Role of the Recombinant DNA Advisory Committee and the Protocol Review Process

NIH Office of Biotechnology Activities

GENE TRANSFER AND THE RECOMBINANT DNA ADVISORY COMMITTEE

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Office of Science Policy
Office of the Director
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NIH Recombinant DNA Advisory Committee (RAC)

- **Federal advisory committee providing advice and recommendations to the NIH Director on all aspects of recombinant DNA research**
  - Proposes changes to *NIH Guidelines* as needed
- **Conducts public review and discussion of science, safety, and ethics of basic rDNA as well as human gene transfer research**
- **Analyzes gene transfer protocols and safety information**
  - Observations and findings of general importance to the field

NIH RAC Expertise

- Virology
  - AdV
  - RV
  - HSV
  - AAV
- Biosafety
- Immunology
- Genetics
- Bioethics
- Public representative
- Internal Medicine
- Pediatrics
- Infectious Disease
- Cardiology
- Pulmonology
- Metabolism
- Hematology
- Oncology
- Neurology
- Clinical Trial Design
- Clinical Data Monitoring
- Law

Gene Transfer and Recombinant DNA Advisory Program

- Protocol Review
- Protocol Oversight
  - GeMCRIS
- Information Resources
  - Webcasts of Meeting
  - Safety Symposiums
  - Guidance Documents

What is human gene transfer?

Human gene transfer is the "deliberate transfer of recombinant DNA or DNA or RNA derived from recombinant DNA into human subjects…"

- **as a marker in cells**
- **to compensate for defective genes**
- **to produce a potentially therapeutic substance**
- **to trigger the immune system to fight disease**

Vaccine Exemption

- Human studies in which:
  - **Induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and**
  - **Such an immune response has been demonstrated in model systems, and**
  - **The persistence of the vector-encoded immunogen is not expected**

Vaccine Exemption

- Scope of exemption:
  - **Exempt from Protocol Submission, Review, and Reporting Requirements (Appendix M-1)**
  - **<u>Not</u> exempt from IBC review or general biosafety requirements of the *NIH Guidelines***

NIH Oversight of Human Gene Transfer Research

- **Unique oversight system**
  - **Rationale**
    - modification of human genome
    - biosafety and risk containment
  - **Agents**
    - Institutes and Centers
    - Office of Biotechnology Activities
  - **Tools**
    - *NIH Guidelines*
    - RAC

Clinical Research Levels of Oversight

FEDERAL

- NIH
  - IC Program Staff
  - NIH OBA
- OHRP
- FDA

LOCAL & NONFEDERAL

- Institutions
  - IBCs
  - IRBs
- Investigators
- Sponsors

Role of the IBC in Human Gene Transfer Research

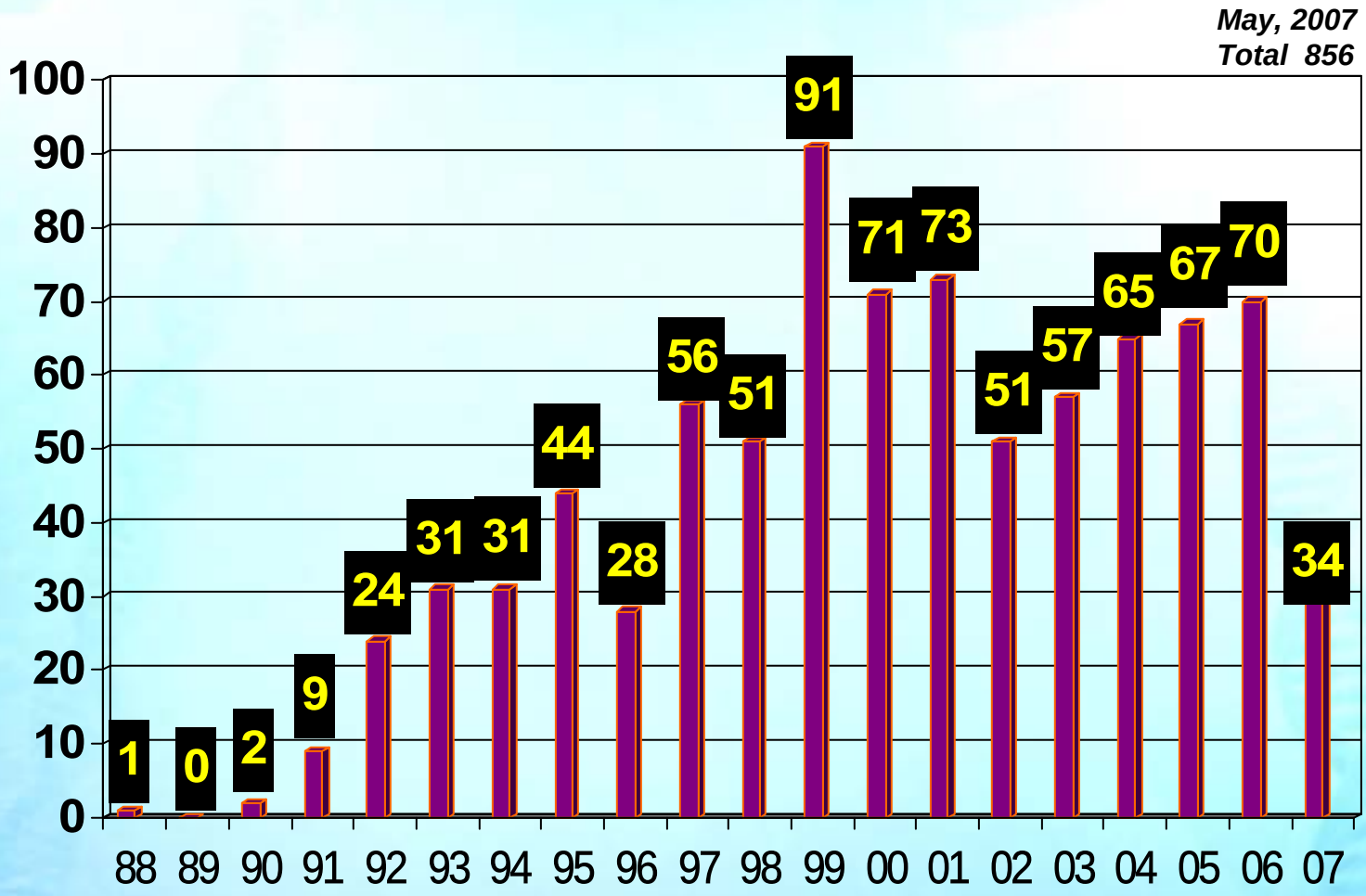
On behalf of the institution, the IBC will:

- **Ensure that all aspects of Appendix M have been appropriately addressed by the PI prior to protocol approval**
- **Consider the responses to RAC's recommendations, if applicable**
- **Approve protocol only after RAC review process is complete**
- **Oversee PI compliance with all surveillance, data reporting and AE reporting requirements**

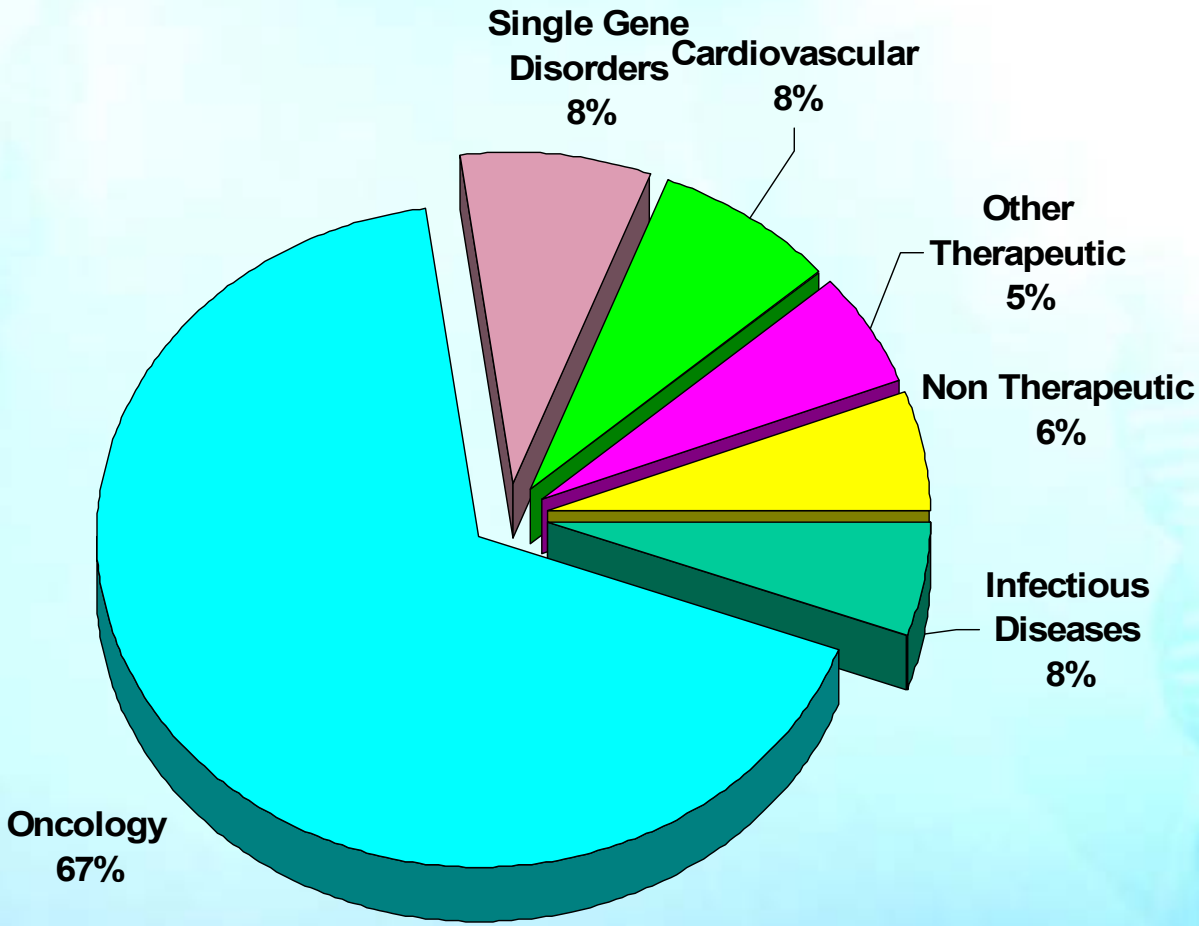
Timing of Federal and Local Protocol Review Processes

- IRB review and approval can occur before or after RAC review
  - In practice IRBs typically await RAC findings
- FDA review and authorization of IND application can occur at any time
  - RAC review prior to FDA IND submission is encouraged

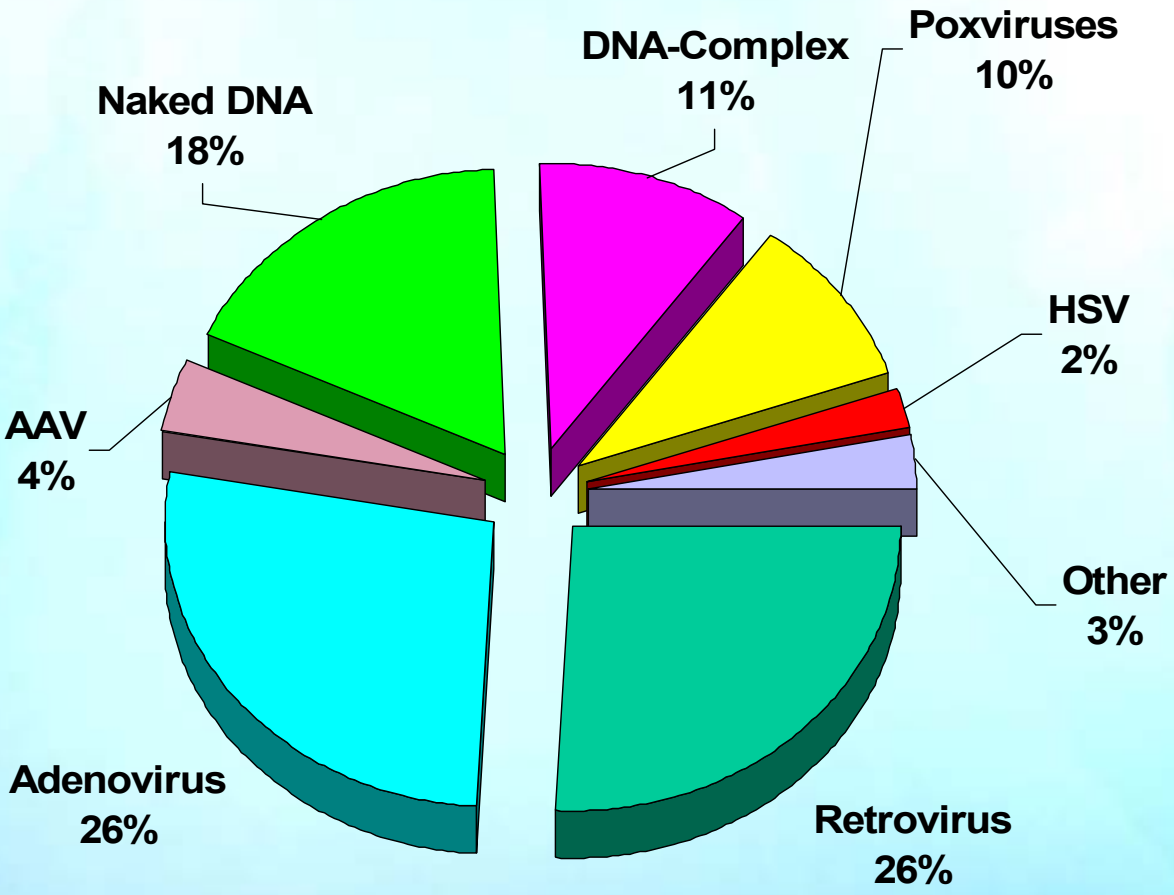
Gene Transfer Trials by Year



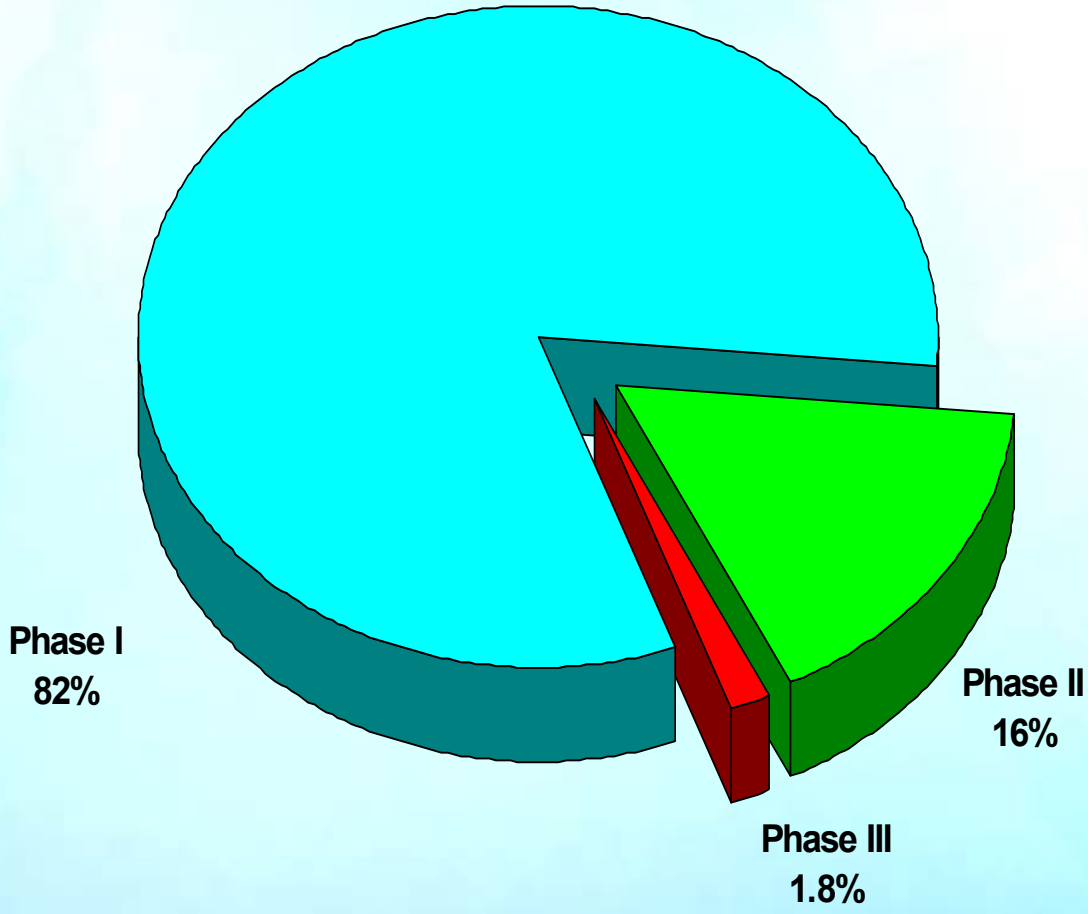
Gene Transfer Trials by Application



Gene Transfer Trials Delivery System



Gene Transfer Trials by Phase



Submission of Protocol

- Letter of assurance
  - IBC contact/IRB contact
  - Guarantees no enrollment until RAC process completed
- Scientific/non technical abstract
- Protocol
- Response to Appendix M
- Proposed informed consent document
- CV of investigators

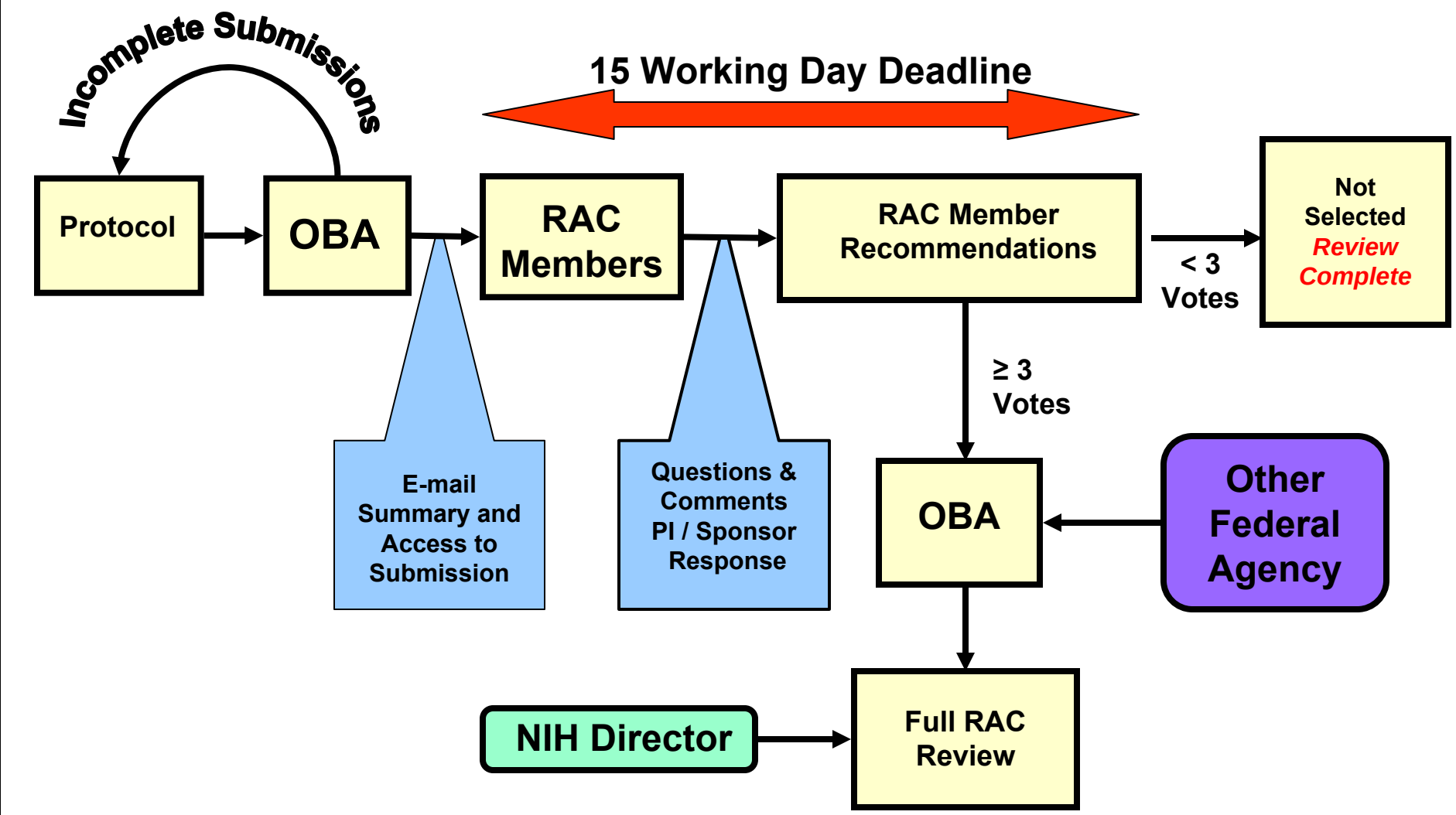
Appendix M

- **Research design, anticipated risks and benefits**
  - Structure, regulatory elements, steps used to derive vector
  - Preclinical studies, including risk assessment studies
  - Gene transfer and expression
  - Clinical procedures
  - Public health considerations
- **Issues Pertinent to the Informed Consent Process**
  - Reproductive considerations
  - Autopsy
  - Long-term follow-up
  - Privacy

RAC Public Review

- RAC recommends (within 15 working days of submission) whether protocol warrants in-depth review and public discussion
  - A new vector or gene delivery system
  - A new clinical application
  - A unique application of gene transfer
  - Other issues considered to require further public discussion

Summary of Human Gene Transfer Protocol Review Process



Purpose of RAC Review and Public Discussion

- **Inform the Scientific Community**
  - Optimize clinical trial design, patient safety, human subjects protections
  - Identify knowledge gaps
  - Discuss findings of general importance to the field
- **Inform the Public**
  - Meaning and significance of the research
  - Technical aspects of the proposal
  - Significant safety, social, and ethical implications of the research

Dissemination of RAC Recommendations

RAC

PI

IRB

IBC

NIH IC

FDA

OHRP

Sponsor

OBA Web site
(minutes, video)

Post-Enrollment Reporting
(Appendix M-I)

- **Within 20 days of enrollment of the first participant, the PI must submit the following to NIH OBA:**
  - **Response to RAC recommendations (if applicable)**
  - **Copy of final protocol**
  - **Copy of final IRB-approved informed consent**
  - **Copy of IRB approval**
  - **Copy of IBC approval**
  - **Any modifications to the Protocol required by the FDA and the FDA IND number**

Post-Enrollment Reporting
(Appendix M-I)

Additional PI reporting:

- Protocol amendments
- Additional Trial Sites
- Serious adverse event reports
  - Possibly associated, unexpected within 15 days, or within 7 days if fatal or life threatening
- Annual reports

Questions?