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The Ethics of Human Subjects Research

Agenda

- What is research?
- Why do we need mechanisms to protect research participants?
- What guidelines protect research participants?
- What makes research ethical?

What is Research?

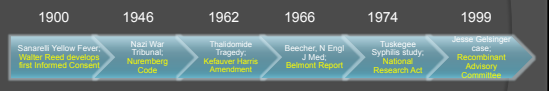
- Research – Systematic activities to advance generalizable knowledge
- Clinical care – activities designed to improve the wellbeing of a patient or client

What is Research?

- Research puts some people at risk for the good of others
  - To gain knowledge
  - Improved diagnosis, treatment
- The inherent risk associated with research creates the potential for exploitation

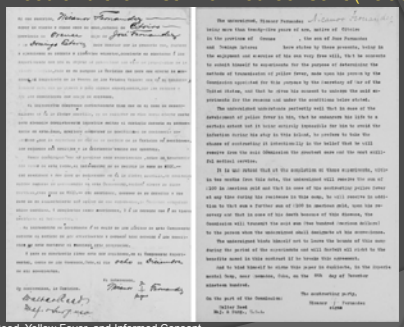
Emanuel et al. JAMA 2000.

"Born in scandal and reared in protectionism."



Levine, Law, Med, Health Care, 1988. Emmanuel et al. Johns Hopkins University Press. 2003.

Walter Reed and the First Informed Consent (1900)



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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Nazi Doctors' Experiments on Prisoners

- Twins (e.g., changing eye color, creating conjoined twins)
- Bone, muscle, nerve transplantation (without anesthesia)
- Freezing (exposure to lengthy periods of below freezing temperatures, some times naked)
- Sterilization (seeking efficient means for mass sterilization, such as drugs, x-ray, etc)
- Poisons and treatments for toxins

Nuremberg Code, 1947

- Actually the third section of the judges' decision at the Nurenberg trial
  - 6 essential elements that made research ethical were submitted to the Counsel for War Crimes
  - Judges added 4 additional elements

Nuremberg Code, 1947

1. Required is the voluntary, well-informed, understanding consent of the human subject in a full legal capacity.
2. The experiment should aim at positive results for society that cannot be procured in some other way.
3. It should be based on previous knowledge (e.g., an expectation derived from animal experiments) that justifies the experiment.
4. The experiment should be set up in a way that avoids unnecessary physical and mental suffering and injuries.
5. It should not be conducted when there is any reason to believe that it implies a risk of death or disabling injury.
6. The risks of the experiment should be in proportion to (that is, not exceed) the expected humanitarian benefits.
7. Preparations and facilities must be provided that adequately protect the subjects against the experiment's risks.
8. The staff who conduct or take part in the experiment must be fully trained and scientifically qualified.
9. The human subjects must be free to immediately quit the experiment at any point when they feel physically or mentally unable to go on.
10. Likewise, the medical staff must stop the experiment at any point when they observe that continuation would be dangerous.

Nuremberg Code, 1947

- Established that "The voluntary consent of the human subject is absolutely essential"
  - Strict interpretation would preclude important areas of medical research (e.g., pediatric medicine, emergency medicine, and mental health).
  - Largely viewed as applying specifically to one population: research on adult prisoners

Declaration of Helsinki, 1964

- Established by the World Medical Association
- Not international law, but largely codified

Declaration of Helsinki, 1964

- 24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is legally incompetent minor, the investigator must obtain informed **consent from the legally authorized representative in accordance with the applicable law**. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed in legally competent persons.
- 25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, **the investigator must obtain that assent in addition to the consent of the legally authorized representative**.

Declaration of Helsinki, 1964

- Revisions in 1983, 1989, 1996, and 2000 addressed specific items such as conformity of review committees with the laws of the country in which the research was to be performed.
- 2000 - removed distinction between therapeutic and non-therapeutic research

North American Atrocities

- Outlined 22 examples of unethical research in the United States
  - Brooklyn Jewish Chronic Disease Hospital – injecting live cancer cells into debilitated elderly patients
  - Willowbrook study – injecting hepatitis into mentally retarded children at a state public institution
- Suggested the critical elements needed
  - Informed consent
  - The more reliable safeguard is "the presence of an intelligent, informed, conscientious, compassionate, responsible investigator"
  - An experiment is ethical or not at its outset. It does not become ethical based on results. The ends do not justify the means.

Beecher, New Engl J Med, 1966

Belmont Report, 1978

- Respect for persons
  - Choices of autonomous individuals should be respected
  - People incapable of making their own choices should be protected
  - Voluntary subjects with adequate information
- Beneficence
  - Participation in research is associated with a favorable balance of potential benefits and harms
  - "Maximize possible benefits, minimize potential harms"
- Justice
  - Equitable distribution of the burdens and benefits of research
  - May not exploit vulnerable individuals or exclude without good reason eligible candidates who may benefit

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1974-1978

The Tuskegee Study

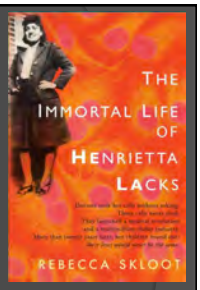
- U.S. Public Health Service project
- 600 low-income African-American males, 400 of whom had syphilis infections, monitored for 40 years
- Free medical examinations were given but participants were not told about their disease
- When penicillin became available in the 1950s, the study continued and participants were withheld treatment. In some cases, researchers intervened to prevent treatment by other physicians
- Many participants died of syphilis. The study was stopped in 1973 only after its existence was publicized in national media


The New York Times

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

Henrietta Lacks

- Cervical cancer patient whose tissue was harvested without her knowledge or consent in 1951
- HeLa cells = first human cells in vitro
  - Billion-dollar industries
  - 11,000 patents
  - Polio vaccine
  - Launched into space
- In 1970's large number of cells became contaminated and family members began receiving requests for cell donation
- In 2013, HeLa genome was sequenced and placed in dbGaP



Hudson and Collins, Nature 2013. Skloot, Crown Publishing 2010.

Jesse Gelsinger

- 18-year old participant in gene therapy trial at U Penn
  - Ornithine transcarbamylase deficiency, an X-linked genetic disease of the liver
    - Spontaneous non-lethal mutation
  - Adenoviral vector gene replacement injected 9/13/99
  - Gelsinger died 9/18/99 after a massive immune response
- FDA investigation
  - Gelsinger should have been deemed ineligible due to high ammonia levels
  - Previous AEs had not been reported
  - Preclinical data had not been reported
  - James Wilson, PI, had conflict of interest

Ethical and Regulatory Guidance

- Local guidance and policy
  - UC Office of the President (UCOP)
  - Local Institutional Review Board (IRB)
- State of California: Dept of Health Services (DHS)
- Federal
  - The Common Rule, Title 45 CFR, Part 46
  - OHRP (Office for Human Research Protections) has jurisdiction over Department of Health and Human Services (DHHS) via 45CFR46
  - FDA (Food and Drug Administration) has jurisdiction over all research involving food, biologics, drugs and devices via 21 CFR

Historical Perspective: US Regulatory System

1906 – Food & Drug Act

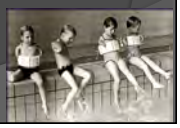
Response to deaths of several children due to contaminated smallpox vaccines

1938 – Food, Drug, and Cosmetics Act

Response Sulfanilamide disaster

1962 – Kefauver-Harris Amendment

Response to thalidomide tragedy



Department of Health and Human Services (DHHS)

- 45CFR Part 46 Common Rule (enforced by OHRP):
- The Common Rule: Federal Policy for the Protection of Human Subjects
  - Subpart A: Basic HHS Policy (basic human subjects, IRB regulations)
  - Subpart B: Pregnant women, Fetuses and Neonates
  - Subpart C: Prisoners
  - Subpart D: Minors

Updates to the Common Rule

Effective July 19, 2018

1. If the institution is federally funded at all, the common rule applies to all research
2. Shorten consent to focus on "essential information that a reasonable person would want to know" but also inform participants that biospecimens might be used for commercial profit, tell them whether they will be informed of clinical findings, and ask if they could be recontacted for additional research
3. Secondary research on identifiable data or specimen will require consent – permits broad initial consent
4. Defines four categories or review (excluded, exempt, expedited, full)
5. No continuing review for excluded and exempt research. Default for expedited research would be no continuing review. For full review, continuing review ceases once recruitment and treatment are complete.
6. Single review for multisite studies

Emanuel, N Engl J Med 2015.

State of CA Health and Safety Code: SECTION 24170-24179.5

- Protection of Human Subjects in Medical Experimentation Act
- Requires "experimental subject's bill of rights"
  - Last page of the Informed Consent Form (ICF)
- Defines Legally Authorized Representative (use of proxy or surrogate)
- Specifies that children 7 years of age or older must also consent to research, not just their parent(s) (LAR)

What Makes Human Subjects Research Ethical?

"Born in scandal and reared in protectionism."

- Ezekiel Emanuel, David Wendler, and Christine Grady recognized the reactive nature of the leading ethical guidelines created in the 50 years since Nuremberg and the resultant lacunae, inconsistencies, and contradictions
- "*Absent a universally applicable ethical framework, investigators, IRB members, funders, and others lack coherent guidance on determining whether specific clinical research protocols are ethical*" (p 2702)

Emanuel et al. JAMA 2000.

Criteria for Ethical Research

1. Social value
2. Scientific validity
3. Fair selection of subjects
4. Favorable risk-benefit ratio
5. Independent review
6. Informed consent
7. Respect for enrolled subjects

Emanuel et al. JAMA 2000.

1. Social Value

- Research must have meaningful value
- 2 reasons that value is an ethical requirement
  - Resources are limited
  - Exploitation is unacceptable
- Research that is nongeneralizable, tests a trifling hypothesis, overlaps substantially with proven knowledge, or will not be disseminated is not ethical

Emanuel et al. JAMA 2000.

2. Scientific Validity

- Methodological rigor is essential for research to be ethical
- If the study will not produce meaningful knowledge, participants are needlessly put at risk
  - Appropriately planned
  - Scientific protocol
  - Analysis plan
  - Adequate power
  - Feasible

Emanuel et al. JAMA 2000.

3. Fair Subject Selection

- Scientific objectives should determine subject selection
- Subjects cannot be selected either due to vulnerability nor to privilege
- Subjects should be selected to minimize risk (those at increased risk should be excluded)
- Groups enrolled should stand to benefit from the research

Emanuel et al. JAMA 2000.

4. Favorable Risk-Benefit Ratio

- Risks to the individual must be minimized
- Benefits to the individual must be maximized
- The benefits to individuals and society are proportionate to or outweigh the risks
- Proportionality is non-quantifiable and inherently subjective

Emanuel et al. JAMA 2000.

The Logic of Clinical Purpose

Placebo is acceptable when

1. Conditions that have no standard therapy at all.
2. Conditions whose standard therapy has been shown to be no better than placebo
3. Conditions in which the standard therapy is placebo
4. Conditions in which the standard therapy has been called into question based on evidence calling into doubt net therapeutic benefit
5. Conditions whose validated optimal treatment is not made freely available to patients, because of cost constraints or otherwise.

Freedman B, IRB, 1990.

Equipoise

- A state of genuine uncertainty within the medical community, not necessarily on the part of the clinical investigator, regarding the comparative therapeutic merits of each arm in a trial.

Freedman B, N Engl J Med, 1987.

5. Independent Review

- Investigators, despite being the first line of protection of subjects, have inherent conflicts of interest
  - Desire to see research completed quickly
  - Desire to obtain funding
  - Desire to advance career
- Approval from an Institutional Review Board or other ethical body is mandatory
  - Ensures social value of research, protection of participants

Emanuel et al. JAMA 2000.

6. Informed Consent

- A detailed but understandable explanation of the risks, procedures, and requirements of study participation
- States that the participant is a volunteer, not obligated to participate and free to withdraw at any time with out any penalty

Informed Consent Does Not

- Bind a participant
- Make a research study ethical

Informed Consent 3 Essential Elements

1. Adequate information is provided
2. The potential enrollee has decision-making capacity
3. Decision is voluntary, without coercion or undue influence

Kim SYH. The informed consent process: Compliance and beyond. In: Clinical trials in Neurology, Design Conduct, analysis. Eds: Ravina B, Cummings J, McDermott M, Poole RM. Cambridge University Press.

- Coercion: when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance
- Undue Influence: an offer of an excessive, unwarranted, inappropriate, or improper reward or other overture in order to obtain compliance

Payments to Research Subjects

- Reimbursement – Participation should be free of charge
- Compensation – Participants can be offered fair wage for the time and effort of participation
- Incentive – Payment beyond fair wage may be necessary to improve the rates and timeliness of study accrual

Gelinas et al., N Engl J Med 2018

Terminology

- Decision-making capacity
- Capacity
- Competence
- Evidencing a choice, understanding, appreciation, and reasoning

Kim SYH. The informed consent process: Compliance and beyond. In: Clinical trials in Neurology, Design Conduct, analysis. Eds: Ravina B, Cummings J, McDermott M, Poole RM. Cambridge University Press.

Surrogate Consent

- Conditions that impair capacity are critical areas of research
- To conduct human studies, alternative methods of consent are required
- In some but not all states a legal path has been laid to attain informed consent from a surrogate decision-maker

Assent

- If a potential participant is deemed unable to provide consent, it might be acceptable to attain consent from a surrogate
- In these cases, the patient must still provide *assent*
  - Affirmative response that they wish to participate

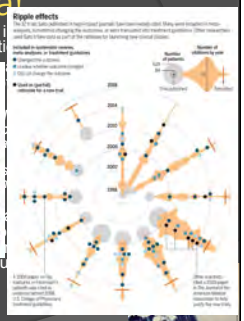
7. Respect for Individuals

1. Confidentiality
2. Opportunity to change mind
3. Updated information
4. Monitor welfare
5. Provide information on study outcomes

Emanuel et al. JAMA 2000.

Don't Make Up Data!

- Sato and colleagues fabricated data i
  trial publications describing 5894 pati
  never approved studies ay other grou



Bolland et al., Neurology 2016. Kupferschmidt, Science 2018.

Summary

- Research gains knowledge essential to medical advances
- Unethical research behaviors have largely driven the development of ethical and regulatory guidelines for research conduct
- Basic elements are essential to ethical clinical research