

# Long-Term Follow-Up in Human Gene Transfer Research: Ethical and Social Issues

James F. Childress  
University of Virginia  
June 1, 2004

- I. Introduction
  - a. Overview
  - b. Preliminary point: shifts in language and perspective
    - i. From research “on” to research “with” human subjects
    - ii. From “research subjects” to “research participants”
    - iii. In short: human research participants are partners and collaborators in the enterprise of research
- II. Elements of an ethical framework: incomplete and still evolving
  - a. Three principles of the Belmont Report (National Commission)
    - i. *Respect for Persons*
      1. Respect the choices of autonomous agents
      2. Protect persons with diminished autonomy
    - ii. *Beneficence*
      1. Do no harm
      2. Maximize possible benefits and minimize possible harms
    - iii. *Justice*: fair distribution of the benefits and burdens of research
  - b. Applications or specifications of these principles
    - i. Respect for persons-- informed consent
      1. Information
      2. Comprehension
      3. Voluntariness
    - ii. Beneficence—assessment of risks and benefits
    - iii. Justice: fair selection of research subjects
  - c. Federal Policy for the Protection of Human Subjects (“Common Rule”) (1991) – codification of several ethical considerations, including
    - i. Criteria for approval of research involving human participants
    - ii. Information components required in disclosure for informed consent
  - d. NIH Guidelines for Research Involving Recombinant DNA Molecules: Appendix M: Points to Consider
  - e. NIH Guidance on Informed Consent for Gene Transfer Research (endorsed by RAC 12/03) <http://www4.od.nih.gov/oba/rac/ic/>
- III. Implications of ethical framework for LTFU in gene transfer studies
  - a. General points:
    - i. Beneficence toward current (and future) participants (and patients) warrants LTFU, but both respect for persons (and their autonomous choices) and justice in the distribution of benefits and burdens set some limits and point some directions
    - ii. Implications of model of partnership and collaboration
  - b. Voluntary and informed consent to participation
    - i. Disclosure of information (with understanding as the goal)
      1. What should be disclosed at the outset?
        - a. Disclosure of the nature and purpose of study, procedures involved, possible benefits and risks, follow-up, etc.
        - b. Possible benefits
          - i. Avoidance of “therapeutic misconception”
          - ii. Research on gene transfer, not therapy for the individual participants
        - c. Risks

- i. For participants & for others in contact with participant
      - ii. Long-term follow-up: important as a way to monitor the safety of the trial in order to protect each current participant and to improve safety for future participants and patients
    - d. In model of research partnership or collaboration, disclosure stresses mutual expectations (including follow-up)
      - i. Participation is optional and may be stopped at any time, but LTFU is an important expectation
      - ii. Nature, schedule, and kinds of follow up, including anticipated procedures
  - ii. Voluntariness:
    - 1. Question about LTFU as an expectation: is it justifiable, i.e., fair and respectful, to exclude potential participants who are unwilling to bear the burden of LTFU? Not depriving of benefit to which otherwise entitled – appropriate expectation in partnership
    - 2. Consent as a process
      - a. Not only a process leading up to the signed consent form, but also on-going process after enrollment because of the participant’s right to withdraw at any time even after gene transfer
      - b. Coercion not justifiable, but encouragement to continue to participate, including through follow-up, is justifiable.
        - i. Encouragement, along with explanation of the value of LTFU
        - ii. Hypothetical exception to the ban on coercion? Suppose that, after experimental gene transfer, a situation developed that put others at serious risk (both probability and magnitude of harm)
  - c. Some special issues
    - i. Request for autopsy as part of LTFU
      - 1. Not typical in non-gene-transfer protocols
      - 2. Recommendation in Appendix M:
        - a. Authorization for autopsy not mandatory for participation
        - b. Indication that potential participant’s permission for autopsy is not being sought but that it will be sought from the next-of-kin, whatever the cause of death, and a request that the participant discuss this matter with his/her family
    - ii. Data and stored specimens
    - iii. Participants who lack competence at the outset or who lose competence
      - 1. For those who lack competence at the outset, permission from guardians for enrollment; if participants become competent, then they may choose whether to continue
      - 2. For those who lose competence during the trial or the LTFU, the permission of guardians will be necessary
    - iv. Disclosure of significant findings to participants both during the trial itself and during the LTFU – as a way to respect persons and to realize the model of collaboration and partnership

#### IV. Conclusions