Subject Selection

Holly Taylor, PhD, MPH
Department of Bioethics
NIH

Disclaimer

The views expressed in this talk are my own. They do not represent the position or policy of the NIH, DHHS, or US government.

Three Aspects of Subject Selection

A. Selection: determining who is eligible
B. Recruitment: inviting eligible individuals
C. Retention: retaining enrolled subjects

Overview

- Protection to Access
  - History and Policy
- Fair Participant Selection
  - Ethical goals
  - Practical considerations

PROTECTION TO ACCESS

Protection to Access

- National Commission Perspective (1970s)
  - Protect vulnerable populations
  - Cannot unduly target prisoners, children, institutionalized persons, poor, etc.
- Contemporary Perspective
  - Allow disadvantaged groups to have *access to what can be learned* through research
  - If research offers particular opportunities, must assure access in a fair way

Assuring Safety

- Mission Statement
  - "The Food and Drug Administration (FDA) is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation." (**ASSURING SAFETY**)

Source: Food and Drug Administration (2019)

Assuring Safety

- Informed by History
  - Patent Medicine
  - Elixir Sulfanimide
  - Thalidomide
  - Diethylstilbestrol (DES)

Assuring Safety

- General Considerations for the Clinical Evaluation of Drugs (FDA 1977)
  - "In general, **women should be excluded** from the earliest dose ranging studies. If adequate information on efficacy and relative safety has been assessed during Phase II [and reproductive testing in animals completed] women of ***childbearing potential*** may be included in further studies…"

Assuring Safety

- General Considerations for the Clinical Evaluation of Drugs (FDA 1977)
  - "A woman of *childbearing potential* is defined as a pre-menopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are single; women whose husbands have been vasectomized or whose husbands have received or are utilizing mechanical contraceptive devices."

Assuring Safety

- How could exclusion of women be problematic?
  - Scientifically?
  - Ethically?

Assuring Access

- Mission Statement
  - "The FDA is responsible …for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health." (**ASSURING ACCESS**)

Source: Food and Drug Administration (2019)

Assuring Access

- AIDS Activism
  - Parallel Track announced 1989
- Evidence about actual level of harm to those enrolled
- Congressional Women's Caucus interest

Assuring Safety

- General Considerations for the Clinical Evaluation of Drugs (FDA 1977)
  - "In general, women shou[illegible]uded from the earliest dose ra[illegible]dequate inform[illegible]d relative safety has been a[illegible]uring Phase II [and reproductive testing in animals completed] women of childbearing potential may be included in further studies…"

Ban lifted in 1993

NIH Inclusion of Women & Minorities as Participants in Research Involving Human Subjects (1994)

- Ensure that women and members of minorities and their subpopulations are included in all human subject research;
- For Phase III clinical trials, ensure that women and minorities and their subpopulations must be included such that valid analyses of differences in intervention effect can be accomplished;
- Not allow cost as an acceptable reason for excluding these groups; and,
- Initiate programs and support for outreach efforts to recruit these groups into clinical studies.

NIH Inclusion of Women & Minorities as Participants in Research Involving Human Subjects (1994)

- Ensure that women and members of mi…es and their subpopulations are included i… …ject research;
- For Phase III clini… …omen and minorities and thei… …be included… …valid analyse… …es in interven… accompl…ied;
- Not allow co… …ason for excluding these groups…
- Initiate p… …ams and support for outreach efforts to recruit these groups into clinical studies.

Inclusion of Children, 1998

Inclusion across the Lifespan, 2017

FAIR PARTICIPANT SELECTION

Ethical Principles

- Collaborative partnership
- Social value
- Scientific validity
- **Fair participant selection**
- Favorable risk benefit ratio
- Independent review
- Informed consent
- Respect for participants

Source: Emanuel, Grady and Wendler (2008)

Goals of Fair Participant Selection

- Distribute burdens and benefits fairly
- Ensure social value of research
- Enhance scientific validity
- Minimize risks to subjects
- Enhance benefits to subjects
- Protect the vulnerable

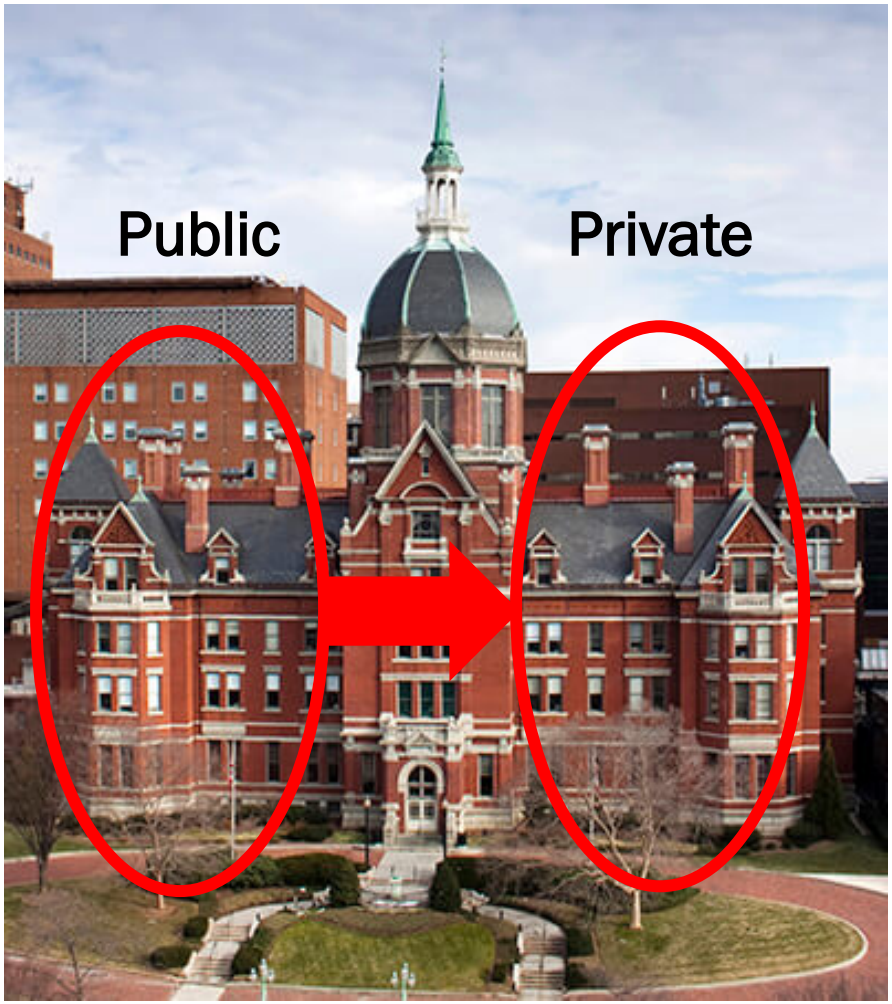
Source: Emanuel, Grady and Wendler (2008)

Distribute Burdens and Benefits

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

- Exclude individuals from this pool only with good reason.

RESEARCH → TREATMENT



RISKS → BENEFITS

RESEARCH → TREATMENT

RISKS → BENEFITS

Distribute Burdens and Benefits

- 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.

Distribute Burdens and Benefits

- 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.

Ensure Value

- Exclude individuals not suitable for answering the scientific question.
  - Exclude individuals who have characteristics/ conditions that make it impossible to assess the intervention being tested (e.g. previous exposure to HIV vaccine; cancer)

Enhance Validity

- Exclude individuals who cannot satisfy the protocol requirements.

Subjects who miss appointments?

Minimize Risks

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

→ Exclude Individuals with poor kidney function from phase II studies of drugs with renal clearance.

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

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.

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 excluded from treatment trials?

Enhance *Aggregate* Benefits?

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

→ Phase 1 study of an experimental treatment for a devastating condition with no current treatments?

Protect the Vulnerable

- There is an order of preference in selecting subjects, for instance, adults before children.

  Belmont Report, 1974

- Exclude vulnerable subjects unless their participation is needed for scientific reasons.

  CIOMS, 2017

Protect the Vulnerable

- 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 who are unable to give informed consent.
  - Lack capacity
  - Have capacity, but not free from influence

Protect the Vulnerable

- Voluntariness
  - Persuasion
    - Influence based on facts
  - Manipulation
    - Informational
    - Of options
  - Undue influence/inducement
  - Coercion
    - Credible threat

Protect the Vulnerable

- 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.

Protect the Vulnerable

- 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.

Protect the Vulnerable

- 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 (e.g. Legally Authorized Representative, Study Partner).

Goals of Fair Participant Selection

- Distribute burdens and benefits fairly
- Ensure social value of research
- Enhance scientific validity
- Minimize risks to subjects
- Enhance benefits to subjects
- Protect the vulnerable

Source: Emanuel, Grady and Wendler (2008)

Three Aspects of Subject Selection

A. Selection: determining who is eligible
B. Recruitment: inviting eligible individuals
C. Retention: retaining enrolled subjects