Responsible Conduct of Research: Human Subjects, Part 1

Objectives

- Define human subjects
- Review the history of unethical research
- Discuss the role of an Institutional Review Board (IRB) and other regulatory guidance

Human Subjects

- Question:
  - What does human subject mean to you?
  - How does research with human subjects differ from patient care?

Human Subjects

- Human subjects are living individuals about whom an investigator conducting research obtains:
  - Data through intervention or interaction with the individual
  - Identifiable private information

Human Subjects

- Participates in a clinical research study
- May or may not benefit from treatment
  - May receive placebo
- May be treated with unapproved treatment

Human Subjects

- Research vs. Practice:
  - If a procedure or intervention is meant to develop generalized knowledge, it is research and must follow ethical and regulatory guidelines
  - If a procedure is conducted for patient care (or quality assurance) and is not part of a research study, it is exempt from IRB review

Human Subjects

- Used in clinical trials to:
  - Gain scientific and medical knowledge that can help others
- Potential consequences:
  - Risks to subjects (and institution)
  - Benefits to subject (e.g., payments; access to medicines, medical care, counseling)
  - Benefits to society
- Weigh the benefits to participants (and society) vs. potential risks

Human Subjects

- Approval needed prior to starting research
- If approval not obtained, all data acquired without approval must be discarded
- If approval lapses while research is ongoing, data may need to be discarded

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- Define human subjects
- Review the history of unethical research
- Discuss the role of an Institutional Review Board (IRB) and other regulatory guidance
- Define vulnerable populations

Unethical or Questionably Ethical Research

- Nazi medical experiments
- Willowbrook
- Tuskegee
- U. of Witwatersrand (SA)
- Dr. Fiddes
- Woo Suk Hwang

WWII: Research atrocities by Nazis

- *In concentration camps (Dachau) and killing camps (Auschwitz)*
  - Immerse prisoners in cold water
  - until they died – ***the intent of the research***
  - Decompress prisoners in high-altitude chambers until they died – ***the intent of the research***
  - Inject many prisoners with typhus
  - No consent obtained
  - many died

- *Nuremberg Medical Trial, 1946-47*
  - 23 German Doctors charged with crimes against humanity for "performing medical experiments upon concentration camp inmates and other living human subjects, without their consent, in the course of which experiments the defendants committed the murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts."
  - 15 convicted

Nuremberg, Germany (December 9, 1946 to August 20, 1947)

The Nuremberg Code (1947)

- As part of the verdict, the Court enumerated some rules for "Permissible Medical Experiments", now known as the “Nuremberg Code”. These rules include:
  - **voluntary consent**
  - **benefits outweigh risks**
  - **ability of the subject to terminate participation**
- *10 rules for “Permissible Medical Experiments”:*
  - voluntary consent, without coercion,
  - good science, done by good scientists,
  - potential benefits justify experiment,
  - harms minimized,
  - degree of risk less than potential benefit,
  - subjects can end their participation, … [and 4 more]
- *A start, but with limited applicability:*
  - medical research only, & only on normal subjects
  - asked "When is research criminal?"

http://www.hhs.gov/ohrp/references/nurcode.htm

Willowbrook: U.S. Hepatitis Study

- Home (state hospital) on Staten Island in N.Y. for severely retarded children.
- Had high incidence of hepatitis.
- Children routinely became infected within 6-12 months of admission – to learned about natural history of hepatitis A and B.
  - deliberately infected mentally retarded children with hepatitis virus
  - administration of hepatitis (apparently told it was a vaccine).
  - coercion of parents
- After 1964, children not admitted unless parents “consented” to experiment

Public Health Service Policy

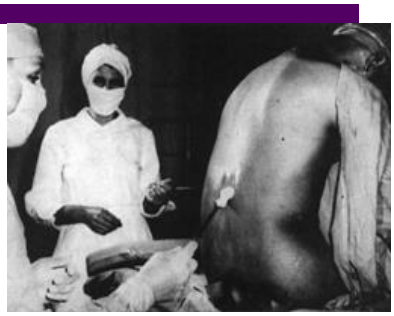
- NIH Director and Surgeon General requested that the National Advisory Health Council review human subject protections
- Council recommended prior institutional review for PHS supported research to:
  - Protect of the rights and welfare of the subjects
  - Assure appropriate methods of informed consent
  - Determine acceptable balance of risks and benefits
- Adopted as Public Health Service policy in 1966
- Beginnings of the Institutional Review Board (IRB)

Tuskegee Syphilis Study

- American medical research project conducted by the U.S. Public Health Service from 1932 to 1972,
- The longest running study in the US
- Motivated by the concern that syphilis might be less harmful in this group
- Examined the natural course of untreated syphilis in black American men.
- The subjects, all impoverished sharecroppers from Macon county, Alabama, were unknowing participants in the study; they were not told that they had syphilis, nor were they offered effective treatment

US Public Health Service Syphilis Study

- *Natural history of **untreated** syphilis in* 405 African American men
  impoverished sharecroppers around Tuskegee, 1932-72
- *Researchers lied to the men*
  - said they treated them for "bad blood"
- *Highly "successful"*
  - dropout rate only 1% over 40 years
  - ***Why was it so "successful"?***
- *The reason: it was "culturally sensitive"*
  - paid for funeral,
  - African American nurse & some doctors recruited
- Not secret!
  - *Updated results published about every 5 years*



(Courtesy National Archives)

- In the light of aforementioned research atrocities, should we continue to conduct research?
- If yes, why?
- If no, why?

Research Establishment Argument?

- Utilitarian perspective
  - The medical and social costs of illnesses justified the need for medical research despite the inherent limitations of the informed consent ideal
  - The need to "play God" is unavoidable
  - Lasagna wrote "How many of medicines great advances might have been delayed or prevented by the rigid application of some currently proposed principles to regulate research at large"

But:

- State has an obligation to protect and promote the liberty and welfare interests of human research participants
  - Promulgates laws
  - Set guidelines
  - Creates oversight structures, e.g., Research Ethics Committee (REC)

Declaration of Helsinki

- **Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects**

  Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, and in Hong Kong in 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996

  "Concern for the interests of the subject must always prevail over the interests of science and society."

1964 World Medical Council Declaration of Helsinki

- Some of the limitations of the Nuremberg code including the unqualified requirement for voluntary consent informed the World Medical Association's decision to develop its own medical ethics guidelines in 1953
- In 1954, the association adopted a resolution that required consent by ill participant or next of kin
- The resolution contained 5 propositions
  - Qualifications of researchers
  - Prudence
  - Responsibility of researchers
  - Respect for participants
  - Confinement of daring procedures to desperate cases

1964 World Medical Council Declaration of Helsinki

- This basically builds on the Nuremberg code and adds additional points
  - Allows for sufficiency of legal guardian's consent
  - Distinction between therapeutic and non-therapeutic research
- In 1975, the declaration was revised
  - It now placed greater emphasis on the need for informed consent
  - Included a requirement for independent review committees
- Subsequent revisions in 1983, 1989, 1996 and 2000 addressed specific items like
  - Conformity of ethics committees with the laws of the country in which the research is being performed

1964 World Medical Council Declaration of Helsinki

  - In 2000, the distinction between therapeutic and non-therapeutic research was removed
  - That the interests of the subject should always be given a higher priority than those of society
  - That every subject in clinical research should get the best known treatment
- They have been incorporated in many national and international guidelines

National Research Act

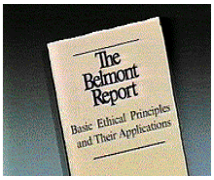
- 1973 Kennedy Hearings “Quality of Health Care - Human Experimentation”
- 1974 National Research Act
  - Established the “National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research”
  - Required IRBs at institutions receiving HEW support for human subjects research

1974 U. S. National Research Act

- This act established the modern research ethics system.
  - The act created U.S. federal regulations that required ethical approval before most kinds of research involving human subjects can be conducted, defined policy and procedures that ethics committees (EC) must follow when reviewing research, and established the criteria that an EC must use to approve research conduct
- It also established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.
- The National Commission which functioned between 1974 and 1978 issued recommendations on research ethics and in 1978, published the Belmont Report

The Belmont Report

Ethical Principles and Guidelines for the Protection of Human Subjects of Research



The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

The Belmont Report

Basic Ethical Principles:

- Respect for Persons
  - Individual autonomy
  - Protection of individuals with reduced autonomy
- Beneficence
  - Maximize benefits and minimize harms
- Justice
  - Equitable distribution of research costs and benefits

Federal Regulations and Policy

- **45 CFR 46 - Basic DHHS Policy for Protection of Human Research Subjects**
  Originally adopted May, 1974, Revised January 13, 1981, Revised June 18, 1991
  Additional protections for vulnerable populations in Subparts B-D

- **Federal Policy for the Protection of Human Subjects - "The Common Rule"** June 18, 1991
  Departments of Agriculture, Energy, Commerce, HUD, Justice, Defense, Education, Veterans Affairs, Transportation, and HHS. NSF, NASA, EPA, AID, Social Security Administration, CIA, and the Consumer Product Safety Commission.

U.S. FDA

- Is not a signatory to the common rule and it developed its own guidelines which are largely similar to the Common Rule

CIOMS Guidelines

- The Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) developed its International Ethical Guidelines for Biomedical Research Involving Human Subjects with special attention to research in developing countries
  - Specifically in response to growing research in HIV/AIDS
  - It took the Nuremberg Code and Declaration of Helsinki into account
  - Its principles are designed with the socioeconomic and political circumstances of developing countries in mind

- Development started in 1982
- Involved consultation with participants from developed and developing countries including health ministry officials, ethicists, philosophers and lawyers
- First version was released in 1993 with 15 guidelines
- Second version was released in 2002 with 21 guidelines

CIOMS guidelines

- Starts with an argument on the necessity of research

- Proclaimed the need for researchers and sponsors to make every effort to ensure that any intervention or product developed or knowledge generated will be made reasonably available for the benefit of the population or community

- The guidelines tackles the issue of placebo trials in guideline 11, articulating conditions when they can be used

ICH-GCP guidelines

- International Committee on Harmonization harmonized tripartite guideline – Guideline for Good Clinical Practice was promulgated in 1996 by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and has been agreed upon by the regulatory agencies in Europe, Japan and the United States
- The ICH-GCP guidelines delineates detailed standards for review committees, investigators and sponsors
- It is particularly targeted at research on drugs or devices seeking regulatory approval
- While it is rooted in the Helsinki Declaration and applicable local codes, it is far more specific than the other codes but not wider in scope
- It is criticized for being lax on the use of placebos in clinical trials

General comments

- These guidelines are still evolving
- Many lack a mechanism for interpretation, implementation, application and enforcement
- In the U.S. the Common Rule is the most widely used and legally binding
- There are some inconsistencies and controversies – particularly with placebo controlled trials
- Failure to comply with the common rule can have dire consequences in the United States but other guidelines often are not legally enforceable

"Cancer researcher sacked for alleged fraud"
Science 2000; 287: 1901-2

- University of Witwatersrand, Johannesburg, South Africa
- Breast cancer treatment with chemotherapy plus bone marrow transplantation
- Researcher "misrepresented his findings" and "failed to obtain approval for the trial before preceding"
- Potential message: "*medical researchers should not be trusted*"

New York Times
May 17, 1999

RESEARCH FOR HIRE: SECOND OF TWO ARTICLES

A Doctor's Drug Studies Turn Into Fraud

By KURT EICHENWALD and GINA KOLATA

Fiddes Case

- Dr. Fiddes president of a clinical research company in Whittier, California in U.S.
  - Conducted over 200 studies for as many as 47 drug companies beginning in the early 1990's
  - Engaged in extensive fabrication and falsification of data
  - Aug. 1997 pleaded guilty to felony charge of conspiracy to make false statements to the FDA in connection with the drug approval process

Fiddes Case

- September 1998 sentenced to 15 months in federal prison
- Ordered to pay $800,000 in restitution
- June 1999 - Disqualified as a clinical investigator by Commissioner of Food and Drug Aministration

Fiddes Case

- Examples of misconduct
  - Made up fictitious study subjects
  - Fabricated lab results by substituting clinical specimens and manipulating lab instrumentation
  - Prescribed prohibited medications to manipulate data

Fiddes Case

- The FDA investigators asked [Fiddes], what evidence of fraud is there in the records reviewed by study monitors and the government?
- What could the watchdogs have seen that would have allowed them to detect his fraud?

Fiddes Case

- ***"Nothing",*** Fiddes replied.
- Had it not been for a disgruntled former employee, he would still be in business.

Woo Suk Hwang's Stem Cell Research

- Claimed to have created personalized stem cell lines – falsification/fabrication
- Used eggs from female research staff – coercion
- Co-author (Gerald Schatten – U. Pittsburgh - PA) may not have contributed to the research – attribution/authorship
- Discovered by anonymous whistleblower – former employee

The Nigerian Experience

- Nigeria experience - Pfizer trovan trial in Kano 1996

- The Microbicide study in West Africa
  - "Family Health International, a US-based nonprofit public health organization, also launched a series of tenofovir PrEP trials in Malawi, Nigeria, Cameroon, Cambodia, and Ghana, with funding from the Bill & Melinda Gates Foundation, but only the Ghana trial is still ongoing. Some of the trials were stopped or suspended after protests from activists over the lack of a lifetime guarantee to treatment for volunteers who happen to become infected during the trial. Others were halted due to ethical or biological questions about these trials or the sites (*Lancet* 366, 1499, 2005; *Science* 309, 2170, 2005; *PloS Med*. 2, e234, 2005). In Malawi the government closed the trial due to concerns that it could foster HIV resistance to tenofovir, a drug they are now using in treatment. In response to these events the International AIDS Society held a global consultation on PrEP research last year where researchers and activists discussed the issues regarding these trials (Building Collaboration To Advance HIV Prevention)."

Source: http://www.iavireport.org/Back-Issues/Pages/IAVI-Report-10(3)-TreatmentasPrevention.aspx [Accessed: Monday 18 Februrary, 2013]

The Nigerian Experience

- **UNICAL dismisses 5, demotes 10 lecturers for academic fraud**
  - The Governing Council of University of Calabar has dismissed five academic staff and demoted 10 others for what it called "academic dishonesty".

Sources: The Guardian Newspaper, Saturday 16 March, 2013 &

- **http://www.punchng.com/news/unical-dismisses-5-demotes-10-lecturers-for-academic-fraud/ [Access Saturday 16 March 2001]**

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- Review the history of unethical research
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Institutional Review Board (IRB)

- Research involving human subjects must be reviewed by an independent committee – Institutional Review Board (IRB)
- The committee must have at least five members and be made up of a variety of people, including a person not affiliated with the institution

IRB

- Once a project is approved, researchers must follow the approved protocol
- If unanticipated harm or risk to subjects arises during the study, the IRB must be informed immediately and re-evaluate the protocol
- If you want to change an approved protocol, IRB approval is needed before instituting the change

What Makes Clinical Research Ethical?

(EJ Emanuel et al)
JAMA 2000; 283:2701-11

- Value - enhancements of health or knowledge must be derived from the research
- Scientific validity – the research must be methodologically rigorous
- Fair subject selection – scientific objectives, not vulnerability or privilege, and the potential for the distribution of risks and benefits, should determine the inclusion criteria for individual subjects

What Makes Clinical Research Ethical?

- Favorable risk-benefit ratio – minimize risks, enhance potential benefits
- Independent review – unaffiliated individuals review the research and approve, amend or terminate it
- Informed consent – informed and voluntary
- Respect for enrolled subjects – privacy protected, opportunity to withdraw, and well being monitored

Small Group Exercise: Case Scenario

- You are part of a research group about to start a “first in man” clinical study of a new anti-cancer drug based on a novel strategy
- The research behind it has been going on for 8 years
- Everyone strongly believes it will work and provide a treatment for currently untreatable cancer
- Side effects may be nasty but short-lived with little evidence of serious consequences
- Construct a list of conflicting/competing interests and other key considerations as you prepare the informed consent document

Consequences

- Declaration of Helsinki (1964)
- Belmont Report (1979)
- Code of Federal Regulations (1981)
- Good Clinical Practices Guidelines (ICH – 1997)
- HIPAA ("Privacy Act" – 2003)

Belmont Report (1979)

1. Respect for persons
2. Beneficence
3. Justice

1. Respect for Persons

- *Autonomy* - individuals should be treated as autonomous agents, capable of making judgments and decisions.
- Protect research subjects, particularly *vulnerable populations* (e.g., children, prisoners, pregnant women).
- *Informed consent*
- Surrogate consent and assent

Protecting Vulnerable Populations

(45 CFR 46 B, C, D)

- Children
- Prisoners
- Pregnant Women
- Others (e.g., critically or mentally ill, demented)

2. Beneficence

- In clinical medicine, the first rule is "do no harm" (*non-malfeasance*); in research, the obligation is to "do good" (*beneficence*)
- Requires a systematic assessment of
  - Risks and benefits
  - Quality of research design (bad science is never ethical)
  - Qualifications of the investigator and associates

3. Justice
"fairness in distribution"

- Selection of subjects - equitable
- Inclusion/exclusion criteria
- Recruitment
  - Exploiting the poor or uneducated (Tuskegee)?
  - Providing an advantage only to the rich or well connected (some cancer research)?
  - Excluding women, minorities, children, etc.

U.S. PUBLIC HEALTH SERVICE SYPHILIS STUDY IN TUSKEGEE ALABAMA

- Followed disadvantaged, rural black men with syphilis to learn about the natural history of the disease. These men were not treated even when effective treatment for syphilis became readily available.
- Illustrates ethical principles of both *beneficence* and *justice*.

Good Clinical Practices *GCP/ICH*

- International ethical scientific standard for designing, conducting, recording, and reporting trials that involve human subjects.
- Compliance provides public assurance that rights, safety, well-being and confidentiality of trial subjects are protected, consistent with principles originating in the Declaration of Helsinki, and that clinical trial data are credible and accurate.

University Policies

Questions & Discussion