Protecting Humans and Animals in Research

Responsible Conduct of Research Series

Historical perspective
Federal Regulations
IRB Issues
Overview

- Protection of humans
  - Historical perspective
  - Federal regulations
  - IRB issues
- Informed consent
- Waiver of informed consent
- Vulnerable populations
- Tissue and data repositories
Overview

- Break!
- Protection of animals
- Questions/Discussion
Historical Perspective

- Research ethics policies
  - From singular events and the reactions to them
- Rarely proactive
Sentinel events

- Nazi war crimes → Nuremberg trial (1948)
- Human radiation experiments, etc. → Declaration of Helsinki (1963)
- Tuskegee Syphilis study → National Commission Belmont Report (1977)
Nuremberg Code - 1947

- Tried for crimes against humanity
- Not for unethical research
- Part of the judgment

http://ohsr.od.nih.gov/nuremberg.php3
Effects Of Nuremberg Code?

- No effect on research
- Medical professionals opinions:
  - Implicit
  - Designed to convict Nazi doctors
  - Not needed by US researchers
- Problems with Nuremberg Code
  - Created *post hoc* to place Nazi actions in an ethical context
  - Did not cover many aspects of research
Declaration of Helsinki

- 1964: World Medical Association
- Reinterpretation of Nuremberg
- Provoked a reaction by medical profession
- Journal editors required that research be performed in accordance with the Declaration

http://www.wma.net/e/policy/17-c_e.html
“Ethics and Clinical Research”
NEJM 274 (1966):1354-60

22 studies performed unethically
- Major journals
- Respected researchers
- Questionable study design
- 2/50 studies mentioned consent
“..[mention of consent in a publication] should be emphasized in all cases for obvious moral and legal reasons, but it would be unrealistic to place much dependence on it...
“A far more dependable safeguard than consent is the presence of a truly responsible investigator.” -Beecher, NEJM 1966

“Until this article we assumed that unethical research could only occur in a depraved regime like the Nazis”

Robert J. Levine, MD
Tuskegee Syphilis Study
Purpose: Describe natural history of untreated syphilis

http://www.dc.peachnet.edu/~shale/humanities/composition/assignments/experiment/tuskegee.html
Events

- 1932: 300 black syphilitic males
- 1933: 300 controls added
- 1943: Penicillin used for military personnel
- 1947: Nuremberg Code
- 1951: Penicillin widely available
- 1966: Local ethics committee review
Syphilis Study: Results

- 28 deaths
- 100 died of related complications
- 40 spouses infected
- 19 cases of congenital syphilis
- >$10 million to > 6000 survivors & family
Syphilis Study: Problems

- No informed consent
- Deception
- Coercion
- Withholding effective treatment
- Lack of continuing review
- Vulnerable population
Belmont Report

- 1974 National Research Act
- Created National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- Ethical foundation for US federal regulations on human subjects research
Underlying ethical principles

- Respect for persons
  - Informed consent
- Beneficence
  - Risk/benefit assessment
- Justice
  - Equitable subject selection
Respect for Persons

- Treat individuals as autonomous agents
- Do not use people as a means to an end
- Allow people to choose for themselves
- Give extra protection to those who have limited freedom or ability to choose for themselves
Beneficence

- Obligations
  - Prevent harm
  - Prevent evil
  - Promote good
- Minimize risks
- Maximize benefits
Justice

- Treat people fairly
- Fair sharing of burdens and benefits of research
  - Who is placed at risk = who benefits from research
1966: All PHS supported research must undergo review to:

- Protect rights and welfare of subjects
- Assure appropriate informed consent
- Determine acceptable risk/benefit balance

Beginnings of the IRB
Regulatory Oversight

- Food and Drug Administration
  * 21 CFR 50, 56, 312, 812

- DHHS Office of Human Research Protection (OHRP)
  * 45 CFR 46: subparts A, B, C, D

- “Common Rule”
  based on 45 CFR 46, subpart A
1991 Federal Policy for Protection of Human Subjects (The Common Rule)
- Adopted by all agencies which conduct, supervise, regulate, fund or sponsor human research
- Informed consent requirements
- IRB approval of any research done
Common Rule Agencies

- Department of Agriculture
- Department of Energy
- National Aeronautics & Space Administration
- Department of Commerce
- Consumer Product Safety Commission
- Agency for International Development
- Department of Housing & Urban Development
- Social Security Administration
Common Rule Agencies

- Department of Justice
- Department of Defense
- Department of Education
- Department of Veterans Affairs
- Environmental Protection Agency
- National Science Foundation
- Department of Transportation
- Central Intelligence Agency
Food and Drug Administration

- Authority
  - Federal Food, Drug and Cosmetic Act
- Regulations
  - IRB 21 CFR 56
  - Informed Consent 21 CFR 50
  - Investigational Drugs 21 CFR 312
  - Investigational Devices 21 CFR 812
FDA Applicability

- Regulated Products
  - drugs
  - devices
  - biologics
  - food/color additives

- Clinical investigations
Burden of Persuasion

- IRB approval is required

- Investigator must convince reviewers that proposed research is acceptable

- Most difficult proposals present risk without direct benefit to individual subjects
Human Subjects Protection: Shared Responsibility

IRB Chair, members, staff

Sponsor Industry, CRO

Institution Institutional officials, leadership

Research Team PI, Co-Investigators Staff

Subject
Milgram Study 1963

Purpose:
- Determine response to authority
- Recruited volunteers to study learning and memory
Persons Needed for a Study of Memory

*We will pay five hundred New Haven men to help us complete a scientific study of memory and learning. The study is being done at Yale University.
*Each person who participates will be paid $4.00 (plus 50c carfare) for approximately 1 hour's time. We need you for only one hour; there are no further obligations. You may choose the time you would like to come (evenings, weekdays, or weekends).

*No special training, education, or experience is needed. We want:
Factory workers Businessmen Construction workers
City employees Clerks Salespeople
Laborers Professional people White-collar workers
Barbers Telephone workers Others

All persons must be between the ages of 20 and 50. High school and college students cannot be used.

*If you meet these qualifications, fill out the coupon below and mail it now to Professor Stanley Milgram, Department of Psychology, Yale University, New Haven. You will be notified later of the specific time and place of the study. We reserve the right to decline any application.

*You will be paid $4.00 (plus 50c carfare) as soon as you arrive at the laboratory.

TO:
PROF. STANLEY MILGRAM, DEPARTMENT OF PSYCHOLOGY,
YALE UNIVERSITY, NEW HAVEN, CONN. I want to take part in this study of memory and learning. I am between the ages of 20 and 50. I will be paid $4.00 (plus 50c carfare) if I participate.

NAME (Please Print) ........................................................
ADDRESS .................................................................
TELEPHONE NO. ................. Best time to call you ....
AGE .......... OCCUPATION .............. SEX ..........
CAN YOU COME:
WEEKDAYS ...... EVENINGS ...... WEEKENDS ........

Fig. 1. Announcement placed in local newspaper to recruit subjects.
Ethical Problems

- Respect for persons - Deception
- Beneficence - Psychological harm

“I observed a mature and initially poised businessman enter the laboratory smiling and confident. Within twenty minutes he was reduced to a twitching, stuttering wreck who was rapidly approaching a point of nervous collapse.”

Stanley Milgram
Milgram Study: Lessons

- People can readily perform unethical acts in the presence of an authority figure

- Authority relationships:
  - PI over staff
  - PI over subject
  - Sponsor over PI
  - Protocol over PI
“A motion has been made and seconded that we stick our heads in the sand.”
Role of the IRB

- Protect the institution
- Can introduce complexity
- Responsibility of PI to terminate if they sense the patient is not really involved in the process
- No one knows how risk is really determined
What is an IRB?

- Not less than 5 members
- Varying backgrounds
- Sufficiently qualified
- Diversity of race, gender, culture
- Lay member(s) (non-scientific)
- Not all of same profession or institution
- Consultants as needed

21 CFR 56.107
45 CFR 46.107
Research approved by the IRB may be subject to further appropriate review and approval or disapproval by institution.

Officials may not approve research if it has not been approved by IRB (45 CFR 46.112 and 21 CFR 56.112).

Lack of institutional support for IRB members, staff, space, professional development, education of researchers is #1 citation in OHRP site visits.
What Does an IRB Do?

- Approve, Disapprove, or Modify
- Conduct Continuing Review
- Observe / Monitor / Audit
- Suspend or Terminate Approval
An EM investigator would like to survey patients about drug use and ED visits.

Questionnaire contains “sensitive” information.

No invasive procedures or follow-up contact planned.

Thinks study might be exempt from review.
Level of risk determines route of review.
What is ‘Harm’?

- Physical (easiest to perceive)
- Psychological
- Social
- Economic
- Legal
- “Dignitary”? 
What is Risk?

- Likelihood of a bad occurrence?
- Magnitude of the potential harm?
- How does it compare to the potential benefit?
- Who derives the benefit?
- Whose risk is it?
Exemption categories

- Educational settings or tests
- Survey procedures
- Interview procedures
- Observation of public behavior
- Research use of existing data
- Public benefit or service programs
- Taste and food quality
Human subject can be identified

AND

Disclosure could place subject at risk
Expedited Review

- Rigor is the same as full review
- Only the number of reviewers is different
For either or both of the following:

(1) Some or all of the research involves no more than minimal risk,
(2) Minor changes in previously approved research (≤ 1 year) for which approval is authorized
Assessment of minimal risk

The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
Expediting Review Categories

1. Clinical studies (No IDE/IND required)
2. Collection of blood samples
3. Noninvasive prospective collection of biological specimens
4. Noninvasive data collection used in clinical practice
5. Data, documents, records, specimens collected for nonresearch purposes
6. Voice, video, digital, or imaging recordings for research
7. Individual or group behavior
8. Continuing review - closed to patient enrollment
9. Continuing review - not greater than minimal risk
Full Review Requirements

- Conducted at convened meeting
- Quorum present
- Nonscientific representative
- All review and discuss
- 45 CFR 46.111 satisfied
- Approval by majority
- Conflict of interest abstain from vote/leave room
- PI informed of outcome in writing
Continuing Review

- Formal re-review of study and consent documents at a set interval
- Occurs during entire study & includes
  - assessment of new information
  - review of adverse reports/subject complaints
  - changes in protocols that affect subjects
  - monitoring as protocol requires
Amendments are common and increasing
- Requires approval by IRB
- Evaluate impact of change on subjects
- Evaluate impact of change on risk/benefit ratio
- Consent may require revision
- Enrolled subjects may require re-consent
- Only “minor” changes may undergo expedited review
- Sponsors require increasing documentation
Unanticipated Problems

- Serious and unanticipated events
- Adverse events (AE)
- Breach of confidentiality
- Subject withdrawal
- Subject complaints
- Protocol deviations
Reporting

- Serious AE or unanticipated problems must be reported in a timely manner.
- Researcher must provide:
  - Interpretation of event
  - Description of precautions to prevent reoccurrence
- Review of should be commensurate with severity.
The investigator must place the subject’s rights, welfare and safety above all other personal and scientific concerns.
Ethical Obligations

- Good science
- Scrupulous honesty
- Protect subjects
  - Early termination of participation
- Obligation not to enroll subjects who cannot give voluntary, informed consent
- Protect rights and welfare