ETHICAL ISSUES IN RESEARCH ON RARE DISEASES

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David Wendler
Department of Bioethics
NIH Clinical Center

Same Old Song

- Research on rare diseases should satisfy the ethical requirements that apply to human subjects research generally.
- For example, research on rare diseases should undergo independent review and minimize risks.

What's Different?

Research on rare diseases also raises some ethical issues that are not present, or are of less importance in research on common diseases.

8 Ethical Requirements

1) Collaborative partnership
2) Social Value
3) Scientific Validity
4) Fair subject selection
5) Favorable risk-benefit ratio
6) Independent review
7) Informed consent
8) Respect for human subjects

Social Value

The Need for Social Value

Human subjects research is ethical only when it has sufficient social value.

Estimating Value

- The value of specific studies on rare diseases may be less clear than research on common diseases.
- In such cases, it is important to explicitly assess the social value of the research.

Internal Value

- In standard cases, reviewers tend to assess only the internal value of clinical research studies.
- This is determined by evaluating whether the benefits produced by the research study (e.g. the value of the information to be collected) justify its risks.

Comparative Value

- There are fewer resources, including fewer subjects, for research on rare diseases.
- Should reviewers also assess *comparative* value: Phase 1 study of an intervention to treat one symptom of a rare disease that would preclude subjects from other studies.

Future Availability

- The value of clinical trials typically depends on their potential to develop new treatments.
- Since industry may not be interested in treatments for rare diseases, it can be important to evaluate prospectively the feasibility of producing treatments (e.g. getting orphan designation).

Need for a Plan

In such cases, it may be important to have a prospective plan that details how any treatments proven effective will be made available to patients.

Scientific Validity

Importance of Validity

- To have social value, research studies must have a valid scientific design.
- Hence, a valid design is an ethical requirement on human subjects research.

Sufficient Power

- Typically, a study must have sufficient power to be valid.
- In some cases, it may be difficult to enroll sufficient subjects in research on rare conditions.

Prospective Plan

- In such cases, investigators should have in place a plan for how they will address the concerns of insufficient power.
- One possibility is to develop a plan to combine the findings with results of similar trials in a meta-analysis.

Collaboration

- In some cases, it may be possible to avoid underpowered trials by combining patient pools.
- This may require collaboration between competing research teams and with patients/advocate groups.

Placebos

There is widespread debate about the conditions under which it is acceptable to conduct placebo-controlled trials.

Scientific Justification

- Many argue that it is unethical to use placebos for “convenience” sake.
- On this view, placebos must be needed for scientific reasons.

Rare Diseases

- It may be necessary for reasons of numbers to conduct placebo-controlled trials.
- Placebo trials can be acceptable when “low frequency of condition” precludes an equivalence trial.

Emanuel, Miller NEJM 2001; 345:916-919

Ethical Concerns

- Reliance on placebo-controlled trials raises important ethical concerns when effective treatments exist.
- PCTs are generally considered acceptable only when risks are minimized and there is no increased risk of serious harm to those in the placebo arm.

Similarity in “Net” Risks?

- Can it be ethical to expose competent adult research subjects to higher risks (e.g. bone marrow biopsy or liver biopsy for research purposes)?
- If so, can it be ethical to conduct PCTs which expose those in the placebo arm to greater risks?

Fair Subject Selection

Subject Selection

- Lack of alternatives makes it especially important to ensure that eligibility criteria are fair, minimize risks and enhance potential benefits.
- Dilemma: enroll less sick who face lower risks or more sick who have greater potential for benefit?

Recruitment

- One of the greatest obstacles to conducting clinical research is enrolling subjects.
- This is especially challenging in research on rare diseases: payment, advertising, finder's fees.

Rare Clinicians

- The rareness of a disease is correlated with a rarity of experts on the disease.
- This increases the chances for conflicts of interest when physicians are both a patient's clinician and researcher.

Managing Conflicts

- Be aware of them
- Disclose
- Obtain independent judgment when higher risks or other concern

Competition for Subjects

- Paucity of potential subjects can lead to competition for subjects.
- This competition increases the potential for unethical practices (e.g. not informing subjects of research alternatives).

Coordination

- Need to consider mechanisms to coordinate.
- Interest groups and the rare disease network might play a role in helping to deal with the issue, highlighting the importance of collaboration.

Informed Consent

Understanding

- The lack of alternatives may increase the chances that subjects fail to understand that they are participating in research.
- In this way, the lack of alternatives may lead to the ‘therapeutic misconception’.

Desperation

- The lack of alternatives also may make some individuals desperate.
- Desperation may impair potential subjects' ability to make decisions.

Assessment

- To address these concerns, investigators and reviewers should consider whether it makes sense to assess potential subjects' consent.

- Assessments can be formal or informal.

Wendler. *Archives Int Med* 2004; 164:2201-2204.

Informal

- Informal assessments involve asking potential subjects to explain the study and their decision in their own words.
- Can you tell me what the study involves? Why do you want to enroll? What could you do otherwise?

Formal

- Formal assessments should be study specific (e.g. not a MMSE).
- Potential formal assessments include post consent quizzes or formal evaluations.
- By investigator or independent party?

The Essential Elements

- Proper assessment requires clear understanding of what is required for potential subjects to provide valid consent for research.
- In general, potential subjects need to understand their own circumstances and the study in question, and make a voluntary decision whether to enroll.

Voluntariness

- Voluntary consent involves potential subjects making their own decision whether to enroll.
- Voluntary consent requires that the decision to enroll is not influenced by inappropriate internal (delusions) or external factors (pressure from others).

Applebaum, et al. *Hastings Cen Rep* 2009; 39:30-39.

Lack of Alternatives

- Subjects with rare diseases may have few, if any, options for treatment other than enrolling in a clinical trial.
- The lack of options *per se* does not undermine the voluntariness of subjects' consent (cf. cancer for which there is one effective treatment).

Validity of Consent

- Valid consent requires potential subjects to understand the essential elements of consent as they apply to the study in question.
- These include: fact that it's research, risks, potential benefits, risks, alternatives, voluntary.

TM

- Bioethicists make a great deal of the therapeutic misconception (TM).
- Commentators claim that subjects need to understand phase of research, fact that interventions are unproven, investigators do not intend to benefit subjects, research is risky, research is unlikely to benefit subjects.

The True Concern

- The TM undermines potential subjects' consent only when it keeps them from understanding one or more of the essential elements of consent.

Dispelling the TM

- Potential subjects should understand how what happens to them (risks, potential benefits, procedures) will be affected by enrolling in research.
- In addition, to understand “it’s research”, potential subjects should understand that they will be contributing to a project to help others.

Underpowered trials

Should underpowered trials inform subjects that participation may only “indirectly” contribute to future benefits?

Halpern, et al. JAMA 2002; 288:363-365.

Research Alternatives

- Informed consent requires subjects to understand their alternatives, and should continue throughout subjects' research participation.
- Does informed consent require that subjects are aware of the possibility of enrolling in other studies?