FDA U.S. FOOD & DRUG ADMINISTRATION

Informed Consent and Ethical Considerations in Clinical Trials

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Disclosures

- **Commercial**
  - Pfizer
    - Sickle Cell Disease Council for Change & Advisory Board
  - Novartis
    - Consultant related to Sickle Cell Disease
- **Other**
  - American College of Emergency Physicians
    - Member, Board of Directors

Learning Objectives

- **Historical perspective on research ethics**
  - Focus on consent
- **Discussion of FDA Federal Regulations**
  - ***Informed Consent of Human Subjects***
    - 21 Code of Federal Regulations (CFR) part 50b
  - ***Institutional Review Boards (IRBs)***
    - 21 CFR part 56
  - ***Investigational New Drug (IND) Applications***
    - 21 CFR 312.10
  - ***Clinical Holds***
    - 21 CFR 312.42

RESEARCH ETHICS:
A HISTORICAL PERSPECTIVE

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Human Subject Research: Balancing Two Goals

Protection of Subject Welfare/Rights

Advancement of Science

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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."

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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?**

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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**

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Tuskegee Syphilis Study

1932 - 1972

Ethical Issues: Consent

- Consent
  - Inadequate disclosure of information
  - Subjects believed they were getting treatment
    - U.S. Government prevented treatment
  - Told that spinal taps were therapy

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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

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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
- **The Common Rule (1981)**
  - No exceptions for emergencies

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International Ethical Guidelines for Biomedical Research Involving Human Subjects

Free

The Council for International Organizations of Medical Sciences (CIOMS) announces the publication of its revised/updated International Ethical Guidelines for Biomedical Research Involving Human Subjects.

https://cioms.ch/shop/product/international-ethical-guidelines-for-biomedical-research-involving-human-subjects-2/

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"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

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Research Regulations FDA and HHS

- Regulatory Scope
  - **Regulated products (FDA)**
  - All human subjects research (HHS)
- Definitions (synonymous)
  - **Clinical Investigation (FDA)**
  - Research (HHS)

https://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/educationalmaterials/ucm112910.htm

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Research Regulations FDA and HHS

- Human Subject (FDA):
  - An individual who is or becomes a participant in research, either as a recipient of the test article or as a control.
- "Virtually Identical" regulations
  - IRB Composition
  - Criteria for approval
  - Record requirements
  - Informed consent requirements

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FDA FEDERAL REGULATIONS

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INFORMED CONSENT:
21 CFR PART 50B

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Informed Consent

- Informed consent ensures that individuals decide:
  - Whether to enroll in research
  - Whether research fits with their own values, interests, and goals.
- Research on individuals who cannot decide:
  - Children and individuals with cognitive impairment
  - Requires surrogate consent

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Informed Consent: Basic Elements (1)

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

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Informed Consent: Basic Elements (2)

5) Confidentiality of records and who can inspect them
6) Discussion of compensation/treatment for research related injury
   For greater-than-minimal risk research
7) Information about subjects rights
   Explanation of whom to contact for questions
8) Statement that participation is voluntary

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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 understanding
- Promoting the voluntariness of the decision
  - Whether or not to participate in the research

See: http://answers.hhs.gov/ohrp/categories/1566

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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

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Quality of informed consent

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

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Informed Consent

It's the process, not the paper!

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INSTITUTIONAL REVIEW BOARDS: 21 CFR PART 56

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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

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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)

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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

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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

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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

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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.

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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

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Research Conduct

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

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

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INVESTIGATIONAL NEW DRUG APPLICATIONS:
21 CFR 312.10

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What is an IND?

- Main purpose is:
  - To provide documentation that it is reasonable to proceed with certain human trials
- Request for an exemption to Federal statute
  - Allows an unapproved drug to be shipped in interstate commerce.
- It is NOT an application for marketing approval

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What is a Drug?

- Articles recognized in
  - Official US Pharmacopoeia,
  - Official US Homoeopathic Pharmacopoeia, or
  - Official National Formulary
- Articles intended for
  - Diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- Articles (other than food and dietary supplements) intended to
  - Affect the structure or any function of the body of man or other animals; and
- Articles intended for use as a component of any article specified above

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Investigational New Drug Types

- **Investigator IND**
  - submitted by a physician who both initiates and conducts an investigation
- Emergency Use IND
  - FDA to authorizes use of an experimental drug in an emergency situation
- Treatment IND
  - FDA authorizes use of promising experimental drugs
    - The final clinical work is being conducted
    - FDA review is occurring

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IND Application Information

- Preclinical data
  - Animal Pharmacology and Toxicology Studies
- Manufacturing Information
  - i.e.: manufacturer, composition, stability
- Clinical Protocols and Investigator Information
  - i.e.: Investigators Brochure, detailed clinical protocol*

*CDER's Pre-Investigational New Drug Application Consultation Program

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CLINICAL HOLDS:
21 CFR 312.42

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What is a Clinical Hold?

- Order by the FDA to an IND holder
- FDA requires:
  - Delay a proposed clinical investigation
  - Suspend an ongoing investigation

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Why a Clinical Hold?

- Unreasonable and significant risk
- Unqualified investigator(s)
- Incomplete/inadequate/erroneous
  - Investigator brochure
  - IND application
  - Investigational plan
- Drug related issues
  - Insufficient amounts
  - Proven lack of effectiveness
  - Already approved for indication

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What does it mean?

- Participants may not be given the investigational drug.
- No new participant recruitment
- Current participants should be taken off drug
  - Unless specifically permitted by the FDA for participant's safety

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Clinical Hold: FDA Initial Actions

- Prior to clinical hold
  - Attempt to resolve the matter with the IND applicant
- The clinical hold order may be made by telephone
  - Or other means of rapid communication or in writing.
- As soon as possible, and no more than 30 days a written explanation will be issued.
  - Identify the studies under the clinical
  - Explain the basis for the clinical hold

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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.

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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

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Challenge Question: Answer

Basic Components of Research Informed Consent

1) Statement that this is research
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4) Disclosure of alternative
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6) Discussion of compensation/treatment for research related injury
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Questions?

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