LSU HEALTH COORDINATOR COMPETENCIES

X

ADHERENCE TO ETHICAL STANDARDS

Research Ethics in the Context of Clinical Research

Objectives

- Describe historical unethical research studies that led to the establishment of ethical guidelines and regulations governing clinical research
- Describe the main ethics principles in the context of human subject research
- Describe the differences between FDA vs. HHS vs. ICH Guidelines, and when each guideline is applicable

Why Do Human Research Subjects Need Protection?

Unethical Historical Research Studies: Nazi Experimentation

Altitude Experiments at Dachau to investigate the limits of human endurance and existence at extremely high altitudes

- Subjects were placed in the low-pressure chamber and thereafter the simulated altitude therein was raised

Twin Experiments to show similarities and differences in their genetics

- Injection of different dyes into the eyes of twins to see whether it would change their color
- Sewing twins together in attempts to create conjoined twins

Sterilization Experiments to development cost effective and efficient methods for large populations

- Injecting women's cervixes with chemicals to block their fallopian tubes
- Exposure of genitalia to radiation to destroy a person's ability to produce ova or sperm

Unethical Historical Research Studies: Nazi Experimentation

Freezing Experiments with the intent of discovering means to prevent and treat hypothermia.

- Forced to sit for several hours in tanks of freezing water or naked in the open air with temperatures as low as −6 °C
- One research assistant testified that some victims were thrown into boiling water for rewarming.

Infectious Disease Experiments to test prevention and treatment

- Individuals, including children, deliberately infected with agents for malaria, typhus, tuberculosis, typhoid fever, yellow fever, infectious hepatitis, tetanus, etc.

Unethical Historical Research Studies: Thalidomide

Thalidomide was approved as a sedative in Europe it the 1950s; it was not approved in the United States by the FDA. However, the drug was prescribed in the US to control sleep and nausea throughout pregnancy.

- It was soon found that taking this drug during pregnancy caused severe deformities in the fetus.
- Many patients did not know they were taking a drug that was not approved for use by the FDA, nor did they give informed consent.
- Some 12,000 babies were born with severe deformities due to thalidomide.

Unethical Historical Research Studies: Tuskegee Syphilis Study

1932: the Public Health Service, working with the Tuskegee Institute, began a study to record the natural history of syphilis in hopes of justifying treatment programs for blacks. It was called the "Tuskegee Study of Untreated Syphilis in the Negro Male."

- The study initially involved 600 black men – 399 with syphilis, 201 who did not have the disease.
- In exchange for taking part in the study, the men received free medical exams, free meals, and burial insurance.

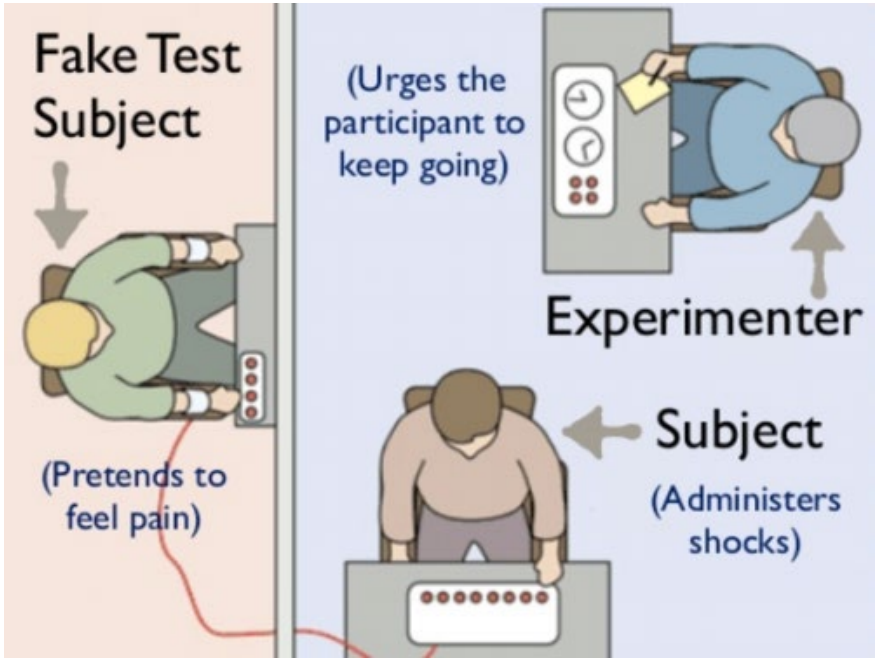
Unethical Historical Research Studies: Tuskegee Syphilis Study

- Although originally projected to last 6 months, the study went on for **40 years.**
- The study was conducted **without** the benefit of patients' informed consent.
- The men were never given adequate treatment for their disease. Even when penicillin became the drug of choice for syphilis in 1947, **researchers did not offer it to the subjects.**
- **The study ended in 1972** when a news article came out with details of what had been going on for 40 years.

Unethical Historical Research Studies: Milgram Experiments

Measured the willingness of participants to obey an authority figure who instructed them to complete a task that conflicted with their conscience

- Participants instructed by the Experimenter to give what participant believes are painful shocks to the student-actor when an incorrect answer is given
- Participants believed actual shocks were being given for incorrect responses
- Many participants realized they were capable of committing acts of extreme violence against others
- Ethical questions raised due to the associated **extreme emotional stress** and insight into personal flaws inflicted upon the participants



Unethical Historical Research Studies: Other Examples

1971: Stanford Prison Experiment

- Study of psychology of imprisonment by setting up a mock prison using volunteer college students, some assuming role of prisoner and others assuming role of guards
- The "guards" ended up brutalizing the "prisoners"
- Concerns included the underestimation of psychological harm

1998: Death of Jesse Gelsinger

- 18-year-old died while taking part in gene transfer experiment to treat an OTC Deficiency
- He developed a massive immune response after his first injection and died within 4 days
- Informed consent was inadequate in describing risks; researchers had conflicts of interest

2010: Publication of *The Immortal Life of Henrietta Lacks*

- 31-year-old died of cervical cancer in the 1950s
- Her cancer cells were used to develop the HeLa cell line that contributes to countless scientific advancements
- Until this book, she received no recognition nor her descendants any compensation
- Concerns with use of biological samples for research purposes without subject consent

History of IRB Regulations

Nuremberg Code (1947)

A result of the Nazi Doctors' trial that formed the basis for the Declaration of Helsinki and the Belmont Report

Declaration of Helsinki (1964)

International statement of ethical principles to guide medical professionals conducting research, including guidelines for consent

National Research Act (1974)

Established a commission that produced recommendations regarding review of research by IRBs and resulted in the creation of 45 CFR 46 or The Common Rule (1978)

The Belmont Report (1978)

Defined three fundamental ethical principles for human subject research:

1. Respect for Persons
2. Beneficence
3. Justice

Common Rule (1978)

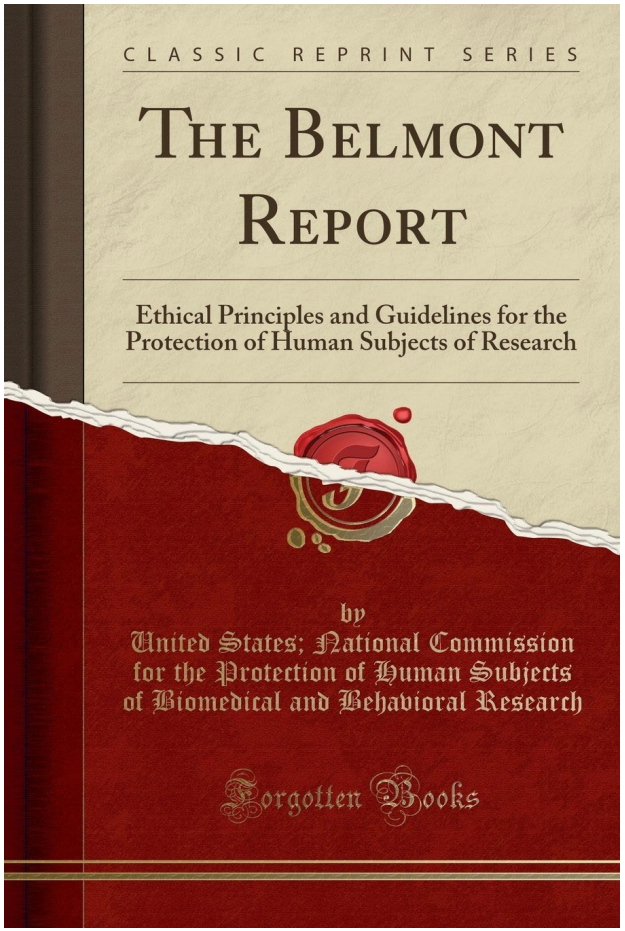
Rule of ethics in the United States regarding biomedical and behavioral research involving human subjects.

HIPAA Privacy Rule (2000)

The rule addresses uses and disclosures of private health information for research purpose

What are the Main Ethical Principals for Human Subjects Research?

Ethical Principles: Belmont Report



- **Ethical Principles and Guidelines** for the Protection of Human Subjects of Research
- **Summarizes the basic ethical principles** identified by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- **Created in reaction to previous human subject violations** (e.g. Nuremberg Trials on human experimentation; Tuskegee Syphilis Experiment, etc.)
- **Named after the conference room** where the Commission convened at the Smithsonian Institution's Belmont Conference Center; held in 1976.

Ethical Principles: Belmont Report

- Individuals should be treated as autonomous agents
- Persons with diminished autonomy are entitled to protection

- Do not harm
- Maximize possible benefits and minimize possible harms
- NOT an act of kindness or charity, but a concrete obligation

- To each person an equal share
- To each person according to individual need
- To each person according to individual effort
- To each person according to societal contribution, and
- To each person according to merit.

Ethical Principles: Belmont Report - Application

Informed Consent

- Sufficient information
- Comprehension
- Voluntariness (no coercion)
- Obtain & document

Assessment of Risks & Benefits

- Procedures w/least risk
- Risks reasonable in relation to benefits
- Justification & additional safeguards for vulnerable populations
- Maintain privacy & confidentiality

Selection of Participants

- *Individual justice*: Select participants equitably
- *Social justice*: Avoid exploitation of vulnerable populations

Ethical Principles: Common Rule

What is it?

- Another term for the Federal Policy for the Protection of Human Subjects or Code of Federal Regulations that govern human subjects research (e.g., 45 CFR 46)
- Initially established by the National Research Act of 1974 and revised multiple times, most recently in 2019
- Adopted by at least 20 federal agencies and departments including NIH, FDA

What does it do?

- Defined human subjects research by level of risk
- Establishes the structure and role of an Institutional Review Board (IRB)
- Establishes procedures for reviewing human subjects research
- Outlines the requirements for researchers' obtaining and documenting informed consent.
- Outlines protections for vulnerable populations (Subparts B-D).

Which Guidelines Do I Follow?

HHS Rule *vs* FDA *vs* ICH

HHS (45 CFR 46)

- Followed when the research involves a human subject

FDA (21 CFR 50 & 56)

- Followed when the research involves a human subject and an FDA-regulated test article, or human subjects research data will be submitted to or held for inspection by the FDA

ICH Good Clinical Practice

- Followed when generating clinical trial data that are intended to be submitted to international regulatory authorities

HHS Rule *vs* FDA

Definition of Research

- HHS: "…a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge."
- FDA: "...any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration."

Definition of Human Subjects

- HHS: a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.
- FDA: an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

HHS Rule *vs* FDA

Inspection of Records

- HHS: Reserves the right to inspect records of studies it funds at a reasonable time and in a reasonable manner; it does not require that subjects provide informed consent for that inspection
- FDA: explicitly requires that subjects be informed that FDA may inspect the records of the study because FDA may occasionally examine a subject's medical records when they pertain to the study.

Record Retention

- HHS: Reserves the right to inspect records of studies it funds at a reasonable time and in a reasonable manner; it does not require that subjects provide informed consent for that inspection
- FDA: explicitly requires that subjects be informed that FDA may inspect the records of the study because FDA may occasionally examine a subject's medical records when they pertain to the study.

HHS Rule *vs* FDA

Exempt Research

- HHS: Exempts 8 categories of research
- FDA: Has a limited number of categories which are exempt

Waiver of Parent/Guardian Permission

- HHS: Multiple circumstances that allow for waiver
- FDA: Waiver is not allowed under any circumstance

Waiver of Documentation of Informed Consent

- HHS: Multiple circumstances that allow for waiver
- FDA: Waiver is not allowed under any circumstance

Investigator Responsibilities

- HHS: Defers to the IRB to determine competence of the investigator(s)
- FDA: Provides expectations and responsibilities within the regulations and requires all investigators to sign Form 1572

LSU Health Coordinator Competencies

- ✓ Onboarding
- ✓ Ethical Standards
- ❑ Protocol Compliance
- ❑ Informed Consent
- ❑ Patient Recruitment & Retention
- ❑ Management of Patients
- ❑ Documentation & Document Management
- ❑ Data Management & Information Technology
- ❑ Financial Stewardship
- ❑ Leadership & Professional Development

Links to Regulations

Belmont Report

Common Rule (45 CFR 46)

FDA Regulations (21 CFR 50 & 56)

ICH Good Clinical Practice