



UNIVERSITY *of* MARYLAND
THE FOUNDING CAMPUS

Informed Consent:

Regulatory & Ethical Considerations

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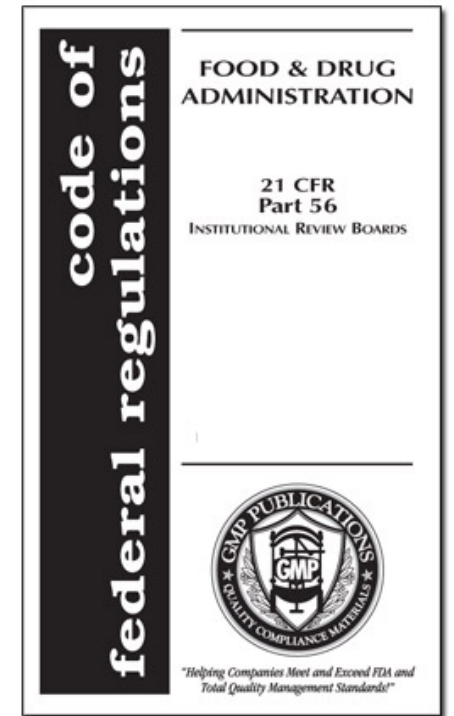
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Learning Objectives

- **Historical perspective on research ethics**
 - Focus on consent
- **Discussion of Federal Regulations**
 - *Informed Consent of Human Subjects*
 - *Vulnerable Populations*
 - *Assent versus Consent*
 - *Waiver of informed Consent vs. Exception from Informed Consent*
 - *Institutional Review Boards (IRBs)*



RESEARCH ETHICS: A BRIEF HISTORICAL PERSPECTIVE

Human Subject Research: Balancing Two Goals



**Protection of
Subject Welfare/Rights**

**Advancement
of Science**



Nuremberg Code (1947)

First Codification of Research Guidelines

- Informed consent
 - No coercion
 - Free to stop any time
- Supporting scientific data and value
- Favorable risk/benefit ratio
 - Anticipated results justify the risks
- Subjects suffering should be avoided
 - No expectation of death/disability

“The voluntary consent of the human subject is absolutely essential.”

Lessons Learned from Nuremberg Trials

- **Medical Practice**

- Clinical Ethics: guided by Hippocratic Oath
 - Patient is silent
 - “dutifully obedient” to the beneficent physician
 - Doctor’s primary obligation is the patient

- **Research**

- Outside of the patient/physician relationship
 - Primary goal is to test a hypothesis
 - Secondary obligation is to participant

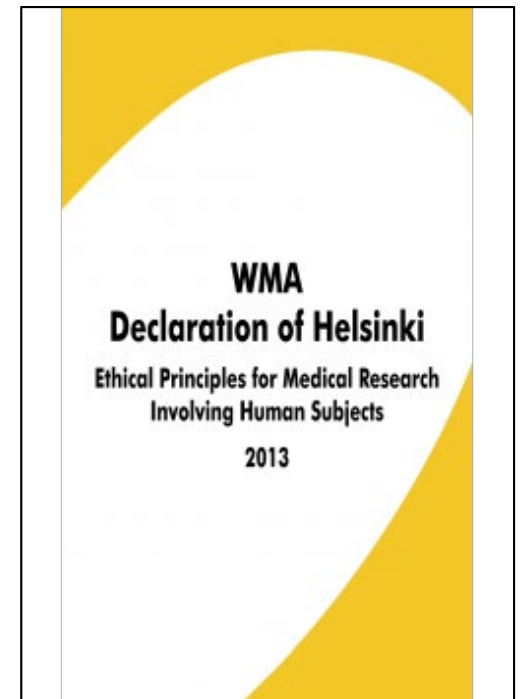
- **Conflict of Roles?**



Declaration of Helsinki

World Medical Association

- Adopted by the 18th WMA General Assembly
 - Helsinki, Finland in June 1964
 - Multiple subsequent amendments
- Updated informed consent
 - Consent individuals
 - Capable of giving informed consent
 - Consent may not always be possible



Tuskegee Syphilis Study (1932 - 1972)

Ethical Imperatives



- Inadequate disclosure of information
- Subjects believed they were getting free treatment
- Told that spinal taps were therapy
- US Government actively prevented men from receiving penicillin (first used in 1943)
- 1972 press reports caused the U.S. Government to stop the study

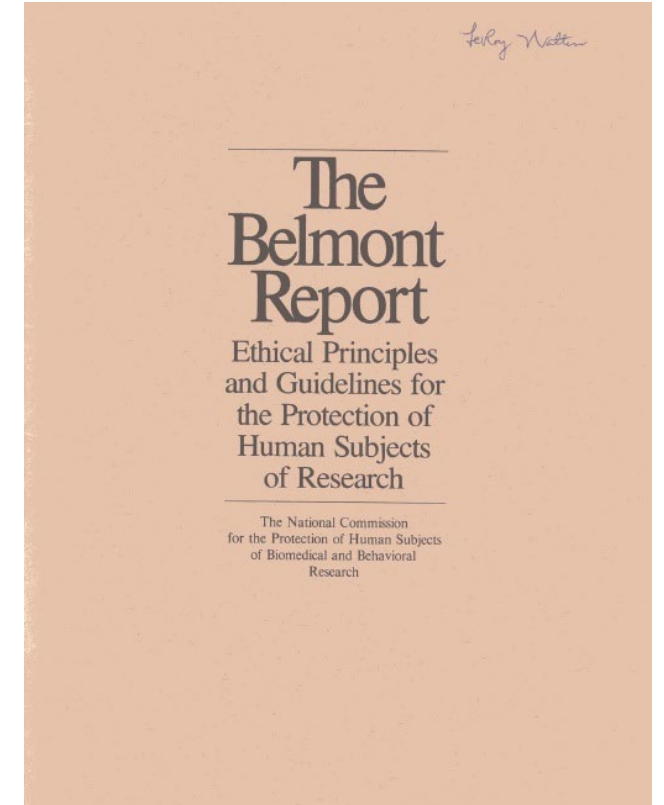
Tuskegee: Ethical Lapses

- Lacking in Social Value
- Scientifically Invalid Study
 - Existing therapy for syphilis
- Unfair Subject Selection
- Unfavorable Risk-Benefit Ratio
- Failure of Independent Review
- Invalid Informed Consent Process
 - No provisions for ongoing consent
- Lack of Respect for Enrolled Subjects:
 - Failure to provide new information
 - Coercive activities

The Belmont Report

April 18, 1979

- **Basic ethical principles**
 - **Respect for Persons**
 - Autonomy
 - **Beneficence**
 - Maximizing benefits while minimizing risks
 - **Justice**
 - Fair distribution of costs and benefits



Key Principles

- **Nuremberg Code 1949**
 - Emphasis on individual, informed, voluntary, legal consent without fraud, deceit, duress
 - Minimizing risks, risks justified relative to benefits
 - Prepared to terminate study when necessary
- **Declaration of Helsinki 1964 *plus revisions***
 - World Medical Association
 - Expanded and includes vulnerable and legally authorized representatives, assent
 - Duty to protect the life, health, privacy, and dignity of subjects
 - Privacy, confidentiality, oversight, etc.
- **Belmont Report 1979**

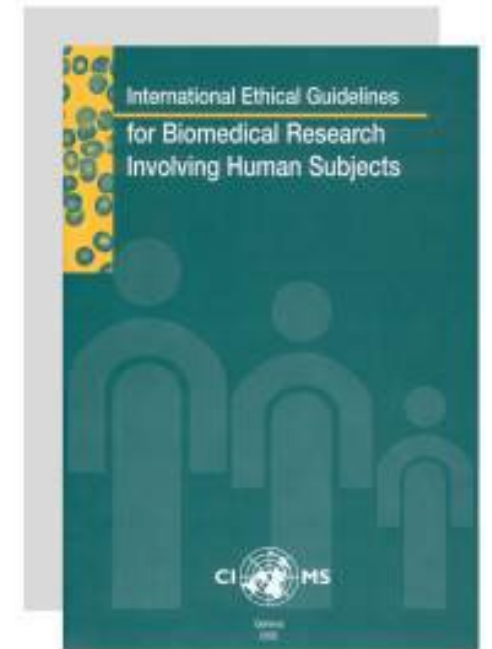
International Codes

CIOMS

- **Council for International Organizations of Medical Sciences**

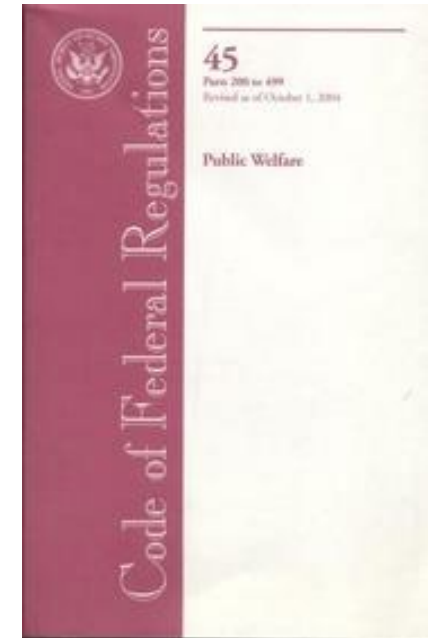
- International Ethical Guidelines for Biomedical Research Involving Human Subjects (2003):

“The challenge to international research ethics is to apply universal ethical principles to biomedical research in a multicultural world with a multiplicity of health-care systems and considerable variation in standards of health care.”



“The Common Rule”

- The HHS regulations, [45 CFR part 46](#) include
 - Four subparts:
 - *Subpart A: the Federal Policy or the “Common Rule”*
 - *Subpart B: pregnant women, human fetuses, and neonates*
 - *Subpart C: prisoners*
 - *Subpart D: children*
 - Published in 1991, revised 2018
- **Separate from FDA regulations**
 - FDA harmonizes with the Common Rule
 - Whenever permitted by law



INFORMED CONSENT

45 CFR 46.116 (HHS)

21 CFR 50.20 (FDA)

What is Informed Consent?

It is a process- not just a document!

- Disclosure to potential participants
 - Needed information to make an informed decision
- Facilitate the participant's understanding
- Promoting the voluntariness of the decision
 - Whether or not to participate in the research

Informed Consent: Basic Elements

- 1) Statement that this is research
Including purpose and duration
- 2) Description of risks
- 3) Description of benefits
- 4) Disclosure of alternatives to research

Informed Consent: Basic Elements (cont.)

- 5) Confidentiality of records and who can inspect them
- 6) Discussion of compensation/treatment for research related injury

Particularly for greater-than-minimal risk research

- 7) Information about subject's rights

Explanation of whom to contact for questions

- 8) Statement that participation is voluntary

Informed Consent

Informed consent helps determine if the research fits subject's values, interests and goals.

- Includes:
 - Disclosure of adequate information to the potential participant.
 - Risks and benefits
 - Required activities of participant
 - Duration of involvement in research
 - Adequate understanding by the participant
 - Voluntariness of the decision

Quality of informed consent

Informed consent in research is important, but imperfect.

- A patient with recurrent breast cancer is sitting in the waiting room.
- She is asked to read and sign a comprehensive consent document detailing all the risks and benefits of experimental chemotherapy with four new agents.
- The informed consent document is 34 pages

Quality of informed consent

- Consent forms are comprehensive
 - Can be complex and incomprehensible
 - Use of the concise summary
- Importance of personal explanation, time to digest
- Ongoing consent process
 - Subject may leave study at any time at his/her discretion

Informed Consent

**It's the process, not the
paper!**

Vulnerable Population

- **Pregnant Women, Human Fetuses and Neonates*** (45 CFR 46, Subpart B)
- **Prisoners*** (45 CFR 46, Subpart C): requires prison advocate review
- **Children*** (45 CFR 46, Subpart D)
- **Cognitively Impaired/ Impaired Decision-Making Capacity**
- **Students/employees**
- **Wards of the State**

* Indicates specific regulations in federal code

Assent Versus Consent

- **Consent:**
 - Permission given by someone who can legally give approval
- **Assent:**
 - Agreement to participant in the research
 - Given by someone not legally able to give approval
 - For children, ability to give assent varies by age
 - Each IRB may determine specific age

Legally Authorized Representative

- Legally authorized representative (LAR) means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research ([45 CFR 46.102\(c\)](#)).

Short Form Consent

- Written consent document stating that the elements of informed consent have been orally presented to the participant or the participant's LAR
 - Short form is signed by the participant or LAR
 - Copy of short form and summary shall be given to the participant or LAR
- IRB has approved a written summary of what will be orally presented
- Must have a witness of the oral presentation
 - Witness shall sign both the short form and a copy of the summary
- Person obtaining the consent shall sign a copy of the summary
- Primarily used when the full consent has not been translated into the participant's language

WAIVER OF CONSENT VS. EXCEPTION FROM INFORMED CONSENT (EFIC)



WAIVER OR ALTERATION OF INFORMED CONSENT

45 CFR 46.116(d)

To Waive or Alter Informed Consent

- **4 Conditions**

- the research involves no more than minimal risk to the subjects;
- the waiver or alteration will not adversely affect the rights and welfare of the subjects;
- the research could not practicably be carried out without the waiver or alteration; **and**
- whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Minimal Risk Research

- The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*

*From: 45 CFR 46.102 i.

Examples of Minimal Risk Research

- Chart review
- Survey
- Physical exam
- Drawing blood
- Review of previously collected specimens
- Collection of stool or sputum specimens

Not adversely affect the rights and welfare of the subjects

- Would the subject population consider their rights were violated?
- Open for interpretation

Research could not practicably be carried out

- Impracticable to conduct the research
 - NOT just impracticable to obtain consent
- Scientific validity would be compromised if consent was required.
- Ethical concerns would be raised if consent were required

Subjects will be provided with additional pertinent information

- When appropriate
 - A debriefing after a “deception research”
 - New information is obtained that directly impacts the safety or welfare of the subjects

**EXCEPTION FROM INFORMED CONSENT
(EFIC) REQUIREMENTS IN EMERGENCY
RESEARCH**

21 CFR 50.24 AND 45 CFR 46.101

EFIC Requirements

21 CFR 50.24 and 45 CFR 46.101

- IRB responsible for the review, approval, and continuing review
- Life-threatening situation, available treatments are unproven or unsatisfactory
 - Collection of valid scientific evidence... is necessary to determine the safety and effectiveness of particular interventions

EFIC Requirements (cont.)

- Obtaining informed consent is not feasible
- The research holds out the prospect of direct benefit
 - Subjects are facing a life-threatening situation that necessitates intervention;
 - Prior animal and preclinical studies support the research
 - Risk/benefit ratio is reasonable, considering the medical condition and potential class of subjects

EFIC Requirements (cont.)

- The clinical investigation could not practicably be carried out without the waiver
- The length of potential therapeutic window is defined (i.e.- short window)
 - Efforts will be made to contact the a legally authorized representative within the window
- The IRB has reviewed and approved informed consent procedures and an informed consent document

EFIC Requirements: Additional Protections

- Consultation with the community
- Public disclosure to the community
- Establishment of an independent data monitoring committee
- Efforts made to contact family members will be summarized and available to the IRB at time of continuing review

What is community consultation?

- Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn

Who is the Community?

- Rule doesn't dictate how or what to do
 - Communities differ
 - Size
 - Homogeneity of population
 - Culture
 - Language
- Effective consultation
 - Multifaceted
 - Informative to IRBs and communities
 - Continuing
- Two-way communication is key

INSTITUTIONAL REVIEW BOARDS:

45 CFR 46 (HHS)

21 CFR PART 56 (FDA)

What is an Institutional Review Board (IRB)?

- The group or committee that is given the responsibility by an institution to review research projects involving human subjects.
- Its primary purposes are
 - to assure the protection of the safety, rights and welfare of the human subjects.
 - determine if Benefit of the research (to the individual or society) *exceeds* the Risk to the participant (healthy volunteer or patient)
- By federal law, the group contains both scientific and non-scientific (community) members

Responsibilities of the IRB

- Protect the rights and welfare of human research subjects
- Determine if **Benefit** of the research (to the individual or society) *exceeds* the **Risk** to the participant (subject, volunteer, patient)

Transactions Reviewed by the IRB

- New Protocols
- Renewals
- Amendments
- Reportable new information
 - Unanticipated Problems Involving Risks to Subjects or Others
 - Adverse Events
 - Includes serious and continuous noncompliance

Important Aspects for IRB Review

- Subjects adequately protected
- Potential Benefits > Risk
- Study design/scientific integrity of research
- Equitable Subject Selection (No Coercion)
- Appropriate Informed Consent
- Privacy & Confidentiality Protection
- Data & Safety Monitoring

Independent Review

- Conducted by individuals unaffiliated with research
- Review includes:
 - Study design
 - Research trial conduct
 - Proposed subject population and protections
 - Risk-benefit ratio
 - Appropriate informed consent

Failure of Independent Review

Independent review is critical for human subjects protection

- An IRB Reviewer of a proposed high-risk protocol does not disclose that he has a financial conflict of interest
 - A positive outcome from this study will cause the value of his stock to skyrocket.

Failure of Independent Review

- Bias/Conflict of Interest (COI) of IRB Reviewers
- Undeclared COI of researchers
- Inappropriate Data Safety Monitoring Plan (DSMP)
 - Level of DSMP determined by complexity of study.
- Incomplete/poorly written consent
 - Decreased participant comprehension

Research Conduct

The principal investigator (PI) is the ***critical component*** in the conduct of

- high quality research, and
- assurance of human research subjects' safety

Challenge Questions

- What research study prompted the development of the Belmont Report?
 - Why is the Belmont Report important?
- Name 6 basic components of research informed consent.

Challenge Question: Answer

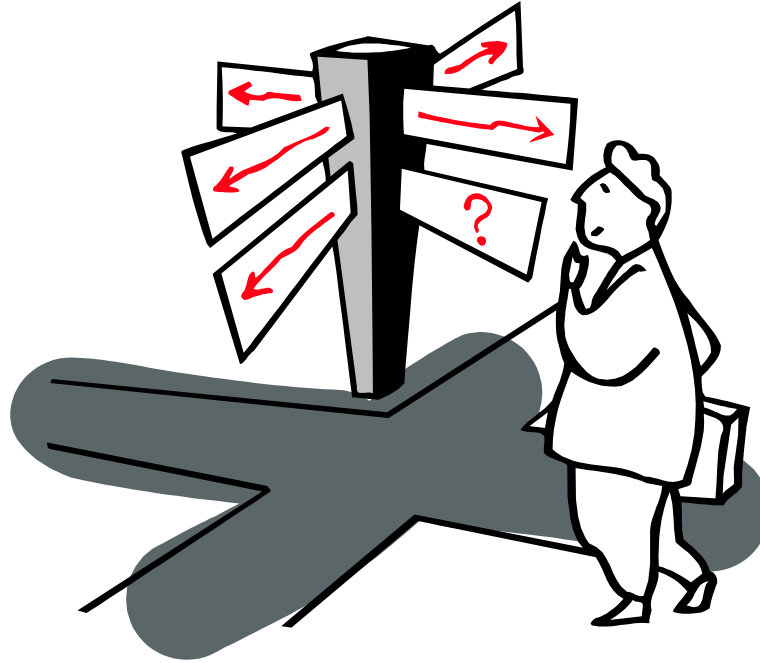
- The Tuskegee Syphilis Study (1932-1972)
 - Developed the key basic ethical principles for research in the U.S.
 - **Respect for Persons**
 - Autonomy
 - **Beneficence**
 - Maximizing benefits while minimizing risks
 - **Justice**
 - Fair distribution of costs and benefits

Challenge Question: Answer

Basic Components of Research Informed Consent

- 1) Statement that this is research
- 2) Description of risks
- 3) Description of benefits
- 4) Disclosure of alternative
- 5) Confidentiality of records and who can inspect them
- 6) Discussion of compensation/treatment for research related injury
- 7) Information about subject's rights
- 8) Statement that participation is voluntary

Questions?



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