Participant 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.

Overview

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

slido.com
#2997361

FAIR PARTICIPANT SELECTION

Participant Selection

- Respect for Persons
- Beneficence
- **Justice**

April 18, 1979

Participant Selection

"Justice is relevant to the selection of subjects of research at two levels:

- 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…

Participant Selection

- …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…

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)

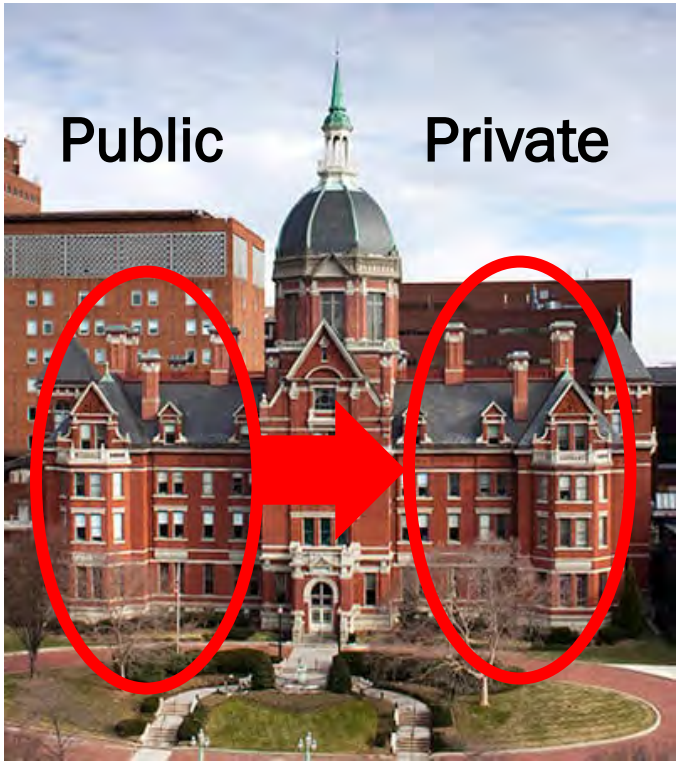
Goals of Fair Participant Selection

- 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

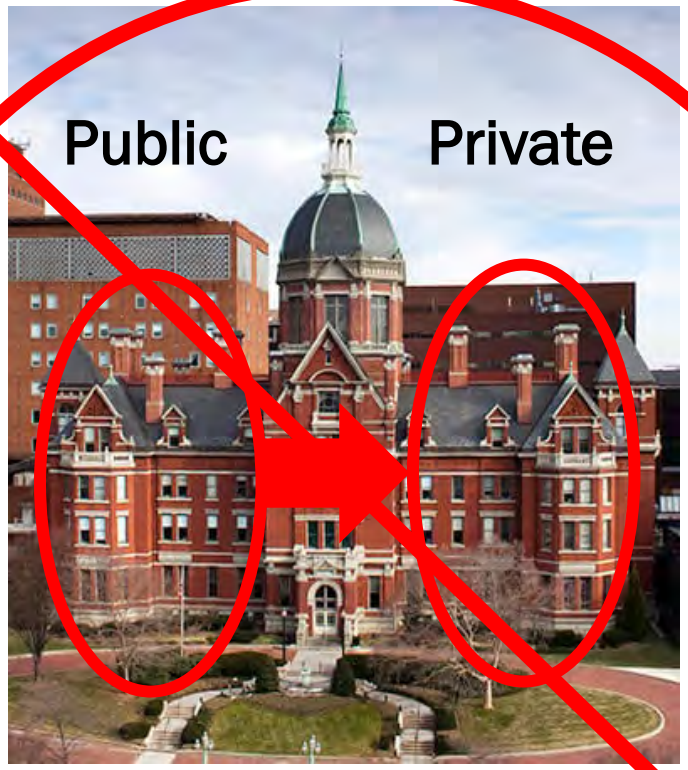
RESEARCH ⟶ TREATMENT



RISKS ⟶ BENEFITS

Distribute burdens and benefits fairly

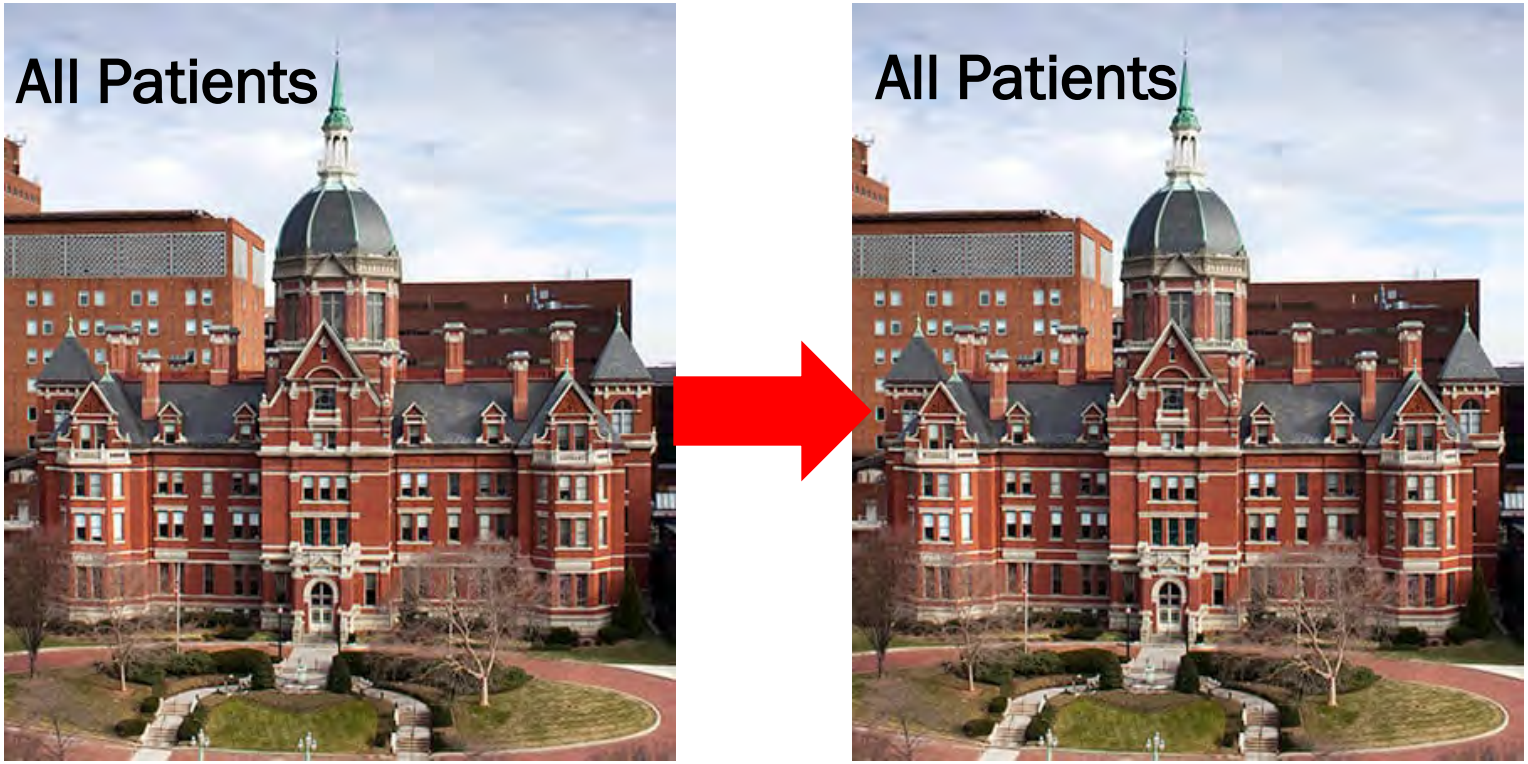
RESEARCH ⟶ TREATMENT



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.

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).

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?
  - Ethically?

slido.com
#2997361

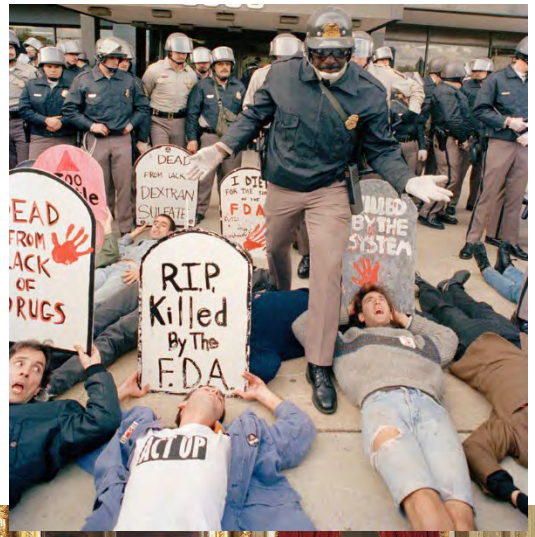
Assuring Access

- 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



FEDERAL INCLUSION POLICY

National Institutes of Health

- NIH budget in FY 2023 was $48 billion
  - 84% of NIH's funding is awarded for extramural research
    - 50,000 competitive grants to more than 300,000 researchers at more than 2,500 universities, medical schools, and other research institutions
  - 10% of NIH funding supports intramural research
    - 6,000 investigators, the majority in laboratories here in Bethesda

Source: NIH (2023)

National Institutes of Health

- Inclusion of **Women and Minorities** in Clinical Research Policy (1986)
- NIH Policy and Guidelines on the Inclusion of **Women and Minorities** as Subjects in Clinical Research (1994, update 2001)
- NIH Policy and Guidelines on the Inclusion of **Children** as Subjects in Clinical Research (1998, update 2017)
- NIH Policy and Guidelines on the Inclusion of **Individuals Across the Lifespan** as Participants in Research Involving Human Subjects (2017)

National Council on Disabilities

- National Council on Disabilities - The Implicit and Explicit Exclusion of People with Disabilities in Clinical Trials (2024)
  - FDA and HHS should develop guidance on eligibility parameters for investigators:
    - Aim to reduce subjectivity in eligibility criteria to eliminate PI bias and participant selection.
    - Provide robust eligibility criteria for protocol teams to access to determine decision making capacity decisions.
    - Broaden inclusion criteria to avoid unnecessary exclusion.
    - Recommend acceptable accommodations be incorporated into inclusion criteria to reduce subjective assessment of a permissible accommodation.
    - Recommend all exclusion criteria be scientifically justified.
    - Recommend inclusion of PWDs in patient advisory boards.

Source: NCD (2024)

Secretary's Advisory Committee on Human Research Protections

- **Considerations for the Design, Review, and Conduct of LGBTQI+ Research**
  - When designing and conducting research involving LGBTQI+ participants, it is essential to incorporate LGBTQI+ considerations into every aspect of the study. SACHRP's recommendations include:
    - Access and Inclusion: Develop and evaluate recruitment plans that promote the representation of LGBTQI+ participants. This involves tailoring recruitment materials and outreach efforts to be inclusive and culturally appropriate.

Source: SACHRP (2024)

Food and Drug Administration

- Regulation of food, **drugs, biologics, medical devices**, electronic products that give off radiation, cosmetics and veterinary products.
  - Review the data submitted related to a drug or device and decide to approve or not
  - All clinical trials regardless of funder submitted with marketing application

Food and Drug Administration

- General Considerations for the Clinical Evaluation of Drugs (1977, withdrawn 1993)
- Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications (1988)
- Guideline for the Study of Drugs Likely to be Used in the Elderly (1989)
- Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs (1993)

Source: NAS (2022)

Food and Drug Administration

- Revision of New Drug Application, Demographic Rule (1998)
- Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials (2018)
- Action Plan to Enhance Collection and Availability of Demographic Subgroup Data (2014)
- Evaluation and Reporting of Age-, Race- and Ethnicity-Specific Data in Medical Device Studies (2017)

Source: NAS (2022)

Food and Drug Administration

- Enhancing the Diversity of Clinical Trial Populations- Eligibility Criteria, Enrollment Practices and Trial Designs Guidance for Industry (2020)
  - Some attention to inclusion of people with disabilities
  - Little attention to inclusion of sexual minorities

Source: NAS (2022)

Food and Drug Administration

- DRAFT - Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies (2024)

Table 1. Enrollment Goals Disaggregated by Race, Ethnicity, Sex, Age Group (Summary)

Enrollment goals must be disaggregated by:[47]

- Race (sponsors should list goals for each category according to FDA guidance for reporting race)[48]
- Ethnicity (sponsors should list goals for each category according to FDA guidance for reporting ethnicity)[49]
- Sex (sponsors should list goals for each category according to FDA guidance for reporting sex)[50]
- Age group (sponsors should list goals for clinically relevant age subsets according to FDA guidance)[51]

"…However, FDA recognizes the broader issues regarding health disparities and differential access to health care and clinical studies that may occur based on other factors, including but not limited to geographic location, **gender identity, sexual orientation**, socioeconomic status, **physical and mental disabilities**, pregnancy status, lactation status, and co-morbidity."

Source: FDA (2024)

Other Players

- Government Accounting Office
- National Academy of Sciences


QUESTIONS