FDA U.S. FOOD & DRUG ADMINISTRATION

Informed Consent and Ethical Considerations in Clinical Trials

Jon Mark Hirshon, MD, MPH, PhD
Professor, Department of Emergency Medicine
Senior Vice-Chairman, IRB
University of Maryland Baltimore

Disclosures

- **Commercial**
  - Pfizer
    - Sickle Cell Disease Council for Change & Advisory Board
  - Global Blood Therapeutics
    - Sickle Cell Disease Access-to-Care Summit, travel reimbursement

- **Other**
  - American College of Emergency Physicians
    - Member, Board of Directors and Vice-President

What We Will Cover

- **Historical perspective on research ethics**
  - Focus on consent
- **Brief Discussion on Federal regulations**
  - Food and Drug Administration (FDA) versus Health and Human Services (HHS) regulations
  - Potential new regulations

Human Subject Research: Balancing Two Goals

Protection of Subject Welfare/Rights

Advancement of Science

Nuremberg Code (1947)

First Codification of Research Guidelines

"The voluntary consent of the human subject is absolutely essential."

- No coercion in informed consent
- Subjects must be free to stop at any time.
- Prior animal data
- Scientific value; Anticipated results justify the risks
- Favorable risk/benefit ratio
- Suffering by subjects should be avoided
- No expectation of death/disability

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 and acts in the patients' best interest
- **Research**
  - Lies outside of the context of the physician-patient relationship
    - Primary goal is to test a hypothesis, secondary obligation is to subject

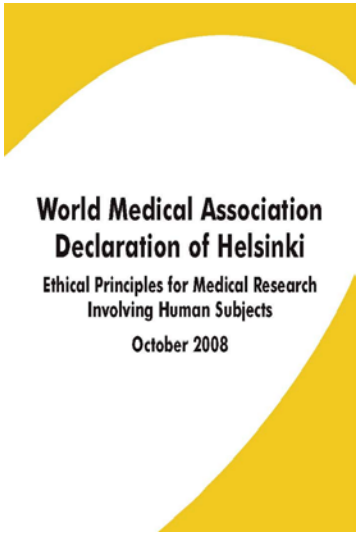
- **<u>Conflict of Roles?</u>**

Declaration of Helsinki

World Medical Association

- Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
  - Subsequent multiple amendments

- **Updated informed consent**
  - **Consent individuals**
    - **Capable of giving informed consent**
    - **Recognizes that consent may not always be possible**



Tuskegee Syphilis Study (1932 - 1972)

- In 1932, medical authorities firmly believed in the efficacy of arsenic therapy for treating syphilis
- Tuskegee, Alabama
  - High prevalence of syphilis
  - Although treatment existed, African-Americans in the rural South were not receiving treatment
  - Lack of funds/Lack of doctors
  - Study natural course of syphilis
  - Enrolled 400 African-Americans males infected with syphilis to study the natural course of syphilis
  - Not an experiment but rather a“study in nature”

Tuskegee Syphilis Study (1932 - 1972)

Ethical Issues

- 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
- 1972 press reports caused the study to stop

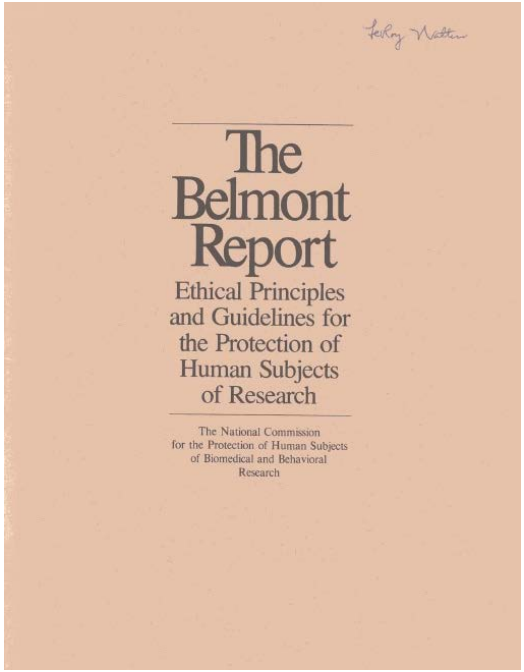
Tuskegee: Ethical Lapses

- Lacking in Social Value
- Scientifically Invalid Study: Existing Therapy for Syphilis
- Unfair Subject Selection
- Unfavorable Risk-Benefit Ratio
- Failure of Independent Review
- Informed Consent Process Invalid; 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



“The Common Rule”

- The HHS regulations, 45 CFR part 46 include
  - Four subparts:
    - subpart A, also known as the Federal Policy or the “Common Rule”;
    - subpart B, additional protections for pregnant women, human fetuses, and neonates;
    - subpart C, additional protections for prisoners; and
    - subpart D, additional protections for children.
  - Published in 1991
- The **Common Rule** regulations are separate from **FDA** regulations

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/

Clinical Research: 7 Ethical Requirements

- Social or Scientific Value
- Scientific Validity
- Fair Subject Selection
- Favorable Risk-Benefit Ratio
- Independent Review
- Informed Consent
- Respect for Potential/ Enrolled Subjects

Emanuel EJ, Wendler D, Grady C. in JAMA 2000;283:2701

Informed Consent in Emergency Research

Consensus Statement From the Coalition Conference of Acute Resuscitation and Critical Care Researchers

Michelle H. Biros, MD, MS; Roger J. Lewis, MD, PhD; Carin M. Olson, MD; Jeffrey W. Runge, MD; Richard O. Cummins, MD, MPH; Norman Fost, MD, MPH

JAMA April 1995

What is Informed Consent?

- ***<u>It is a process- not just a document!</u>***
  - (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

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

Informed Consent

- Informed consent ensures that individuals themselves decide:
  - whether to enroll in research and
  - 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

- Guidelines require several items to be disclosed to potential subjects:
  - Purpose and duration of participation
  - Procedures and identification of which are experimental
  - Risks/Benefits
  - Alternatives
  - Confidentiality of records
  - Compensation of injuries
  - Person to contact for answers to questions
  - Voluntariness and right to withdraw

Quality of informed consent

- **Informed consent in research is important, but imperfect.**
  - Consent forms are complete, but complex (often incomprehensible)
  - Importance of personal explanation, time to digest
  - Ongoing consent process
  - Subject may leave study at his/her discretion

Respect for Enrolled Subjects

The ethical requirements of research do not end with a signed consent document.

- Respecting enrolled subjects includes:
  - Protecting confidentiality
  - Permitting withdrawal
  - Providing new information
  - Monitoring welfare throughout the study

Informed Consent

It’s the process, not the paper!

Clinical Leadership & Infection Control

Minneapolis hospital enrolled ER patients in ketamine studies without consent, FDA finds

Written by Harrison Cook | October 29, 2018 | Print | Email

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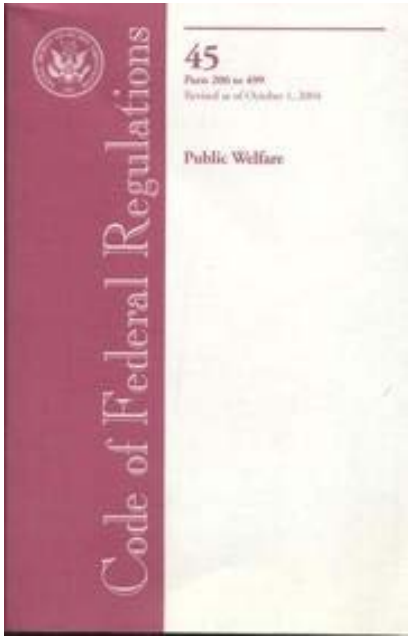
Federal inspectors found Minneapolis-based Hennepin County Medical Center tested antipsychotics and ketamine on emergency room patients without their consent, which violates human research regulations, according to *STAT*.

https://www.beckershospitalreview.com/quality/minneapolis-hospital-enrolled-er-patients-in-ketamine-studies-without-consent-fda-finds.html

FEDERAL REGULATIONS



Definitions

- ***"Medical Practice"*** (IRB is not involved)
  - **Interventions designed solely to enhance the well-being of the patient**.
  - Provides diagnosis, prevention or therapy with the expectation of a successful outcome.

- ***"Experimental"***
  - **Defined as new, untested or different**.
  - An experimental procedure is not automatically categorized as research.
  - A new "experimental" procedure should be formally researched (investigated) to determine if is safe and effective.

Research Definition (HHS)

- ***"Research"*** (IRB is involved)
  - **Activities designed to contribute to generalizable knowledge**.
  - Tests a hypothesis and draws conclusions.
  - Research is described in a formal protocol and a set of procedures designed to reach an objective.
  - The line between practice and research is often blurred.
  - Research and practice can occur simultaneously

Definition of a Human Subject (HHS)

- A “human subject” (participant, volunteer) is a <u>living individual about whom an investigator conducting research obtains:</u>
  - Data through intervention or interaction with the individual

    or
  - Identifiable private information

From: 45 Code of Federal Regulations (CFR) 46.102

Responsibilities of the IRB and Human Research Protections Program

- 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)

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

Research Regulations FDA

- Need for drug and device review and approval
  - investigational new drug application (**IND**)
  - investigational device exemption (**IDE**)

CHANGES TO THE FEDERAL REGULATIONS GOVERNING HUMAN SUBJECTS RESEARCH

Revised Common Rule

Significant Changes

- IRB Operations
  - Single IRBs for multi-site cooperative research
  - External IRBs
  - For specific research activities, continuing review will no longer be required

Significant Changes

- Scope
  - Definitions
    - human subjects,
    - clinical trial research
    - identifiable biospecimen
    - identifiable private information/vulnerable population
  - Tribal law
- Exemption categories expanded

What Has Already Been Implemented?

- Clinical trials
  - Definition expansion for NIH research
  - Registration/reporting enforcement
- Certificates of confidentiality
- NIH requirements for Good Clinical Practice (GCP) training
- Single IRBs (sIRB)
  - For multi-site cooperative research

sIRB Objectives

- NIH and revised Common Rule compatible
- Enhance and streamline the IRB review process for multi-site research
- High standards and protections for human subjects maintained
- Efficient and effective
- Eliminate redundancy

sIRB- When Do They Apply?

- Applies to
  - U.S. institutions engaged in cooperative research for the portion of the research conducted in the U.S.
- Does not apply to:
  - When more than single IRB review is required by law (including tribal law)
  - When determined by a Federal department or agency
  - Foreign sites
  - Training awards (e.g.: K, T and F awards)

sIRB- Local Responsibilities

- Conflict of Interest (COI) management plans
- HIPAA may be handled locally
- Ensuring that investigators/study staff are qualified and meet standards to conduct research
- Responsible for the safe and appropriate performance of the research
  - Includes monitoring study compliance.

sIRB Challenges

- Implementation ongoing nationally
  - Only a small number of institutions are currently functional as a sIRB
- CICERO currently not configured to operate as a single IRB for large multi-site studies
  - UMB is committed to ensuring the successful implementation of a sIRB for these trials requiring reliance agreements

Upcoming Changes

- Revised Common Rule
  - Published in Federal Register
    - January 19th, 2017
  - Implementation date??
    - ~~January 19, 2018~~
    - ~~July 19, 2018~~
    - January 21, 2019?

Human Subject Definition

- Human subject - a living individual about whom an investigator conducting research:
  - Obtains information or **biospecimens** through intervention or interaction with the individual, and uses, studies, or analyzes the information or **biospecimens**; or
  - Obtains, uses, studies, analyzes, or generates identifiable private information or **identifiable biospecimens**

Exempt Studies- Expansion

- Significant expansion
  - Scholarly and journalistic activities
    - Oral history, Journalism, Biography, Literary Criticism, Legal Research, Historical Scholarship
  - Public health surveillance activities
    - "conducted, supported, requested, ordered, required or authorized by a public health authority (PHA)"
      - Intent for governmental public health agencies
- Multiple other categories added or revised

Informed Consent

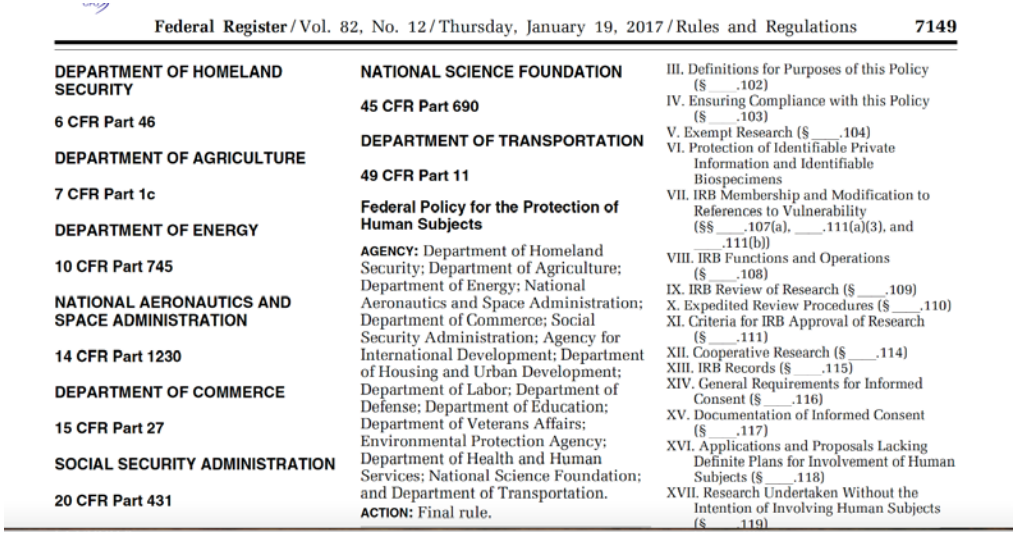
- New language/clarity
  - Basic and additional elements of informed consent
- Broad consent
- Recruitment/screening waivers
- Clinical trials consent forms
- Electronic consent
- Legally authorized representatives

Continuing Review

- No longer required (examples)
  - Research approved by expedited review
  - Exempt research requiring limited IRB review
  - Research in which interventions have been completed:
    - Data analysis including analysis of identifiable private information or identifiable biospecimens
    - Data from clinical care accessed as part of follow-up
- The IRB can still require continuing review but this must be documented.
- Guidance forthcoming from oversight agencies and UMB

Many more Common Rule changes…

- Federal Register
  - https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf



Federal Register / Vol. 82, No. 12 / Thursday, January 19, 2017 / Rules and Regulations 7149

DEPARTMENT OF HOMELAND SECURITY

6 CFR Part 46

DEPARTMENT OF AGRICULTURE

7 CFR Part 1c

DEPARTMENT OF ENERGY

10 CFR Part 745

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

14 CFR Part 1230

DEPARTMENT OF COMMERCE

15 CFR Part 27

SOCIAL SECURITY ADMINISTRATION

20 CFR Part 431

NATIONAL SCIENCE FOUNDATION

45 CFR Part 690

DEPARTMENT OF TRANSPORTATION

49 CFR Part 11

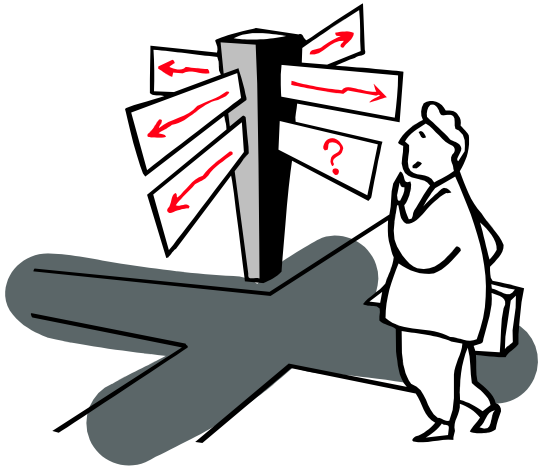
Federal Policy for the Protection of Human Subjects

AGENCY: Department of Homeland Security; Department of Agriculture; Department of Energy; National Aeronautics and Space Administration; Department of Commerce; Social Security Administration; Agency for International Development; Department of Housing and Urban Development; Department of Labor; Department of Defense; Department of Education; Department of Veterans Affairs; Environmental Protection Agency; Department of Health and Human Services; National Science Foundation; and Department of Transportation.

ACTION: Final rule.

III. Definitions for Purposes of this Policy (§ ____.102)
IV. Ensuring Compliance with this Policy (§ ____.103)
V. Exempt Research (§ ____.104)
VI. Protection of Identifiable Private Information and Identifiable Biospecimens
VII. IRB Membership and Modification to References to Vulnerability (§§ ____.107(a), ____.111(a)(3), and ____.111(b))
VIII. IRB Functions and Operations (§ ____.108)
IX. IRB Review of Research (§ ____.109)
X. Expedited Review Procedures (§ ____.110)
XI. Criteria for IRB Approval of Research (§ ____.111)
XII. Cooperative Research (§ ____.114)
XIII. IRB Records (§ ____.115)
XIV. General Requirements for Informed Consent (§ ____.116)
XV. Documentation of Informed Consent (§ ____.117)
XVI. Applications and Proposals Lacking Definite Plans for Involvement of Human Subjects (§ ____.118)
XVII. Research Undertaken Without the Intention of Involving Human Subjects (§ ____.119)

Questions?



Email: jhirshon@umaryland.edu