Fair Subject Selection

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Three Aspects of Subject Selection

A. Selection: determining which groups of individuals are eligible
B. Recruitment: approaching individuals in eligible groups for enrollment
C. 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 an understanding of the circumstances to determine which factors are more important in a given case.

A. 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

- Early clinical trials often posed significant risks and frequently enrolled vulnerable subjects (e.g. Tuskegee, prisoners).
- This led to an emphasis on protecting individuals, often by excluding them from research.

More Recent History

- In the 1980s, early HIV trials offered the best (sometimes only) chance of treatment.
- Advocates argued that, in these cases, exclusion can be unfair.
- This view was later endorsed by advocates of breast cancer research.

Research as Potentially Beneficial

- “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 Textbook

→ Should the regulations for prisoners or pregnant women be revised to reflect this new approach?

1. Distributing Burdens and Benefits

- To ensure fairness, investigators and IRBs should begin by assuming everyone is eligible for a given trial.
- 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 is eligible to 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.

2. 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?

3. Enhancing Validity

- Exclude individuals who cannot satisfy the protocol requirements.
- For instance, subjects who cannot make the required clinic visits.

Withdrawal from clinical trials individuals who miss appointments?

Minimizing Risks

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

- Individuals with poor kidney function are typically excluded from phase II studies of drugs with renal clearance.

→ Exclude pregnant women (women of child bearing potential)?

The Justification?

- In some cases, enrollment may be in the interests of subjects who face higher risks (individuals with poor kidney function).
- Exclusion of these subjects cannot be justified on the grounds that it protects them.

Possible Argument

- When there are more potential subjects than subject slots: excluding ‘riskier’ subjects minimizes aggregate risks.
- This suggests protections are not just about individual research subjects.

Response

- Individuals may be excluded only to promote the legitimate goals of research: promote science, protect participants.

- If enrollment is in an individual's interests, they should not be excluded because they face greater risk than others.

MacKay J Med Ethics 2016;42:672–677

5. Enhancing 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.

Enhance Aggregate Benefits?

- Should investigators and IRBs increase the number of subject slots beyond what is needed scientifically?

- Example: phase 1 study of an experimental treatment for a devastating condition with no current treatments.

6. 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 unable to give 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: trial of a treatment for severe Alzheimer disease must 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 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?

- For example, should individuals who cannot consent due to Down's Syndrome be excluded from a phase II study of a new chemotherapy?

Tension

- Emphasis on individual interests supports inclusion of those who cannot consent when the potential benefits outweigh the risks.
- Does the importance of minimizing aggregate (moral) risks support excluding those who cannot consent in these cases?

Additional Safeguards

- Informed consent is a primary research safeguard.
- Hence, when subjects unable to consent are eligible, additional safeguards should be included to protect them.

Benefits of Research

- More recent debate has focused on the fair distribution of the benefits OF (versus IN) research.

→ Should individuals without health insurance be included in or excluded from treatment trials?

B. 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 need 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.

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.

Community vs. Individual Benefit

- Many commentators argue that communities, especially those in lower-income countries, should benefit from the clinical trials they host.

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

Methods of Recruitment

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

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 recruit and refer patients pose a conflict of interest?

→ To what extent might use of incentives encourage investigators to refer and 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?

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.

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

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

Ads in Real Life: Drugs and Models

- Ad about heroin addiction and research.
- Discusses woman who was addicted and through research was able to stop.
- The ad included a picture of a smiling woman.

A New Worry

- Significant worry over paying subjects to enroll in research (does it undermine understanding or accurate reporting?).

- More recently, recognition of the benefits of research participation has led to debate over the ethics of charging individuals to participate in clinical trials.

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.

C. RETENTION

- To collect valid data, recruited subjects need to be retained.
- Data suggest that enrolled subjects can 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?

- Is it appropriate for researchers to 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 (and good judgment!) can help to address these ethical challenges.