Bedside to Bench or Bench to Bedside: The Ethics of the Investigator-Participant Relationship

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Steven Joffe, MD, MPH

Emanuel and Robert Hart Professor

Department of Medical Ethics and Health Policy

Perelman
School of Medicine
University *of* Pennsylvania

Ethical & Regulatory Aspects of Clinical Research
National Institutes of Health
Bethesda, MD
September 26, 2018

Disclosures

- I have no relevant financial relationships to disclose
- 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 but constrained by the moral status of persons

Hastings Cent Rep 38(2):30, 2008

Are you involved in the conduct of clinical trials?

Are you involved in the conduct of scientific experiments?

Elements of a rigorous experiment

Clearly state the question or hypothesis

Identify the intervention under study (the causal agent)

Describe the outcomes and the methods used to measure them

Specify the experimental conditions, including the materials and controls

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 ~1960s, physicians, investigators, & policymakers recognized need for an ethics of research with sick patient-participants

- Especially research with potential to benefit participants

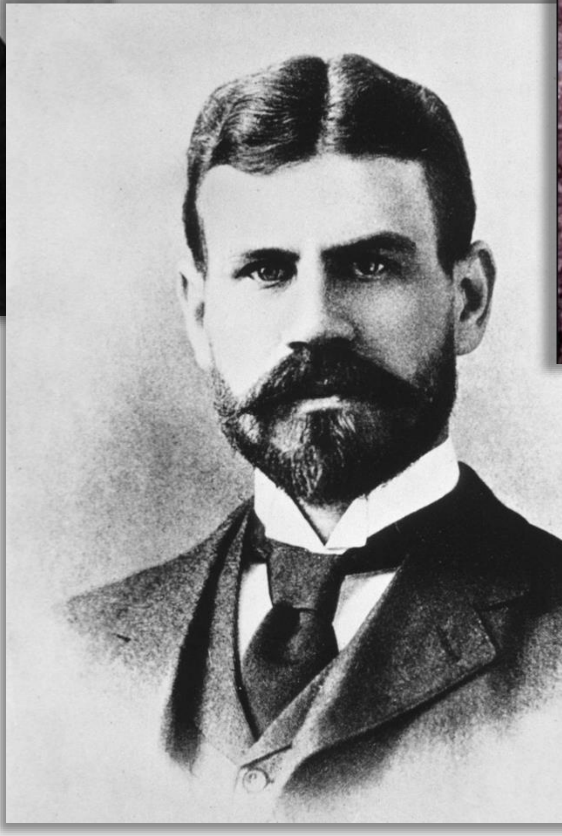
Walter Reed's yellow fever experiments (1900)

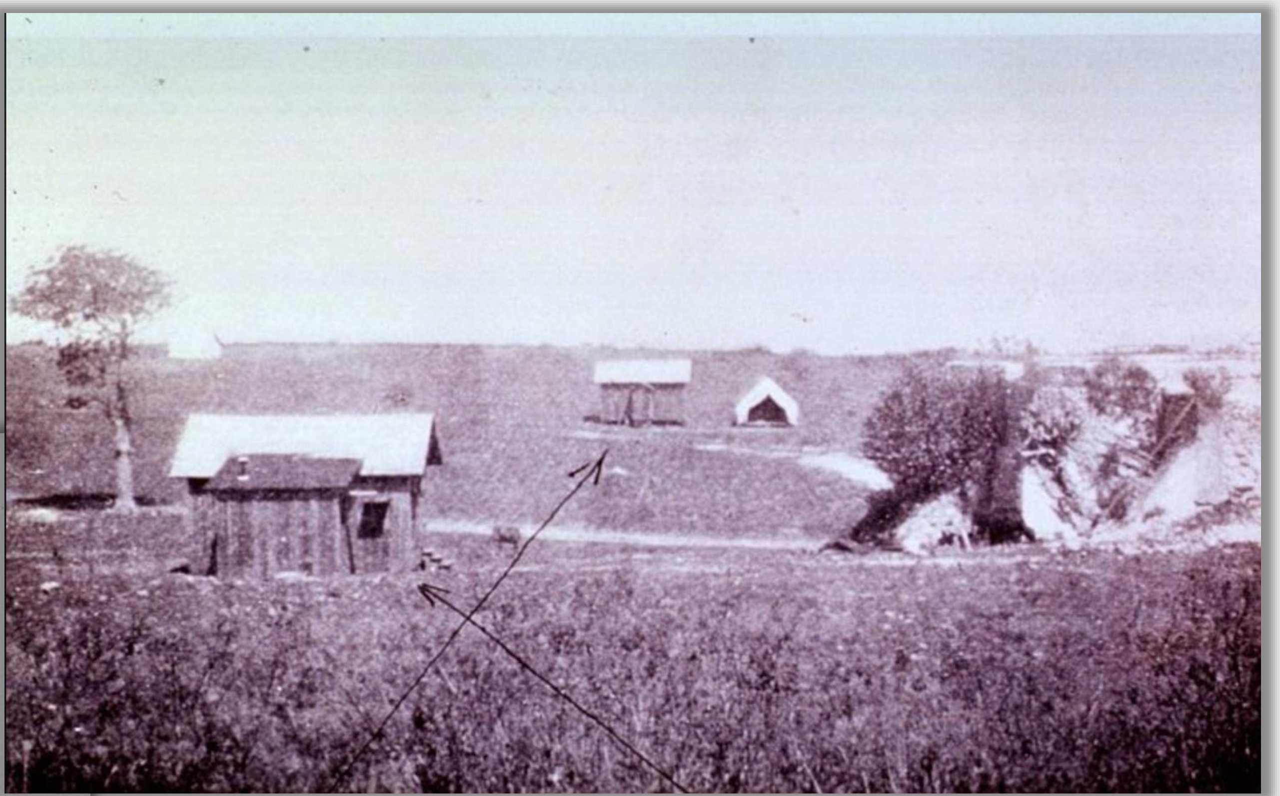
How is yellow fever transmitted?

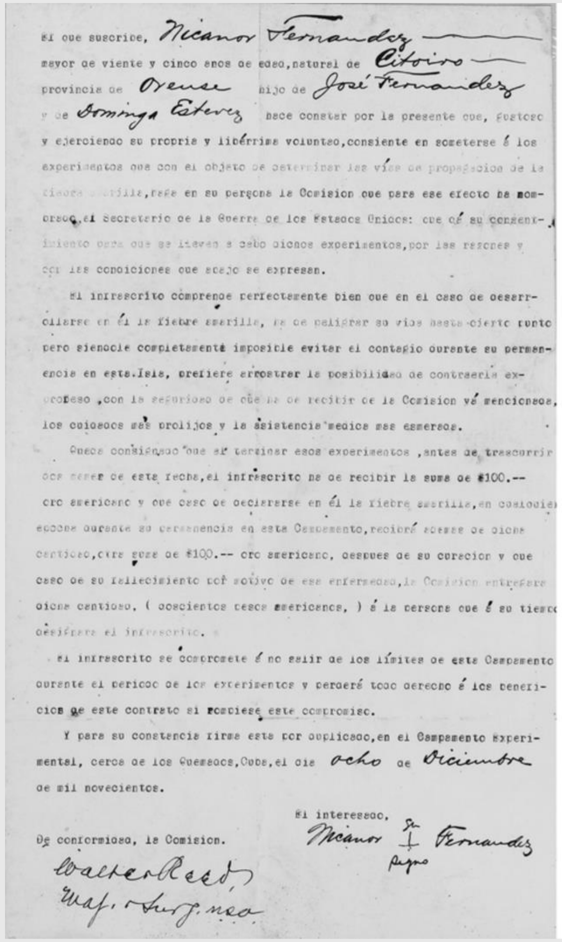
- Fomites (droplets from infected person)?
- Bite of mosquito (Carlos Finlay)?

Reed intentionally exposed volunteers to bites from carrier mosquitos

- Observed for signs of disease
- Innovations included consent and payment







El que suscribe, Nicanor Fernandez mayor de viente y cinco anos de edad, natural de Citoiro provincia de Orense hijo de José Fernandez y de Dominga Estevez hace constar por la presente que, gustoso y ejerciendo su propria y libérrima voluntad, consiente en someterse á los experimentos que con el objeto de determinar las vías de propagación de la fiebre amarilla, haga en su persona la Comision que para ese efecto ha nombrado el Secretario de la Guerra de los Estados Unidos: que dá su consentimiento para que se lleven á cabo dichos experimentos, por las razones y con las condiciones que abajo se expresan.

El infrascrito comprende perfectamente bien que en el caso de desarrollarse en él la fiebre amarilla, ha de peligrar su vida hasta cierto punto pero siendole completamente imposible evitar el contagio durante su permanencia en esta Isla, prefiere arrostrar la posibilidad de contraerla ex-profeso, con la seguridad de que ha de recibir de la Comision yá mencionada, los cuidados más prolijos y la asistencia medica mas esmerada.

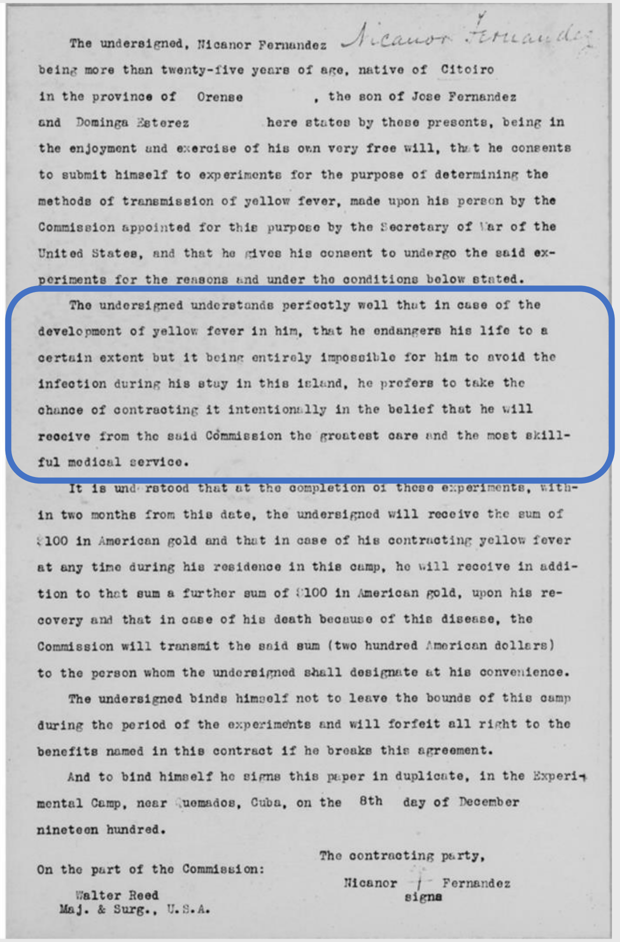
Queda convenido que al terminar esos experimentos, antes de trascurrir dos meses de esta fecha, el infrascrito ha de recibir la suma de $100.-- oro americano y que caso de declararse en él la fiebre amarilla, en cualquie época durante su permanencia en este Campamento, recibirá además de dicha cantidad, otra suma de $100.-- oro americano, despues de su curacion y que caso de su fallecimiento por motivo de esa enfermedad, la Comision entregará dicha cantidad, (doscientos pesos americanos,) á la persona que á su tiemp designare el infrascrito.

El infrascrito se compromete á no salir de los límites de este Campamento durante el periodo de los experimentos y perderá todo derecho á los beneficios de este contrato si rompiese este compromiso.

Y para su constancia firma esta por duplicado, en el Campamento Experimental, cerca de los Quemados, Cuba, el dia ocho de Diciembre de mil novecientos.

El interesado,
Nicanor su + signo Fernandez

De conformidad, la Comision.
Walter Reed,
Maj. & Surg. USA



The undersigned, Nicanor Fernandez Nicanor Fernandez being more than twenty-five years of age, native of Citoiro in the province of Orense, the son of Jose Fernandez and Dominga Esterez here states by these presents, being in the enjoyment and exercise of his own very free will, that he consents to submit himself to experiments for the purpose of determining the methods of transmission of yellow fever, made upon his person by the Commission appointed for this purpose by the Secretary of War of the United States, and that he gives his consent to undergo the said experiments for the reasons and under the conditions below stated.

The undersigned understands perfectly well that in case of the development of yellow fever in him, that he endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his stay in this island, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said Commission the greatest care and the most skillful medical service.

It is understood that at the completion of these experiments, within two months from this date, the undersigned will receive the sum of $100 in American gold and that in case of his contracting yellow fever at any time during his residence in this camp, he will receive in addition to that sum a further sum of $100 in American gold, upon his recovery and that in case of his death because of this disease, the Commission will transmit the said sum (two hundred American dollars) to the person whom the undersigned shall designate at his convenience.

The undersigned binds himself not to leave the bounds of this camp during the period of the experiments and will forfeit all right to the benefits named in this contract if he breaks this agreement.

And to bind himself he signs this paper in duplicate, in the Experimental Camp, near Quemados, Cuba, on the 8th day of December nineteen hundred.

The contracting party,
Nicanor + Fernandez
signs

On the part of the Commission:
Walter Reed
Maj. & Surg., U.S.A.

From: Walter Reed, Yellow Fever, and Informed Consent

Mil Med. 2016;181(1):90-91. doi:10.7205/MILMED-D-15-00430

Nuremberg Code (1947)

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

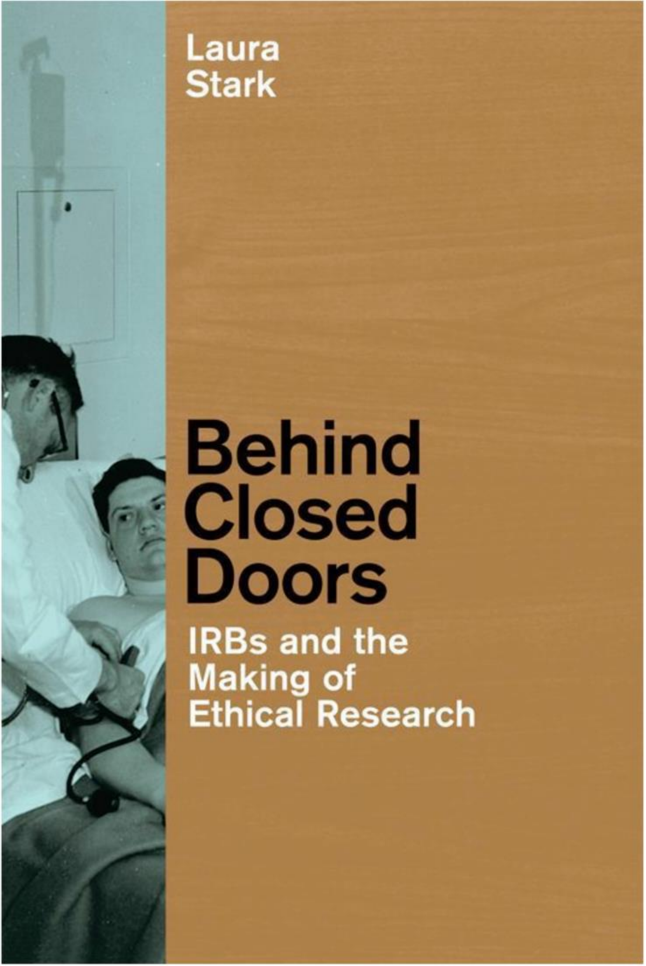
Implicitly applies to experiments, performed on volunteers, that lack the prospect of benefit to participants

Experiments at NIH Clinical Center

Clinical Center opened in 1953

- Needed volunteers for experiments
- Found source in conscientious objectors to military service, especially members of peace churches
- Roots in World War II “Guinea Pig Units”

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



Laura
Stark

Behind
Closed
Doors

IRBs and the
Making of
Ethical Research

Figure 3. Thyroid study on a Mennonite Normal patient at the Clinical Center, 1958. Courtesy of the Mennonite Church USA.

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

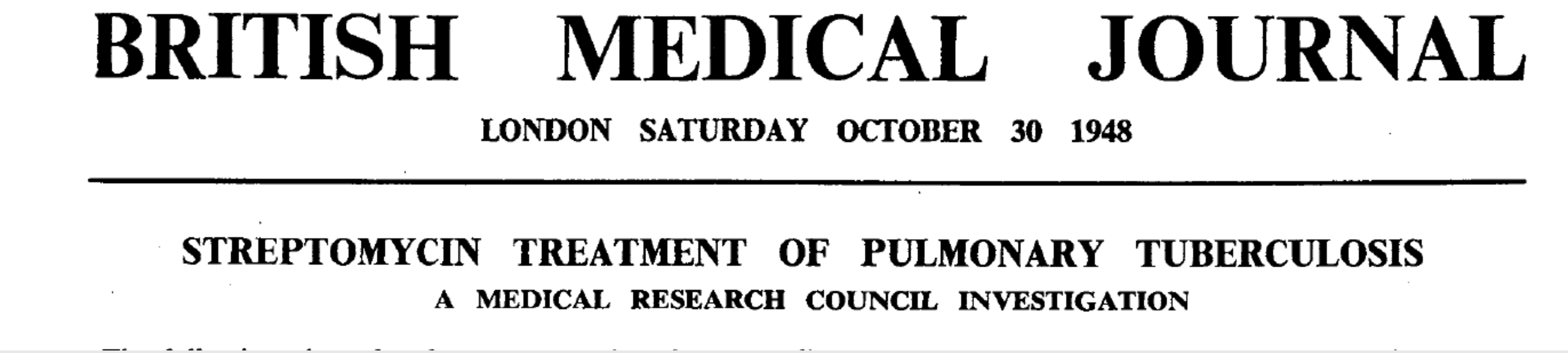
Advent of randomized controlled trials

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	• Prospect of benefit
• Clear distinction between clinician-patient and investigator-participant relationship	• Blurs boundary between clinician-patient and investigator-participant relationship



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%
- “Considerable radiological improvement” in 51% vs. 8%

Regulatory requirement for evidence of drug efficacy

Kefauver-Harris Amendment of 1962 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/ForConsumers/ConsumerUpdates/ucm322856.htm

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"…

The ethical challenge of randomized controlled trials

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)

“The role of the scientist is quite different. The clinical scientist is concerned with answering questions—i.e., determining the validity of formally constructed hypotheses”

“[The goal of the RCT] is not to deliver therapy. It’s to answer a scientific question so that the drug can be available for everybody once you’ve established safety and efficacy” (quoting Tony Fauci)

NEJM 324:1585, 1991

Randomized clinical trials are “of mice but not men”

Conflicts with physicians’ role

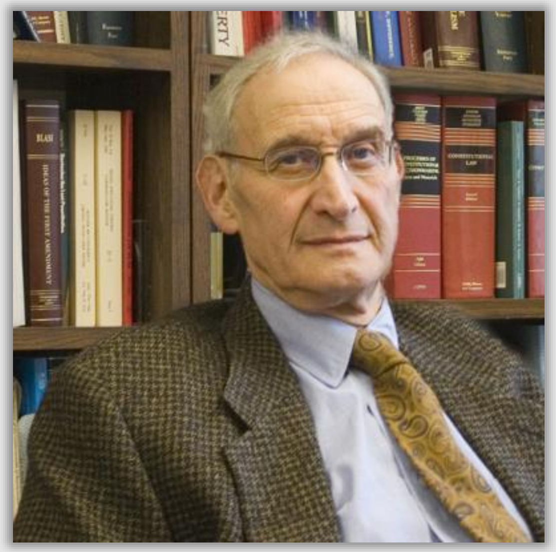
- No role for physicians’ imperfect knowledge
- Can’t modify technique based on evolving information
- Limit physicians’ access to emerging data
- Physician cannot simultaneously be a fiduciary for the patient while aiming at knowledge to benefit future patients
- “Techniques appropriate to the laboratory 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

Charles Fried: physician can ethically participate in an RCT if s/he is personally indifferent between the treatments under study

- Central concern is to preserve personalized care, physician’s fiduciary role



Fried C. Medical experimentation: personal integrity and social policy. NY: American Elsevier Publishing Co., 1974.

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

Benjamin Freedman recognized instability of Fried's answer to the RCT dilemma

- Argued instead that boundaries of acceptable clinical practice define whether RCT is ethical or not
- "clinical equipoise"

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, the physician may participate
    - Even if s/he has a personal preference for one treatment over the other

NEJM 317:141, 1987

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

“There exists…an honest, professional disagreement among expert clinicians about the preferred treatment.”

“At this point…there is no consensus within the expert clinical community about the comparative merits of the alternatives to be tested.”

“A state of clinical equipoise is consistent with a decided treatment preference on the part of the investigators. They must simply recognize that their less-favored treatment is preferred by colleagues whom they consider to be responsible and competent.”

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…

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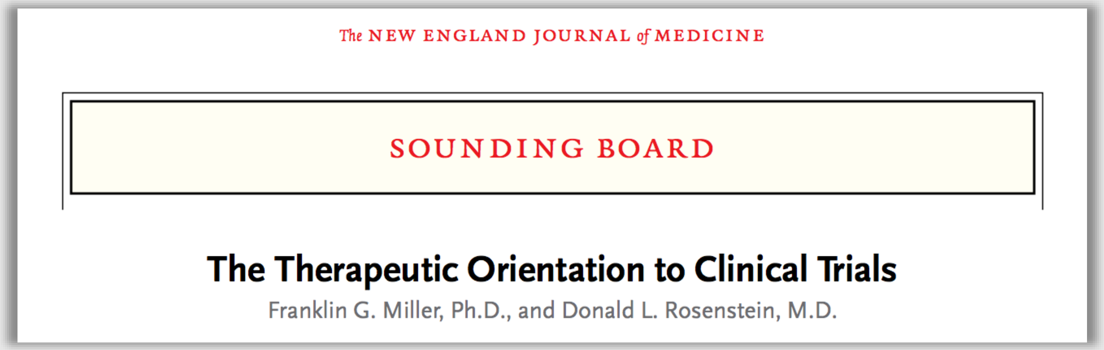
- “For the most part, the term ‘practice’ refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy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

The Patient-Physician Relationship

Professional Integrity
in Clinical Research

Franklin G. Miller, PhD; Donald L. Rosenstein, MD; Evan G. DeRenzo, PhD

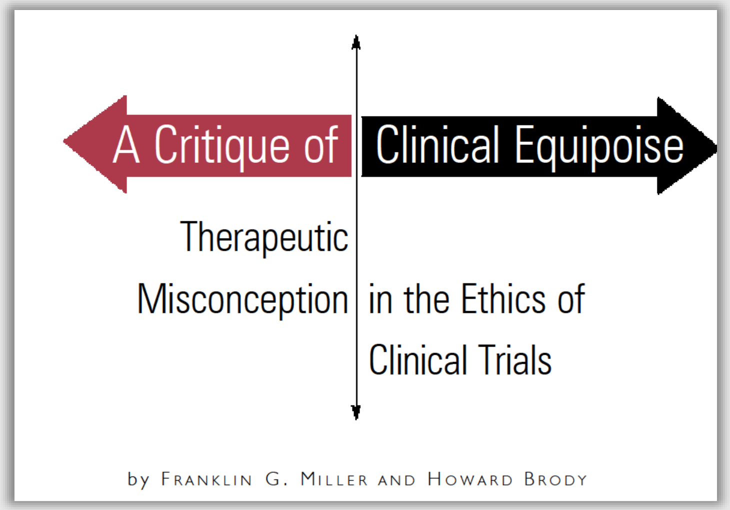


The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

The Therapeutic Orientation to Clinical Trials

Franklin G. Miller, Ph.D., and Donald L. Rosenstein, M.D.



A Critique of Clinical Equipoise

Therapeutic Misconception in the Ethics of Clinical Trials

by Franklin G. Miller and Howard Brody

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
- Blinds investigators to 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

Being simultaneously a clinician & investigator is hard

IRB

ETHICS & HUMAN RESEARCH

SEPTEMBER-OCTOBER 2009 • VOLUME 31, NUMBER 5

Competing Commitments in Clinical Trials

by Charles W. Lidz, Paul S. Appelbaum, Steven Joffe, Karen Albert, Jill Rosenbaum,

Competing Commitments in Clinical Trials

BY CHARLES W. LIDZ, PAUL S. APPELBAUM, STEVEN JOFFE, KAREN ALBERT, JILL ROSENBAUM, AND LORNA SIMON

Being simultaneously a clinician & investigator is hard

We surveyed 1250 contact individuals associated with clinical trials listed on Centerwatch.com

- Response rate 72% (744/1034 with valid email addresses)
- How often have you faced various conflicts between protocol requirements and participants' best medical interests during last 2 years?
    - How did you respond to the conflict?

IRB 31(5):1, 2009

Being simultaneously a clinician & investigator is hard

Conflict	% Experiencing Conflict at Least Once in Prior 2 years	Responses
Patient eligible, not in his/her best medical interest to enroll	70%	- 55% had not offered trial to participant at least once

Being simultaneously a clinician & investigator is hard

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Patient *eligible*, not in his/her best medical interest to enroll	70%	- 55% had not offered trial to participant at least once
Patient *ineligible*, but in his/her best medical interest to enroll	69%	- 22% had recruited at least one ineligible participant

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Protocol prohibited medication that was in participant's best medical interest to receive	52%	• 28% had given restricted medication at least once

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Adjusting dose of study med outside protocol-permitted range was judged to be in participant's best medical interest	48%	- 16% had adjusted med outside permitted range at least once

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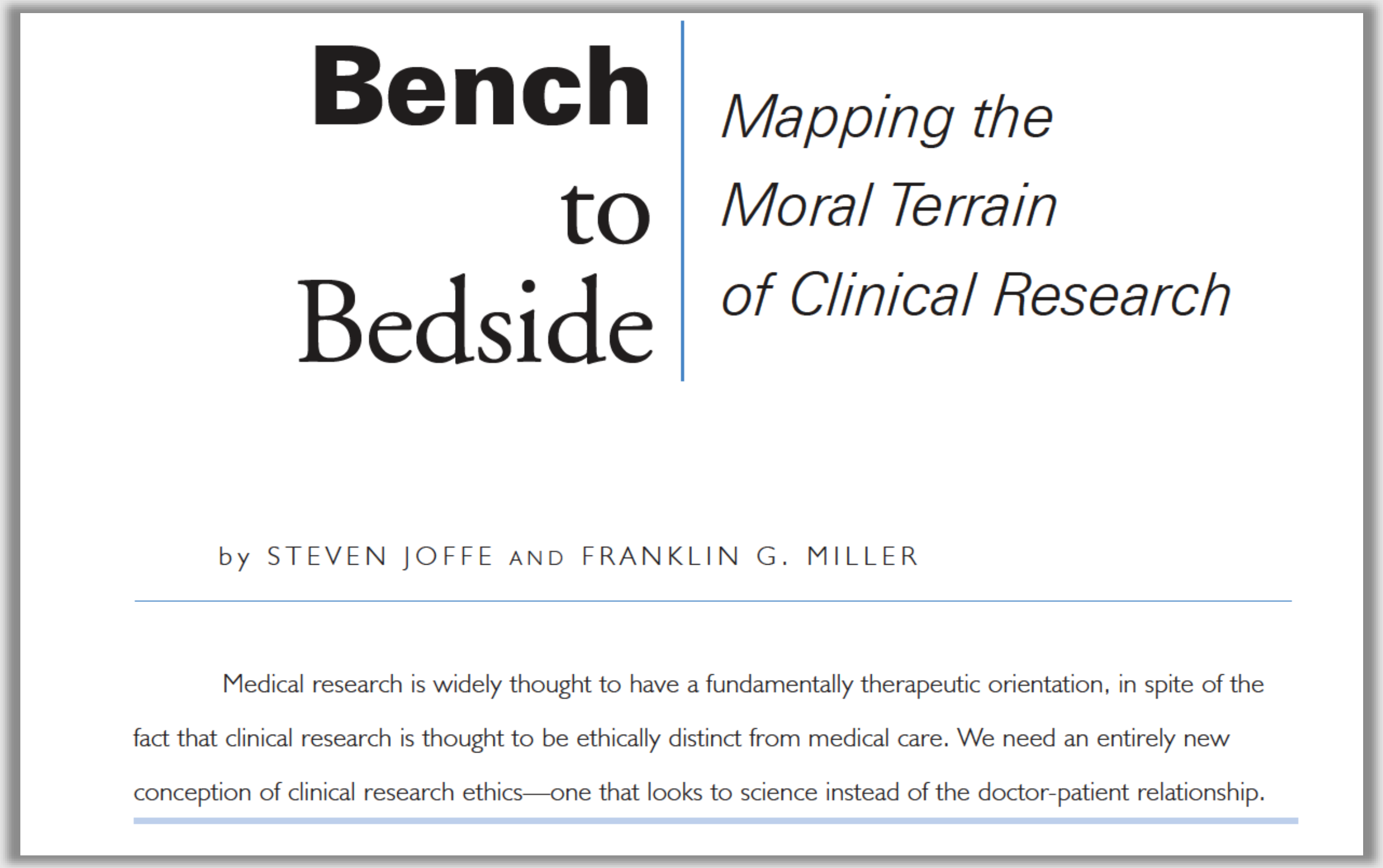
Adjusting dose of study med outside protocol-permitted range was judged to be in participant’s best medical interest	48%	• 16% had adjusted med outside permitted range at least once
Participant met trial termination criteria, but staying in trial was judged to be in his/her best medical interest	36%	• 9% had kept at least one participant in a trial despite their meeting termination criteria

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 store of valid generalizable knowledge
- Relevant in some way to human health and disease
- $34.8 billion NIH budget request for FY2019 signifies extent of our public commitment to this goal

Hastings Cent Rep 38(2):30, 2008

A bench-to-bedside approach

Internal norms

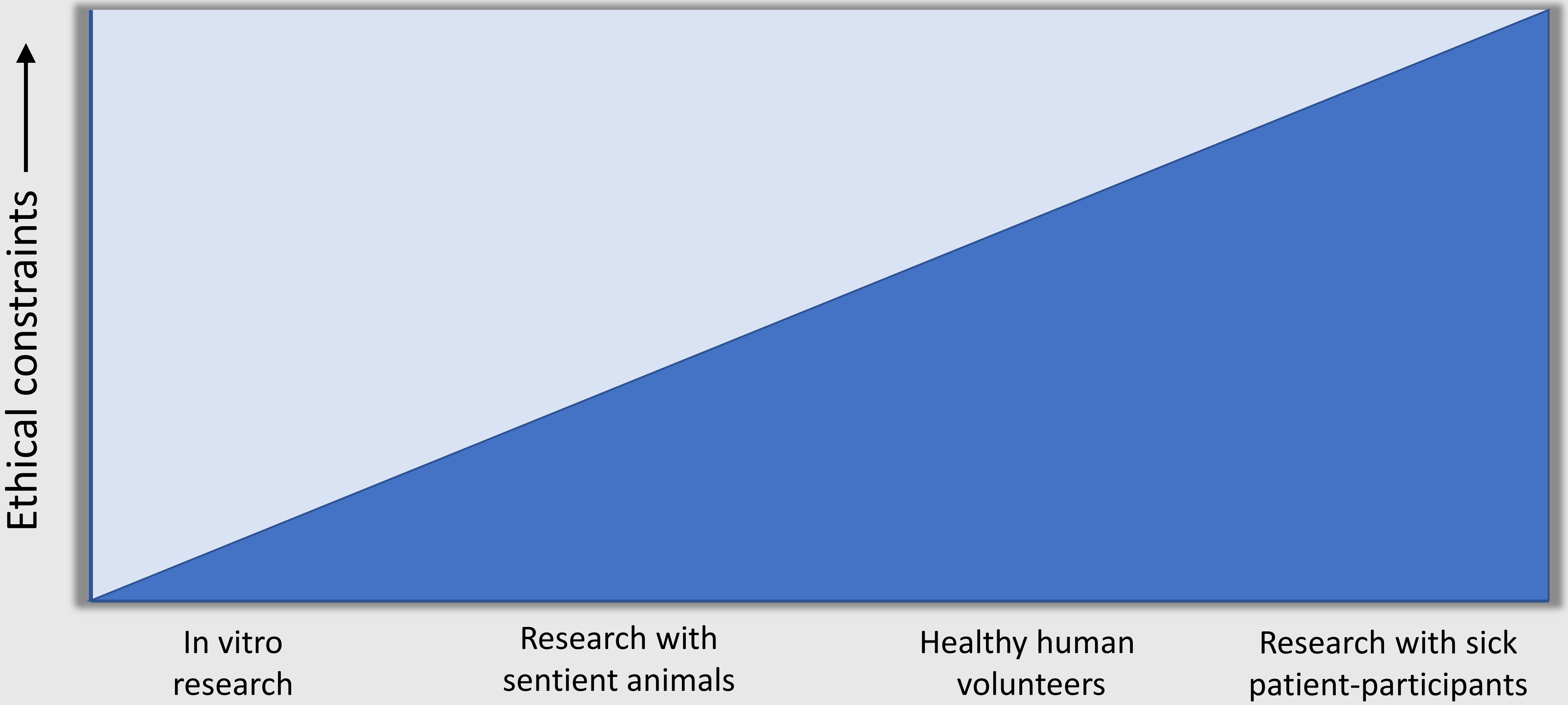
- Adherence to the scientific method
    - E.g., specify question or hypothesis, intervention under study, experimental materials and conditions, outcomes and methods for measuring them
- Adherence to the norms of scientific integrity
    - Avoid fabrication, falsification, and plagiarism
    - Attribute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

Hastings Cent Rep 38(2):30, 2008

A bench-to-bedside approach

Hastings Cent Rep 38(2):30, 2008

A bench-to-bedside approach



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
- Increasingly numerous & rigorous as you move from *in vitro* work→ research with sentient animals→healthy human volunteers→sick patient-participants

Hastings Cent Rep 38(2):30, 2008

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
- 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 relationship to 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

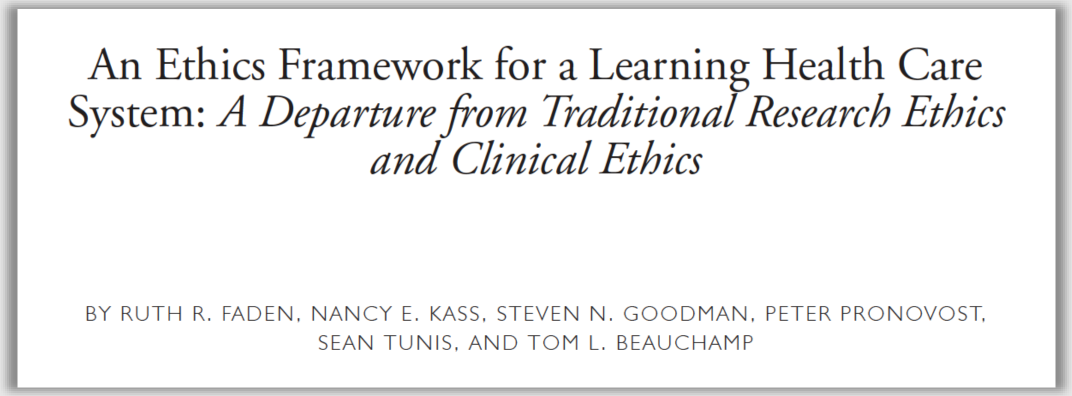
The investigator-participant relationship in the context of the learning healthcare system

Can
RESEARCH
and
CARE
Be Ethically Integrated?

BY EMILY A. LARGENT, STEVEN JOFFE, AND FRANKLIN G. MILLER

The Research-Treatment Distinction:
A Problematic Approach for Determining Which Activities Should Have Ethical Oversight

BY NANCY E. KASS, RUTH R. FADEN, STEVEN N. GOODMAN, PETER PRONOVOST, SEAN TUNIS, AND TOM L. BEAUCHAMP



An Ethics Framework for a Learning Health Care System: *A Departure from Traditional Research Ethics and Clinical Ethics*

BY RUTH R. FADEN, NANCY E. KASS, STEVEN N. GOODMAN, PETER PRONOVOST, SEAN TUNIS, AND TOM L. BEAUCHAMP

Hastings Cent Rep 41(4):37, 2011
Hastings Cent Rep 43(1):S4, 2013
Hastings Cent Rep 43(1):S16, 2013

Thank you!

joffes@upenn.edu

@SteveJoffe

Perelman
School of Medicine
UNIVERSITY of PENNSYLVANIA