Human Subject Research – An Overview

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What is “Research”?  

Research is an activity that permits conclusions to be drawn, and develops or contributes to generalizable knowledge.
What is “Human Subject”? 

*Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or

(2) Identifiable private information.
What is Not Human Subject Research

An activity is research not Involving Human Subjects if:

• there is no interaction or intervention with living individuals, and

• neither the provider of the specimens/data nor the recipient can link the specimens/data with identifiable individuals (living or dead) or

• the provider of the specimens/data is not an investigator or collaborator in the research activity, and

• the specimens/data have no code linking them with identifiable individuals, or it is impossible for the recipient to use the code to identify someone because the provider of the specimens/data is prohibited from releasing identifiers.
Clinical Care vs. Research

• Clinical care
  – provides direct benefit to the patient

• Research
  – Contributes to generalizable knowledge
  – Special attention to possible harm to the subject
  – Regulations place the responsibility for ethical conduct on researchers
  – Researchers need to hold themselves to the highest standards of integrity and accountability
Milestones in Ethical Development

• 1932–72 Tuskegee experiment on syphilis
• 1939–45 Nazi experiments
• 1944–74 Human radiation experiments by U.S. government
• 1946 Nuremberg Trial of doctors responsible for Nazi experiments
• 1947 Nuremberg Code outlining ethical principles required for research
• 1948 United Nations adoption of Universal Declaration of Human Rights
Milestones in Ethical Development

• 1953 NIH policy, first U.S. federal policy introducing independent reviewers to examine research, forerunners of IRBs
• 1963–66 Willowbrook Study, involving hepatitis research on mentally retarded children, raising issues of access to care, consent, and coercion
• 1964 Declaration of Helsinki international agreement on recommendations for the ethical conduct of medical research
• 1972 Public exposure of Tuskegee syphilis study
• 1974 First federal protections for human research participants
Milestones in Ethical Development

- 1979 Belmont Report promoting three principles for research
- 1980 Food and Drug Administration regulations
- 1982 Council for the International Organization of Medical Sciences (CIOMS) publication of the International Ethics Guidelines for Biomedical Research Involving Human Subjects
- 1985 U.S. Public Health Service Task Force on Women’s Health issues report encouraging inclusion of women in research
- 1990 Society for Women’s Health Research
- 1993 Public exposure of U.S. human radiation experiments
- 1993 NIH Revitalization Act (include women and minorities)
- 1993 NIH Office of Research on Women’s Health
Milestones in Ethical Development

• 1997 Food and Drug Modernization Act (FDAMA) requiring the FDA, NIH, and pharmaceutical industry to develop guidance on the inclusion of women and minorities in trials
• 1998 Pediatric Rule passed by Congress, stipulating that new drugs for children must include specific pediatric labeling information
• 2000 Further publicized ethical abuses - establishment of Office of Human Research Protections (OHRP)
• 2009 Qatar Policies, Regulations and Guidelines for Research Involving Human Subjects
Nuremberg Code (1947)

• Good for society not attainable by other means

• Experiments that avoid unnecessary physical and mental suffering and injury

• Balance degree of risk with the humanitarian importance of the research

• Researcher responsibility

• Voluntary consent required

• Shortcomings noted- Beecher 1959
  – If not able to give consent then research would not be done
  – No research in the mentally ill – how to advance knowledge?
Declaration of Helsinki

• World Medical Association – 1964

• Codes existed for delivery of health care but not for research

• Identified research as that involving human subjects including research on identifiable human material or identifiable data

• Interest to the wellbeing of the subject far outweighs the benefit to society

• Research Ethics Committee – review the research protocol

• Special populations
  – Economically and medically disadvantaged
  – Those unable to give consent
  – Those who may be subject to giving consent under duress
  – Those who will not benefit from the research
  – Where research is combined with medical care
Declaration of Helsinki

• Therapeutic research
  – Offers some potential benefit to the subject
  – Consent can be procured from a legal guardian
    • Surrogate consent
    • Ensures that children, mentally ill can participate

• Nontherapeutic research
  – Purely investigational
  – Consent can never be waived

• Has been revised 4 times
Limitations of Helsinki

• Ignored in the US and problems persisted

• NEJM article 1966 Beecher identified 22 cases of research that involved patently unethical practices in the use of human subjects in research
  – Use of mentally ill patients for the study of diseases not related to mental illness
  – Cold war studies
  – CIA studies

• Despite the existence of ‘codes’ researches were not adopting them into their research

• Call for further reform in research ethics and conduct
  – Beecher introduced the concept of voluntary peer review
  – Prompted a call for mandatory peer review and legislation governing research practices
Code of Federal Regulations

• Director of the NIH developed new standards for the Public Health Service (PHS) that required
  – Committee review for all human subjects research
  – Review focused on subject rights and welfare, methods used to obtain consent and the risk benefit ratio
  – Although signed in 1966 did not come into effect until 1974
  – The same year the Dept of Health, Education and Welfare (now the DHHS) published regulations for the protection of human subjects in the federal register
    • Under title 45 CFR part 46
Tuskegee - 1932

- Conducted by the US Dept of Health Services
- Undertaken with good motives but in the Context of racism
- Observational study 400 African-American males in Alabama with known syphilis

• Belief was that men would not stop dangerous sexual behavior and had different form of disease

• Ethical concerns
  - Available treatments in 1932 were poor but not given
  - Withheld an approved therapy when it became available in 1940’s
  - Controlled subjects access to penicillin - deception
  - Prevented enlistment in the Army because the disease would have been treated
Moral justifications for Tuskegee

• Knowledge worth sacrifice of few
• No point losing knowledge by stopping study
• Subjects were going to get syphilis anyway
• No effective cures
• Subjects gave consent
Response to Tuskegee

• Public and professional outrage led to
  – The Tuskegee Advisory Panel in 1973
  – Recommended termination of the study
  – Determined governments policies for reviewing scientific procedures and consent practices in federally funded research were inadequate

• A Federal Advisory Board (1974-78)
  – “National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research”
  – Result was the “Belmont Report of the National Commission” in 1979
  – 3 ethical principles central to the research enterprise
Charge of the Commission

• Boundaries between research and clinical care

• The role of risk benefit analysis in determining the appropriateness of research

• Appropriate guidelines for selection of human subjects

• Nature and definition of informed consent
The Belmont Report

• Purpose of the report is to provide three principles (prescriptive judgments) that will ‘assist researchers, subjects, reviewers and interested citizens with an understanding of the ethical issues inherent in HSR’

• Statement consists of 3 parts
  – Distinction between research and medical practice
  – Establishment of 3 ethical principles
  – Remarks regarding application of the principles
The Belmont Report

• Practice
  – Interventions designed solely to enhance the wellbeing of the patient and that have a reasonable expectation of success

• Research
  – An activity designed to test an hypothesis, permit conclusions to be drawn, develop or contribute to generalizable knowledge
The Belmont Report - Three Ethical Principles

• Principle of respect for persons
  – Individual autonomy
  – Protection of individuals with reduced autonomy

• Principle of beneficence
  – Requires a risk benefit assessment be made
  – Maximize benefits and minimize harms

• Principle of justice
  – Equitable distribution of research costs and benefits
How to Apply the 3 Principles

• Autonomy - Informed consent
  – Information
  – Comprehension
  – Voluntariness

• Beneficence – determination of the risk and benefits
  – Peer review – risks are justified
  – Investigator – study design
  – Subject – the determination to participate

• Justice
  – Selection of subjects described by the researcher
  – Reviewed during the peer review process
  – Determined to be equitable
The Common Rule

- Further review by the president’s commission 1980-1983 and other panels

- Mid 1980’s no standard government policy that coordinated the diverse regulations of all federal agencies

- 1986 the “Common Rule” proposed and then codified in 1991

- Essentially identical to the 1981 DHHS policy
  - CFR 46 Subpart A

- But by executive order extended that basic structure to the regulations of all 15 federal agencies and the CIA
The Common Rule

• First time after more than 25 years in the making a comprehensive regulatory framework existed that formally governed all human subjects research conducted by the federal government or in facilitates receiving federal funds

• The common rule
  – Mandates role of the IRB
  – Defines requirements for informed consent
  – Codifies special requirements for vulnerable populations
    • Pregnant women, fetuses, IVF
    • Prisoners
    • Children
  – Requires institutional assurance of compliance
Pillars to Protect for Human Subjects Research

• Consent

• Peer Review

• Research Integrity
  – Duty to protect subjects
  – Carry out studies per protocol
  – Communicate with subjects
  – Report findings honestly

• Conflict of Interest
Questions/Comments