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

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Ethical & Regulatory Aspects of Clinical Research
National Institutes of Health
Bethesda, MD
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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 and 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, along with 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 late 1940s, physicians, investigators, & policymakers recognized need for an ethics of research with sick patient-participants

- Especially research with potential to benefit participants

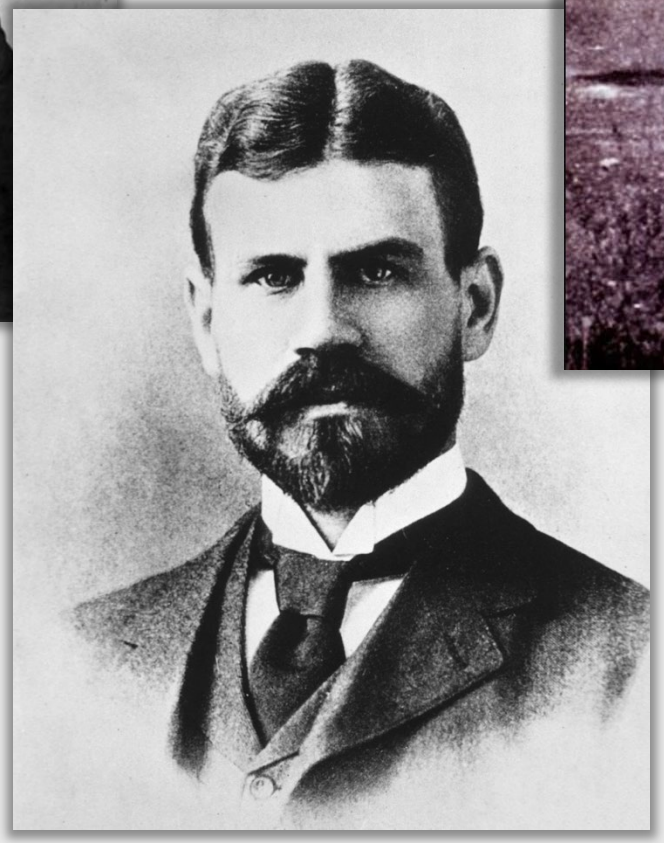
Walter Reed's yellow fever experiments (1900)

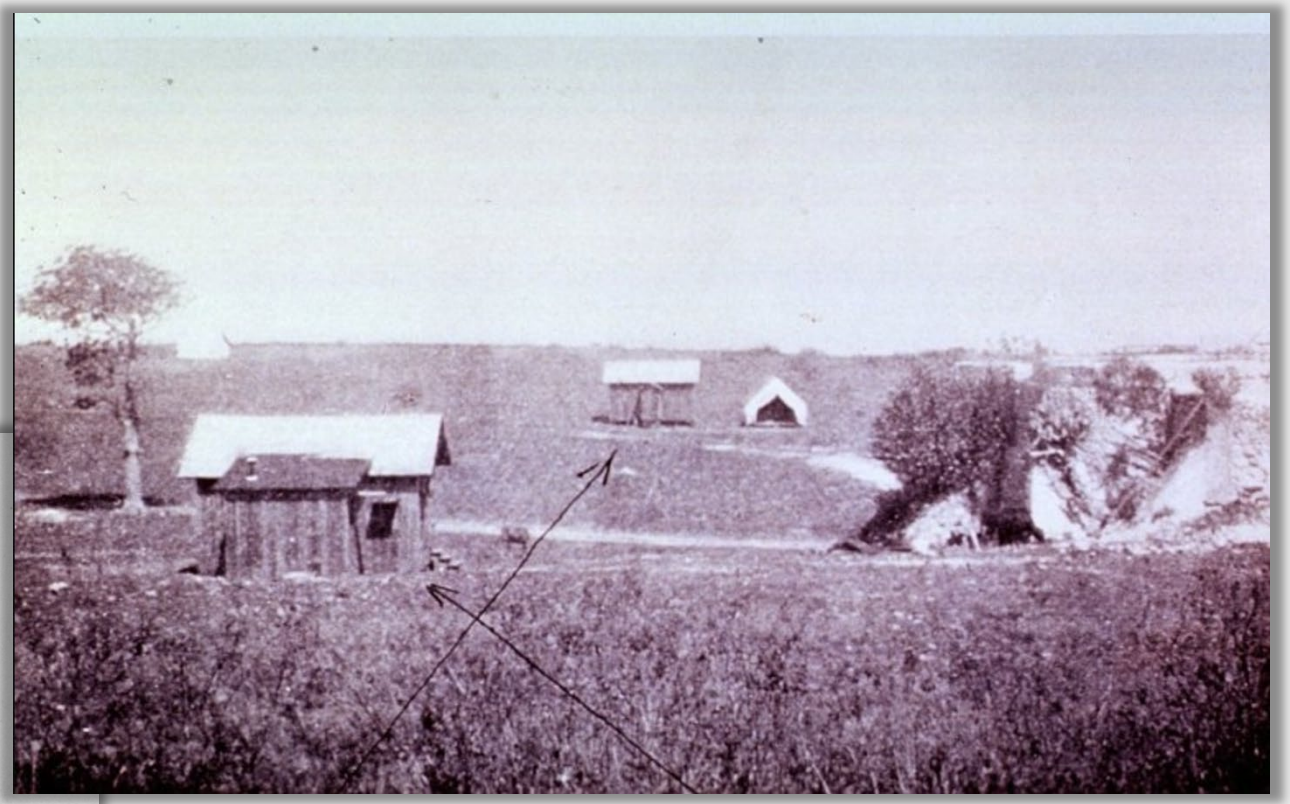
How is yellow fever transmitted?

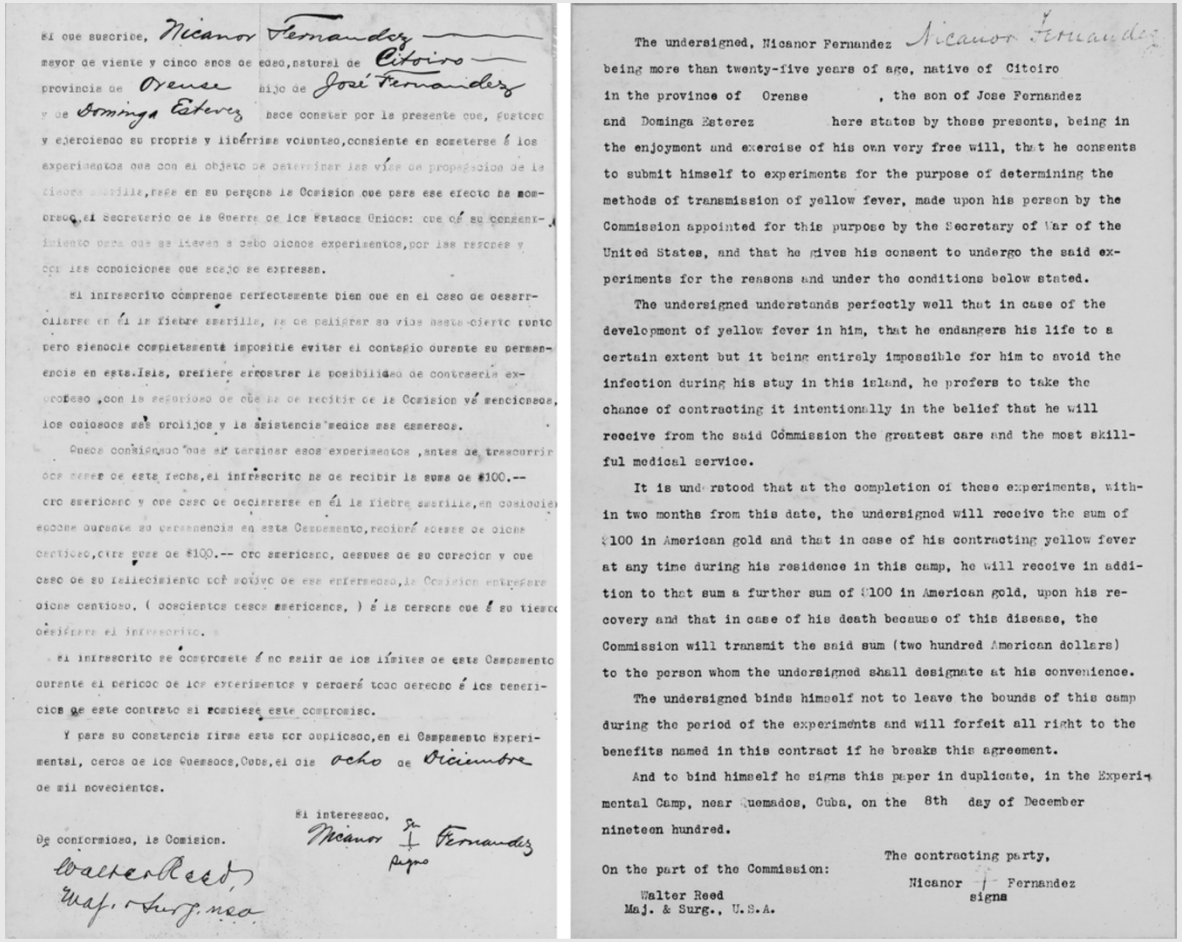
- Fomites (droplets from infected person)?
- Bite of mosquito (Carlos Finlay)?

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 años de edad, natural de Citoiro
provincia de Orense hijo de José Fernandez
y de Dominga Esterez hace constar por la presente que, gozando
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, trate en su persona la Comision que para ese efecto ha nom-
brado el Secretario de la Guerra de los Estados Unidos: que de su consenti-
miento hace con se hacen a cabo dichos experimentos, por las razones y
con las condiciones que abajo se expresan.

El infrascrito comprende perfectamente bien que en el caso de desarr-
ollarse en él la fiebre amarilla, se de peligrar su vida hasta cierto punto
pero siendole completamente imposible evitar el contagio durante su perman-
encia en este Isla, prefiere arrostrar la posibilidad de contraerla ex-
puesto, con la seguridad de que se le recibir de la Comision vé asistencias,
los cuidados mas prolijos y la asistencia medica mas eficaces.

Hasta considerando que al terminar esos experimentos, antes de trascurrir
dos meses de esta fecha, el infrascrito se de recibir la suma de $100.--
oro americano y que caso de declararse en él la fiebre amarilla, en cualquier
epoca durante su permanencia en este Campamento, recibirá ademas de dicha
cantidad, otra suma de $100.-- oro americano, despues de su curacion y que
caso de su fallecimiento con motivo de esa enfermedad, la Comision entregara
dicha cantidad, (doscientos pesos americanos,) á la persona que él su tiempo
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 benefi-
cios de este contrato si rompiese este compromiso.

Y para su constancia firma este por duplicado, en el Campamento Experi-
mental, cerca de los Quemados, Cuba, el dia ocho de Diciembre
de mil novecientos.

El interesado,
Nicanor X Fernandez
Papa

De conformidad, la Comision.
Walter Reed
Maj. & Surg. U.S.A.

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 ex-
periments 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 skill-
ful medical service.

It is understood that at the completion of these experiments, with-
in 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 addi-
tion to that sum a further sum of $100 in American gold, upon his re-
covery 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.

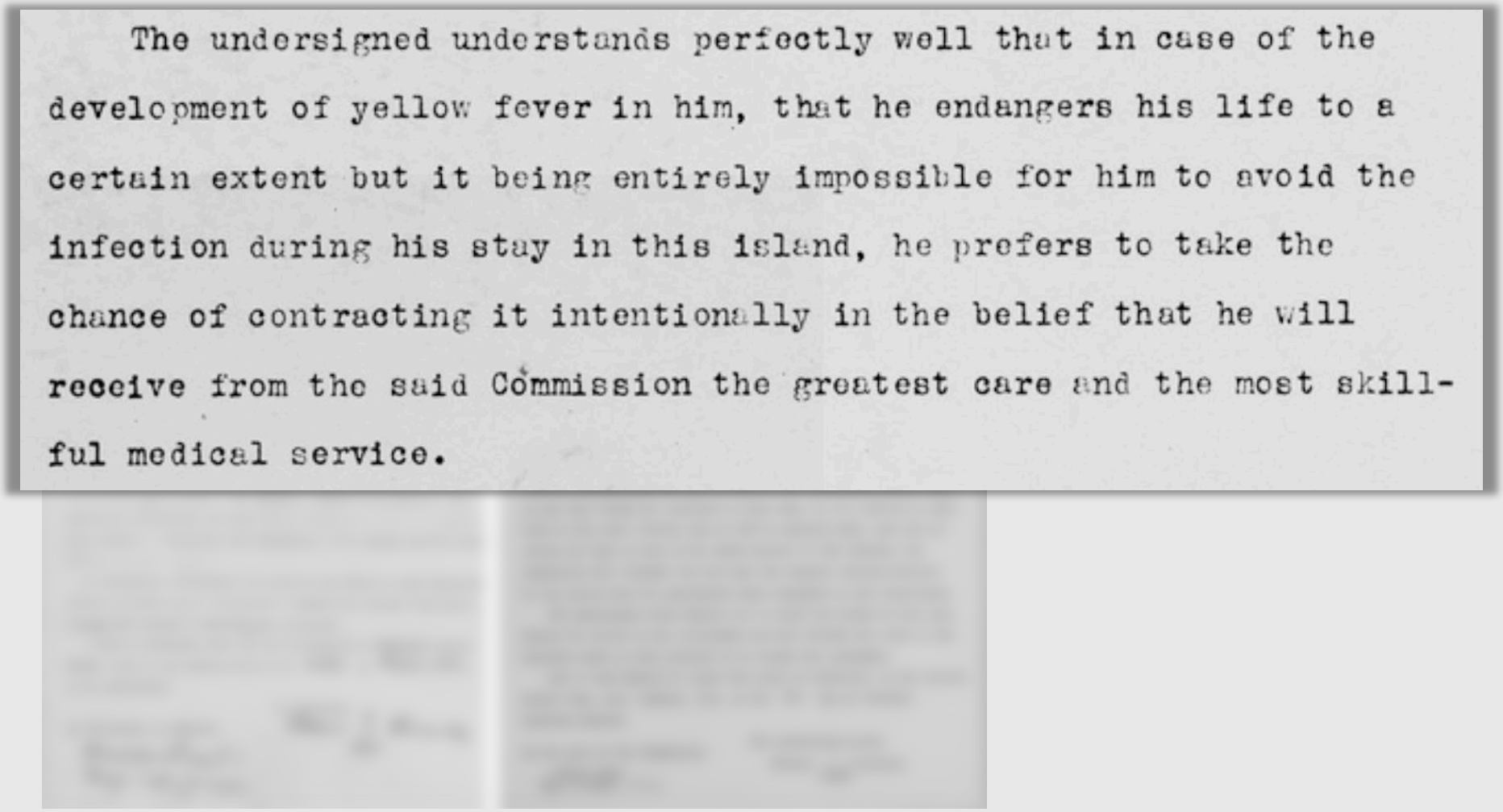
The undersigned binds himself not to leave the bounds of this camp
during the period of the experiments and will forfeit all right to the
benefits named in this contract if he breaks this agreement.

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

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

The contracting party,
Nicanor X Fernandez
signs

From: Walter Reed, Yellow Fever, and Informed Consent
Mil Med. 2016;181(1):90-91. doi:10.7205/MILMED-D-15-00430



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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

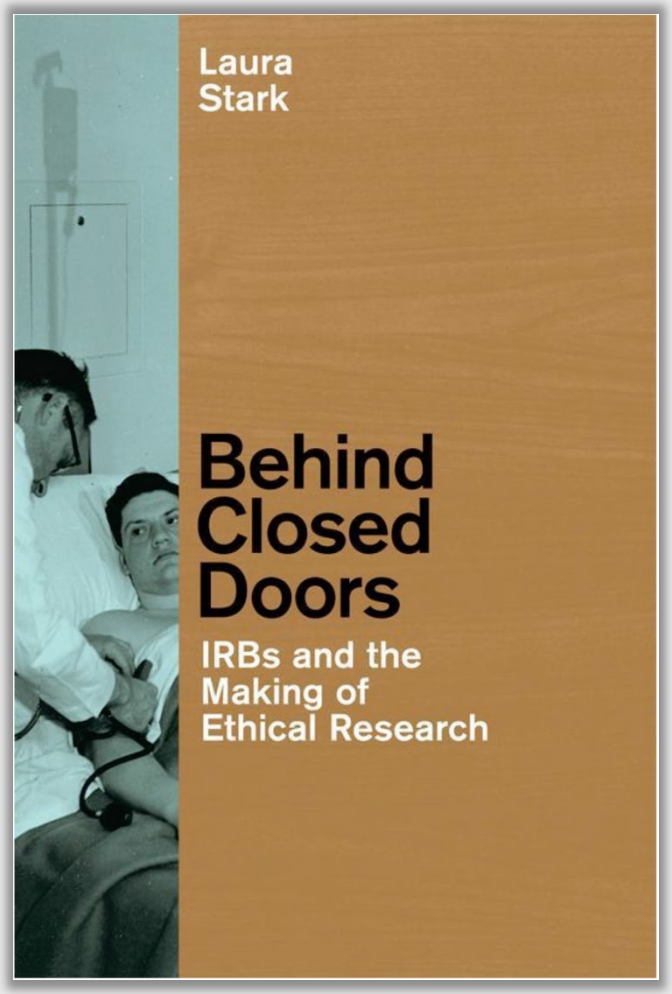
Code implicitly applies to experiments (performed on volunteers) that lack the prospect of benefit to participants

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



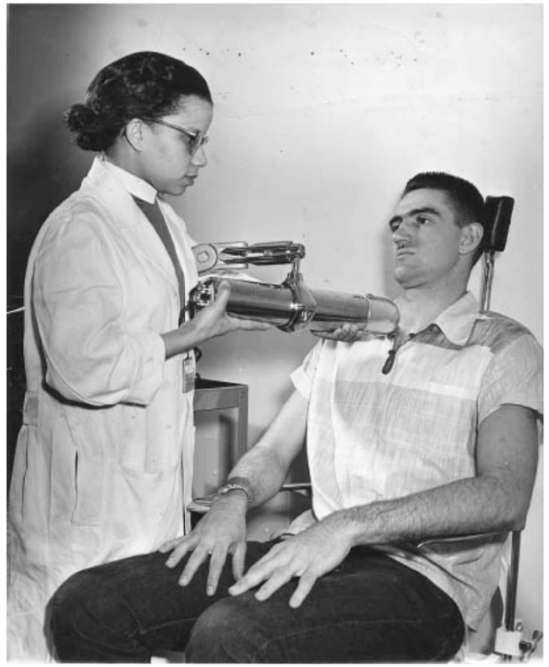


Figure 3. Thyroid study on a Mennonite Normal patient at the Clinical Center, 1958. Courtesy of the Mennonite Church USA.

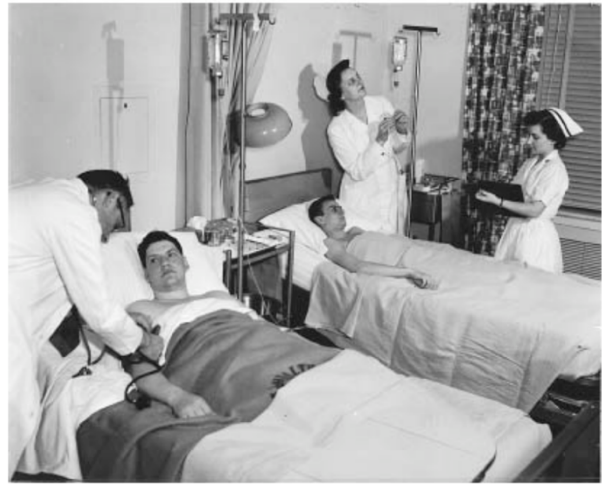


Figure 5. Normal patients enrolled in studies at the NIH Clinical Center, 1958. Courtesy of the Mennonite Church USA.

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

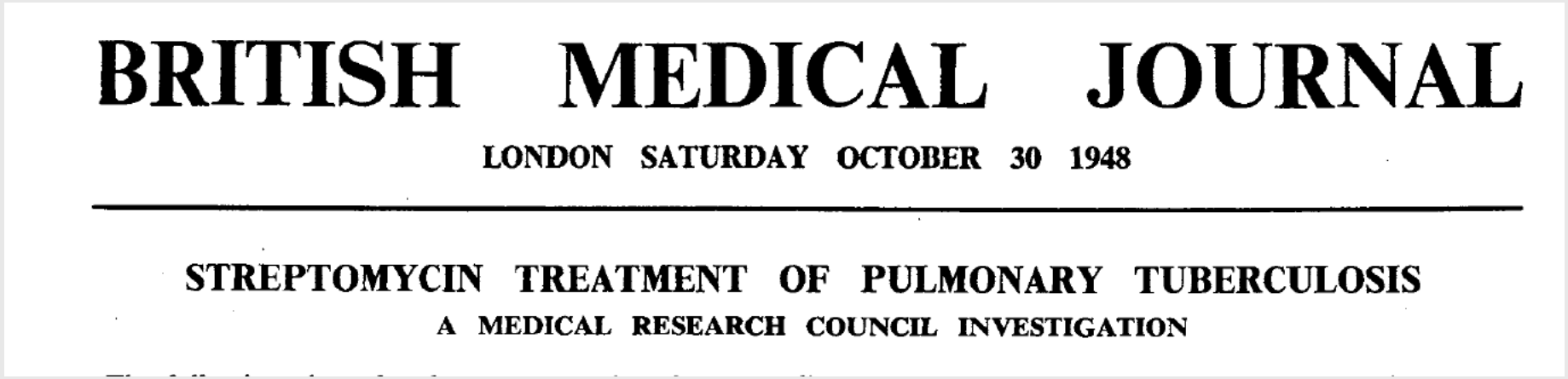
Advent of randomized controlled trials

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

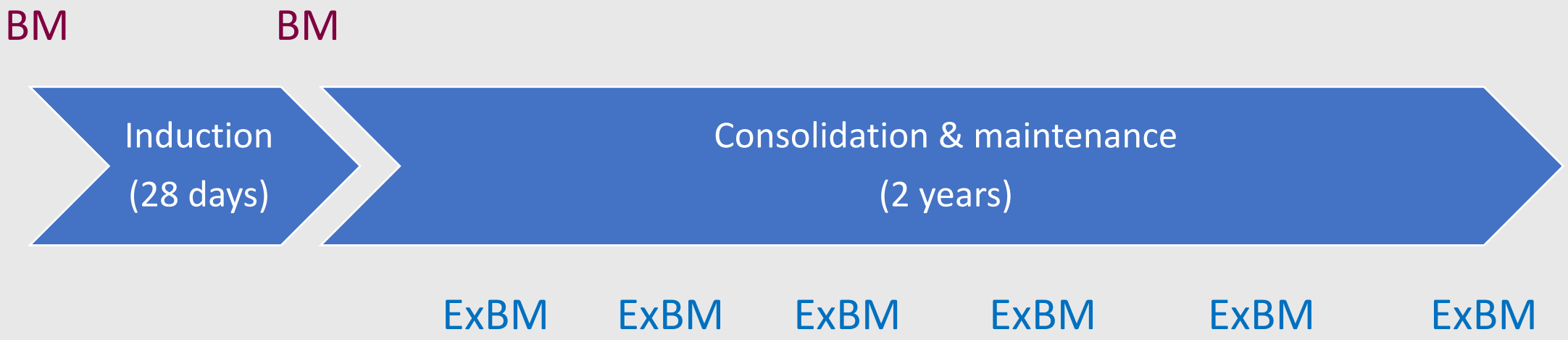
- “It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of this mission”
- “The Declaration of Geneva of the World Medical Association binds the doctor with the words, “The health of my patient will be my first consideration”…

An example of the problem

NCI-sponsored randomized clinical trial of different chemotherapy regimens for childhood acute lymphoblastic leukemia

- Embedded in trial: does detection of “minimal residual disease” at various time points predict risk of relapse?

Study timeline



BM = Bone marrow aspirate

Randomized controlled trials pose a particular 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)

“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

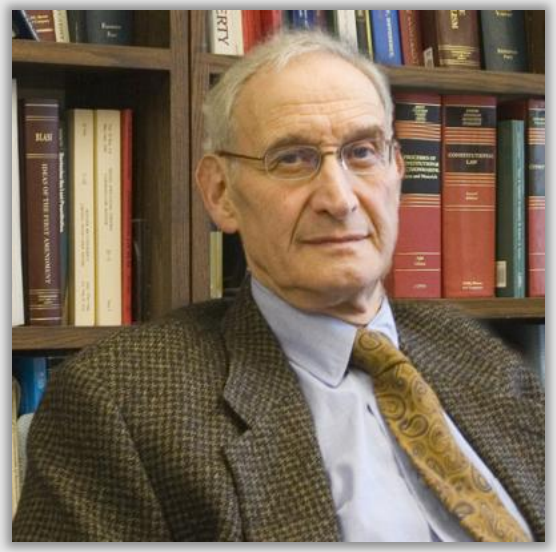
- No role for physicians’ imperfect knowledge
- Can’t modify technique based on evolving information
- Limit physicians’ access to emerging data
- Physician cannot simultaneously be a fiduciary for the patient while aiming at knowledge to benefit future patients
- “Techniques appropriate to the laboratory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

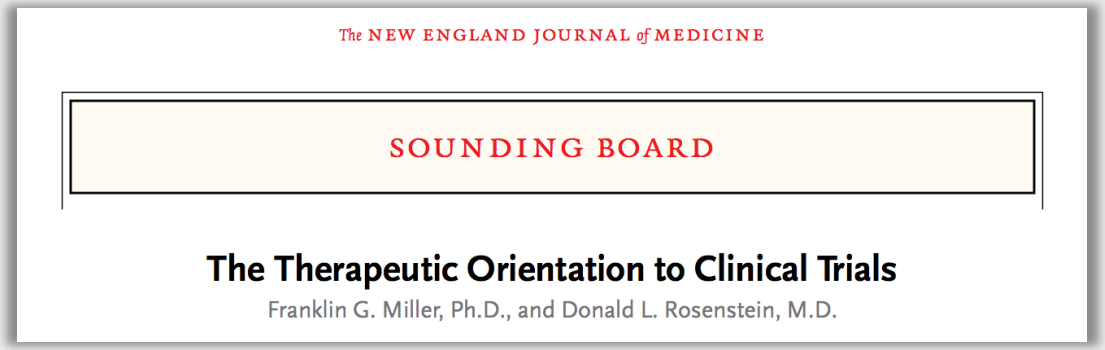
- “For the most part, the term ‘practice’ refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy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

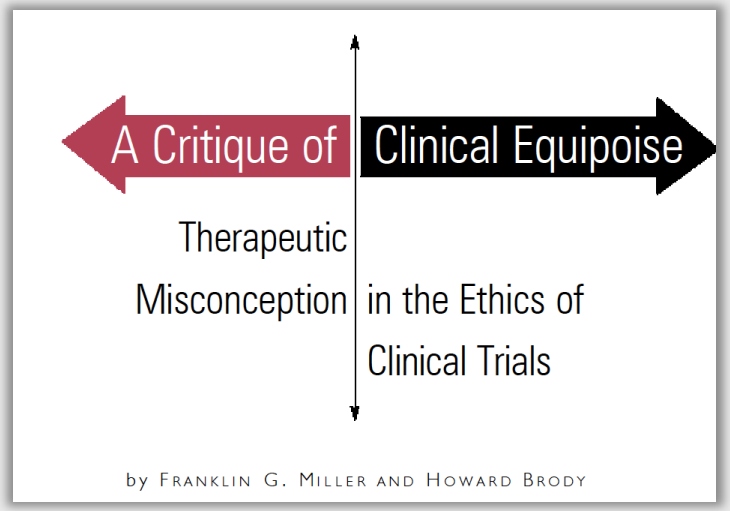
But research and care fundamentally differ…

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
- Blinds investigators to the inherent conflicts between scientific pursuit and participant protection
- 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

Competing Commitments in Clinical Trials

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

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, 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%
- 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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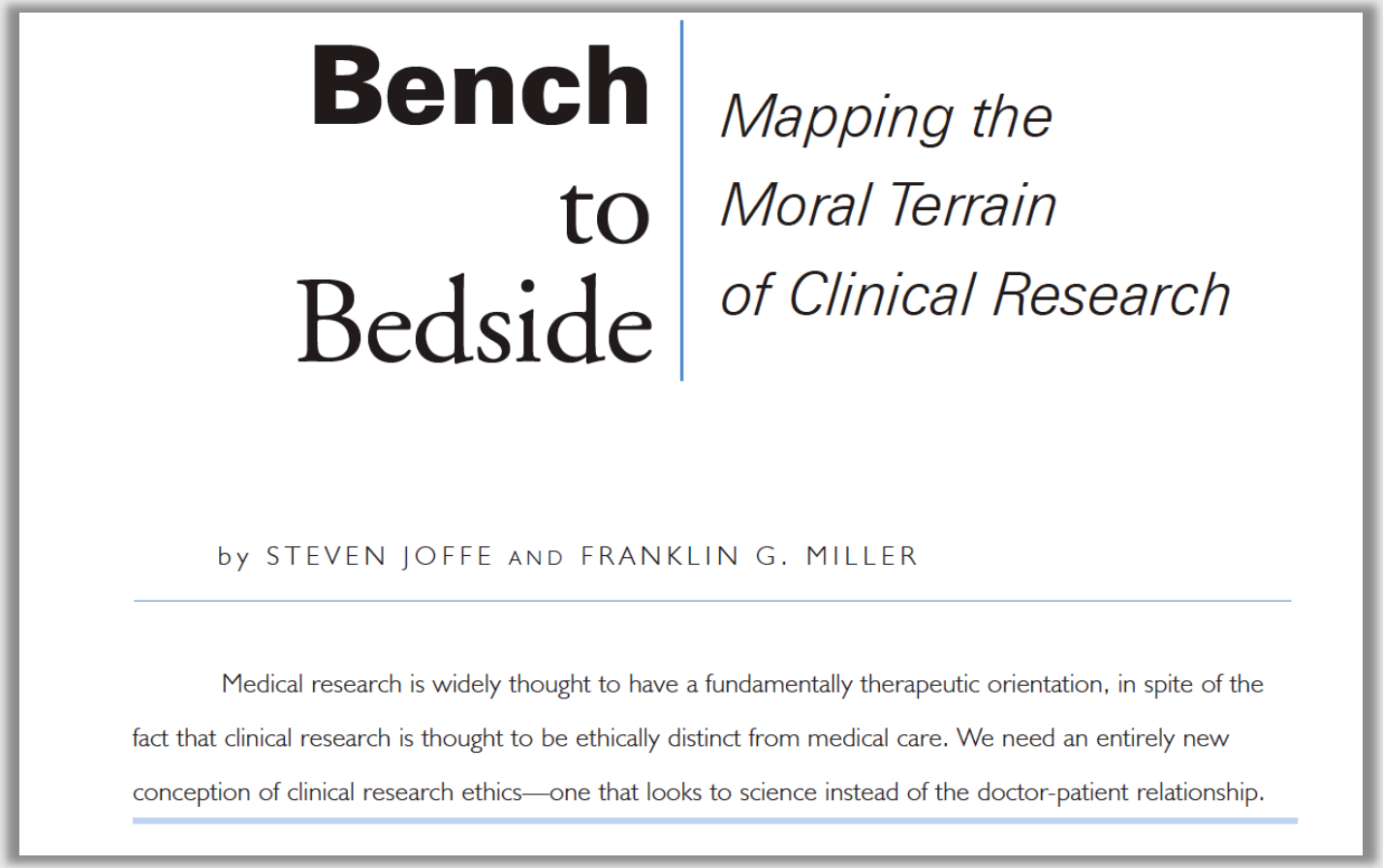
Adjusting dose of study med outside protocol-permitted range was judged to be in participant's best medical interest	48%	• 16% had adjusted med outside permitted range at least once
Participant met trial termination criteria, but staying in trial was judged to be in his/her best medical interest	36%	• 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 stock of valid generalizable knowledge
- Relevant in some way to human health and disease
- $34.4 billion NIH budget request for FY2020 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

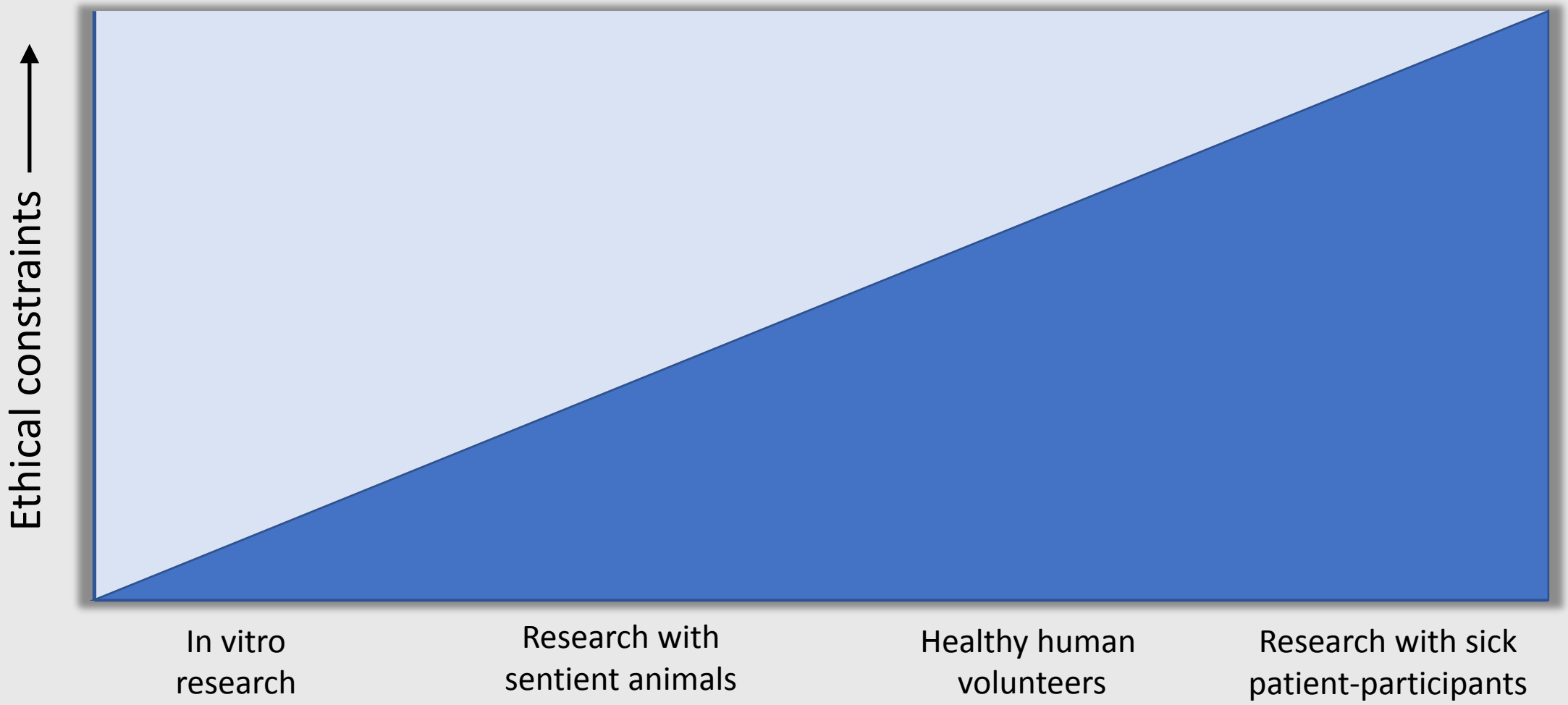
A bench-to-bedside approach

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



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 (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 envision 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!

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