YSEMA · Introduction to Research

Lecture 2 · June 5, 2024

Research Ethics

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Recap – 1st Lecture

Objectives

- Describe, discuss, and define the history of protection of human subjects
- Describe and discuss the need for protection of human subjects
- Outline and discuss the Belmont Principles
- Describe the functions of the IRB
- List the elements of informed consent

Ethical Issues in Research

- Researchers have not always treated their human subjects appropriately.
- People have been subject to research without their consent.
- Many have endured harsh treatments, and some have had fatal outcomes.
- Researchers have faked data and have submitted false research reports.

Stanford President Will Resign After Report Found Flaws in His Research

Marc Tessier-Lavigne was cleared of accusations of scientific fraud and misconduct. But the review said his work had "multiple problems" and "fell below customary standards of scientific rigor."

https://www.nytimes.com/2023/07/19/us/stanford-president-resigns-tessier-lavigne.html?unlocked_article_code=1.vE0.mIeM.t8zlZDhNyJ_l&smid=url-share

Historical Context: *Why are IRBs and regulations necessary?*

Sulfanilamide (1937)

Courtesy of the FDA.

High altitude experiment at Dachau

Harvard Law School Library. Nuremberg Trials Project.

The poison squad (1906)

Courtesy of the FDA.

1920 Fitter Families competition

American Philosophical Society.

Buck v. Bell, 274

TABLE 2.1 Examples of Nazi Human Torture during WWII[11]

War Related
- Extreme cold exposure to study hypothermia and warming
- Atmospheric pressure chambers to study altitude effects
- Forced saltwater ingestion
- Simulated war wounds using, bullets, ground glass, wood fragments
- Induced abscesses

Reconstructive Surgery
- Bone breaking, bone transplants, bone grafting
- Soft tissue resection and grafting

Infectious Diseases
- Inoculation with viruses for vaccine creation
- Malaria experiments
- Intentional tuberculosis exposure

Biochemical Agents
- Poison gas exposures
- Induced chemical burns
- Testing of poisoned bullets

Eugenics
- Surgical sterilization and castration
- Intrauterine injections of iodine and silver nitrate
- Testicular and ovarian radiation exposures

The Nuremburg Code 1947

- Consent should be **informed**, **voluntary**, **and** **non-coercive**.
- Experiments should be **useful and necessary.**
- Human experiments should be based on animal research.
- Physical and mental suffering should **be avoided.**
- Death and disability should **not be expected.**
- **Risk should not exceed the humanitarian importance.**
- Human subjects should be protected from remote harms.
- **Only qualified scientists** should conduct research.
- Subjects should be **free to end an experiment.**
- Scientists should **prepare to end** experiments.

Tuskegee Study of Untreated Syphilis in the Negro Male (1932-1972)

This Photo by Unknown Author is licensed under CC BY-SA

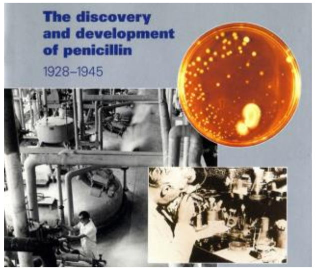
- 399 Black Males from Macon County, Alabama
- The goal was to “observe the natural history of untreated syphilis”
- Under the guise of receiving free medical care for “bad blood”
- Physicals, hot meals, and burial stipends provided
- Treatment was deliberately withheld to observe the progression of the disease

In 1997, President Bill Clinton formally apologized on behalf of the United States to the victims of the study, calling it shameful and racist: **"What was done cannot be undone, but we can end the silence. We can stop turning our heads away. We can look at you in the eye and finally say, on behalf of the American people, what the United States government did was shameful, and I am sorry."**

Began the study

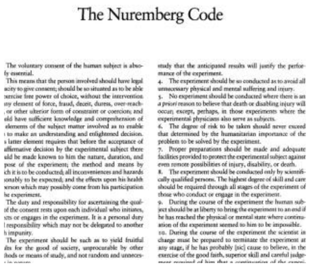
1932

Penicillin becomes treatment of choice for syphilis



1943

Nuremberg Code



The Nuremberg Code

The voluntary consent of the human subject is abso-
ly essential.
This means that the person involved should have legal
acity to give consent; should be so situated as to be able
xercise free power of choice, without the intervention
ny element of force, fraud, deceit, duress, over-reach-
, or other ulterior form of constraint or coercion; and
uld have sufficient knowledge and comprehension of
elements of the subject matter involved as to enable
to make an understanding and enlightened decision.
s latter element requires that before the acceptance of
affirmative decision by the experimental subject there
uld be made known to him the nature, duration, and
pose of the experiment; the method and means by
ch it is to be conducted; all inconveniences and hazards
sonably to be expected; and the effects upon his health
erson which may possibly come from his participation
he experiment.
The duty and responsibility for ascertaining the qual-
of the consent rests upon each individual who initiates,
cts or engages in the experiment. It is a personal duty
l responsibility which may not be delegated to another
h impunity.
The experiment should be such as to yield fruitful
lts for the good of society, unprocurable by other
thods or means of study, and not random and unneces-

study that the anticipated results will justify the performance of the experiment.

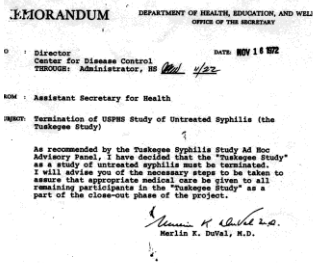
4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seemed to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably [sic] cause to believe, in the exercise of the good faith, superior skill and careful judge-

1947

Declaration of Helsinki

1964

Tuskegee study finally ended



.EMORANDUM DEPARTMENT OF HEALTH, EDUCATION, AND WEL
OFFICE OF THE SECRETARY

O : Director DATE: NOV 16 1972
Center for Disease Control
THROUGH: Administrator, HS 11/22

ROM : Assistant Secretary for Health

UBJECT: Termination of USPHS Study of Untreated Syphilis (the Tuskegee Study)

As recommended by the Tuskegee Syphilis Study Ad Hoc Advisory Panel, I have decided that the "Tuskegee Study" as a study of untreated syphilis must be terminated. I will advise you of the necessary steps to be taken to assure that appropriate medical care be given to all remaining participants in the "Tuskegee Study" as a part of the close-out phase of the project.

Merlin K. DuVal M.D.
Merlin K. DuVal, M.D.

1972

In 1979, the National Commission released the *Belmont Report* and established three fundamental ethical principles for conducting research involving humans.

1. **Respect for Persons (Autonomy)**
2. **Beneficence**
3. **Justice**

Additional Readings & Resources

- https://www.cdc.gov/tuskegee/about.html
- https://www.mcgill.ca/oss/article/history/40-years-human-experimentation-america-tuskegee-study
- https://www.jstor.org/stable/3561468

How Is Research Approved?

- **Informed consent**
- **Assessment of risks and benefits**
- **Equitable selection of subjects**
- **IRB approval:** An institutional review board (IRB) is the institutional entity charged with providing ethical and regulatory oversight of research involving human subjects.
- **Privacy Rule:** Requires additional approval by a privacy board when research involves identifiable health information held by health-related entities.

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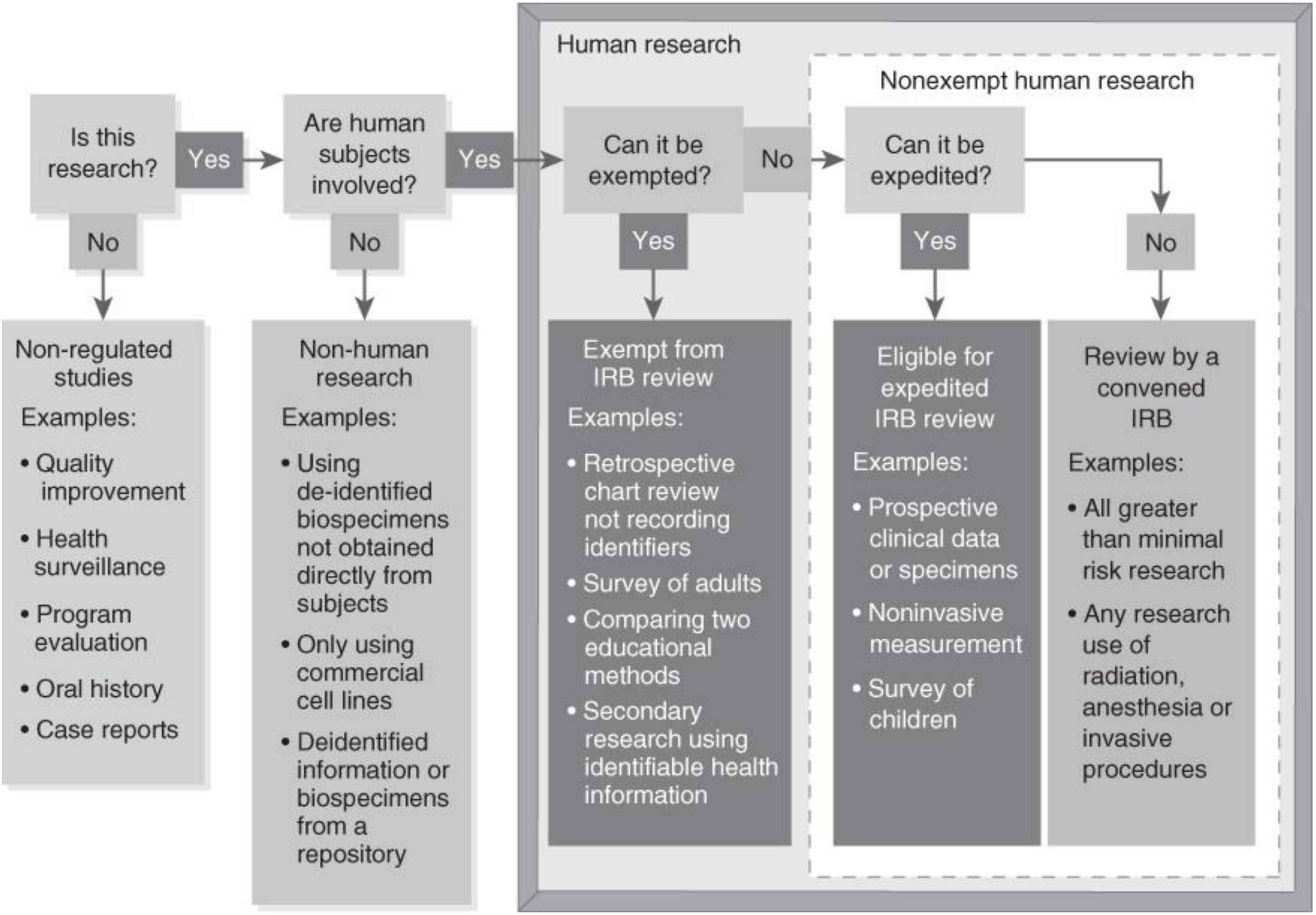
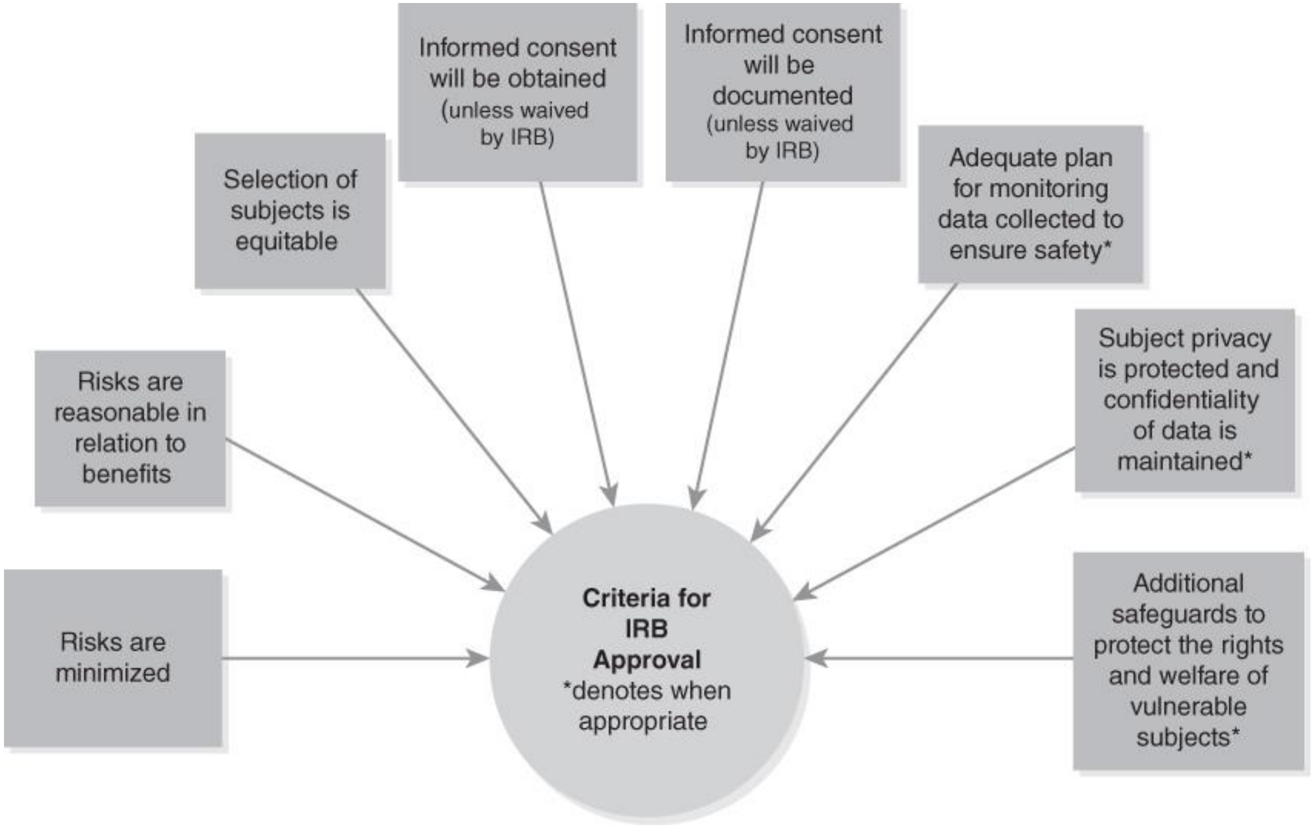
Determining whether *human subjects* are involved in research



Criteria for IRB Approval of Nonexempt Regulated Research

Convened IRB must review regulated research that does not meet criteria as either exempt or expedited.

- Committee of at least five members with varying backgrounds, expertise, diversity, and affiliations
- Uses same criteria regardless of whether it is reviewed by expedited review or the convened IRB



Informed consent will be obtained (unless waived by IRB)

Informed consent will be documented (unless waived by IRB)

Selection of subjects is equitable

Adequate plan for monitoring data collected to ensure safety*

Subject privacy is protected and confidentiality of data is maintained*

Risks are reasonable in relation to benefits

Risks are minimized

Additional safeguards to protect the rights and welfare of vulnerable subjects*

Criteria for IRB Approval
*denotes when appropriate

Elements of Informed Consent

A statement that the study involves research

- An explanation of the purposes of the research
- The expected duration of the participant's participation
- A description of the procedures to be followed
- Identification of any procedures that are experimental

Description of any reasonably foreseeable risks or discomforts

Benefits that may reasonably be expected

- To the participants (if applicable)
- To others

Alternative procedures or treatment, if any, that might be advantageous to the participant

Confidentiality of records

- The extent, if any, to which confidentiality will be maintained

Elements of Informed Consent

Injury-related care or compensation (for research involving more than minimal risk)

- Whether any compensation and medical treatments are available if an injury occurs
- If so, what they consist of, or where further information may be obtained

Contact information: Whom to contact?

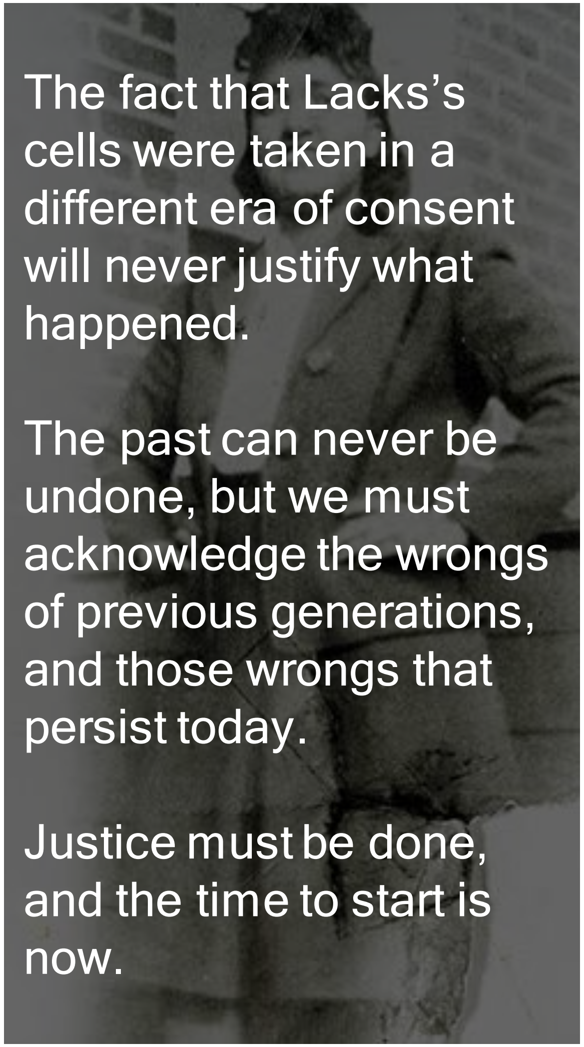
- For answers to pertinent questions about the research and participants' rights
- In the event of a research-related injury to the participant

Participation remains voluntary—no penalty or loss of entitled benefits

- By refusing to participate
- By discontinuing participation at any time

If identifiable specimens are collected, a statement on whether, if subsequently de-identified, the specimens will be used for future research or not. WHY?

Historical Context: *Henrietta Lacks and HeLa Cells*



The fact that Lacks’s cells were taken in a different era of consent will never justify what happened.

The past can never be undone, but we must acknowledge the wrongs of previous generations, and those wrongs that persist today.

Justice must be done, and the time to start is now.

“I want scientists to acknowledge that HeLa cells came from an African American woman who was flesh and blood, who had a family and who had a story,” - Her granddaughter Jeri Lacks-Whye

- Henrietta Lacks was an African-American woman whose cancer cells were **taken without her consent in 1951.**
- These cells, known as ***HeLa cells***, became the first immortal human cell line and have been used extensively in research, including COVID-19 vaccine research.
- Lack of informed consent: Henrietta Lacks was not told that her cells would be used for research.
- Identifiability and privacy: The use of identifiable specimens raised concerns about privacy and the rights of patients. Her Cells, her Genome.
- Researchers must inform participants if their identifiable specimens will be de-identified and used for future research.

Nature **585**, 7 (2020) *doi: https://doi.org/10.1038/d41586-020-02494-z*
https://hela100.org/herstory

Elements of Informed Consent

Additional information, when determined to be appropriate by the IRB

- A statement that the particular treatment or procedure may involve unforeseeable risks
- Anticipated circumstances under which the participant's participation may be terminated by the investigator without regard to the participants consent
- Any additional costs to the participant that may result from participation in the research
- The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the subject
- A statement that significant new findings developed during the research that may relate to the participant's willingness to continue participation will be provided to the subject
- The approximate number of participants involved in the study
- Statement whether specimens may be used for commercial profit and if subjects will share in the profit
- Statement whether clinically relevant research results will be disclosed to subjects and if so under what conditions
- Statement whether research might include whole genome sequencing

What Are the Investigator's Responsibilities?

- Obtaining approval for a new project
- Ensuring the study continues to meet the IRB criteria
- Communicating regularly with the IRB under certain circumstances
- IRB approval is necessary to make changes to a research study unless the modification is necessary to eliminate an immediate hazard to the participants
- Each IRB establishes a mechanism for requesting approval of modifications.

Tracking Adverse Events and Reporting UPIRSOs

Unanticipated Problem Involving Risks to Subjects or Others (UPIRSO)

Data safety monitoring plan allows investigators to:

- Track adverse events that occur
- Continuously monitor them to determine whether changes should be made to the research plan to minimize risks to participants.

Only adverse events that meet the criteria of an Unanticipated Problem Involving Risks to Subjects or Others (UPIRSO) must be reported immediately to the IRB.

What to do if we have unexpectedly positive outcomes?

Additional Responsibilities

- Complete and maintain training on human-subjects protection.
- Follow the IRB-approved protocol and the regulations and policies related to research and privacy.
- Supervise project workers to ensure they follow the protocol and rules that govern research.
- Place the protection of research participants first.
- Verify IRB approval before allowing research to begin or before implementing changes.
- Keep participants informed and ensure they are willing to continue participating.
- Ensure informed consent occurs at the beginning of research participation and continues throughout a participant's involvement in the research.
- Regularly collect and assess information about safety or unexpected problems.
- Conduct regular literature reviews for new information that may affect the study or participants.
- Ensure those working on the project are qualified and are authorized, by education, training, experience, and certifications, to perform delegated tasks.
- Provide ongoing communication with study staff.
- Confirm that the data collected are accurate.
- Maintain organized records.

Questions

Read

The Ethics of Research pg. 271

Chapter 3: From Topics to Questions

Chapter 4: From Questions to a Problem

> **“Scientific research? Only when not at the cost of ethics - and first of all, those of the researchers themselves.**
>
> *-Aleksandr Solzhenitsyn*