The IRB

Purpose, Function, and Proposals for Improvement

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Disclaimers/Disclosures

- No statement in this presentation should be construed as an official position of the National Human Genome Research Institute, National Institutes of Health, or Department of Health and Human Services.
- The speaker declares no financial conflicts of interest.

What is an Institutional Review Board (IRB)?

- "The IRB is an administrative body established to protect the rights and welfare of human research subjects…" (OPRR 1993)
- Also known as:
  - independent ethics committee (IEC)
  - ethical review board (ERB)
  - research ethics board (REB)

NHGRI Institutional Review Board

(circa 2007)

NIH General Medicine IRB Panel #1

(circa 2018)

NIH IRB Panel #1

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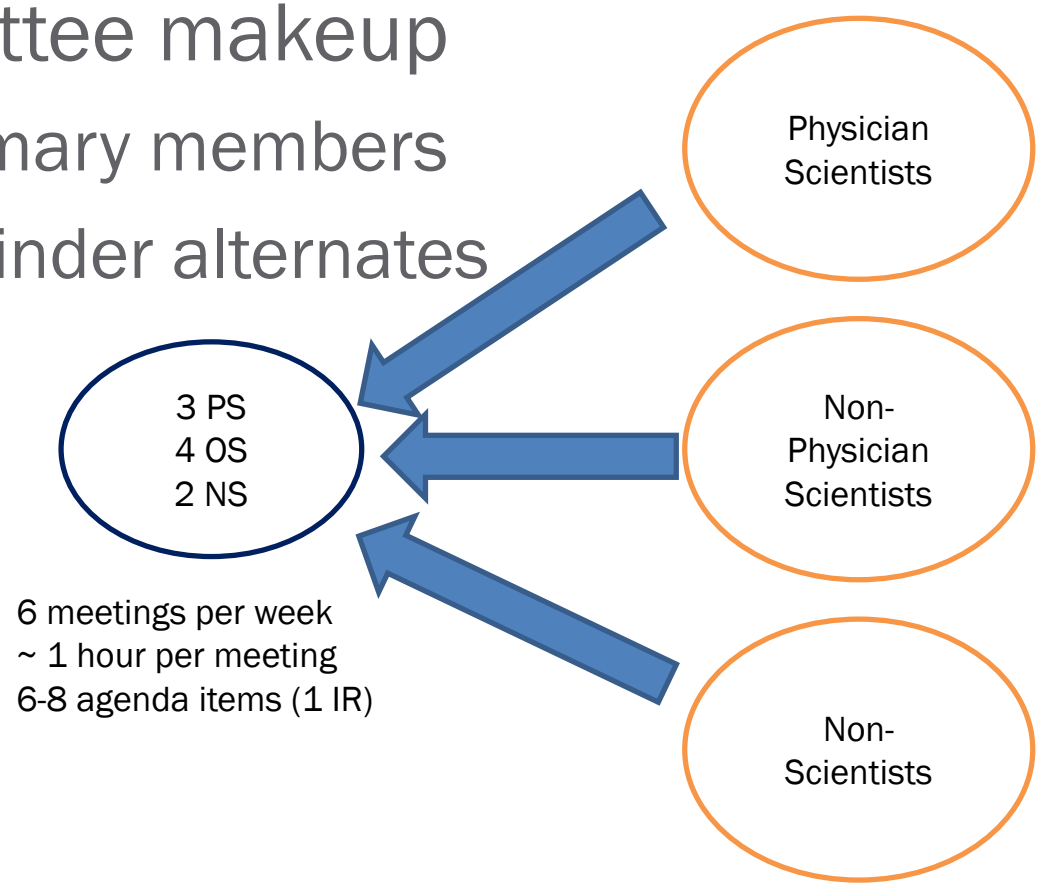
- Committee makeup
  - 9 primary members
  - remainder alternates

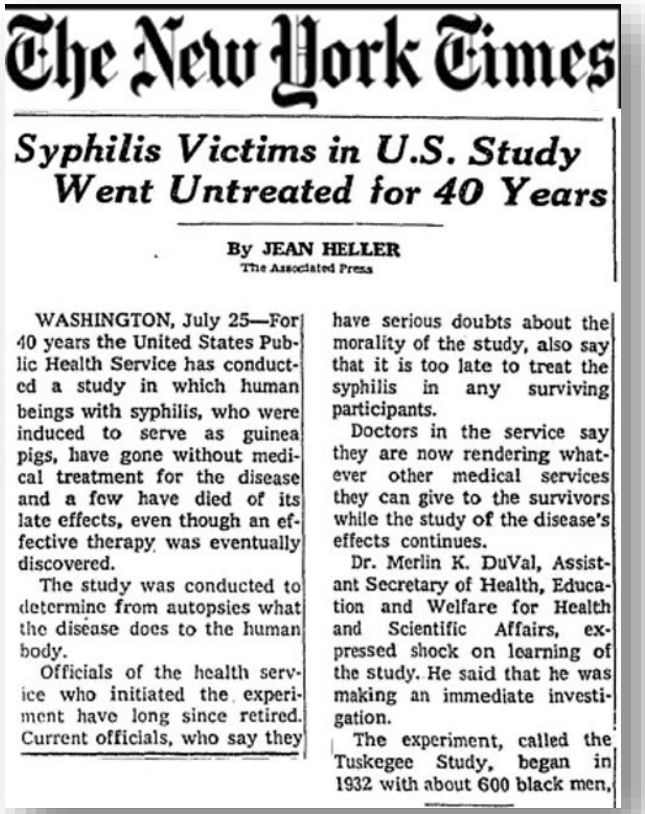


Roadmap

- Brief history and background of IRBs and their function
- Proposals for improving IRB functions

Why Were IRBs Created?

- Response to scandal and tragedy
  - US: PHS Tuskegee Study of Untreated Syphilis in the Negro Male
    - 1932-1972



The New York Times

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER
The Associated Press

WASHINGTON, July 25—For 40 years the United States Public Health Service has conducted a study in which human beings with syphilis, who were induced to serve as guinea pigs, have gone without medical treatment for the disease and a few have died of its late effects, even though an effective therapy was eventually discovered.

The study was conducted to determine from autopsies what the disease does to the human body.

Officials of the health service who initiated the experiment have long since retired. Current officials, who say they have serious doubts about the morality of the study, also say that it is too late to treat the syphilis in any surviving participants.

Doctors in the service say they are now rendering whatever other medical services they can give to the survivors while the study of the disease's effects continues.

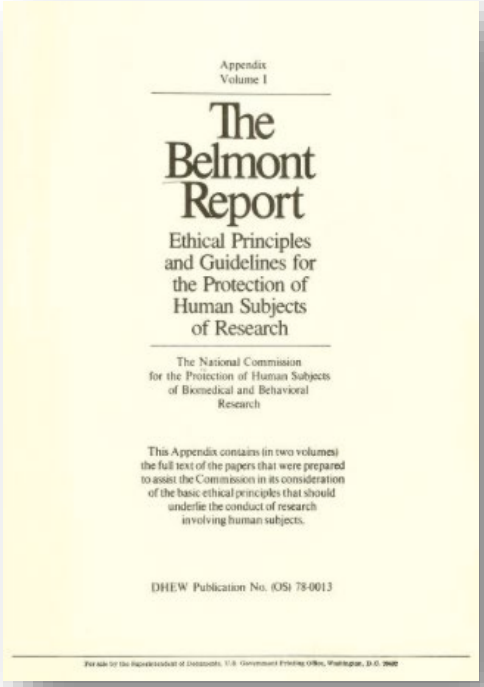
Dr. Merlin K. DuVal, Assistant Secretary of Health, Education and Welfare for Health and Scientific Affairs, expressed shock on learning of the study. He said that he was making an immediate investigation.

The experiment, called the Tuskegee Study, began in 1932 with about 600 black men,

History of IRBs in the U.S.

- 1974 DHEW National Research Act
  - National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
  - Belmont Report (1978)

- 1981 45 CFR 46
  - codified IRBs and informed consent


Appendix
Volume I

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

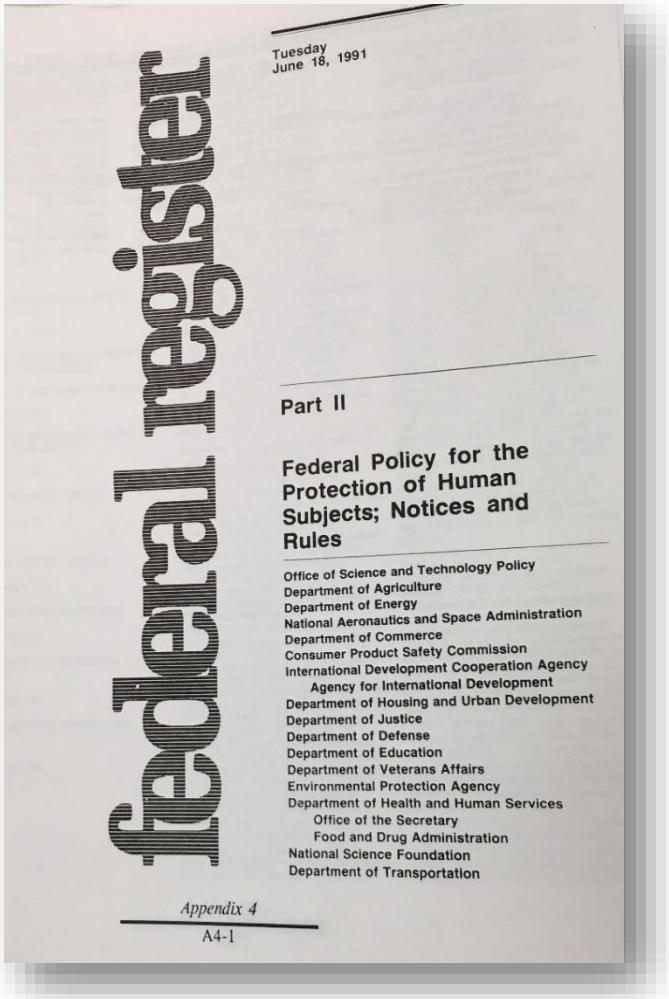
This Appendix contains (in two volumes) the full text of the papers that were prepared to assist the Commission in its consideration of the basic ethical principles that should underlie the conduct of research involving human subjects.

DHEW Publication No. (OS) 78-0013

History of IRBs in the U.S.

- 1991 “Common Rule”
- Parallel FDA regs:
  21 CFR 56

- 2017 Revised Common Rule
  - Implementation delayed until 2019



Ethical Requirements: Independent Review

- Review of research (design, population, risk/benefit) by unaffiliated individuals to:
  - Minimize impact of potential researcher COI
  - Assure public/social accountability

Emanuel *et al* (2000) *JAMA*

IRBs at a Glance

- >4000 IRBs in the United States
  - And 100s more in 113 countries

Bartlett (2008) *JEHRE*

- Approx. between 14-40 members
- Meet 1-2x/month → weekly!
- Staffed by full time administrators
  - Credentialing/professionalization
- Chair ~ 20% (at NIH: 15-100%)

IRB Membership
45 CFR 46.107/21 CFR 56.107

- At least 5 members with varying backgrounds
  - Qualified, diverse, not all men or all women or same profession
  - One scientist, one non-scientist
  - One unaffiliated member
  - No conflicts
  - Special areas of expertise

NIH Membership Requirements

- Non-affiliated members
- Member representing participant perspective
- Bioethicist
- Statistician or epidemiologist
- Pharmacist or pharmacologist

At majority of IRB meetings

Non-Scientist

- "A member whose education, training, background, and occupation would incline him/her to view research activities from a standpoint other than any biomedical or behavioral scientific discipline" (SOP 2)
  - "…to fully appreciate risks associated with the study without being blinded by the lure of scientific advancement." (Allison *et al* 2008)

Roles of Non-Scientists (n=25)

	Agree	Disagree
• Layperson	68%	32%
• Public representative	28%	72%
• Community Representative	16%	84%
• Research subject advocate*	16%	84%

- *vs. non-NIH studies: majority of NS members describe themselves as representing or giving a voice to human subjects*

Allison, Abbott, Wichman (2008) *IRB*

IRB Functions and Operations

- Reviews:
  - Initial protocols
  - Continuing review
  - Amendments
  - Unanticipated problems, non-compliance
  - Protocol deviations
  - Closures

Expedited Review

- When no more than minimal risk and involves certain categories of procedures (see OHRP guidance)
  - To be updated every 8 years

Summary of Key Common Rule Changes (per OHRP)

- **"Promoting individual autonomy"**
  - Changing requirements of informed consent
  - Adding broad consent option for secondary research
- **"Reducing administrative burden, streamlining IRB processes"**
  - Removing activities from the definition of research
  - Expanding exempt research
  - Updating and simplifying expedited review
  - Eliminating certain continuing reviews
  - Using single IRB review

Q: Does IRB Review Work?

A: We don't really know

- No controlled trials
- No underlying theory or framework of **quality** or **effectiveness**
- Lack of longitudinal assessment
- Little research with key stakeholders beyond boards/researchers

Nicholls *et al* (July 30, 2015) *PLOS ONE*

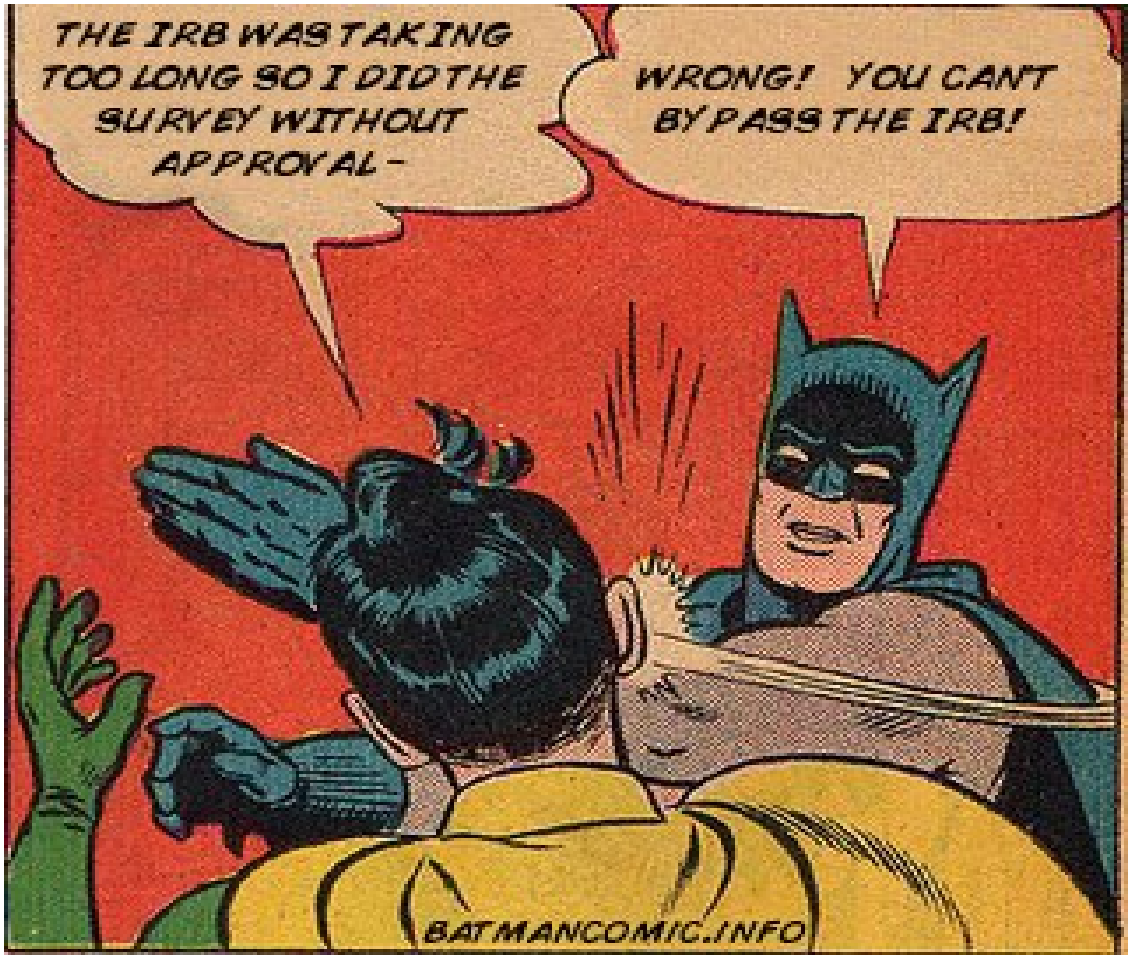
review of 198 empirical studies

Transformative Effects of IRBs

- "Unquestionably, their very existence has tempered the inevitable propensity of researchers to pursue investigations without dispassionately weighing the risks they are asking others to assume or fully informing their subjects of them."

Edgar and Rothman (1995) *Milbank Q*

Transformative Effects of IRBs



https://thomashunter.name/batman/

Problems with the Current System

1. Structural problems
    - Repetitive IRB reviews, inconsistencies in regulations, absence of resources
2. Procedural problems
    - Time consuming, inadequate guidance, overly focused on consent forms
3. Performance assessment problems
    - Absence of data

Emanuel *et al.* (2004) *Ann Int Med*

Problem: Repetitive IRB Review

- Multisite research is reviewed at each engaged institution, dissipating limited resources. Does it…
  - Foster local efforts to uphold ethical standards for research?
  - Capitalize on IRB's knowledge of local research environment and community standards?

Emanuel *et al.* (2004) *Ann Int Med*

Proposed Solution: Single IRBs

- Simple definition:
  - *A single IRB of record for a multicenter clinical trial.*
- Detailed definition:
  - *A properly constituted IRB to which sites cede all [sic] regulatory responsibility for scientific oversight and integrity of the protocol from initial review to termination of the research, including review of informed consent.*

Flynn *et al.* (2013) *PLOS ONE*

Lack of Enthusiasm for sIRBs

- Stakeholder concerns:
  - Institutional liability
  - Loss of community representation
  - Loss of knowledge of local subjects and investigators
  - Quality of sIRB review
  - Loss of revenue from IRB fees
  - Feasibility of working with multiple outside IRBs

Loh and Meyer (2004) *Acad Med*
Klitzman (2011) *BMC Med Ethics*
Flynn *et al.* (2013) *PLOS ONE*

Final NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research

Notice Number: NOT-OD-16-094

Key Dates

Release Date: June 21, 2016

Effective Date: New Date - January 25, 2018 as per issuance of NOT-OD-17-076

NIH Policy - sIRB

...to establish the expectation that a single IRB (sIRB) of record will be used in the ethical review of non-exempt human subjects research protocols funded by the NIH that are carried out at more than one site in the United States.

Effective date: January 25, 2018

NIH Policy - sIRB

Rationale:

- No evidence that multiple IRB reviews enhance protections for human subjects
- Use of single IRBs may lead to enhanced protections for research participants by:
  - eliminating the problem of distributed accountability
  - minimizing institutional conflicts of interest
  - refocusing IRB time and resources toward review of other studies

Final Common Rule - sIRB

"Creates a requirement for US-based institutions engaged in cooperative research to use a single IRB for that portion of the research that takes place within the United States, with certain exceptions. This requirement becomes effective 3 years after publication of the final rule."

https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects

Undiagnosed Diseases Network | Seven clinical site locations

- Bethesda, MD (NIH Undiagnosed Diseases Program)
- Boston, MA (UDN Clinical Site at Harvard Medical School)
- Durham, NC (Duke University and Columbia University)
- Houston, TX (Baylor College of Medicine, Texas Children's Hospital, and Baylor CHI St. Luke's Medical Center)
- Los Angeles, CA (UCLA Undiagnosed Diseases Clinic)
- Miami, FL (University of Miami School of Medicine)
- Nashville, TN (Vanderbilt Center for Undiagnosed Diseases)
- Philadelphia, PA (Children's Hospital of Philadelphia and University of Pennsylvania) ***not currently reviewing applications****
- Salt Lake City, UT (University of Utah – Intermountain West)
- Seattle, WA (Pacific Northwest Undiagnosed Diseases Clinical Site at University of Washington and Seattle Children's Hospital)
- Stanford, CA (Center for Undiagnosed Diseases at Stanford)
- St. Louis, MO (Washington University in St. Louis)

http://www.genome.gov/27550959

UDN Protocol

- 18 Reliance Agreements
  - Coordinating Center
  - Clinical enrollment sites
  - Cores
    - Sequencing
    - Model organisms
    - Metabolomics
  - Biorepository
  - Monitor

UDN Consent Forms (n=150!)

- Main study (144)
  - 16 consent/assent forms (English + Spanish) x 9
  - Plus use of NIH or local short forms
- Patient web pages sub-study (2)
- Site specific (2 x 2)

CTS Clinical and Translational Science
Open Access

Citation: Clin Transl Sci (2018) 11, 28–31; doi:10.1111/cts.12512

TUTORIAL

Implementing the Single Institutional Review Board Model: Lessons from the Undiagnosed Diseases Network

Kimberly Splinter[1,*], Sara Chandros Hull[2,3], Ingrid A. Holm[4,5], Tara L. McDonough[3], Anastasia L. Wise[3], Rachel B. Ramoni[6] and Members of the Undiagnosed Diseases Network

"The UDN experience demonstrates both the envisioned efficiencies and investments required to make a single IRB model successful."

NIH Policy on Use of a Single IRB for Multi-Site Research

Exceptions:

- *Where review by the proposed sIRB would be prohibited by a federal, tribal, or state law, regulation, or policy*
- *If there is a compelling justification*

Exceptions (public comment)

- IHS: “Multi-site studies with central IRB approval should be required to seek IHS or Tribal IRB approval, as appropriate, for research conducted within the jurisdiction of federally recognized AI/AN Tribes”

Exceptions (public comment)

- Tribal IRBs ensure that research
  - is conducted in a community engaged manner
  - does not deplete or divert limited tribal resources away from direct patient care
  - findings are first shared with tribal leadership, tribal communities, and key stakeholders

Revised Common Rule: Acknowledging Tribal Sovereignty

"Thus, if the official governing body of a tribe passes a tribal law that provides additional protections for human subjects, the Common Rule does not affect or alter the applicability of such tribal law …"

Federal Policy for the Protection of Human Subjects/Final Rule 2017, 7158, Executive Summary II.E.2

PRIM&R Webinar

Preserving a Role for Tribal Review of Research in the Context of Single IRB Policies

Tuesday, September 20 • 1:00-2:30 PM ET

http://www.primr.org/webinars/sept2016/

Beyond Belmont: Ensuring Respect for AI/AN Communities Through Tribal IRBs, Laws, and Policies

Sara Chandros Hull, National Institutes of Health
David R. Wilson (Diné), National Institutes of Health

We concur with Friesen and colleagues (2017) that it is timely to reflect on the history of the Belmont Report and its role in the development of research regulations, especially its failure to account for harms to communities and transparency in research. We would like to amplify the authors' comments about the relevance of these failures as they pertain to American Indian and Alaska Native (AI/AN) communities—and clarify a few important nuances. Transparency and trust are key issues that continue to beleaguer AI/AN communities and their perception of scientific research (Havasupai Tribe of the Havasupai Reservation v. Arizona Board of Regents and Therese Ann Markow 2008; American Journal of Medical Genetics [AJMG] 2010). It would have been fitting for the Belmont Report to address "respect for communities" in response to the harm caused to the African American community by the Public Health Service Tuskegee Syphilis Study, especially given that the study was an important catalyst in the establishment of both the National Research Act and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1974. Realistically, however, it seems unlikely that the Belmont Report, a historical document that has stood intact for nearly 40 years, will be revised to formally incorporate a new principle that focuses on community respect and trust—which makes it all the more important to understand how the interests of AI/AN communities can be protected under the newly updated U.S. federal regulatory framework ("the final Common Rule").

Friesen and colleagues (2017) acknowledge that the issue of community harms is relevant to AI/AN tribes through their inclusion of case examples and alluding to the sovereign authority that tribes have to establish research regulations. However, their concern that it is

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Thank you!