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

Human Subject Research: Balancing Two Goals

Protection of Subject Welfare/Rights

Advancement of Science

Advancement of Science

Protection of Subject Welfare/Rights
**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
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

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
• The Common Rule (1981)
  • No exceptions for emergencies
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/

“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

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
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

**FDA FEDERAL REGULATIONS**

**INFORMED CONSENT:**
21 CFR PART 50B
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

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

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
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

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
- Importance of personal explanation, time to digest
- Ongoing consent process
  - Subject may leave study at his/her discretion
Informed Consent

It’s the process, not the paper!

INSTITUTIONAL REVIEW BOARDS:
21 CFR PART 56

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

- 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

INVESTIGATIONAL NEW DRUG APPLICATIONS:
21 CFR 312.10

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
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

Investigational New Drug Types

- Investigator IND
  - Submitted by a physician who both initiates and conducts an investigation
- Emergency Use IND
  - FDA to authorize 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

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
CLINICAL HOLDS:
21 CFR 312.42

What is a Clinical Hold?
• Order by the FDA to an IND holder
• FDA requires:
  – Delay a proposed clinical investigation
  – Suspend an ongoing investigation

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
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

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

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

Basic Components of Research Informed Consent

1) Statement that this is research
2) Description of risks
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5) Confidentiality of records and who can inspect them
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Questions?

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