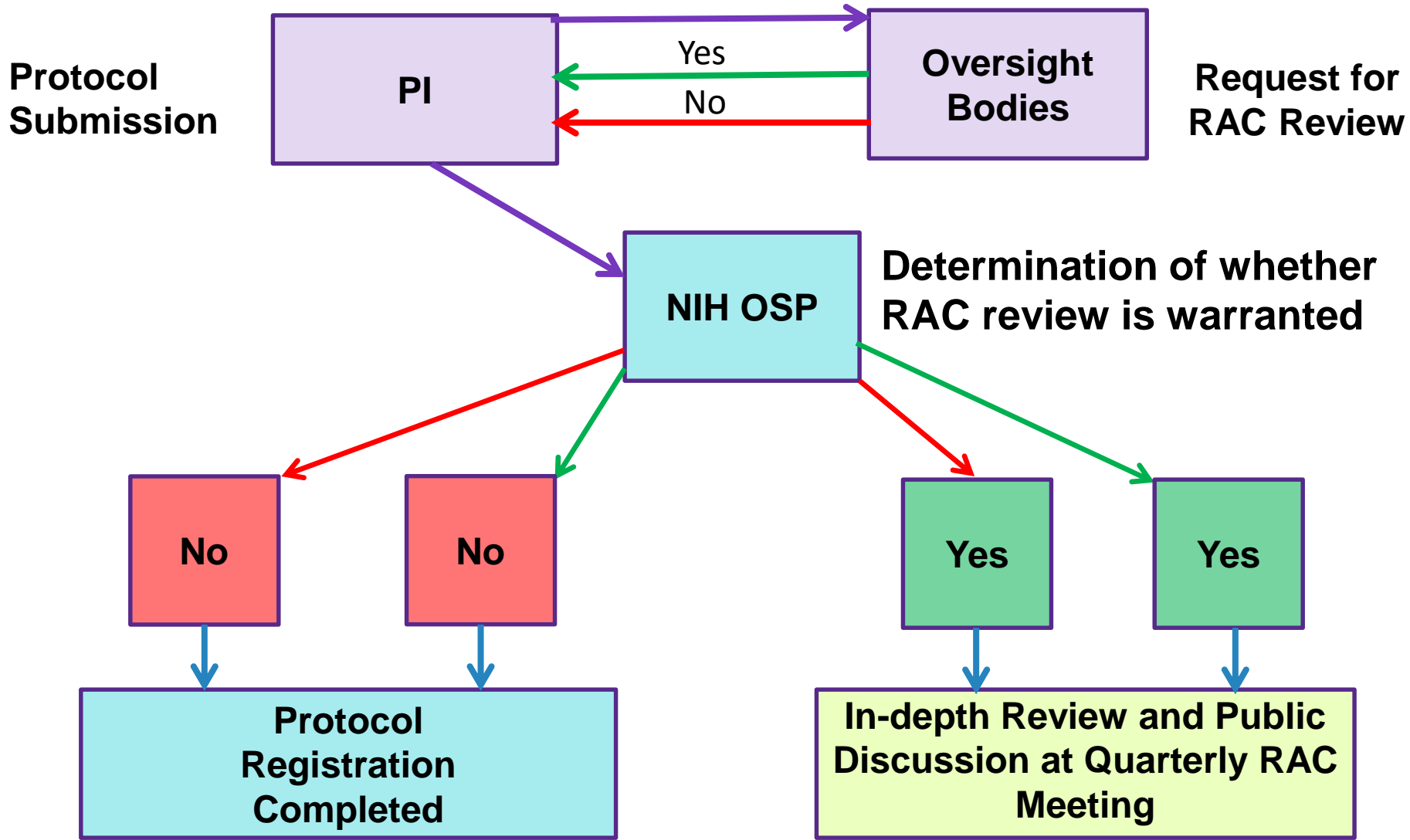
1. An oversight body (an Institutional Biosafety Committee [IBC] or an Institutional Review Board [IRB]) determines that a human gene transfer protocol submitted to it for approval would significantly benefit from RAC review; and
2. One or more of the criteria below are satisfied:
 - ➔ a. The protocol 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

Roles of NIH OSP

- **NIH determines whether protocol satisfies the review criteria and informs PI within 10 working days**
 - Oversight bodies do not request RAC review
 - If NIH concurs, registration process will be complete
 - IBC may approve protocol
 - If NIH does not concur, the NIH Director may select the protocol for in-depth review and public discussion at RAC meeting
 - One or more oversight bodies request RAC review
 - If NIH concurs, protocol is selected for in-depth review and public discussion at RAC meeting
 - If NIH does not concur, NIH informs PI and oversight bodies
 - Registration process will be completed
 - IBC may approve protocol

Protocol Review and Submission Process



RAC Review

- No changes to process for in-depth RAC review and public discussion
- If selected, protocols submitted by an eight week deadline will be reviewed at the next quarterly RAC meeting
- Following the RAC meeting, OSP will send a letter with RAC's comments and recommendations to PI and oversight bodies



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 human gene transfer protocols registered with the NIH

Reporting Requirements

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

Benefits

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

OSP Resources for Research Community and Public

- GeMCRIS
- Safety symposia, policy conferences, and scientific workshops
- Publications
- Archived webcasts, minutes, slides, FAQs and guidances

Questions, 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**

- For General Inquiries:
SciencePolicy@od.nih.gov
- For Queries related to the
NIH Guidelines:
NIHguidelines@od.nih.gov

Additional Resources

- **Subscribe to the OSP listserv**
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 - “Under the Poliscope”
<http://osp.od.nih.gov/under-the-poliscope>



Bringing Science Policy Into Focus