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Introduction to Research Ethics with Human Subjects Informed Consent and Capacity

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No Conflict of Interest

Objectives

- Discuss historical influences on research ethics and the seven tenets of research ethics.
- Identify the nine required elements for informed consent.
- Identify regulatory and ethical components to human protection related to participant capacity.
- Identify the functional elements of capacity/competence determination with
- Evaluate IC elements with respect to children and adults and the legally authorized representative (LAR)

Applied Ethics

- Bioethics
  - Clinical Ethics
  - Research Ethics
- Business Ethics
- Social Ethics
- Environmental Ethics
- Professional Ethics

What is Research Ethics?

- ensure that biomedical research is conducted responsibly in a way that serves the interests of individuals, groups and/or society as a whole
- to protect human and animal participants
- to examine specific research activities and projects for their ethical soundness (management of risk, protection of confidentiality and the informed consent process)
- International and Domestic influences

- Importance: builds trust, public accountability and public support for science (trust that scientific data is correct)

Yellow Fever Research

- 1901

Walter Reed

Clara Maas

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Events leading to current research regulations

Examples of unethical research:

a) Nazi experiments:

- Mengele's studies on twins
- Hypothermia
- High altitude

b) response: Nuremberg Code & Trial (1946-49)

Tuskegee's syphilis study (1932-1972)

- The facts

- The Consequences
  - 1969: Blue ribbon panel on whether study should continue: *Why only blacks? Why don't they get treatment?*
  - 1974: US National Research Act: federal regulations, IRB, informed consent
  - 1979 Belmont Report

HeLa

George Gey

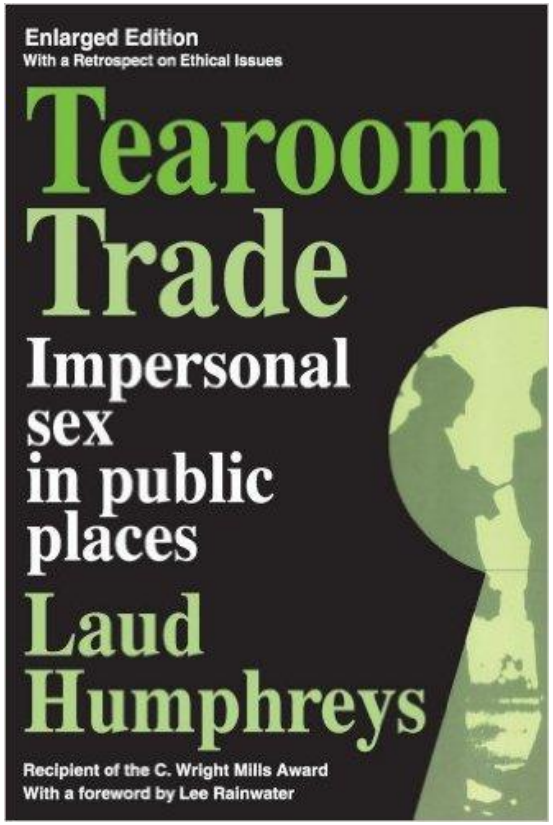
Henrietta Lacks

Henry Beecher's paper Ethics and Clinical Research, *NEJM*, 1966 – 22 examples:

- **Willowbrook State School, NY:** study the national progression of hepatitis in children

- **Jewish Chronic Disease Hospital, NY:** injecting pts. with cancer cells without consent

1961-1962 Stanley Milgram electric shock therapy studies. publishes Obedience to Authority in 1974.



Laud Humphreys

Time-line of Regulations

- 1946 -1949 Nazi Trails and Nuremberg Code (developed to evaluate the conduct of Nazi doctors: *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10", Vol. 2, pp. 181-182. Washington, D.C.: U.S. Government Printing Office, 1949).*
- 1964 Declaration of Helsinki, World Medical Association(2001)
- 1974: National Research Act
- 1979: Belmont Report (by National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research)
- 1993, 2002: WHO International Guidelines

Regulations: Key Contributions

- **1946 -1949:** Nuremberg Code: consent is "absolutely essential", participants free to withdraw, soundness of research, qualified researchers
- **1964:** Declaration of Helsinki: well-being of subjects take precedence over society's, written consent required, access to benefits, limited use of placebo, avoiding dependency
- **1979:** Belmont Report: 3 principles of research ethics – respect for persons, beneficence, justice

Ethical Principles from Belmont

- RESPECT: not merely giving information but empowerment (creating conditions enabling free decisions) - the informed consent process
  - RESPECT extends to a person's culture, community
  - preventing THERAPEUTIC MISCONCEPTION
- BENEFICENCE: mental, physical, social well-being; reducing risk, protecting participants, access to benefits for the community where research is conducted
- JUSTICE: fair distribution of risks/benefits; equitable recruitment of participants, protecting the vulnerable – disabled, or socio-economic vulnerability to exploitation

Key US Regulations and Guidelines

- Common Rule 45CFR.46
  - Subparts B,C,D
- FDA Regulations (US21CFR 50 & 56)

The International Conference on Harmonization (ICH-GCP)

An international quality standard that is provided by the International Conference on Harmonisation (ICH)

Goals: Harmonize technical procedures and standards; improve quality; speed time to market.

In 1997, the FDA endorsed the GCP Guidelines developed by ICH

ICH guidelines have been adopted into law in several countries, but used as guidance for the FDA in the form of GCP

13 Tenets of ICH-GCP

Ethics:

1. Ethical conduct of clinical trials
2. Benefits justify risks
3. Rights, safety, and well-being of subjects prevail

Protocol and science:

4. Nonclinical and clinical information supports the trial
5. Compliance with a scientifically sound, detailed protocol

Responsibilities:

6. IRB/IEC approval prior to initiation
7. Medical care/decisions by qualified physician
8. Each individual is qualified (education, training, experience) to perform his/her tasks

13 Tenets of ICH-GCP

Informed Consent:

9. Freely given from every subject prior to participation

Data quality and integrity:

10. Accurate reporting, interpretation, and verification
11. Protects confidentiality of records z Investigational Products
12. Conform to GMP's and used per protocol

Quality Control/Quality Assurance

13. Systems with procedures to ensure quality of every aspect of the trial

Ethical Framework of Research -

- **Value**—enhancements of health or knowledge must be derived from the research.
- **Scientific validity**—the research must be methodologically rigorous
  - "good ethics = good science"
- **Fair subject selection**—scientific objectives, not vulnerability or privilege-based, distribution of benefits
- **Favorable risk-benefit ratio:** minimize risk, risks to subject proportional to benefits

(Emanuel 2000)

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Ethical Framework of Research -

- **Independent review**

-Review the design, population, risk benefit ratio by individuals unaffiliated with the research

- **Informed voluntary consent**

- **Respect for enrolled subjects:** privacy protected, right to withdraw, monitoring is necessary and sufficient to make clinical research ethical.

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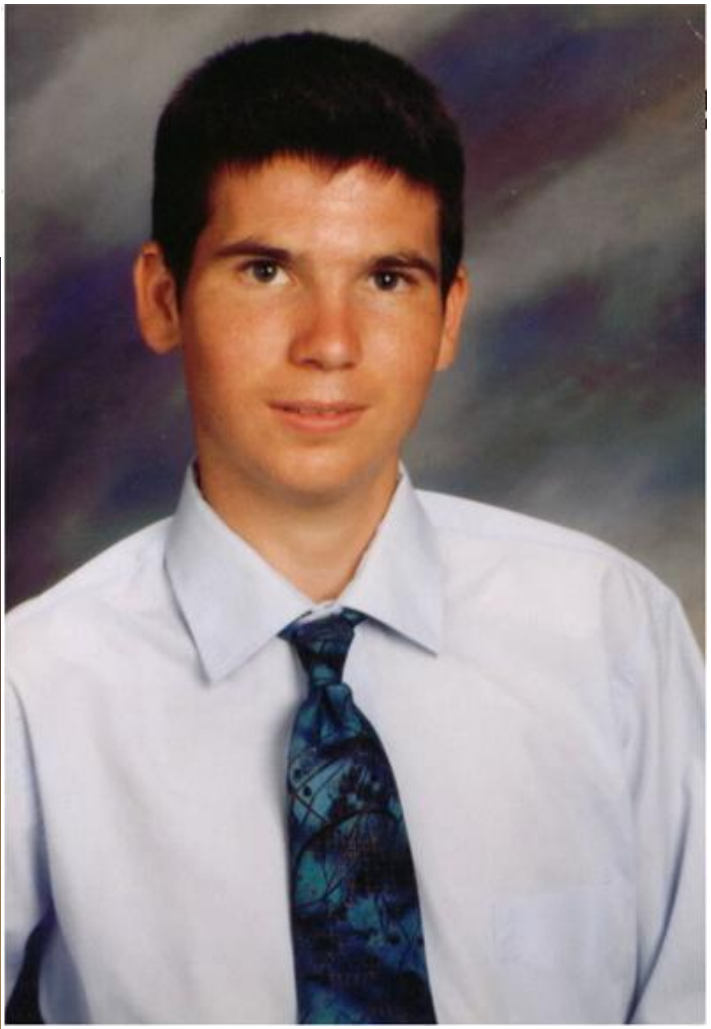

James Wilson

Jessie Gelsinger

2001 Ellen Roche

GU · HU · MHRI · ORNL · WDCVAMC

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Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) Study Group of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development

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Dr. Alexander Neumeister,

Ethical Empowerment

- To influence research from an ethical perspective
- Be knowledgeable in ethical principles and models
- Respect, Transparency and Honesty
- Facilitating discussion and encouraging engagement-promote structure; role modeling
- ANA Code- advocacy and communication
- Research team members gain power through establishing positive, collegial, working relationships with physicians, reserchers and all the members of the team. Productive relationships increase your power to base decisions on ethical principles.

Informed Consent

The person involved should be so situated as to be able to exercise free power of choice and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decisions –

The Nuremberg Code

Informed Consent

The informed consent process involves four key ethical features:

(1) disclosing to potential research subjects information needed to make an informed decision;

(2) facilitating the understanding of what has been disclosed; and

(3) promoting the voluntariness of the decision about whether or not to participate in the research.

(4) ensuring participant capacity to participate in consent fully or partially

Special Considerations

- Emergency
- Pregnant women, fetus and neonates
- Children
- **individuals with impaired decision making capacity or economically or educationally disadvantaged persons**
- Minorities/Non-English speakers
- Prisoners
- Incapable participants

Particularly Vulnerable

- Some people with mental illness, including certain elderly patients suffering from dementia.
- Substance abusers, who may be vulnerable to coercion.
- Homeless patients, who may perceive a benefit to participating in a research study, such as being able to sleep in a hospital.
- Patients who are desperately ill and particularly vulnerable to therapeutic misconception.

Informed Consent

- If the investigator can reasonably interact with the research participant, an informed consent document should be completed.
  - Consent form templates are available on the website
  - Depending on the project, consent may be implicit (e.g. completing and returning a survey may be considered consent to participate)
  - You may not be required to use the informed consent document, but instead the IRB may ask that you use a cover letter describing confidentiality and voluntary participation.

Broad Consent

- Covers both the subject of the investigator's current research and future unspecified research using the same data or biospecimens
- Commercial profit
- Genome sequencing
- Data sharing

Nine Required Elements of Informed Consent Document

1. Statement that the study involves research, the purpose of the research, and the expected duration of the subject's participation, description of the procedures, identification of any procedures that are experimental.
2. Description of risks or discomforts
3. Description of benefits
4. Alternative procedures or treatments
5. Confidentiality of records

Elements (continued)

6. Greater than minimal risk studies – description of medical treatment for injury and who is responsible for payment.
7. Who to contact for answers pertaining to research subject rights and who to contact in the event of research-related injury
8. Statement that participation is voluntary, refusal to participate will involve no loss of benefits, subject may discontinue participation at any time without penalty
9. Study must be registered with ClinicalTrials.gov if it meets the criteria

New Consent Regulations

beginning of the informed consent include a concise explanation of the following:

- (a) the fact that consent is being sought for research and that participation is voluntary
- (b) the purposes of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research;
- (c) the reasonably foreseeable risks or discomforts to the prospective subject;
- (d) the benefits to the prospective subject or to others that may reasonably be expected from the research; and
- (e) appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the prospective subject.

Additional Issues with Consent Process

- Incidental findings
  - Anticipate/unanticipated findings
- Secondary findings
- Process for disclosures to participants

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IRB Review of Informed Consent

An IRB can waive or alter some or all the required elements of informed consent:

45 CFR 46.116© IRB may waive or approve an alteration of informed consent in some research examining state or local public benefit or service programs or certain features of those programs.

45 CFR 46.116(d) IRB may waive or approve an alteration of informed consent in research that meets four specified criteria.

45 CFR 46.408© IRB may approve waiver of parental permission in certain research involving children.

Waiver of **documentation** of informed consent

An IRB may waive the requirement to obtain a signed consent form for some or all subjects if it finds either:

- That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research and the subject's wishes will govern; or
- That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (e.g., drawing a blood sample, or asking shoppers in a mall about the ambient lighting or temperature).
- Emergency Conditions with stipulations

Waiver of Informed Consent **Elements**

- An IRB may approve research for which some or all of the elements of informed consent at 45 CFR 46.116 (a) and (b) have been altered, or for which some elements have been left out.
- The IRB may approve such research in which investigators will leave out or alter elements of informed consent, so long as the research meets the criteria for approving research in 45 CFR 46.111, and the research meets the criteria specified in the HHS regulations for leaving out or altering those elements.

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Why Do We Need to Improve Informed Consent?

Even after signing a consent form, many still do not understand basic information about the risks and benefits

Factors:

- Low health literacy
- Limited English proficiency
- Cognitive impairments
- Confusion about the purpose of consent process
- Feeling of intimidation, and stress or time pressure

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Electronic Informed Consent

- Greater than 18 years of age
- Online consent must present each required element one at a time.
- Low risk studies only
- Must be able to print copy of consent
- Technology must ensure privacy and confidentiality
- Full signature regulations

Consider the Possible Risks for Social and Behavioral Studies

- Invasion of privacy
- Loss of confidentiality
- Psychological trauma
- Embarrassment and humiliation
- Social stigma
- What else?

Coercion and Undue Influence

- Study teams
- Participant families

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Capacity Elements

Elements

- (1) Understanding
- (2) Appreciation
- (3) Reasoning
- (4) Choice
- (5) Values- Altruism

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Clinical Assessment of Capacity- Understanding

- 1. To understand what entering and remaining in the study is and why.
- 2. To understand in broad terms the nature of the study.
- 3. To understand the potential benefits and risks of participating.
- 4. To understand what will be the consequences of not being in the study.

Marginally Capable

- Children
- Mentally Ill
- Disease Progression
- Diagnosis
- Legally Incompetent
- Fluctuating capacity

Vulnerable population

(Marginally) Capable Participant:

- Assumption that the subject is unable to understand
- Assumption that proxy can evaluate the risks and benefits of the research
- Assumption that subjects may agree to research in order to please
- Proxy may persuade the subject to participate
- Proxy could prevent participation even when subject indicates desire to participate
- At what level of capacity is proxy consent desirable or required
- Are there obligations of proxy for investment in research?
  - Relief of suffering
  - Preservation and restoration of function
  - Quality and extent of life

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Capacity Considerations by Age 0-7; 7-14; 14-21 years

- 18 years presumed capable
- < 7 years-lack cognitive function for autonomy;
- 7-14 years- at age 7 distinguish right from wrong
- 14-21 years- at age 14 legally and socially accountable for actions
- Cognitive development → moral development → autonomy development

- Assess willingness and consistency

Assessment of Capacity-Process

- Affirming- no dissent
- Two step consent
- Post-consent – written test
- Standardized cognitive tests
- Independent assessment
- UCSD Brief Assessment of Capacity to Consent
  - UBACC
- MacArthur Competence Assessment Tool
  - MacCat-CR

Criteria for Legally Authorized Representative

- must have decision making capacity
- must know the patient and his/her values
- no undue conflict of interest
- no serious emotional conflict

Rights of a LAR

- To be fully informed
- To review the informed consent
- To make any and all decisions
- To withdraw the participant at any time

Responsibilities of a LAR

- 24/7 availability
- Be present and accountable
- Must follow any directives made by the participant
- Act in a way that agrees with their religious and moral beliefs
- Act in a way that the person would
- Act only after you are fully informed and understand
- Be knowledgeable
- Ask questions

The on-going process of Informed Consent

To meet the federal requirements for informed consent, the consent process must have all of the following attributes:

- An investigator (or approved designee) will obtain the informed consent of the potential participant or the participant's legally authorized representative, unless the requirement for consent has been waived or altered by the IRB.
- The circumstances of the consent process will provide the participant or legally authorized representative sufficient opportunity to consider whether to participate.
- The circumstances of the consent process will minimize the possibility of coercion or undue influence.
- The information provided during the consent process will be presented in language understandable to the research participant or the participant's legally authorized representative.
- The information being communicated during the consent process is free of exculpatory language through which the participant or legally authorized representative is made to waive or appear to waive any of the participant's legal rights or to release (or appear to release) the investigator, sponsor, or facility (or its agents) from liability for negligence.

Tips

- Speak plainly
- Write to grade level of audience
- Use active voice, short words
- Make it simple
- Don’t dictate
- Break it down
- Be straightforward
- Quiz the potential participant
- Don’t rush a decision

Tips

- Ask what the subject *expects* and *hopes for* in terms of benefits
- Assess perceptions of risks and benefits to ascertain if risks may be *under*estimated or benefits *over*estimated
- Ask about motivations for participation
- Highlight key differences between research and usual clinical care

Tips
Images, video, multimedia

- Useful for showing things that are hard to describe in text or are difficult concepts for many people
  - study procedures
  - probabilities
- Should not replace in person, individualized consent, but may be a helpful supplement

ICF Required Language

- avoidance of pregnancy
- research related Injury
- commercial interest language
- contact information
- Payment

See Template

The witness

Impartial Witness as “a person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject’s legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

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Just Process of Research

- Collaboration Issues –Authorship, Data ownership, management
- Conflict of interest
- Scientific Misconduct
  - fraud, data fabrication, plagiarism

Authorship- Example

- Vittone- conception and design, IRB, IC development, data acquisition, interpretation, drafting
- Coleman- conception and design, analysis, interpretation, drafting
- Giffin- conception and design, interpretation, drafting
- Vargas- conception and design, interpretation
- Sloss- data acquisition
- Anderson- data analysis, drafting
- Yearwood- data analysis, drafting
- Spencer- conception and design, data acquisition, analysis, interpretation, drafting, final proof

Protocol Creep

Consider the Possible Risks for Social and Behavioral Studies

- Invasion of privacy
- Loss of confidentiality
- Psychological trauma
- Embarrassment and humiliation
- Social stigma

More Issues for Survey Participants

- Compensation
- Hawthorne Effect
- Timing to Recruit
- Excessive data collection

Risks for Bench Science

- Data selection- reproducibility
- Funding- creates COI
- Peer review-COI
- Use of biobanks
- Use of discarded tissue

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Therapeutic misconception

The therapeutic misconception occurs "when subjects consent to participate in clinical research because of the belief that they will receive the same individually focused treatment that they would receive in a non-research clinical context." (Lidz 2002)

- ✓failure to appreciate the distinction between the imperatives of clinical research and of ordinary treatment

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New Regulations

- Single IRB-Jan 2018 (NIH)
- Common Rule Revisions (2020)
  - Informed Consent (format/exec summary)
  - Broad data consent (unspecified research)
  - Exempt research (expanded to 8 categories)
  - sIRB
  - Criteria for IRB approval-vulnerable is expanded
  - IRB Review (Cont Review)

Retraction Watch

- The mission of the Center for Scientific Integrity, the parent organization of Retraction Watch, is to promote transparency and integrity in science and scientific publishing, and to disseminate best practices and increase efficiency in science.
- http://retractionwatch.com/the-center-for-scientific-integrity/

Compassionate Use

- Compassionate use grants individuals access to a drug or device that hasn't been approved for sale or use in the United States by the Food and Drug Administration (FDA).
- Normally patients in the U.S. have access to such unapproved medical products only by enrolling in a clinical trial. Compassionate use does not involve enrolling in a clinical trial

Right to Try

- the laws don't require a manufacturer to actually provide the investigational medical products upon request.
- Right-to-try laws raise an important ethical concern: They create false hope in desperately ill people that they can obtain something they may, in fact, not be able to get.

Emergent Use

- Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)].
- Informed Consent is still required
- Conditional exceptions

Pediatric Tenets

- Capacity to assent
- Voluntariness
- Risk/Benefit (and mitigation plan)
- Mandatory Reporting
- Privacy/Confidentiality Risk
- Recruitment
- Payment

Top Vittonian Concerns in Research Ethics

- Peer Review Bias
- Replicability
- Informed Consent (capacity)
- Use of BIG DATA
- Participant self report data
- Privacy and Anonymity
- Skill of the Primary Investigator
- Role Conflict
- Inclusion of participants of culture, gender, age,etc
- Recruiting

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Resources

- NIH Course PHRP: http://phrp.nihtraining.com/users/PHRP.pdf
- Time-line: http://www.niehs.nih.gov/research/resources/bioethics/timeline/index.cfm
- What is Ethics of Research? (Cases, Definitions), by D. Resnik, NIEHS IRB Chair: http://www.niehs.nih.gov/research/resources/bioethics/whatis/
- HHH Final Rule Research Misconduct- http://www.ori.dhhs.gov/sites/default/files/42_cfr_parts_50_and_93_2005.pdf
- IRB Role & Responsibilities: http://www.niehs.nih.gov/about/boards/irb/index.cfm

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