Fair Subject Selection and Vulnerability

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Goals

Selection and Recruitment should:

1. Distribute burdens and benefits fairly
2. Ensure social value of research
3. Enhance scientific validity
4. Minimize risks to subjects
5. Maximize benefits to subjects
6. Protect the vulnerable

Potential Conflicts

- In some cases, these different goals may conflict.

- For instance, minimizing risks to subjects may decrease the social value of the research.

Tradeoffs

In cases of conflict, investigators, ethics review committees, and sponsors must “balance” the competing goals.

Subject Selection

- Subject selection involves determining which subjects may enroll in the research.

- Subject selection is determined by the study's inclusion/exclusion criteria.

Research as a Benefit

- Exclusion without a good reason may be unfair or discriminatory.

- People are clamoring for access to clinical trials...demanding they, and others like them, are owed such as a matter of justice. (Levine, 1994)

Fairness

- To ensure fairness, begin by assuming everyone is eligible.
- Exclude individuals from this pool only with good reason.

Priority of Science

- The scientific goals of the study should be the primary consideration in determining who can enroll.

- This involves ensuring the value of the study and enhancing its validity.

Ensuring Value

- Exclude individuals not suitable for answering the scientific question.

- For instance, individuals with conditions that make it impossible to assess the drug being tested (e.g. brain tumors).

Enhancing Validity

- Also exclude individuals who cannot satisfy the protocol requirements.

- For instance, subjects who cannot (or do not) make the required clinic visits.

Minimize Physical Risks

- To minimize risks, exclude individuals who would face significantly higher risks.

- Individuals with poor kidney function might be excluded from a phase II study of a drug with renal clearance.

Maximize Benefits

- Select subjects who are more likely to benefit from participation.

- A study of a new anti-HIV drug might focus on individuals with low CD4 counts.

Protecting the Vulnerable

- There is an order of preference in selecting subjects, for instance, adults before children. (Belmont Report)
- Exclude vulnerable subjects unless their participation is needed for scientific reasons. (CIOMS)

Vulnerable Subjects

- In general, vulnerable subjects are those who are significantly less able to protect their own interests.

- In the context of clinical research, vulnerable subjects typically are those not able to give voluntary informed consent.

Address Vulnerability First

- In some cases, it is possible to address individuals' vulnerability without excluding them.

- Individuals who do not understand English are vulnerable (in the US), but this vulnerability can be addressed by translators and translated documents.

Subjects Who Can’t Consent

- Exclude individuals unable to consent, unless there is a compelling reason to enroll them.
- Scientific necessity is the most obvious reason to enroll those who cannot consent.

Lower Risks?

- Should individuals who cannot consent be enrolled when they face significantly lower risks than individuals who can consent?

- For example: a phase I study that can be conducted with relatively low risks in children or high risks in adults.

The Prospect of Benefit

- Should subjects who cannot consent be excluded from trials that offer the potential for medical benefit?

- Should an individual unable to consent be enrolled in a phase II study of a new chemotherapy for lung cancer, if the study could equally well be completed with individuals who can consent?

The Justification?

- In some cases, enrollment may be in ‘riskier’ subjects’ (e.g. individuals with poor kidney function) best interests.

- Thus, a general exclusion of these subjects cannot be justified on the grounds that it protects them.

Research vs. Clinical Care

- It is important to distinguish research from clinical care.
- Excluding ‘riskier’ subjects minimizes the aggregate risks of research.
- Applies to moral (can’t consent) as well as physical risks (renal clearance example)?

Additional Safeguards

- Informed consent is a primary research safeguard.

- Hence, when enrollment of subjects unable to consent is justified, the study should include additional safeguards to protect them.

Sufficient Evidence

- Adults no longer able to consent should be enrolled only with sufficient evidence that it is consistent with their preferences and interests.

- Some commentators require this evidence to be documented in a formal advance directive.

Surrogates

- Subjects unable to consent should be enrolled only with the permission of an appropriate surrogate.

- Are health care surrogates sufficient for research purposes (evidence that those close to us are bad predictors of our preferences)?

Subject Recruitment

Subject recruitment involves active attempts to enroll specific individuals or groups within the pool of eligible subjects.

Finding the Right Community

- In many cases, the choice of communities from which to recruit is determined by institution location.

Selecting a Community

- In other cases, investigators have a choice of possible communities.

- In these cases, the principles of subject selection apply in deciding which community to select.

Goals of Selection and Recruitment

1. Distribute burdens and benefits fairly
2. Ensure social value
3. Enhance scientific validity
4. Minimize harm
5. Maximize benefit
6. Protect the vulnerable

Declaration of Helsinki -2000

Medical research is only justified if there is a reasonable likelihood the populations in which the research is carried out stand to benefit from the results of the research.

Social Value/Community Benefit

- To what extent must communities benefit from research involvement?
- To what extent must the community benefit specifically from the research results?

Community vs. Individual Benefit

Should the requirement of benefit be added to the conditions on selection of individual subjects?

Recruitment

- Targeted recruitment
- Inviting referrals from colleagues
- Advertising
- Inviting one’s own patients

Recruitment for good reasons

- Do not focus recruitment on individuals who are (or appear to be?) vulnerable

- Ensure subjects are recruited for reasons of science, not compromised position.

(Belmont Report)

Incentives to Enroll Subjects

- Investigators are under considerable pressure to recruit subjects, sometimes receiving financial incentives. (US Inspector General 2000)
- Physicians receive payments for referring their patients to trials.

Concerns about Incentives

- Do incentives to refer patients pose a conflict of interest?

- To what extent might use of incentives encourage investigators to enroll riskier/inappropriate subjects?

Advertising

- What effect does advertising have on recruitment?
- Does advertising affect consent?
- May benefits be advertised?
- Must risks be advertised?

IRBs and Advertising

- "The IRB should review the methods and material that investigators propose to use to recruit subjects."
- Ads should not claim that investigational interventions are safe or effective.
- IRB should evaluate the "relative size of type used and other visual effects."

www.fda.gov/oc/ohrt/irbs/toc4.html#recruiting

Ads in Real Life: Bar Coaster

Research Subjects Wanted

Earn $50-$1295

Call
555-555-5555

Christine's Research Institute

Proposed T.V. Ad

- Thumping music; Tie-dye colors rotating on screen.
- VOICE OVER: Attention alcohol Users...If you are currently using alcohol you are a candidate for a new research study being done at Dave's Institute.
- We are enrolling men and women, eighteen to forty, to study the effects of alcohol on the brain.
- This study pays up to 3500 dollars and includes room and board in our dorm-like facility. Call today.

Effect of Ads

- Do advertisements affect which groups enroll?
- Does advertising affect understanding? Does it affect motivations (does it matter?)

Payment

- What role should payment play in recruiting research subjects?

- Is it acceptable to advertise payment?

Is Alan Here Yet?

- Some argue that payment may coerce individuals.
- Others worry that payment may represent an undue inducement.