Subject Selection

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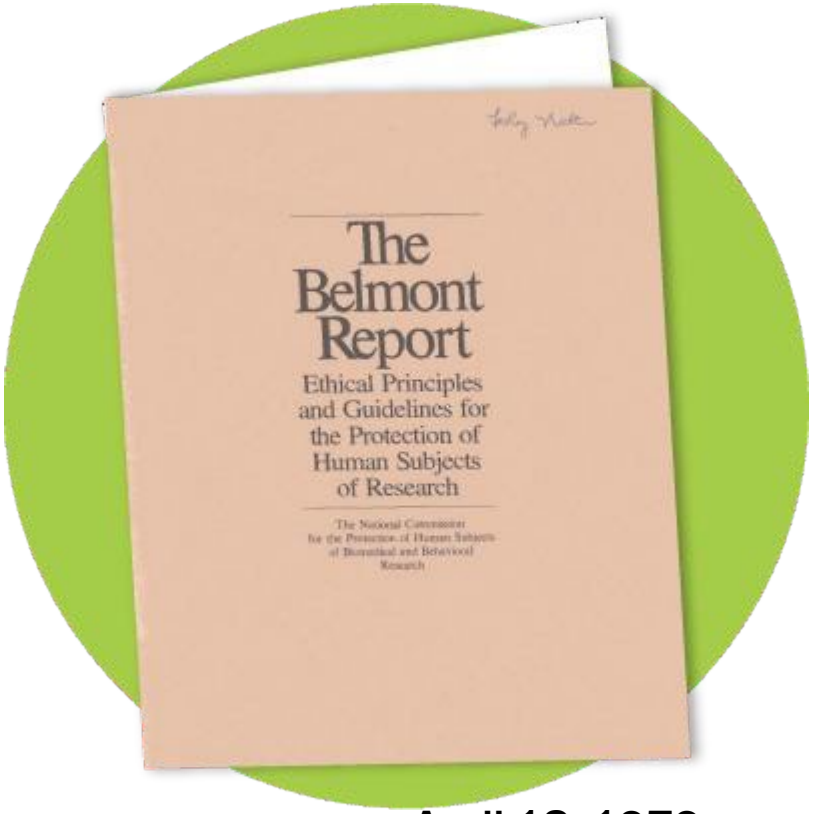
Subject Selection

- Respect for Persons
- Beneficence
- Justice



April 18, 1979

Subject Selection

"Justice is relevant to the selection of subjects of research at two levels: the individual and the social.

- Individual justice in the selection of subjects would require that researchers exhibit fairness: thus, they should not offer potentially beneficial research only to some patients who are in their favor or select only "undesirable" persons for risky research...

Selection of Subjects

- …Social justice requires that distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons…

Selection of Subjects

…Thus, it can be considered a matter of social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions."

Three Aspects of Subject Selection

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

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Inclusion of Children

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 (1990s)
  - 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

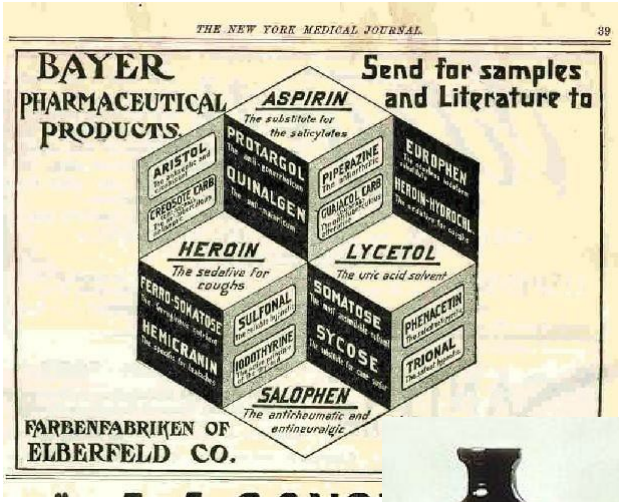
Assuring Safety

- **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

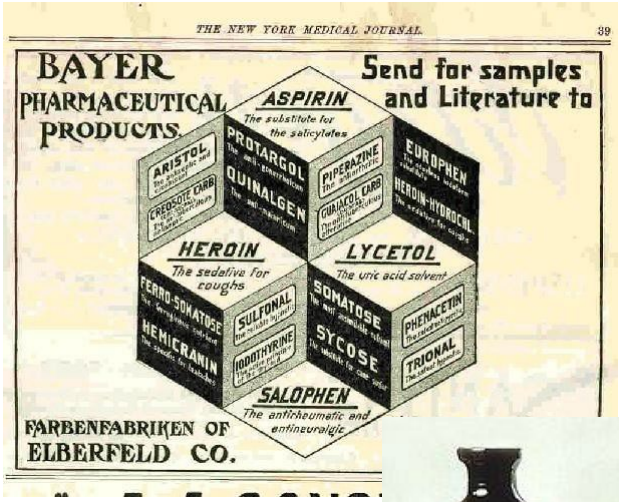
- Informed by History
  - Patent Medicine
  - Elixir Sulfanimide
  - Thalidomide
  - Diethylstilbestrol (DES)



Assuring Safety

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

None were clinical trials



Francis Kelsey

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?
    - Generalizability
    - Clinical Care
  - Ethically?
    - Fair distribution of benefits and burdens of research

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

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)

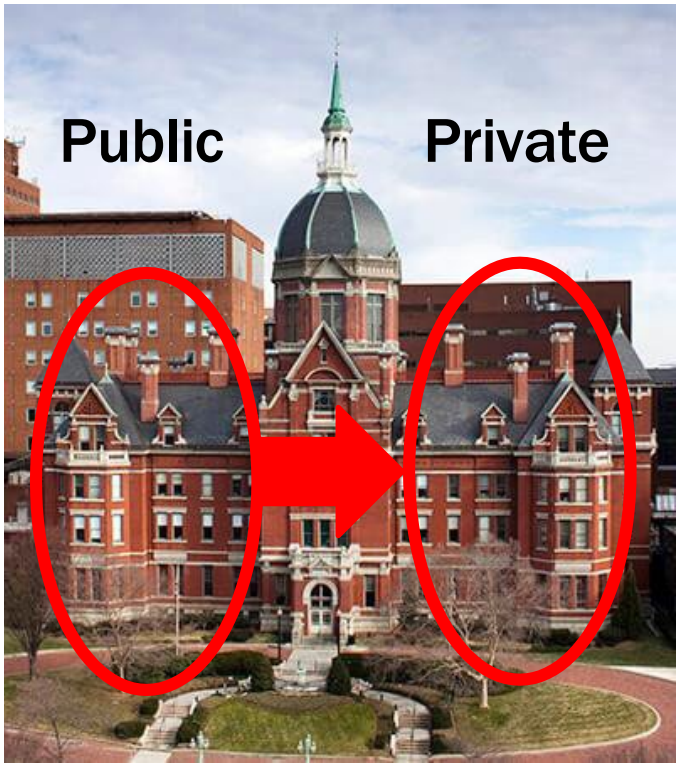
Goals of Fair Participant Selection

- 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 fairly

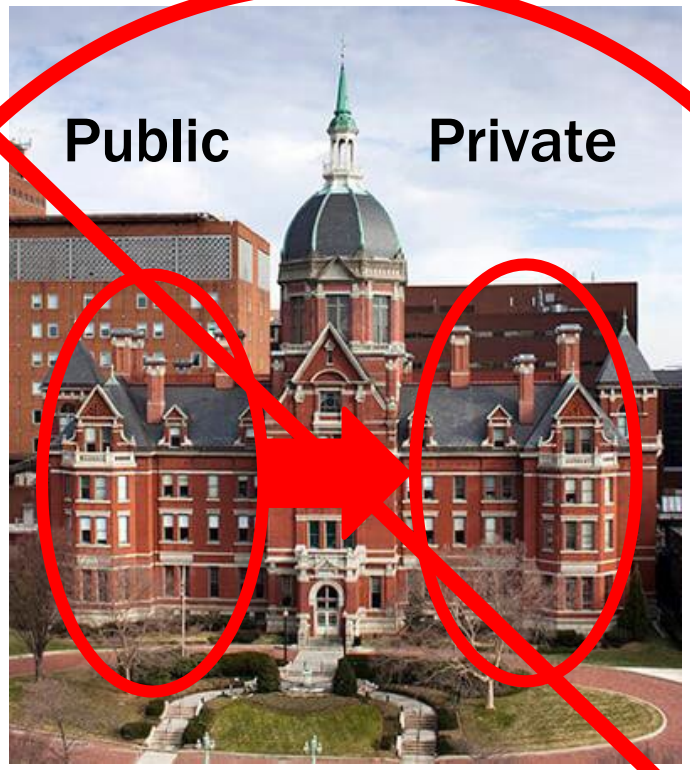
RESEARCH ⟶ TREATMENT



RISKS ⟶ BENEFITS

Distribute burdens and benefits fairly

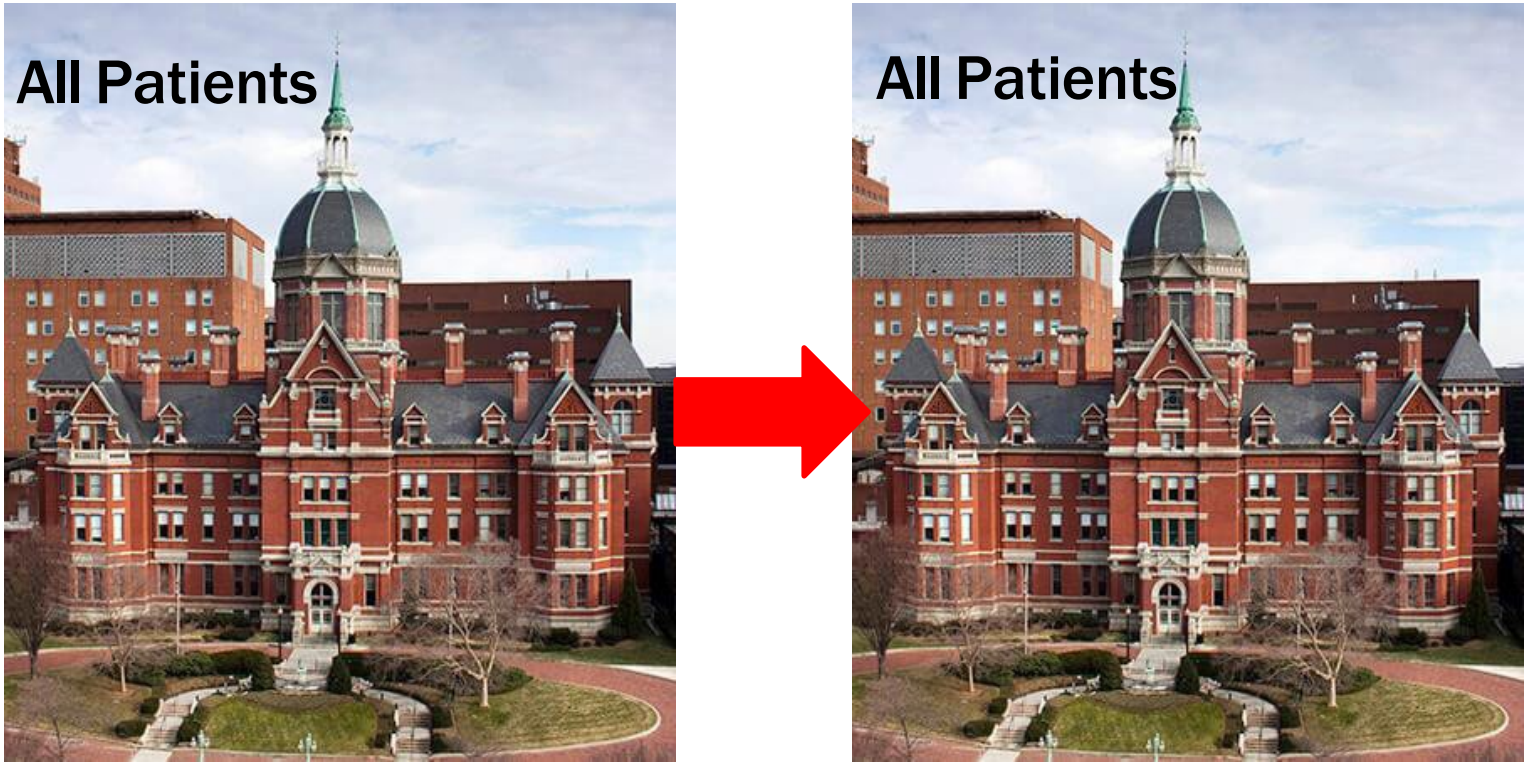
RESEARCH ⟶ TREATMENT



RISKS ⟶ BENEFITS

Distribute burdens and benefits fairly

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 Social 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 Scientific Validity

- Exclude individuals who cannot satisfy the protocol requirements.

Subjects who miss appointments?

Minimize Risks to Subjects

- 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 to Subjects

- 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?

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

- Who is vulnerable according to 45 CFR 46?
  - Pregnant Women, Human Fetuses and Neonates (Subpart B)
  - Prisoners (Subpart C)
  - Children (Subpart D)

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).

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QUESTIONS