



Ethics: Case Presentations and Discussion

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Disclaimer

- The views expressed in this presentation are those of the speakers and do not necessarily represent the policy of either the Food and Drug Administration or the Department of Health and Human Services.

Cases

- Challenges in Funding Research
 - Cases #2-4
- “First-in-Human” Studies in Children
 - Case #6
- Individual/Institutional Conflict of Interest
 - Case #1
- Limits of Parental Discretion
 - Case #5

Challenges in Funding Research

Case #2:

- Parents of a 4 yr old child with an incurable neurodegenerative condition hear about a gene therapy clinical trial that you are running. The trial only has room for 5 children and is filling up fast. The family volunteers that they would like to help fund your research to the tune of \$1 million. Although this is not discussed explicitly, you feel as if the gift is contingent on the child's enrollment in the trial.

Challenges in Funding Research

Case #3:

- Parents of a 3 yr old child with a neurodegenerative disorder visit a major university medical center that is proposing conducting a stem cell clinical trial. They arrive at the medical center for evaluation and find out that the trial is not yet funded. The family is asked to meet with the university development office, where they are told that the trial will only take place if the families can fund it.

Challenges in Funding Research

Case #4:

- Parents of an 8 yr old child going blind from a neurodegenerative disease find out you are doing a trial of gene therapy for their child's disease, that may restore vision. They would like to pay specifically for their child to have the gene therapy procedure done. They are not interested in helping to fund the study in general.

Questions/Issues

- Case #2: Parents desperate for treatment for their child. Investigator tempted by offer of gift to support research. Is it ethical to accept the gift?
- Case #3: Is it fair to pressure families to pay for clinical trials? If the trial goes forward, will families who supported the trial be invited to have their children enrolled first?
- Case #4: Is it a conflict of interest for an investigator to accept payment to support a clinical trial from parents of a child who would be enrolled?

Discussion Points (1 of 3)

- **Context**

- Incurable disease; unproven interventions; no alternate treatments
- Parents willing to sacrifice much in hope of improving their child's chances for extended or quality of life
- Investigators looking for early funding from an “angel investor” (http://en.wikipedia.org/wiki/Angel_investor)

- **Therapeutic Misconception**

- Confuses research with treatment
- Unrealistic expectation of benefit

Discussion Points (2 of 3)

- **Independent Assessment**
 - Scientific Credibility
 - Appropriate Balance of Risk and Potential Benefit
- **Equitable Selection of Subjects**
 - Fair distribution of scarce resource?
 - Selection Procedures
 - “first come, first served”
 - “to each according to their ability to pay”
 - “lottery”

Discussion Points (3 of 3)

- Role of Disease-Based Advocacy Groups
 - Funding Mechanism?
 - Respect for Community? Control of Community Resources?
 - Intellectual Property?
 - Sharing of Data/Trial Results?
 - Buffer between Desperate Parents and Overly Optimistic Scientists?
 - Establish Pool of Eligible Subjects?

“First-in-Human” Studies

Case #6

- A four year old boy is diagnosed with a progressive neurometabolic disorder, for which there is no FDA-approved treatment. Recently published studies of an animal model of this disease show that treatment with a drug approved for other indications doubles the life span of the animal, when injected in the first week of life. Treatment begun when the animals are symptomatic shows no benefit. The authors of a commentary accompanying the published animal data suggest that human studies would be premature.

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“First-in-Human” Studies

- The parents of the affected child persuade their treating physician to develop a compassionate use protocol to give the drug to their child by intravenous infusion every two weeks, indefinitely. The protocol is approved by the IRB and the FDA.
- Parents announce on their blog that their child is receiving “FDA approved therapy” for his disease and is “doing well”. Physicians treating this illness are deluged with requests from other parents to prescribe this drug for their children

Questions/Issues

- Is it ethical to perform pilot/phase I clinical trials in children, even when terminally ill with no other specific treatment?
- What standard of evidence (animal/human studies) is required or desirable before initiating therapeutic trials in children with rare diseases?
- What is the impact of compassionate use studies on the community of people with the rare disease in question?
- How do anecdotal reports of uncontrolled observations from compassionate use studies affect progress in the field?
- How does ad hoc compassionate use of experimental agents influence recruitment to randomized trials?

Questions/Issues

- Should all affected individuals have equal opportunity to access such studies?
- Who should initiate experimental treatment protocols?
- How can investigators and regulators most effectively educate families and patients regarding the scientific and ethical principles governing human studies?

Discussion Points

- “First-in-Human” Trials in Children
 - Prospect of Direct Benefit
 - Setting Justifiable Risk in the Context of the Disease and Available Alternatives
- Expanded Access, Emergency IND and “Compassionate Use” Protocols
 - Standard of Evidence for Individual, Intermediate, and Treatment INDs
- Need for informed consent and IRB review

Conflict of Interest

Case #1

- An investigator submits a research protocol for a clinical trial of a therapy for which the institution holds a patent. There is a potential for millions of dollars to the institution if the therapy is successful. Given the institutional conflict of interest, the IRB elects to review the protocol with “extra care” due to the presence of the financial conflict (confided to the investigator by the compliance officer). The IRB continues to review protocol amendments, but consults a single external reviewer as to its decisions. One of these consultations prompts a reversal in the IRB’s approval of a specific age group, disqualifying a previously screened potential subject from enrolling in the trial.

Questions/Issues

- Who should review research protocols when the institution has a conflict of interest in the therapy being tested?
- What are the problems with using external IRB's, and why may institutions be reluctant to use them?
- What are the potential pitfalls for investigators, institutions, and pharmaceutical companies when the institution conducting a clinical trial has a significant financial interest in the therapy being tested? What are the obligations of each party, and how can they best be met?

Questions/Issues

- What industry-academic collaborations are acceptable, and what should academicians do with regard to consultancies, stock options, honoraria, and research funds? Are academic-industry partnerships desirable? Will the court of public opinion agree?

Discussion Points

- **Impact of Conflict of Interest on Scientific and Ethical Review**
 - Trial Conduct and Data Integrity
 - Mechanisms to Reduce Investigator Bias
 - Difficulties in Small Clinical Trials
 - Human Subject Protection
 - Recruitment
 - Informed consent process (including empirical studies)
 - Safety and Adverse Event Reporting
- **Institutional Conflict of Interest/Mitigation Strategies**
 - IOM Report

Limits of Parental Discretion

Case #5

- An infant girl has an abnormal newborn screening test for Krabbe disease (KD). She is two weeks of age and is brought in by her parents for confirmatory testing which shows that she is at "high risk" for developing KD because her GALC enzyme activity is very low. GALC mutational testing shows she has a novel compound heterozygote for two mutations that have never been seen together, but separately have been seen in children with the early infantile form of KD. Therefore, the evidence and the opinion of experts suggest that she may be at "high risk" for developing early onset KD.

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Limits of Parental Discretion

- There is a suggested protocol in place for evaluating children at "high-risk" of early onset KD. It includes head MRI, LP, EMG/NCV, ABR, SSEPs. The most important of these are the MRI and LP, which are the two studies the parents have the greatest concerns about because they do not want the infant sedated nor do they want a "needle in her back." The potential treatment (hematopoietic stem-cell transplantation) is one that the parents associate with a high morbidity and mortality. They are aware that since the start of KD newborn screening in NY state, two infants have been transplanted and one died of complications of the transplant.

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Limits of Parental Discretion

- The parents voice concerns about the premise of the KD newborn screening program. They feel that they are being pushed into being part of a research project disguised as clinical care, and they do not want their daughter to be a "guinea pig" for novel treatments. As far as they can see, their daughter is "fine" and to all appearances, a normal baby. Until that changes, they will not allow anyone to sedate her or "put a needle in her back."
- The physicians' concern is that when the child does become abnormal, it will be too late to provide transplantation.

Questions/Issues

- How is this case different from the case of an infant who has screened positive for congenital hypothyroidism?
Can a family refuse to obtain confirmatory testing or treat their child with supplemental hormone?
- The parents are angry about being put in a position of making urgent and frightening medical decisions in the face of substantial uncertainty about both risk of developing disease and efficacy of proposed treatment. Are they too hostile and suspicious to work rationally on behalf of their infant?

Discussion Points

- Parental Refusal of Medical Treatment
- Role of Independent (Peer?) Counseling
- Innovative or Established Treatment

Fetal Therapy

- Could prenatal therapy for lysosomal storage diseases (e.g. ERT to mom with transplacental targeting) ever be studied in a clinical trial?

Discussion Points

- 45 CFR 46, Subpart B