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Human Gene Transfer Research

"Informed Consent in Human Gene Transfer Trials: The Role of the IBC"

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I. Background: Review of human gene transfer research

A. Complex science

B. Complex regulatory oversight

1. Food and Drug Administration
   - Reviews safety and efficacy

2. NIH Recombinant DNA Advisory Committee
   - Reviews and publicly discusses selected protocols
   - Scientific, medical, ethical, legal, social issues
3. IBC
   - For all experiments involving deliberate transfer of recombinant DNA, or DNA or RNA derived from recombinant DNA, into any human research participants, reviews trial design, biosafety and containment, and compliance with NIH Guidelines with focus on minimizing risk to individual, close contacts, health care workers, community
   - Approves/disapproves gene transfer protocols

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4. IRB
   - Conducts risk/benefit assessment relative to participants
   - Approves/disapproves gene transfer protocols

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C. IBC's Consideration

1. Documents submitted for IBC review

- RAC comments, if any
- IBC application form
- Human subjects IRB application form
- Human subjects consent form
- Clinical protocol
- Investigational brochure
- Appendix M of NIH Guidelines

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2. Application Review Process

- IBC reviews application form to assess:
  - Containment of vector, potential for environmental release
  - Risk of vector to subjects, family members, the environment
  - Potential benefits vs. biohazard or other toxicity risk
  - Precautions that will be taken to prevent spread of virus/vector
  - Measures that will be undertaken to mitigate risks, if any, to public health
  - Whether are any pre-existing patient medical conditions among recruited subjects that may amplify risks of using the vector

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- If IBC approves, IRB receives copy of IBC approval letter and deliberations and modified ICD after IBC changes are implemented
  - IRB deliberations should include considerations noted by IBC of vector based complications associated with the gene transfer that could affect assessment of risk/benefit to subject
- No participant may be enrolled until RAC review process has been completed and PI has obtained IBC approval, IRB approval, and all applicable regulatory authorizations

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II. Informed Consent and IBCs

A. In reviewing recombinant DNA research for compliance with NIH Guidelines, IBCs must ensure that issues raised by RAC in public review and PI's response are considered (NIH Guidelines for Research Involving Recombinant DNA Molecules, Section IV-B-2-b-(1))

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B. In reviewing recombinant DNA research for compliance with NIH Guidelines, IBCs must ensure that all aspects of Appendix M have been appropriately addressed by PI (NIH Guidelines, Section IV-B-2-b-(1))

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- Appendix M – III: Informed Consent
  - PIs must indicate how subjects will be informed about study and manner in which consent will be solicited;
  - Should indicate how ICD makes clear special requirements of gene transfer research

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- Communicating About Study to Potential Participants (Appendix M-III-A)
  - Who is responsible? If PI is also treating MD, what procedures will be used to avoid possible conflicts of interest?
  - How will information be disclosed in understandable manner?
  - How long will potential participants have to decide?
  - How will assent be obtained (as applicable)?

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- Informed Consent Document (Appendix M-III-B) – Should include the following:
- *General (Appendix M-III-B-1)*
  - Description/Purpose of Study
  - Alternatives
  - Voluntary Participation
  - Possible Benefits, if any
  - Possible Risks, Discomforts, Side Effects
  - Costs

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* *Specific to Gene Transfer Research (Appendix M-III-B-2)*
  - Reproductive considerations
  - Long-term follow-up
  - Request for autopsy
  - Interest of media and others in the research

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- Appendix M-IV: Privacy
  - Provisions that will be made to honor subjects' wishes as to whether, when, how their identity is publicly disclosed
  - Provisions for maintaining confidentiality of research data

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- Appendix M-V: Special issues for response by PIs
  - Steps that will be taken to ensure that accurate and appropriate information is made available to the public with respect to public concerns that may arise
  - If patents will be sought for research products or procedures, steps that will be taken to permit as full communication as possible among investigators and clinicians concerning research methods and results.

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C. Selected Informed Consent Issues Raised by RAC and Relevant to Appendix M: Therapeutic Misconception

1. The Problem

History:

- Term coined by Applebaum and Lidz 1982

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Definition:

- Refers to participant's failure to appreciate purpose and nature of potential benefit of the research
  - Implications: May impede meaningful decisions to enroll

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– Explanations:

Applicable Generally

- Socialization to believe physicians always provide personal care
- Ill participants tend to trust their well-being to authority figures

Particularly prevalent for trials of novel technologies and/or treatment for urgent condition

- Persons who are critically ill more desperate
- Public and clinicians regard the novelty as heralding revolutionary advances
- Clinician - developer of the novel therapy often conducts his/her own trials

Sometimes applicable

- Trial Design
  Example: Phase I/II Study of Repeat Intra-Articular Administration of tg AAC94

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2. Lines of Defense

- The Informed Consent Document
  - Terminology
    *"Physician" vs. "Investigator"
    *"Patient" vs. "Subject"
    "Therapy" or "Treatment" vs. "Research Participation" or "The Investigational Agent"

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- Study Purpose Description Examples:
  - Phase I ICFs fail to state safety and dosage as aims
  - Purpose, study agent, and benefits descriptions entangled:
    - "The purpose of the research study is to determine the safety of special cells that may make your own immune system fight your leukemia"
    - "The purpose of this study is to develop a new kind of cancer treatment that works by helping the body's immune system attack cancer cells."

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Suggestions:

- Partition “purpose,” “agent,” “possible benefits” sections
- Briefly describe classic study phases
- Avoid first-person pronouns

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- Study Benefits Description
  - Avoid implication that logic driving PI's hypothesis is fact.

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– Description of Alternatives

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- The Informed Consent Process
  - Conduct or supplement discussion with discussion by individual not on prospective subject's treatment team
  - Decision monitoring
  - Clear disclosure of PI's role