Historical Perspectives on Human Participant Protection

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- Those who cannot remember the past are condemned to repeat it

  George Santayana, *The Life of Reason*

A complete timeline for the informed consent development is found at: *http://www.research.umn.edu/consent/mod1soc/mod1sec4.html*

The Nuremberg Doctors Trial of 1946

- The Nuremberg trial (United States v. Karl Brandt et al.) “The Nazi Doctors Trial”
- 23 defendants (20 physicians)
- Charged with murder, torture and other atrocities
- 15 found guilty; 7 sentenced to death
- Resulted in the Nuremberg Code (1947)

“The Nazi Doctors Trial”

- Medical experiments with legitimate concerns
  - High altitude exposure
  - Cold water exposure
  - Wounds, burns, amputations
  - Chemical and biologic agent exposures
- Hundreds of Participants
- 25-50% mortality; the rest maimed

The Nuremberg Code

- Informed consent of *volunteers* must be obtained without coercion
- Human experiments should be based on prior animal studies
- Anticipated scientific results should justify the experiment
- Only qualified scientists should conduct medical research
- Physical and mental suffering and injury should be avoided
- There should be no expectation of death or disabling injury from the experiment

Historical Perspectives on Human Participant Protection

- Post War years
  - 1953: the World Medical Association began drafting what became known as the “Declaration of Helsinki (1964)

Declaration of Helsinki

- Re-affirmed Hippocratic Oath; Nuremberg Code
- Established concept of independent review (IRB's)
- Participation voluntary and can withdrawn anytime
- Established concepts of:
  - Minimizing risk
  - risk/benefit ratio
  - special groups

The “Milgram Study”

- The Investigator
  - Stanley Milgram social psychology researcher
  - Interested in obedience and human’s response to authority (after reading accounts of Nazi Holocaust)
  - Published study in 1963

The "Milgram Study"

- The Experiment
  - Adult volunteer recruited from newspaper ad
  - Participants part of a triad: Participant, investigator and learner (confederate of PI, giving wrong answers)
  - Participant asked questions, administered shocks for wrong answers or nonresponsiveness
  - After 1/3 of shocks learner said: Stop!
  - After 2/3's of shocks learner silent/non-responsive
  - At debriefing Participants said they were only following instructions (just like the Nazi defendants)

The "Milgram Study"

- The Impact
  - Criticism centered upon the deception, extreme psychological stress without informed consent
    - When deception is involved, true informed consent cannot be obtained
  - Fed Regs allow deception:
    - in limited conditions
    - With IRB approval
  - Fed Regs instruct PI's & IRB's to consider other than physical harm
    - Including psychological, social, legal and economic

The Willowbrook Study

- Began 1956 to early 1970's Willowbook Hospital Staten Island, New York
- Newly institutionalized (& "retarded") children were infected with Hepatitis A
- Not voluntary, misleading informed consent
- Purpose: study natural course & effects of gamma globulin
- Rationalization: would have become infected anyway (poor hygiene in facility)

The Thalidomide Tragedy

- Background
  - Approved as sedative in Europe late ’50’s
  - Not approved by FDA but samples supplied to US physicians
    - Paid to do “research studies” of safety/efficacy
  - 1961 extreme harm to unborn babies (not mothers) if taken in first trimester; worldwide ban
- Hearings
  - Participants not informed of experimental nature of drug
  - Participants not asked to give consent

The Thalidomide Tragedy

- The Impact
  - Passage of the Drug Amendments of 1962 (to the Food Drug and Cosmetic Act
  - 1963 FDA issued regulations with a consent requirement (albeit with widespread exemptions)
  - 1966 FDA pressured to rewrite regulations
    - Required consent (except in certain emergencies or with experimental therapeutic research in children)
    - Required documentation of consent in writing and informing Participants they might receive a placebo

The Jewish Chronic Disease Hospital Study

- 1963
- Population: elderly and senile or demented patients
- Protocol: injected with live cancer cells
- Not part of informed consent
  - Would “only upset them”
  - No evidence there would be any harm

Beecher article

- NEJM June 16, 1966
- 22 medical studies performed unethically
- Major universities
- Respected researchers
- Major journals
- Questionable study design
  - Placebo controlled strep throat study
  - Transplantation of melanoma
- No informed consent

The San Antonio Contraception Trial

- 1971
- Purpose: To study effects of contraception in Mexican-Americans
- Design: midpoint substitution of placebo for oral contraceptive
- Placebo not part of informed consent

Zimbardo's Prison Simulation

- 1972
- Population: Stanford U undergrads
- Complete informed consent lacking
- Protocol some made guards, some prisoners
  - Placed in an underground dungeon
  - 2 week stay planned
- Study terminated after 6 days
  - Guards became sadistic
  - Prisoners became psychotic

The Tuskegee Study of Untreated Syphilis in the Negro Male ("The Syphilis Study")

- Background
  - Existing treatment (mercury/arsenic) highly toxic
  - Designed to demonstrate the need to establish treatment programs
  - Evolved from genuine concern for minority health problems
  - Initially not designed to deny treatment on long term basis
  - Involved 200-300 syphilitic black males
  - Followed for 6-8 months

The Syphilis Study

- The Experiment (October 1932)
  - Enrollment encouraged by offer of free medical care
  - Men not informed of their disease or lack of benefit
  - Study was to end with LP's in May 1933
  - Second phase started late '33 to add scientific validity
    - Control group and autopsies of study Participants added
  - 1943 PCN accepted as treatment
    - Participants exempted from military duty to avoid Rx
  - 1951 PCN generally available but still withheld
  - Availability used to further justify the study
    - Protocol a "never again" opportunity

The Syphilis Study

- The Expose
  - Story published NY Times/Washington Star **7/72**
  - Outrage widespread; esp. since a PHS study
- The Reaction
  - Congressional hearings 3/73; study stopped; Rx given
  - 4/73 survivors medical expenses to be paid for life
  - 1975 Rx for spouses with syphilis & children (with congenital syphilis)
  - 1997 President Clinton apologized
    - Called for renewed emphasis on research ethics

The Syphilis Study

- The Reaction (continued)
  - 1974 Congress passed the National Research Act
    - Required regulations for protection of human Participants
      - Including informed consent & IRB review of research
  - 1979 National Commission issued the "Belmont Report"

The Belmont Report
1979

- Resulted from the 1974 National Research Act
- Developed by the National Commission for Protection of Human Participants of Biomedical and Behavioral Research
- Describes three Basic Ethical Principles
  - Respect for Participants
  - Beneficence
  - Justice

The Belmont Report
3 Basic Ethical Principles

1. Respect for persons:
   - Acknowledge and treat individuals as autonomous
   - Protect individuals with diminished capacity

The Belmont Report
3 Basic Ethical Principles

2. Beneficence:

An obligation to first:

- To do no harm – Hippocrates
- Maximize possible benefits- Claude Bernard
- Minimize possible risks- ” ”

Belmont Report
3 Basic Ethical Principles

3. Justice:
   - Fairness in the distribution and getting what is deserved
     - Who ought to receive the benefits
     - Who ought to bear the risks
       - Formulations to consider
         - To each person an equal share
         - To each person according to need
         - To each person according to effort
         - To each person according to societal contribution
         - To each person according to merit

The Belmont Report
(1979)

- 1981 DHHS and FDA published convergent regulations based on Belmont Report
  - Mandated community members on IRB's
  - Specific elements of informed consent listed
- 1991 the "Common Rule" adopted
- Recognized as cornerstone of human Participants protection by OHRP and NBAC
- After 15 years, NBAC decided this report needed to be taken to next level

Human Radiation Experiments

- November 1993
  - Albuquerque Tribune series (New York Times)
    - Between 1947 and 1974
      - Plutonium injected into unknowing Participants
      - Gov't sponsored; several major universities involved 1000's
    - Congressional report
      - Gov't experiments: 13 facilities; intentional release of radiation into environment; hundreds of times
- January 1994 Advisory Committee on Human Radiation Experiments (ACHRE)
  - Created by President Clinton
- 1995 Committees Final Report accepted
  - Created National Bioethics Advisory Commission (NBAC)

The University of Rochester Study

- 1996; 19 y.o. normal female Participant; answered ad for bronchoscopy to harvest cells
- Bronchoscopy very difficult, multiple doses of topical lidocaine
- Repeatedly asked & agreed to continue
- Returned in cardiac arrest secondary to lidocaine overdose
- Many COI's; Participant should have been withdrawn

The UCLA Schizophrenia Study

- 2000
- Schizophrenic patient at UCLA
- Medications withdrawn during a 2 week washout period
- Participant committed suicide during washout period

National Bioethics Advisory Committee (NBAC) Report

- Final report approved May 2001
- Sweeping recommendations made
- Particularly concerned about informed consent
  - Too complicated, difficult to read, misleading
  - Vulnerable (by situation, not impairment) ***participants***
  - Treatment v. research (“gene therapy”)
- Particularly concerned about conflicts of interest
  - PI, institution, IRB
- Advocate
  - Increased community membership on IRB
  - Include participants on IRB
  - Increase education in research ethics
  - Certification of investigators, IRB members and staff
  - Accreditation of sponsors, institutions and IRB’s

The Johns Hopkins Asthma Study

- 2001
- Research tech participated as control
- 2 days later developed symptoms of "URI"
- Progressed quickly to ICU, ARDS and death
- PI missed pre-PubMed studies (1960's, 1970's)
- Many questions raised, esp. coercion of employees

The University of Pennsylvania Gene Therapy Trial

- 1999
- Jesse Gelsinger 19 y.o. with ornithine transcarbamylase deficiency
- Disease under good control with diet & med
- Injected with adenovirus vector in attempt to replace enzyme
- Developed multi organ failure; died
- Animal toxicity data withheld; efficacy data exaggerated
- PI with multiple COI's

Conclusion

- It is the responsibility of the researcher to provide the participants with information regarding the purpose, benefits, and risks of participating in both the interview and surveys.
- It is also the responsibility of the researcher to obtain the participants consent and explain on an eighth grade level any questions the participants may have regarding their consent and participation.

Conclusion

- The researcher is also responsible for ensuring the confidential nature of the information collected and making sure that the information collected is stored safely to maintain anonymity of the participant. Any potential conflict of interest should be identified and explained accordingly.
- In addition, the researcher should make sure that the participants are aware of the fact that they are free to terminate their participation and any given point.

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  George Santayana, *The Life of Reason*

- Those who don't know the past are bound to repeat it

  Ron Simon, *The Reason of Life*

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