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

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NIH Oversight of Human Gene Transfer Research

- **Unique oversight system**
  - **Rationale**
    - **Ethical, safety and scientific concerns associated with**
      - **modification of human genome**
      - **biosafety and risk containment**
  - **Agents**
    - **Institutes and Centers**
    - **Office of Biotechnology Activities**

Clinical Research
Levels of Oversight

FEDERAL

NIH

- IC Program Staff
- NIH OBA

OHRP

FDA

LOCAL & NONFEDERAL

Institutions

- IBCs
- IRBs

Investigators

Sponsors

NIH Recombinant DNA Advisory Committee (RAC)

_____ recommendations to the NIH Director regarding recombinant DNA research

- **Unique public forum for the discussion of science, safety, and ethics of recombinant DNA research**
- **Reviews and analyzes clinical gene transfer protocols and safety information**
- **Observations and findings of general importance to the field**
- **<u>Not</u> an approval process**

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

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**
- **Recombinant DNA Advisory Committee Review Process**
- **Safety and Annual Reporting Requirements**

Goal

- **To assure research participants that, prior to their enrollment* in a trial that is either novel or raises ethical and/or safety concerns, their local IRBs, IBCs, and investigators are apprised of the outcome of public RAC review and discussion**

***In the *NIH Guidelines*, "enrollment" means obtaining informed consent**

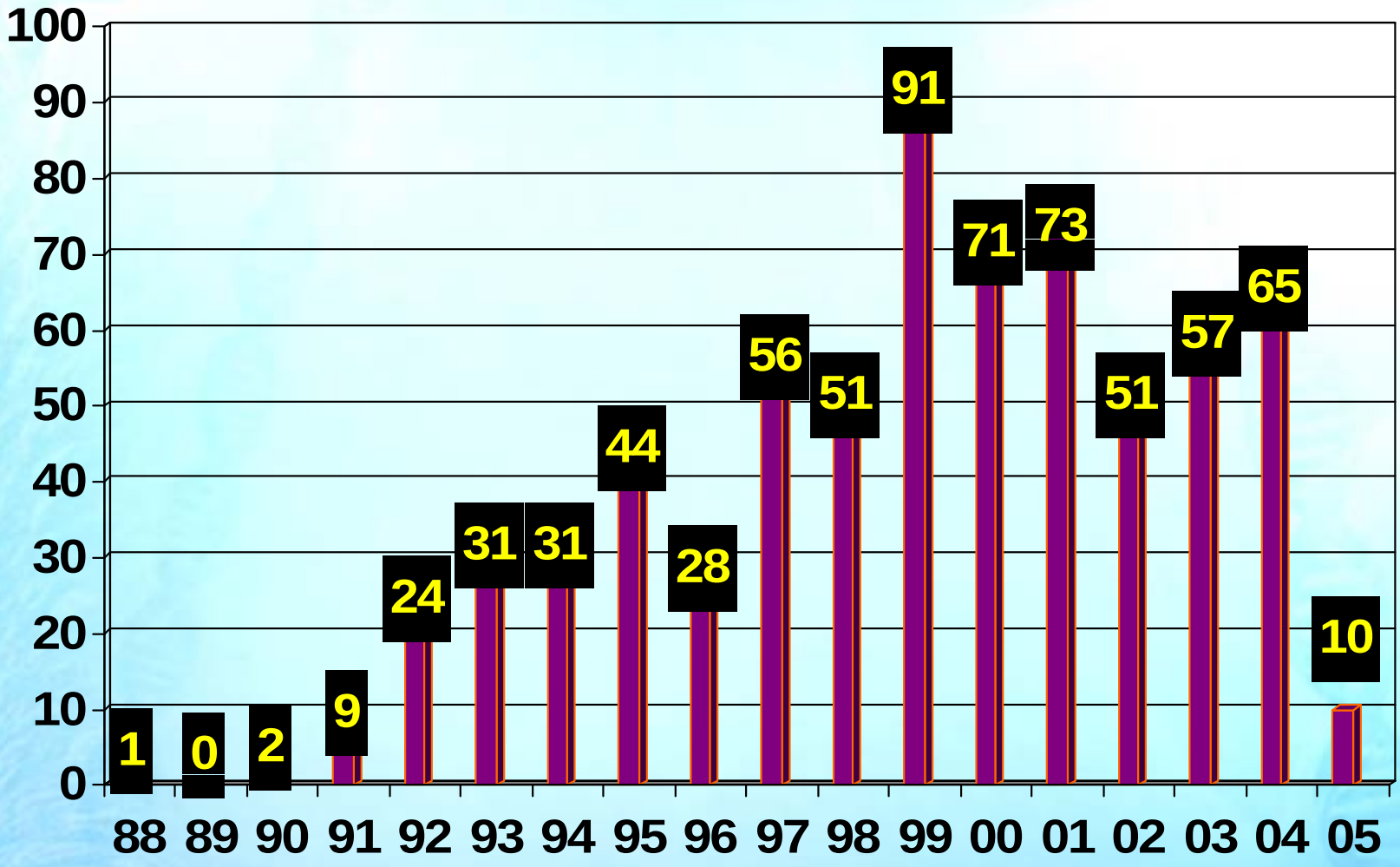
RAC Protocol Review Process

- **All protocols registered with NIH OBA and undergo initial RAC review**
- **RAC recommends (within 15 working days of submission) whether protocol warrants in-depth review and public discussion**
  - **Novel approach and/or**
  - **Significant scientific, safety, and/or ethical issues**

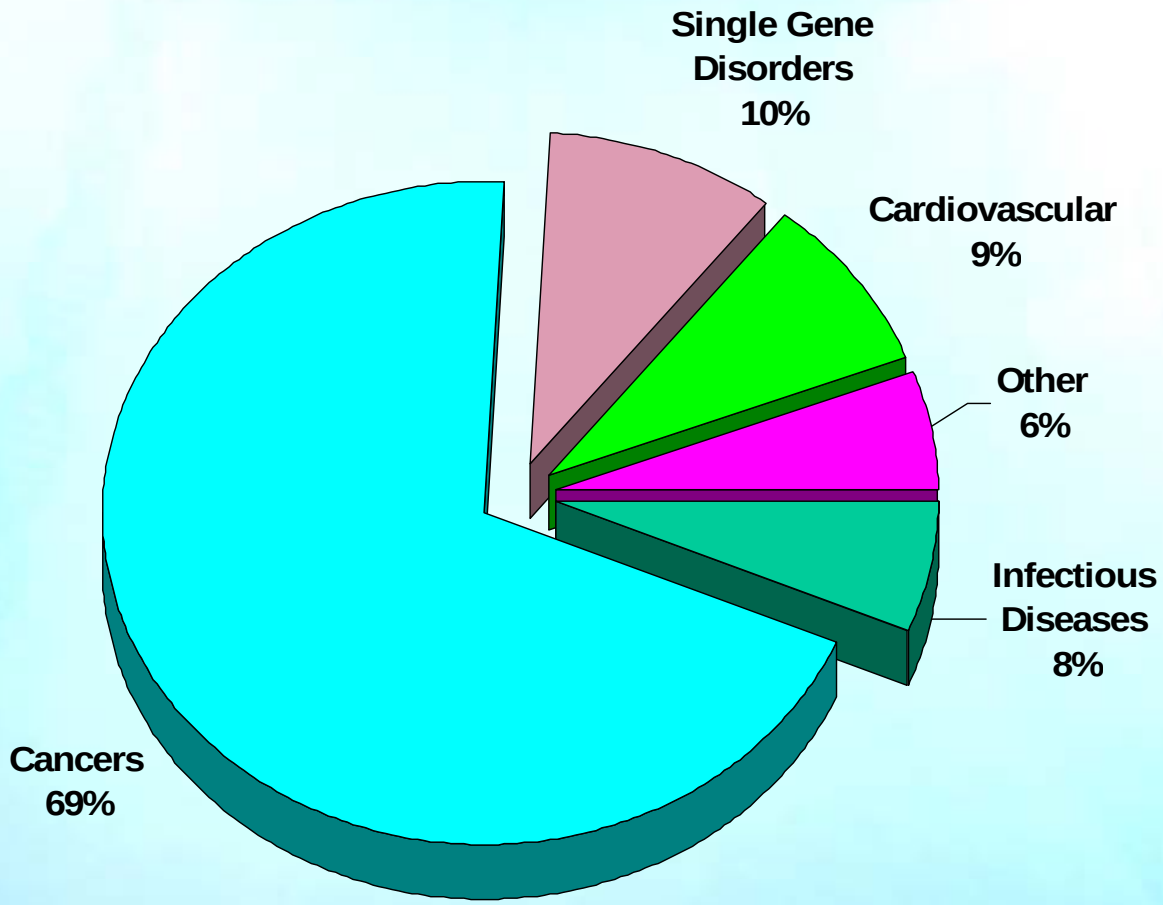
RAC Review of Selected Protocols

- **20-30% of protocols are selected**
- **In-depth review by RAC members and, as needed, *ad hoc* experts**
- **Discussed by entire RAC at quarterly public meeting**

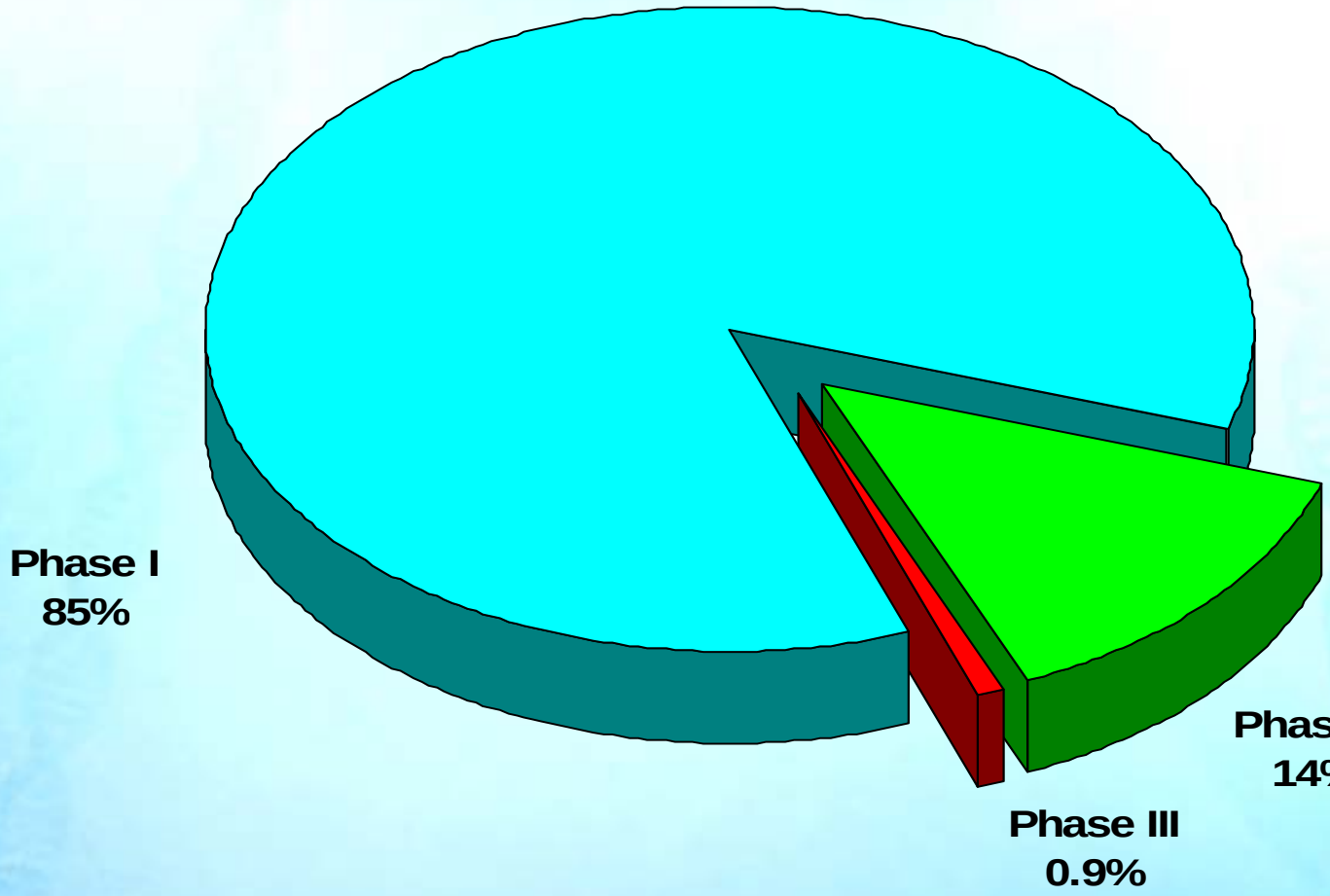
Gene Therapy Trials by Year



Gene Therapy Trials by Clinical Indication



Gene Therapy Trials by Phase



Dissemination of RAC Recommendations

RAC

PI

IRB

IBC

NIH IC

FDA

OHRP

Sponsor

OBA Web site
(minutes, video)

Timing of Federal and Local Protocol Review Processes

- **Final IBC approval cannot occur until RAC review is completed**
- **IRB review and approval can occur before or after RAC review**
- **FDA review and authorization of IND application can occur at any time**

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**

Post-Enrollment Reporting
(Appendix M-I)

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

Post-Enrollment Reporting
(Appendix M-I)

- **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**
      - **Additional information pertinent to understanding gene transfer product**

Post-Enrollment Reporting
(Appendix M-I)

- **Roles and Responsibilities**
  - **PI is responsible for reporting safety information**
  - **PI may delegate to another party, such as a corporate sponsor, the role, but not the responsibility, of reporting safety information to NIH**
- **Reports must be sent to:**
  - **Institutional Review Board**
  - **Institutional Biosafety Committee**
  - **NIH/OBA**
  - **FDA**

New Resources from the NIH Office of Biotechnology Activities

Genetic Modification Clinical Research Information System (GeMCRIS)

A public database of human gene transfer trials registered with the National Institutes of Health

GeMCRIS

Genetic Modification Clinical Research Information System
Version 2.0

Home | Search | User Help

Support

- Feedback
- Frequently Asked Questions
- Contact Us
- Browser Requirements

Welcome to the NIH Genetic Modification Clinical Research Information System (GeMCRIS). GeMCRIS is a comprehensive information resource and analytical tool for scientists, research participants, institutional oversight committees, sponsors, federal officials, and others with an interest in human gene transfer research. GeMCRIS allows users to access an array of information about human gene transfer trials registered with the NIH, including medical conditions under study, institutions where trials are being conducted, investigators carrying out these trials, gene products being used, route of gene product delivery, and summaries of study protocols.

To facilitate access to this information, GeMCRIS offers a number of preformatted reports. You can also create your own query tailored to your particular information needs. To get started, use the "Search" menu item above, or click the "Frequently Asked Questions" link on the left to learn more about using the system.

We are seeking comments on GeMCRIS's utility and ease of use. Please take a moment to respond to the questions on the form provided through the "Feedback" link on this page. Your input is critical to ensuring that the system meets the needs of all its diverse users.

Related Information

- About The RAC
- NIH Guidelines
- Documents (With Quarterly Reports)

Site Map

GeMCRIS: Underlying Philosophy

- **Creating a system that would:**
  - **Promote public access to information and understanding about gene transfer research**
  - **Facilitate investigator compliance with adverse event reporting**
  - **Harmonize NIH and FDA approaches to data collection**
  - **Assist NIH and FDA in conducting oversight of human gene transfer trials**

GeMCRIS: Key Protocol Information

- Protocol title
- Study phase
- Clinical indication(s)
- Investigator(s)
- Clinical trial site(s)
- Scientific abstract
- Non-technical abstract
- Investigational strategy
- Vector
- Transgene
- Route of administration

Key Features of GeMCRIS: On-line AE Reporting

- **Tools for streamlined and effective communication and analysis of safety data**
  - **One AE reporting format**
    - **Copies can be sent to FDA, IRB, IBC**
  - **Uniform "Core" data elements**
  - **Controlled medical vocabularies**
  - **On-line adverse event reporting**
- **Objective: To facilitate**
  - **Investigator compliance**
  - **Agency oversight**
  - **Data sharing**

Adverse Event Reports: Core Data Elements

- Date and description of event
- Seriousness and severity
- Suspected cause(s)
- Attribution (gene transfer product, underlying disease)
- Relevant clinical observations and history
- Description of gene transfer product
- Route and site of administration
- Dosing information

Accessing GeMCRIS:

Connect to:

http://www.gemcris.od.nih.gov/

New Resources from the NIH Office of Biotechnology Activities

NIH Guidance for Informed Consent for Gene Transfer Research

A new resource for investigators, IRBs, IBCs, potential research participants, and others concerned with informed consent in gene transfer trials

Informed Consent Guidance for Gene Transfer Research

Impetus

- RAC review of informed consent documents revealed that investigators were having difficulty conveying important concepts pertinent to gene transfer research and to human subjects research more generally
  - inappropriately positive description of benefits
  - therapeutic misconception
  - presumptive use of the first person pronoun (“I understand that...”)

Appendix M-III-A

Communication about the Study to Potential Participants

MAIN POINTS

- Informed consent is a communication process, not a form.
- Various methods and tools exist to improve comprehension of information.

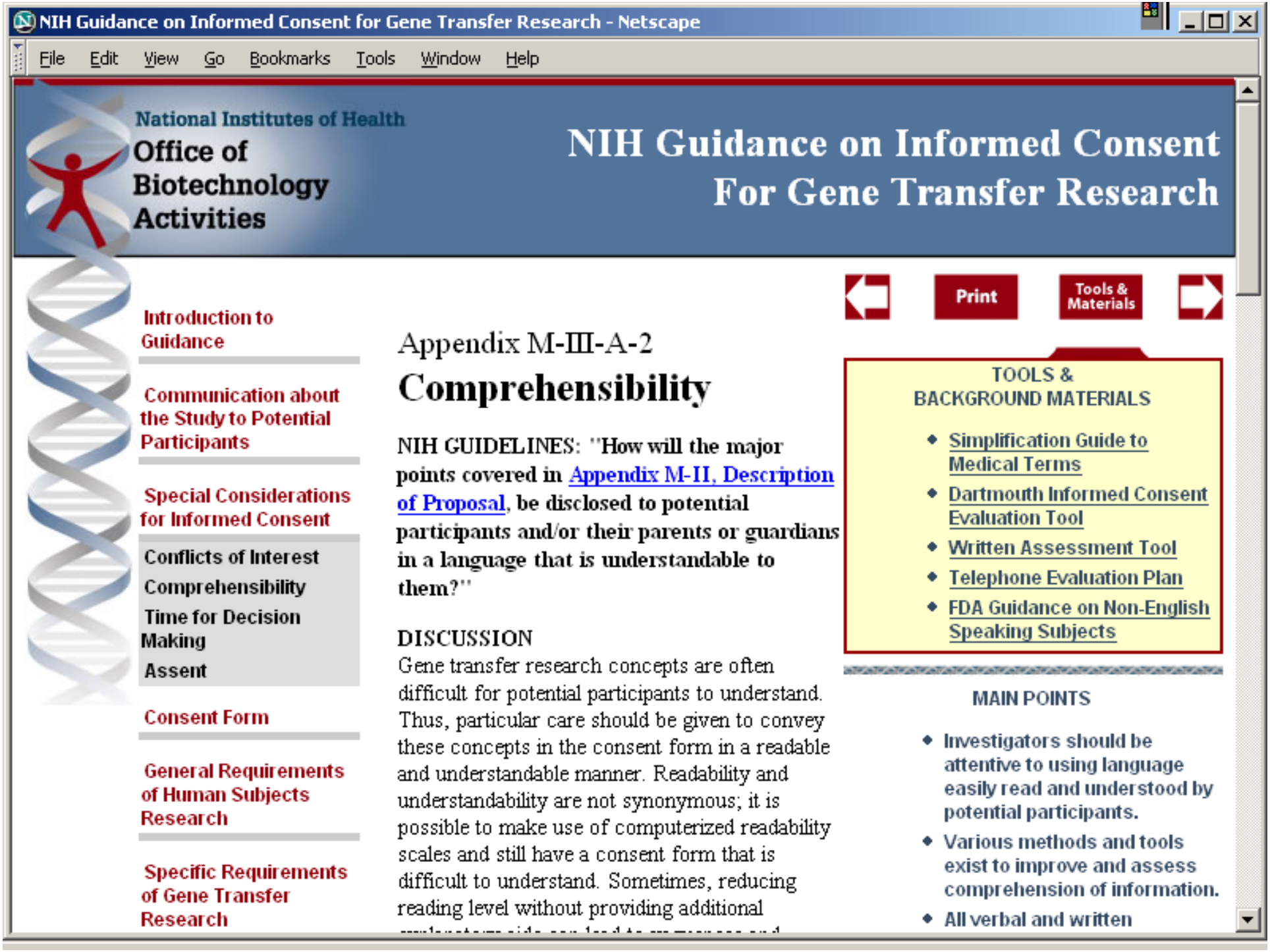
DISCUSSION

Informed Consent - A Process, Not a Form:

Informed consent is much more than a document or obtaining a participant's signature on a consent form. Informed consent is a process of communication between an investigator and a potential research participant.

The purpose of the consent process is to:

- Ensure that potential participants understand that they are being asked to participate in research, and that they appreciate the differences between research and treatment
- Foster potential research participants' understanding of what to expect from participation in a study
- Encourage and respond to questions about study participation
- Facilitate discussion, reflection, and free and informed decision making


NIH Guidance on Informed Consent for Gene Transfer Research - Netscape
File Edit View Go Bookmarks Tools Window Help
National Institutes of Health
Office of Biotechnology Activities
NIH Guidance on Informed Consent For Gene Transfer Research
Introduction to Guidance
Communication about the Study to Potential Participants
Special Considerations for Informed Consent
Conflicts of Interest
Comprehensibility
Time for Decision Making
Assent
Consent Form
General Requirements of Human Subjects Research
Specific Requirements of Gene Transfer Research
Print
Tools & Materials
Appendix M-III-A-2
Comprehensibility
NIH GUIDELINES: "How will the major points covered in Appendix M-II, Description of Proposal, be disclosed to potential participants and/or their parents or guardians in a language that is understandable to them?"
DISCUSSION
Gene transfer research concepts are often difficult for potential participants to understand. Thus, particular care should be given to convey these concepts in the consent form in a readable and understandable manner. Readability and understandability are not synonymous; it is possible to make use of computerized readability scales and still have a consent form that is difficult to understand. Sometimes, reducing reading level without providing additional
TOOLS & BACKGROUND MATERIALS
Simplification Guide to Medical Terms
Dartmouth Informed Consent Evaluation Tool
Written Assessment Tool
Telephone Evaluation Plan
FDA Guidance on Non-English Speaking Subjects
MAIN POINTS
Investigators should be attentive to using language easily read and understood by potential participants.
Various methods and tools exist to improve and assess comprehension of information.
All verbal and written

Morning Session: The Fundamentals

- Introduction to the National Institutes of Health Office of Biotechnology Activities
- Overview of the Current *NIH Guidelines for Research Involving Recombinant DNA Molecules*
- Requirements for IBCs in the *NIH Guidelines*
- Open Forum
- Break
- Role of the Recombinant DNA Advisory Committee and the Protocol Review Process
- Case Studies