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 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).

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 be enrolled in a phase II study of a new chemotherapy that could be evaluated in 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, exclusion of these subjects cannot always be justified on the grounds that it protects them.

Possible Argument

- Excluding 'riskier' subjects minimizes the aggregate risks of research.
- Does this apply to moral risks (e.g. increased chance that enrollment is inconsistent with individuals' preferences) as well as physical risks?

Additional Safeguards

- Informed consent is a primary research safeguard.
- Hence, when subjects unable to consent are not excluded, additional safeguards should be included 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 values.
- What about adults who were never able to consent?

Surrogates

- Subjects unable to consent should be enrolled only with the permission of an appropriate surrogate.
- Are health care surrogates? Next of kin? sufficient for research (evidence that those close to us are poor predictors of our preferences)?

Autism Study

- Proposed enrollment of a 30 year old with severe autism.
- Study involves 2 research blood draws and behavioral observation.

Autism Study

- The clearly caring parents are asked whether they think the potential subject is willing to participate and help others.
- "We have no idea. But, we would like to enroll him because we think this research is so important."

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

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?

Declaration of Helsinki -2008

Research with disadvantaged or vulnerable populations is only justified if the research is responsive to their health needs and priorities and there is a reasonable likelihood that they will benefit from the results of 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?
- Is good advertising bad, and bad advertising bad?

IRBs and Advertising

- Direct advertising for study subjects is the start of the informed consent and subject selection process.
- IRB should evaluate the "relative size of type used and other visual effects."

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

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 and includes room and board. 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?
- FDA: Advertisements may state that subjects will be paid, but should not emphasize the payment or the amount.

Ads in Real Life: Bar Coaster

Research Subjects Wanted

Earn $50-$1295

Call
555-555-5555

Dave's Research Institute

Concerns

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

The Real World

- 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 obtain inaccurate information, and 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.

Summary

- Subject selection, recruitment and retention are central to the ethics of clinical research.
- Yet, these issues have not received the attention they deserve in practice, or in the literature.