The Complicated Role of the Clinician-Investigator

Steven Joffe, MD, MPH

Art and Ilene Penn Professor
Interim Chair
Department of Medical Ethics and Health Policy

Perelman School of Medicine
University of Pennsylvania

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Disclosures

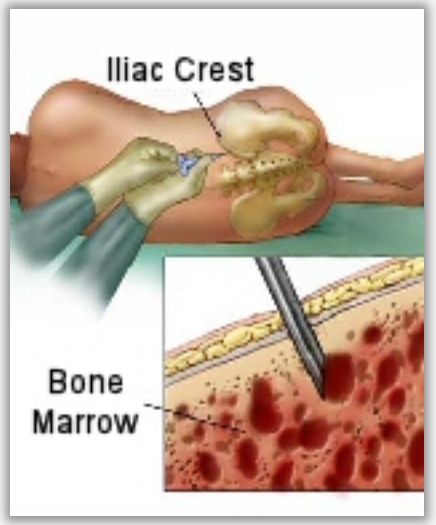
- I received research support from Pfizer through May 2020
- I will not be discussing unapproved uses of medical products

Objectives

1. Describe the historical roots of the investigator-participant relationship
2. Explain the therapeutic orientation to clinical research and its problems
3. Define an ethics of the investigator-participant relationship grounded in the ethics of science and the moral status of persons

A case

- In the 1990s, at Dana-Farber Cancer Institute, children with acute lymphoblastic leukemia (ALL) received one month of intensive “induction” followed by 2 years of maintenance chemotherapy
  - Question: does detection of microscopic “minimal residual disease” during remission identify children at high risk of relapse?
  - Research intervention: screening bone marrow aspirate every 4 months during maintenance chemo
  - How should we think about the ethics?



An irresponsibly brief history of ethics of human experimentation

Early history focused on (usually healthy) “volunteers” participating in research without a prospect of direct benefit

Starting in late 1940s, physicians, investigators, & policymakers recognized need for an ethics of research with sick patient-participants

- Especially research with potential to benefit participants

Nuremberg Code (1947)

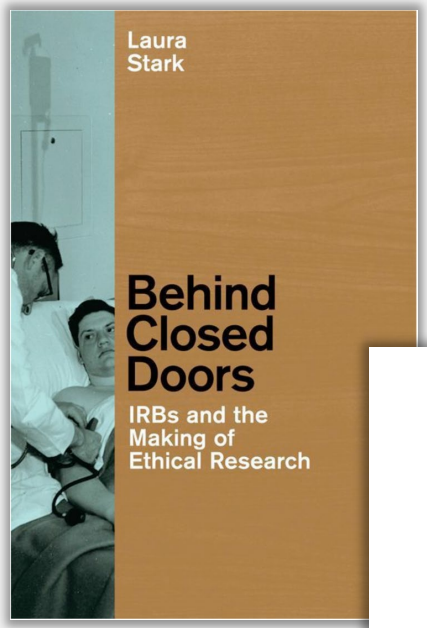
Response to atrocities conducted by physician experimenters in the Nazi concentration camps

Code implicitly applies to experiments (performed on volunteers) that lack the prospect of benefit to participants

Experiments at NIH Clinical Center

Opened in 1953

- Needed volunteers for experiments
- Found source in conscientious objectors to military service, especially members of peace churches



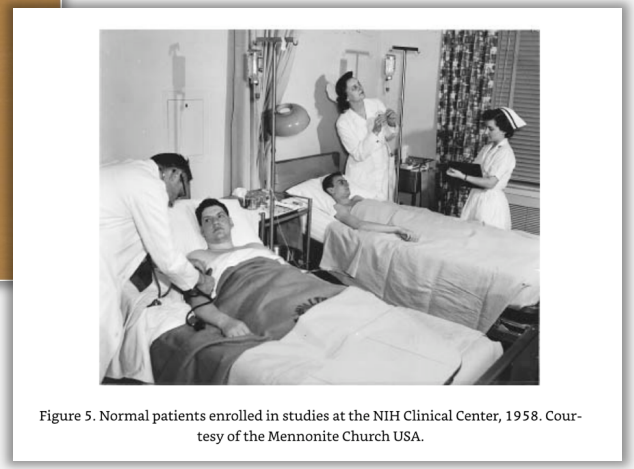


Figure 5. Normal patients enrolled in studies at the NIH Clinical Center, 1958. Courtesy of the Mennonite Church USA.

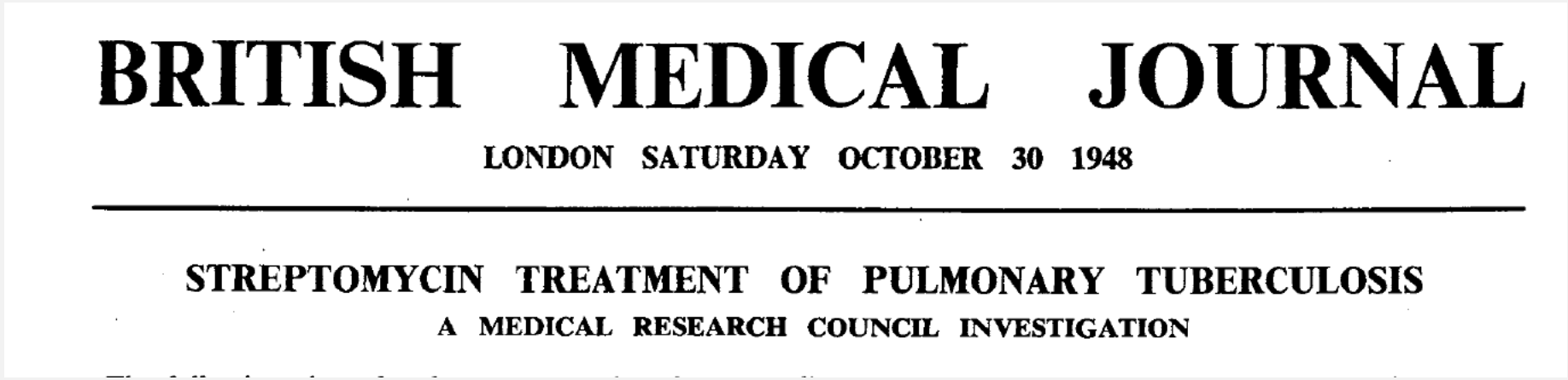
Laura Stark, *Behind Closed Doors.* Chicago:U. Chicago Press, 2012

Increasing consciousness, starting in late 1940s, of the need for an ethics of research involving sick patients

- Advent of randomized controlled trials
- Regulatory requirement to demonstrate efficacy of new drugs
- Declaration of Helsinki

Why does this matter?

Pure experiments in volunteers	Efficacy trials in sick patient-participants
• No prospect of direct benefit • Clear distinction between clinician-patient and investigator-participant relationships	• Prospect of benefit • Blur distinction between clinician-patient and investigator-participant relationships



BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

107 patients with pulmonary TB randomized to streptomycin + bedrest vs. bedrest alone

- 6-month mortality 7% vs. 27%

Regulatory requirement for evidence of drug efficacy

1962 Kefauver-Harris Amendment to the Federal Food, Drug, and Cosmetics Act of 1938

- Response to thalidomide tragedy
- Required that “evidence of effectiveness be based on adequate and well-controlled clinical studies conducted by qualified experts”
- Required that participants give informed consent

https://www.fda.gov/about-fda/histories-product-regulation/promoting-safe-effective-drugs-100-years

Declaration of Helsinki (orig. 1964)

Promulgated by the World Medical Association

Grounds ethics of research in the ethics of the doctor-patient relationship

- “It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of this mission”
- “The Declaration of Geneva of the World Medical Association binds the doctor with the words, “The health of my patient will be my first consideration”…

Randomized controlled trials pose a paradigmatic ethical challenge

In ordinary care…

- clinicians use their clinical judgment when recommending treatment to patients (“personalized care”)
- clinicians don’t withhold treatments that they believe might be advantageous to patients
- clinicians don’t use placebos
- clinicians don’t blind themselves & their patients to what the patient is receiving

Randomized clinical trials are “of mice but not men”

“the physician must produce unswervingly the virtues of loyalty and fidelity to his patient” (quoting Leon Kass)

Physician cannot simultaneously be a fiduciary for the patient while aiming at knowledge to benefit future patients

“Techniques appropriate to the laboratory may not be applicable to humans. We must develop and use alternative methods for acquiring clinical knowledge.”

NEJM 324:1585, 1991

Reconciling the methodology of RCTs with physicians' obligations to their patients

Benjamin Freedman's solution: "clinical equipoise"

- boundaries of acceptable clinical practice define whether RCT is ethical or not

NEJM 317:141, 1987

Reconciling the methodology of RCTs with physicians' obligations to their patients

Logic of Freedman's argument

- Physicians' treatment of their patients must remain within the bounds of acceptable medical practice
- The community of expert physicians defines the boundaries of acceptable medical practice
- So long as all treatments within an RCT are consistent with acceptable medical practice, physicians may participate

NEJM 317:141, 1987

But research and care fundamentally differ…

The Belmont Report (1979)

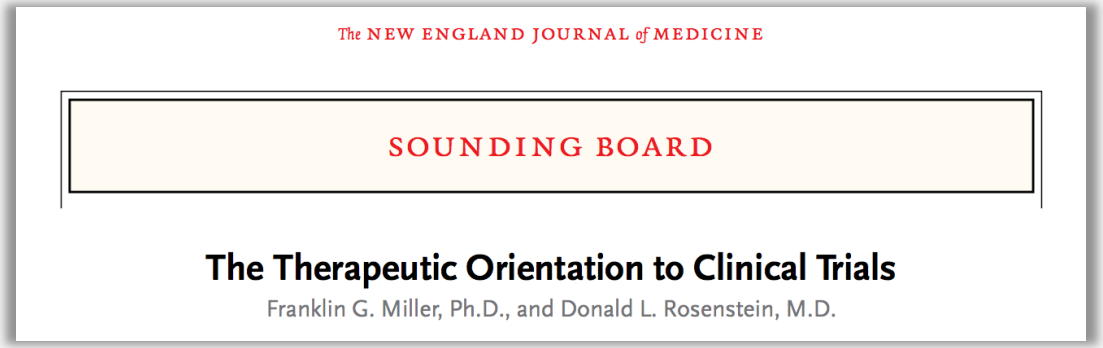
- “For the most part, the term ‘practice’ refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals.”

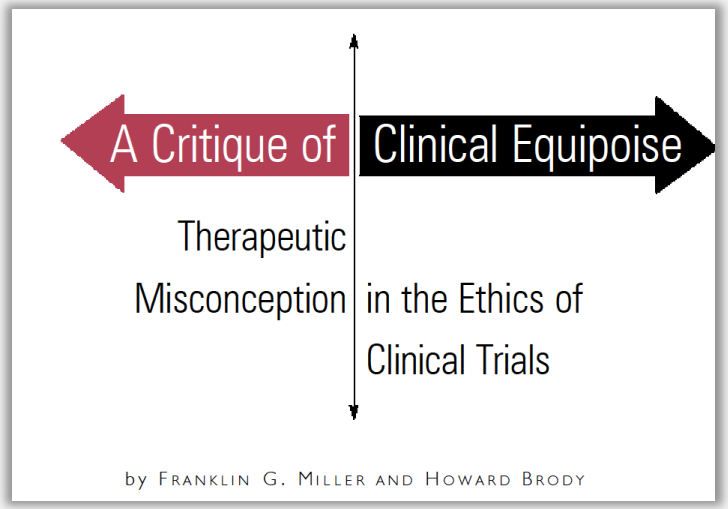
But research and care fundamentally differ…

The Belmont Report (1979)

- "For the most part, the term 'practice' refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term 'research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge…"

…and so the investigator-participant and clinician-patient relationships must differ too





JAMA 280:1449, 1998
Hastings Cent Rep 33(3):19, 2003
NEJM 348:1383, 2003

…and so the investigator-participant and clinician-patient relationships must differ too

Pervasive therapeutic orientation to clinical trials (the conventional view) leads to ethical problems

- Impedes informed consent by promoting therapeutic misconceptions
- Obscures the inherent conflicts between the pursuit of science and the protection of participants
- Interferes with investigators' ability to develop a sense of professional integrity

NEJM 348:1383, 2003

…and so the investigator-participant and clinician-patient relationships must differ too

"To avoid exploitation and misplaced trust, an investigator approaching a patient about enrollment in a study should describe his or her own role as primarily that of a scientist in pursuit of knowledge aimed at improving medical care for future patients, rather than as that of a personal physician dedicated to promoting the individual patient's health. Making the relationship with patient-subjects a partnership in pursuit of science will require positive efforts on the part of physician-investigators to counteract therapeutic misconceptions about clinical trials."

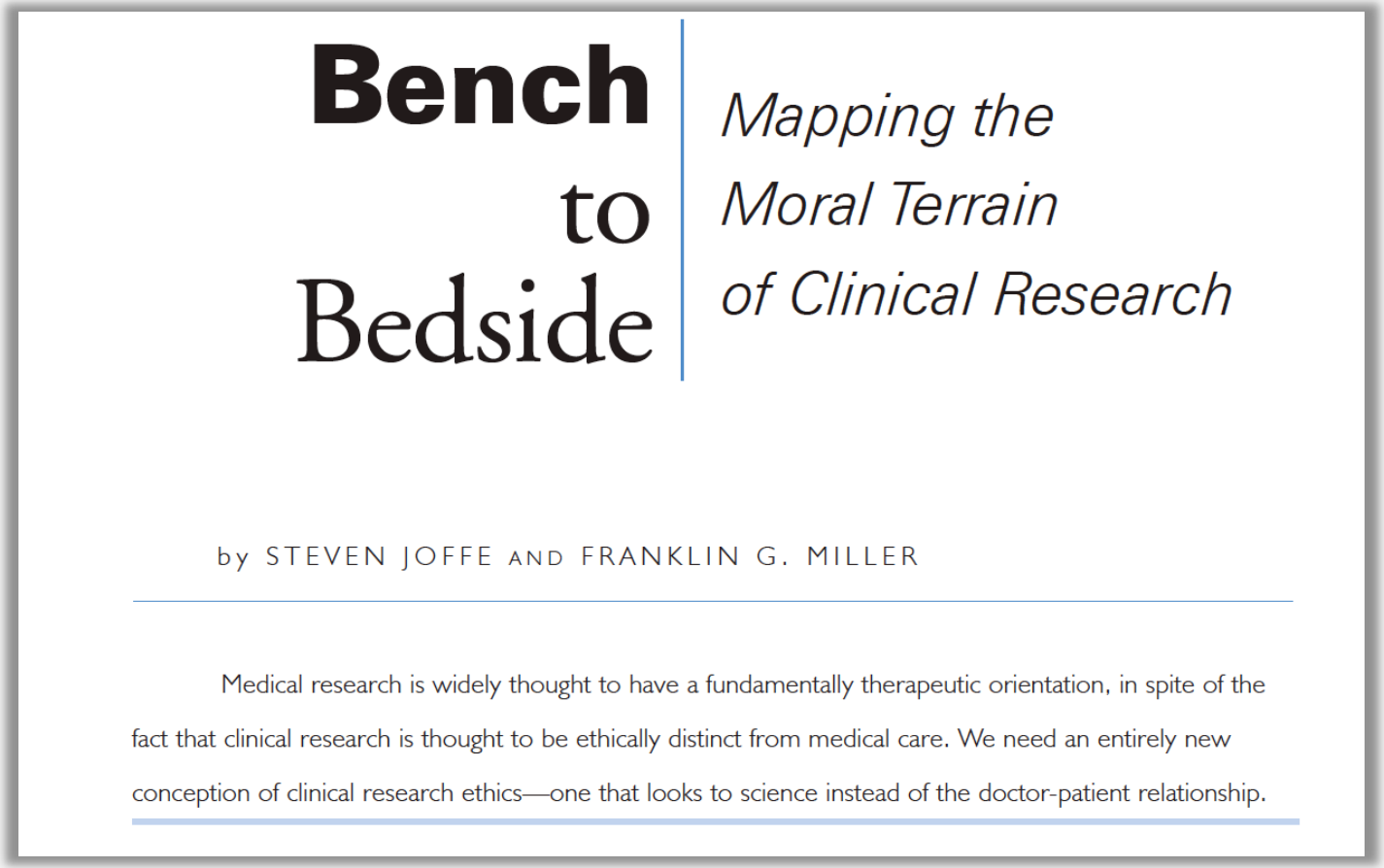
NEJM 348:1383, 2003

Reconceptualizing the investigator-participant relationship

Conventional view starts from the foundation of the clinician-patient relationship, modified (within limits) to fit the demands of research

If the conventional view is wrong, we need a rich, comprehensive alternative framework that specifies the obligations of investigators to their patient-participants

A bench-to-bedside approach



Bench to Bedside

Mapping the Moral Terrain of Clinical Research

by STEVEN JOFFE AND FRANKLIN G. MILLER

Medical research is widely thought to have a fundamentally therapeutic orientation, in spite of the fact that clinical research is thought to be ethically distinct from medical care. We need an entirely new conception of clinical research ethics—one that looks to science instead of the doctor-patient relationship.

Hastings Cent Rep 38(2):30, 2008

A bench-to-bedside approach

Three domains characterize ethical biomedical science

- Goals and objectives
- Internal norms
- Ethical constraints

Hastings Cent Rep 38(2):30, 2008

A bench-to-bedside approach

Goals and objectives

- Add to the stock of valid generalizable knowledge
- Relevant in some way to human health and disease
- ~$43 billion FY21 NIH budget signifies extent of our public commitment to this goal

Hastings Cent Rep 38(2):30, 2008

A bench-to-bedside approach

Internal norms

- Adherence to the scientific method
  - E.g., specify question or hypothesis, intervention under study, experimental materials and conditions, outcomes and methods for measuring them
- Adherence to the norms of scientific integrity
  - Avoid fabrication, falsification, and plagiarism
  - Attribute credit, ensure fairness in peer review, etc.

Hastings Cent Rep 38(2):30, 2008

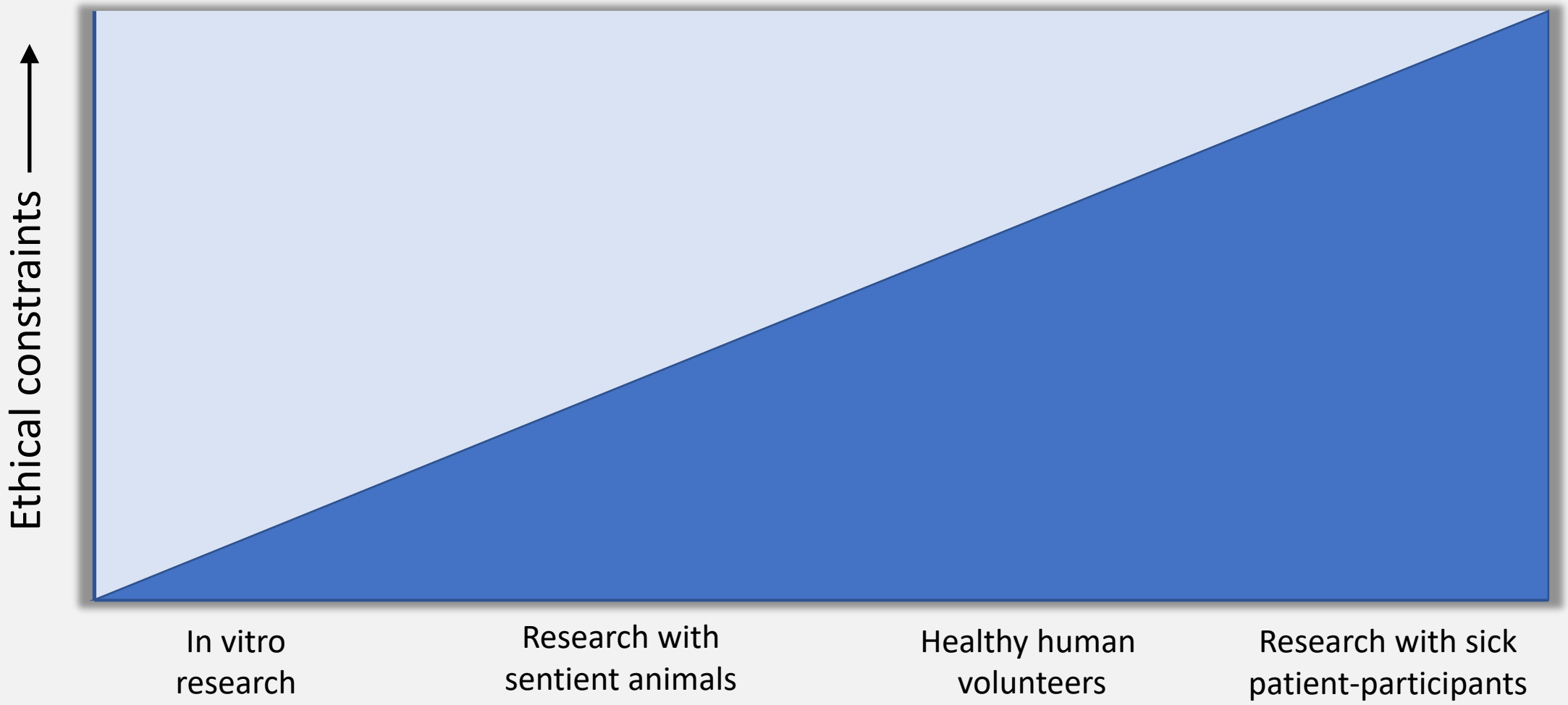
A bench-to-bedside approach

Ethical constraints

- Exist even for the most basic *in vitro* work
  - E.g., safety of research personnel & surrounding communities
  - E.g., ensure beneficent use
- Increase in number & rigor as you move from *in vitro* work→ research with sentient animals→non-patient volunteers→sick patient-participants

Hastings Cent Rep 38(2):30, 2008

A bench-to-bedside approach: ethical constraints



A bench-to-bedside approach

Ethical constraints on research with sentient animals

- All constraints on *in vitro* research, plus
- Minimize risk, burden, harm, etc. for animal subjects
  - *Reduce* number of animals
  - *Refine* procedures to minimize pain etc
  - *Replace*, whenever possible, with *in vitro* models or less sentient animals
- Independent review of research (i.e., IACUCs)

Hastings Cent Rep 38(2):30, 2008

A bench-to-bedside approach

Ethical constraints on research with healthy human volunteers

- All constraints on animal research, plus
- Avoid unacceptable levels of risk
- Uphold respect for persons, e.g., informed consent, privacy
- Ensure fairness in subject selection (justice)
- Satisfy ancillary care obligations
- Fairly compensate participants

Hastings Cent Rep 38(2):30, 2008

A bench-to-bedside approach

Ethical constraints on research with sick patient-participants

- All constraints on research with healthy human volunteers, plus
- Minimize risks associated with withholding/deferring therapy
- Maximize potential for direct benefit (consistent with achieving aims of the study)
- Ensure honesty regarding nature of participation in research
- Adopt caring attitude that acknowledges status as ill persons

Hastings Cent Rep 38(2):30, 2008

Virtues of the bench-to-bedside approach

Represents a single comprehensive ethical framework for the full spectrum of biomedical research

vs the conventional view, which posits different ethics for animals, human volunteers, and sick patient-participants

- (and fails to recognize any continuity with the ethics of *in vitro* science)

Hastings Cent Rep 38(2):30, 2008

Virtues of the bench-to-bedside approach

Acknowledges that trials are experiments designed to acquire important knowledge

- Avoids erroneous ethical guidance stemming from the conventional view
- Allows clear thinking about placebos, research-specific procedures, and other features of rigorous experiments designed to achieve valid results

Hastings Cent Rep 38(2):30, 2008

Virtues of the bench-to-bedside approach

Clarifies meaning of ethical principles in research vs. clinical care

- e.g., beneficence means different things in the two contexts

Highlights positive as well as negative obligations of investigators

- E.g., maximizing benefits, returning summary results

Promotes ethical honesty & integrity in research

Hastings Cent Rep 38(2):30, 2008

To summarize

- Early conceptions of the investigator-participant relationship envisioned a volunteer in a pure physiology experiment
- Rise of clinical trials conducted in sick individuals led to a therapeutic model rooted in the ethics of the clinician-patient relationship
- Reconceptualizing the investigator-participant relationship as rooted in the ethics of science has many advantages over the therapeutic model

Thank you!

joffes@upenn.edu

@SteveJoffe

Perelman School of Medicine
University of Pennsylvania