



Phase I Trials for Adult and Pediatric Disease: Ethics, Design, & Decisions

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Human Research Ethics in a Nutshell

- **Respect for persons**
 - Supporting autonomy of subjects
 - Informed consent
 - Privacy & confidentiality
- **Beneficence/Nonmaleficence**
 - Minimizing risks of harm through study design and conduct
 - Monitoring and long-term follow-up
 - Maximizing benefit to society
 - Balancing risks of harm and potential for benefit
- **Justice**
 - Subject selection
 - Use of results

Issues to Address

- Envisioning the Research Trajectory
- Identifying Preclinical Data Needed
- Transition to FIH trials
- Who should be first and why?
- Phase I: goals and design
- Dealing with uncertainty
- Direct benefit: a special challenge
- Informed consent: general issues
- Pediatric subjects: how different?

Ethics Meets Science in GTR

- Does preclinical evidence support research safety and validity?
- Does the study have sufficient value (safety, fairness, payoff)?
- Guidelines, monitoring, and long-term follow-up
- Detecting rare events in animal and human studies
- Collection and testing to monitor shedding, biodistribution, vertical transmission risk
- Ethics of study design
- Assessing subject selection & consent form
- Minimizing uncertainty and risks of harm
- Discussing uncertainty and reasonable expectations

Moving from Bench to Bedside I

- Choosing disorders as research targets:
 - need (severity, prevalence, lack of effective standard treatment or symptom control)
 - science (easy to study, transgenes/vectors available, generalizability of new knowledge)
 - society (advocacy group interest, available funding)
- Think early about:
 - research goals & products
 - harm-benefit balance & probable affordability
- What preclinical information is needed?
- What would it take to gather more?
- When is it time to move to humans?
 - no more can be learned without human data
 - can we learn about both effects and mechanisms?
 - can we minimize harms to human subjects?

Moving from Bench to Bedside II

- Has enough preclinical information been collected so that the only reasonable way to learn more is to move to humans?
- Has enough been done to reduce the risks of harm to humans, and to maximize the likelihood that the gene transfer intervention will ultimately show benefit in humans?
- Has the point of irreducible uncertainty been reached?
- Is the amount of irreducible uncertainty small enough that it is fair to subjects to ask them to become involved in the research?

FIH Trials in GTR

- Appropriate design of human GT studies depends on the population of patients chosen as first subjects:
 - nature of their disease
 - severity of their disease stage
- Preclinical research into a particular combination of gene, target cell, disease, and route of administration must be sufficiently developed and sufficiently informative to move to human studies.
- First-in-human trials must be able to:
 - provide sufficient knowledge
 - adequately inform subjects
 - protect them from harm as far as possible
- Investigators and oversight bodies must examine whether a particular clinical trial can do so
 - using the design proposed
 - under all relevant circumstances

Selection of Patients as Subjects Should Reflect Research Goals

- minimizing risks of harm -- for which subjects can the risks of the intervention be meaningfully minimized?
- maximizing contribution to generalizable knowledge -- from which subjects can maximally useful data (amount, meaning, interpretability) be obtained?
- both goals must be met; they can conflict; this presents challenging ethical/design questions.

Who Should Be First?

- Should subjects be more like “healthy volunteers”?
 - adults with relatively stable disease
 - informed and unpressured decisions about participation
 - possible to minimize risks of harm
 - reliable and interpretable data
- Should subjects be more like the sickest patients?
 - most often asked in early-phase trials (e.g., oncology)
 - treatment possibilities exhausted
 - not tempted to forgo a “bird in the hand”
 - may value potential benefits more, or risks less

Subject Selection I

- Which first subjects can be sufficiently protected from harm?
- Which first subjects can provide useful enough data to move forward?
- Very sick subjects may be at greater risk of harm, but may value chance of benefit highly
- Disease effects, intervention effects, and effects of prior treatment may be hard to disentangle in very sick subjects
- Healthier subjects may sometimes be too well to provide data needed to move to later-phase trials
- Which first subjects are most likely to benefit (is this a research question)?

Subject Selection II

- Who should be first
 - when there is no effective treatment?
 - when standard treatment is imperfect?
 - when there is effective standard treatment?
 - when risks of harm are minor to moderate?
 - when the risks of harm are great?
 - when uncertainty is great?
 - when the condition is life-threatening?
 - when the condition is less serious?
 - when in the disease course— late or early?
- When should investigators return to preclinical studies
 - to reduce risks of harm and uncertainty?
 - to increase likelihood of benefit from the line of research?

Balancing Harms & Benefits

- Nuremberg Code:
 - “The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.”
- Declaration of Helsinki:
 - “Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.”
- Belmont Report:
 - “It is commonly said that benefits and risks must be “balanced” and shown to be “in a favorable ratio”. The metaphorical character of these terms draws attention to the difficulty of making precise judgments. However, the idea of systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible.”

Informed Consent Guidance: Study Purpose

- You were asked to be in this study to help the investigators learn more about the type of disease you have. The investigators will try to keep the risks of harm to you from being in the study as low as possible. They believe that being in the study will not keep you from getting any treatments you may need for your disease.

--NIH Guidance on Informed Consent for Gene Transfer Research, <http://www4.od.nih.gov/oba/rac/ic/>

Informed Consent Guidance: Study Purpose cont' d

- This study will enroll people with your disease [CHOOSE WHICHEVER APPLIES]
- Whose disease has been treated unsuccessfully by all standard means
- Who will continue to receive standard treatment
- Who can probably put off standard treatment during the study
- Who can probably stop or change standard treatment during the study

Harm-Benefit Assessment in GTR: Factors to consider

- variability in diseases and interventions
- variability in risks of harm
 - vector toxicity
 - Insertional mutagenesis
 - germline transmission
- lack of good animal models
- hard to predict dose-dependent safety and efficacy
- potential for permanent changes
- long-term risks of harm
- heightened uncertainty
- “irrational exuberance” about potential benefits?

Phase I Issues

- Goals of First-in-Human Trials:
 - Safety
 - Dosage information
 - Information needed to decide next research steps
 - Proof of concept
 - Preliminary data potentially signaling efficacy
- What does it mean to be a research subject?
 - LTFU
- What does “success” mean?
- Consequences of “failure”?

Safety & Risks of Harm

- What risks of harm are expected?
- What risks of harm are conceivable?
- Describe the risks of harm
 - nature
 - severity
 - duration
 - likelihood
- Can they be minimized?

Potential for Benefit

- Does available information & reasoning about potential for benefit *from the line of research* support moving to humans?
- When *in the line of research* might subjects experience meaningful direct benefits?
- Does available information & reasoning support the expectation of meaningful direct benefit for subjects *in this trial*?
- Describe potential direct benefit *when relevant*:
- Direct Benefit
 - resulting from receipt of the intervention(s) being studied
- Dimensions of Direct Benefit
 - *Nature*
 - clinical endpoint?
 - surrogate endpoint?
 - *Magnitude*
 - size (improvement? cure?)
 - duration (temporary? permanent?)
 - *Likelihood* (affected by dosage group, design, number of subjects?)

Potential for Direct Benefit: Ambiguous Expectations?

PI: “Oh, it’s a long shot. It’s a long shot.”

Q: “If you were just to say yes or no what would you say?”

PI: “Ah that’s tough, that’s actually, I’m really conflicted about that. I guess if you really push me, I’d have to say no, but I would like to say yes, but I don’t think that would be honest at this point. It’s a little bit too early... to work out.”

Q: “I can also punch here ‘don’t know’ .”

PI: “Well, no, I don’t know. Nobody knows.”

Q: “Would you like to answer that instead of yes or no?”

PI: “No I’ll put no. It’s the moral response.”

Reasonable Disagreement

- Investigators, regulators, & patient-subjects might disagree
 - about the meaning of the available data
 - about the harm-benefit balance
 - about how to value the risks of harm & chance of benefit under the circumstances
- RESEARCH IS NOT TREATMENT
- Frequency vs. Belief:
 - Researchers' expectations for the study and patient-subjects' hopes for themselves CAN DIFFER if risks are minimized and clear information is shared

Informed Consent

- Explain why is it necessary to learn from humans & fair to ask them to participate
- Explain the harm-benefit balance
- Describe risks of harm and their minimization
- Describe direct benefits subjects may experience, *if any*, and how likely or unlikely
- Explain how and why research is not treatment
- Emphasize research partnership & avoid inducing therapeutic misconception

Pediatric Considerations

- When should pediatric patients be first subjects?
 - nature of disorder (pediatric only; other?)
 - what can best be learned from whom
 - nature and amount of preclinical data
- Special protections needed?
 - disease severity
 - availability of alternatives
 - best order for interventions
 - standard first?
 - standard later?
- Examples besides SCID:
 - cystic fibrosis, Canavan, Batten, LCA, WAS, CGD, others?
- Conformity with Adult Considerations
- Conformity with Subpart D?