

Drinker Biddle

**American Society of Gene & Cell Therapy  
2010 Clinical Trials Training Course**

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**Session V (Part 1):**

**Bioethics, Research Integrity and Conflicts of  
Interest**

**May 18, 2010 2:25-3:25 pm**

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## Disclosure

- > No financial relationships to disclose.

## Overview:

- > Setting the Stage: The Importance of Addressing Ethical Issues in Gene Transfer Research
- > Selected Ethical Issues in Gene Transfer Research
  - Trial Development
  - Trial Design
  - Informed Consent
  - Privacy and Confidentiality
  - Safety Monitoring

## Setting the Stage: The Importance of Addressing Ethical Issues in Gene Transfer Research

- > Shared ethical challenges/issues with all research involving new biotechnologic developments
- > Heightened importance due to public perceptions/fears, history of the field
  - Public's fear of potential hazards following discovery that genes from different species of bacteria could be recombined in laboratory, leading to 1975 Asilomar Conference's call for research restrictions, leading to legislative proposals to govern laboratory research and court actions

- Hemophilia B trial – Detection of vector in participants' semen, concern about germ line modification
- Death of Jesse Gelsinger (1999)
- X-linked SCID trial – unexpected vector-induced leukemia in 2 of 11 participants in Paris trial (2002-03)

## Selected Ethical Issues in Gene Transfer Research

### > Trial Development

- Evaluating diseases/conditions for which gene transfer trials are appropriate
  - Life-threatening diseases vs. less serious conditions, enhancement
    - Arguments to restrict to former
      - » Access concerns
      - » New definitions of “normal”
      - » Risk/benefit balance
    - Counter Arguments
      - » Sometimes difficult to distinguish “disease” (achondroplasia) from “trait” (short stature)

- » Sometimes difficult to evaluate if risk/benefit calculus is favorable. Example: in utero gene transfer trial for alpha thalassemia – If fetus survives until birth, would it be a benefit if it has to endure life-time suffering?
- o Observations:
  - » Current prevalent thinking seems to be that should be restricted to life-threatening diseases; yet—
  - » RAC has approved trials for hyperactive bladder function, ED and blindness; and—
  - » Seems inevitable that will be increasing demand for studies for less serious conditions; which means—
  - » Challenging risk/benefit analyses

– Germ line vs. somatic cell

■ Arguments Pro:

- If goal is to prevent or alleviate disease or disability, more efficient than repeating gene therapy generation after generation
- In chemo and clinically indicated irradiation, inadvertent germ line genomic changes can't be excluded, and this risk is acceptable
- Preimplantation genetic diagnosis and implantation of healthy embryos is not acceptable alternative – it prevents individual's birth following PGD, not manifestation of disease in the individual

- Arguments Con
  - Misuse – Eugenics
  - Permanent alteration of human gene pool, unnatural, “playing God”
  - Potential for deleterious unforeseen negative effects on future generations
  - Is alternative to prevent germ line transmission of inherited disorder – preimplantation genetic diagnosis and implantation of healthy embryos
  - Very expensive, won’t merit high social priority
  - Violates rights of subsequent generations to inherit genetic endowments, or to decide about whether their genetic constitution should have been modified

## > Trial Design

### – Subject selection

#### ▪ Children

○ Dilemma with respect to children with non-life-threatening diseases:

- » Possibility of latent reactions in individuals with still-developing tissues who are likely to live long enough to experience them
- » May be different for life-threatening progressive disorders unresponsive to conventional therapy where no adult patients are available
- » Applicable Regulations: 45 C.F.R. 46 Subpart D and FDA guidance on assent of children

- » Issues:
  - Addressing minor's dissent
  - Addressing subjects once they reach age of majority for continued Study participation/long term follow-up
- Incapacitated adults
  - Dilemma: While voluntary informed consent is a key safeguard in human subjects research, important clinical research is aimed at addressing diseases, disorders, conditions that affect cognition, awareness, decisionmaking capacity, and excluding persons with impaired consent capacity can disregard autonomy and delay answers to important scientific questions that could lead to new treatments and diagnostic and preventive strategies

- Applicable Regulations: Common Rule and FDA regulations call for equitable selection of subjects and provision of additional safeguards to protect rights and welfare of subjects vulnerable to coercion or undue influence (including mentally disabled); no additional regulations regarding mentally disabled
- Issues:
  - » Assessing consent capacity – how, when
  - » Identifying and evaluating decisions of LARs – when, how
  - » Respecting subject's right to withdraw
  - » IRB review: consideration of additional safeguards, e.g.
    - Consent monitor
    - Waiting periods

- Advanced vs. moderate disease vs. health volunteers; availability vs. unavailability of alternatives
  - Goal: Acquire meaningful data, minimize subject risks, through trial with acceptable risk/benefit balance
  - Dilemmas:
    - » May be increased benefit for less sick individuals, but sicker may have little to lose
    - » If subjects have severe illness, attributing causes for adverse events may be confounded by underlying medical issues
    - » If subjects have severe illness, not likely to survive and experience theoretically predicated latent adverse effects

- » If are no alternatives, may be increased benefit, but this could cause concern about decisionmaking process; if are alternatives, may be better decisionmaking process, but risk/benefits balance may be problematic
  - Example: X-linked SCD when allogenic BMT available
- Observation:  
Need for careful scrutiny of conflict of interest issues and informed consent

- > Informed Consent: The Therapeutic Misconception
  - Definition: Misconception that participating in research is same as receiving individualized treatment (Applebaum, Roth, Lidz)
  - Ethical significance: May impact prospective participant's ability to make meaningful, autonomous enrollment decision

– Reasons:

- Belief that physicians always provide personal care
- Tendency, when ill or distressed, to trust well-being to authority figures
- Novel biotechnologies viewed as revolutionary advances
- Trial design (sometimes)

– Responses:

- The Informed Consent Document
  - Terminology
  - Study Purpose Description
  - Study Benefits Description
  - Description of Alternatives
- The Informed Consent Process

- > Privacy and Confidentiality: Special Challenges in Gene Transfer Research
  - Media and others may have interest in innovative character of the research and participants
  - Long-term follow-up and desire for autopsy information may require retaining participants' consent information and links to study results for many years
  - Stored biospecimens often involved
  - Adverse event reporting, discussion

> Safety Monitoring

Goals: Assure that integrity and safety of research remain intact and that anticipated and unanticipated harms are detected and contained

Activities: Review of informed consent process, protocol adherence, adverse event reporting, research data collection, continuing (annual) review of risk/benefit profile

Responsible Entities: IRBs (ERBs), DSMBs, Study Sponsors, Investigators

Concerns:

*General*

- Confusion about monitoring responsibilities
- Imperfect communications, integration among reviewing groups
- Unclear review standards

*Gene transfer trials*

- Review bodies' lack of experience and expertise in gene transfer research
- Distinctive risks to subjects including, e.g., long latency of risks due to continuous, life-long exposure to transgenes or vectors, use of active agents (as opposed to chemicals), variability in response to some vectors

- Risks to descendants of subjects due to inadvertent modification of germ cells
- Risks to public through use of vectors for which recombination or transmission are safety concerns
- Scarcity of safety, toxicity information gathering, which adversely impacts risk/benefit balance – risks are justifiable if trial can make contribution to scientific knowledge

## Recommendations:

- Enhance safety monitoring
- Assure follow-up, autopsy
- Track medical records of gene transfer trial participants