Fair Subject Selection

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Three Aspects of Subject Selection

1. Selection: determining which groups of individuals are eligible
2. Recruitment: actively approaching individuals in the eligible groups
3. Retention: retaining enrolled subjects

Goals

Selection, Recruitment, and Retention should:

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

Potential Conflicts

- In some cases, there may be conflicts between the 6 goals.
- Minimizing risks to subjects (e.g. excluding the very sick) may decrease the social value of the research.

Tradeoffs

- In cases of conflict, investigators, ethics review committees, and sponsors must “balance” the competing goals.
- These determinations require judgment based on an understanding of the circumstances to determine which factors are more important in that case.

1. 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 Risky

- A good deal of early clinical trials posed significant risks and were conducted in vulnerable subjects (e.g. Tuskegee, research with prisoners).
- This led to an emphasis on fairness as the fair distribution of risks and burdens.

Research as Potentially Beneficial

- Prompted by early HIV (and breast cancer) trials, people started arguing that exclusion can be unfair.

- “Against this backdrop…the focus shifted from fair distribution of research burdens and risks to fair distribution of research benefits.

Meltzer and Childress, ch 35, Oxford Textook

Balancing the Two Claims

- 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.

Generalizability

- To the extent possible, it is important to ensure that interventions are tested in different populations (e.g. men and women).
- Enrollment of a broad range of subjects helps to promote this goal.

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).

Competing Trials

- Sometimes two or more trials will recruit from the same (small) group.

→ Is it acceptable to exclude individuals from one study in order to increase the potential subjects for another study?

Enhancing Validity

- Exclude individuals who cannot satisfy the protocol requirements.
- For instance, subjects who cannot (or do not) make the required clinic visits.

Minimize 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.

Enhance 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.
- Is it the only reason?

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 cognitively impaired adults or high risks in cognitively intact adults.

Prospect of Benefit?

- Should individuals who cannot consent be excluded from trials that offer potential clinical benefit?
- Should individuals who cannot consent due to Down's Syndrome be enrolled in a phase II study of a new chemotherapy?

Benefits of Research

- More recently, debate over fair subject selection has focused on the fair distribution of the benefits that result from the study.

→ Individuals without health insurance: Reason to include from a treatment trial or reason to exclude?

2. SUBJECT RECRUITMENT

Subject recruitment involves active attempts to attract specific individuals within the pool of eligible subjects.

The Need to Recruit

- According to a 2007 survey by Center Watch, over 70% of clinical trials are delayed due to difficulty enrolling a sufficient number of subjects.
- To be ethical, clinical trials needs to recruit a sufficient number of subjects to obtain valid data.

The Ethics of Recruitment

- This provides an *ethical* reason to recruit (and retain) subjects.
- Yet, recruiting (and retaining) research subjects raises important ethical issues.

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 6 goals of subject selection apply in deciding which community to select.

Goals of Selection, Recruitment, Retention

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

Choosing a Site

- Where research is conducted can have a significant impact on who enrolls.
- Low inclusion of racial minorities in some studies likely traces more to study site than widely discussed concerns regarding trust in researchers.

Social Value/Community Benefit

- To what extent should host communities benefit from research involvement?
- Must the community benefit specifically from the results of the research?
- This has become the focus of debate in the ethics of multinational research.

Declaration of Helsinki, par 20

"Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group... In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research."

Community vs. Individual Benefit

- Should the requirement of benefit be added to the conditions on selection of individual (vulnerable) subjects?

Methods of Recruitment

- Targeted recruitment
- Inviting referrals from colleagues/clinicians
- 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

- May benefits be advertised? Must risks?
- Some commentators seem to suggest that good advertising is bad, and bad advertising is bad?

IRBs and Advertising

- Direct advertising for subjects is the start of the consent and subject selection process.

- IRBs should determine that ads are: not coercive; do not promise a cure; use appropriate font size and visual effects; explain that test articles are investigational; do not emphasize payment or the amount

http://www.fda.gov/RegulatoryInformation/Guidances/ucm126428.htm

Proposed T.V. Ad

- Thumping music, swirling tie-dye colors: “Attention alcohol users...you are a candidate for a new research study.
- We are enrolling men and women, 18-40, to study how alcohol affects the brain.
- This study pays up to $3500. Call today.

Effect of Ads

- Does advertising affect which groups enroll?
- Does advertising affect understanding?
- Does it affect subjects' motivations (does it matter?)

Payment

- What role should payment play in recruiting research subjects?
- Is it acceptable to advertise payment?

Ads in Real Life: Bar Coaster

Research Subjects Wanted

Earn $50-$1295

Call
555-555-5555

Dave's Research Institute

Coercion?

- Some argue that payment may coerce individuals.
- However, coercion concerns threats to make individuals worse off, not offers to benefit them.

Undue Inducement

- Others worry that payment may represent an undue inducement: individuals focus on the payment so much that they make decisions contrary to their interests.

- One way to address this concern is to ensure that the study is not excessively risky for eligible subjects.

Deception?

- 100 individuals who had participated in at least two trials: 32% concealed health problems; 28% concealed medications, 14% pretended to have a condition.

- Concealment was correlated with greater interest in monetary rewards.

Devine et al. Clinical trials 2013

Other Challenges

- Data suggest that many problems recruiting subjects trace to mundane, practical concerns: awareness of studies, transportation, parking, child care.

- Investigators (and IRBs?) should address these concerns.

3. RETENTION

- To collect valid data, recruited subjects need to be retained.
- Some data suggest that enrolled subjects sometimes experience problems in their personal lives as a result of their participation in clinical research.

Lazovski J, et al. *JERHRE* 2009; 4:89-97.

Ethical Concern

- Loss of enrolled subjects undermines scientific validity and wastes resources.
- Future research is needed to identify ways to encourage subjects to continue to participate, and retain them, without undermining their right to withdraw.

More Questions

- Is it appropriate to emphasize the social/scientific value of a study to encourage enrollment and retention?

- Should researchers throw parties for their subjects?

Summary

- Subject selection, recruitment and retention are central to clinical research.
- The ethical challenges they raise have not received the attention they deserve.
- The 6 goals can help to address these ethical challenges.