

Randomized Controlled Trials (RCTs): Ethics and Feasibility

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Outline

- 1 Ethics and Feasibility of RCTs
- 2 External Validity, Generalizability, and Interpretability
- 3 Challenges of Understanding Society
- 4 Today's Opportunities and Challenges
- 5 This Week's Readings

Brief History of Ethics of Human Experimentation

MEDICAL NEWS

33

WMA's Declaration of Helsinki Serves as Guide to Physicians

Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.

5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

- Nuremberg Code, 1947
- Declaration of Geneva, 1948
- **Declaration of Helsinki, 1964**
- Revelations in the 1960s and 1970s: Willowbrook State School and Tuskegee syphilis study
- **Belmont Report, 1978**
- U.S. Common Rule, 1981
- IRBs, FDA, **NIH principles** and enforcement

Respect for Persons

Informed Consent

Participants must be able to:

- ① freely consent to participating,
- ② choose to stop participating at any time, and
- ③ understand the goals of the experiment and their role in it.

Equipoise

Clinical Equipoise

There must be genuine uncertainty about which arm is better for the patients involved. A valid scientific question must be asked and there must be knowledge that can be gained from the research.

Other Justifications for Randomization

Besides equipoise, there can be other justifications used for randomization (especially outside of medical trials):

- Limited resource availability
- Necessity for gathering information/improving implementation and quality
- Investigator (or funder) preference

Beneficence

Primum non nocere

Do no harm. Maximize potential benefits (to research participants and society) and minimize potential risks (to research participants and society).

Justice

Research Justice

There should be reasonable, non-exploitative, well-considered procedures administered fairly. Potential benefits and risks should be distributed fairly across all parties as much as possible.

Whose Ethics?

These are principles that (at least in theory) guide human experimentation in much of the world, especially the U.S. and Western Europe. But that does not mean they are the **right** or **only** ethical considerations.

Feasibility, Resources, and Ethics

- Is the ethical study feasible?
- Is the feasible study ethical?
- Is this an ethical use of resources? Is it statistically sound?

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Generalizability

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[← Home](#) / [Science & Research](#) / [Science and Research Special Topics](#) / [Real-World Evidence](#)

Real-World Evidence

<https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence>

Is the sample of participants representative of the target population?

- Inclusion/exclusion criteria
- Self-selection into study sample
- Generalizability of the intervention: acceptability and feasibility in routine practice
- Can a controlled experiment ever represent the real world?

Efficacy vs. Effectiveness

Definitions

Efficacy is often used to refer to the outcome measure from a clinical trial: the well-controlled measure of cause and effect. **Effectiveness** is used to refer to the real-world effect, accounting for imperfect implementation, a different mix of patients and conditions, counterbalancing effects, etc.

See this *Washington Post explainer* for an explanation in the context of COVID-19 vaccines.

Interpretability

Are the results **interpretable** to the target audience? Do they generate significant understanding of the world? Do they point the way to a potential action to improve outcomes?

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Addressing Ethical or Logistical Limitations

Question

What are our options if the ideal RCT is unethical or infeasible?

Addressing Ethical or Logistical Limitations

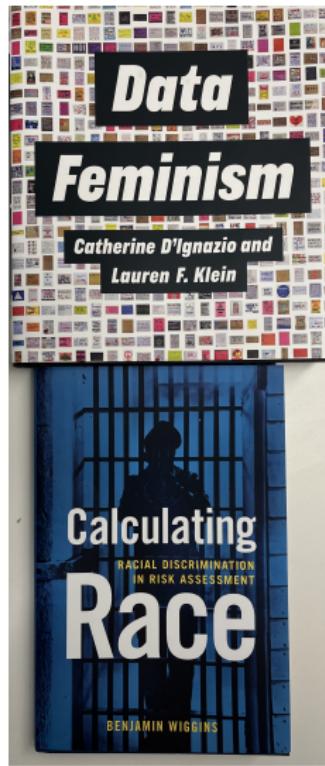
- Change the intervention
- Change the outcome
- Change the study population
- Find a “natural experiment” where the intervention is randomized for another reason
- Conduct an observational study

Addressing Ethical or Logistical Limitations

- Change the intervention (risk to consistency and generalizability)
- Change the outcome (risk to internal validity and generalizability)
- Change the study population (generalizability lost)
- Find a “natural experiment” where the intervention is randomized for another reason (hard to identify)
- Conduct an observational study (exchangeability lost)

What Are We Measuring?

- Race ≈ genes, ethnicity, social class, culture, effect of others' perceptions
- Gender ≈ sex chromosomes, hormones, gender identity, gender expression, effect of others' perceptions
- “Socioeconomic status” ≈ wealth, income, education, neighborhood, family background, race, etc.



What Are We Comparing?

Infeasible/unethical

We can't generally randomize or assign race, gender, education, "class", background, etc.

WHAT DO WE MEASURE WHEN WE MEASURE RACE?

Camara Jones, *American Journal of Epidemiology*, 2001

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Camara Jones, *American Journal of Epidemiology*, 2001

- We affect the *perception* of one of those
- We affect income or wealth in a narrow, short-term way
- We randomize an incentive to change something (e.g., neighborhood)

What Are We Controlling?

"Race," Racism, and the Practice of Epidemiology 301



FIGURE 1. The impacts of racism on health, illustrating the relation between institutionalized racism, personally mediated racism, and internalized racism and various factors that contribute to race-associated differences in health outcomes. SES, socioeconomic status.

Camara Jones, *American Journal of Epidemiology*, 2001

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- We can't control or adjust for most of these factors
- What we do control for reveals what we consider "extraneous" to the main question and risks diluting the effect
- Some take the view that causal inference on "non-modifiable factors" is meaningless

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Where Do We Go From Here?

- The most interesting questions are the most challenging to answer!
- We must show humility in our interpretations.
- Data-gathering is no substitute for other sources of knowledge-making.

Where Do We Go From Here?

Megan T. Stevenson, *BU Law Review*, 2023

That being said, the constraints that remain appear to be deep, structural, and hard to shift. That doesn't mean they are immovable, but just that they usually aren't moveable with the type of intervention evaluable via RCT. As for how to move them—I don't know. Moreover, I don't think we *can* know, or at least not with the high levels of confidence promised by the engineer's view. We will proceed, but must do so with the humility of uncertainty.

Challenges: Research Ethics in 21st Century

EDUCATION

Harvard professor who studies dishonesty is accused of falsifying data

JUNE 26, 2023 · 1:15 PM ET

 Juliana Kim

[109] Data Falsificada (Part 1): "Clusterfake"



Posted on June 17, 2023 by Uri, Joe, & Leif

This is the introduction to a four-part series of posts detailing evidence of fraud in four academic papers co-authored by Harvard Business School Professor Francesca Gino.

The Stanford Daily

Stanford president resigns over manipulated research, will retract at least three papers

More: Toxic fatigue failed to address manipulated papers, fostered unhealthy lab dynamic, Stanford report says.



Washington Post photo of Mark Tessier-Lavigne, former Stanford president, that went viral on the internet. Photo: AP/STANFORD UNIVERSITY

By Steve Baker
Jun 16, 2023 10:00 AM

Andrew Lawrence

 @by_drew
Sat 6 Jan 2024 11:00 EST

Harvard's Claudine Gay was ousted for 'plagiarism'. How serious was it really?

Gay resigned amid claims of plagiarism, but was it the person being accused rather than the violation itself that brought about her downfall?

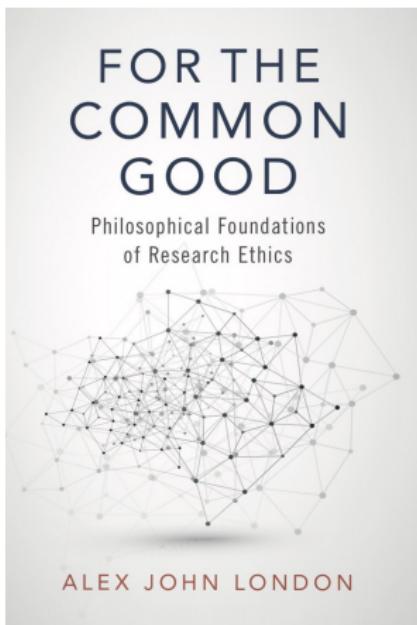


AP Handout photo of Claudine Gay, resigned on 2 January. Composite: Reuters

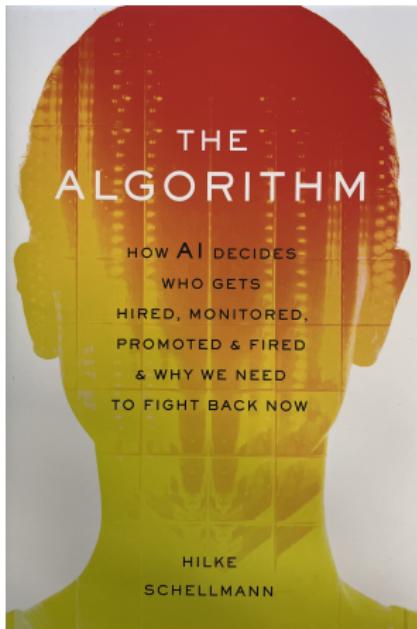
- P-Hacking
- Publication bias
- Fabricated data or analysis
- Plagiarism/AI use

Challenges: RCT Ethics in 21st Century

- Acceptable/unacceptable risks
- Costs/rewards/incentives of trials
- Publishing, reporting, and confidence
- Generalizability and representativeness
- Research justice



Challenges: Data Ethics in 21st Century



- Data dominance
- “Objective” veneer on subjective decisions
- Garbage in = Garbage out
- Non-transparency
- Who bears responsibility?

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Consider While Reading

- What is the scientific question of interest? How do you think that was shaped by the available data/the feasibility of the experiment?
- What are the interventions? Do they reflect real-world interventions? Are they chosen by the question of interest or by convenience?
- What is the purpose of randomization and (if any) blinding in these studies? What biases are reduced? What is lost by randomizing/blinding?
- What particular ethical considerations arise with these interventions/outcomes/populations?