Responsible Conduct of Research: IRB ethics & review

William L. Gannon, Ph.D.
Graduate Studies
Academic Integrity & Ethics Program (AIRE)
Human Research Protections Office (HRPO)

Institutional Review Board (IRB)

- Research: why do it and what is it?
- Why is there so much regulation?
- Ethical bases…
- What do Institutional Review Boards (IRB) do?

Fast Facts:
- How many studies are submitted/year?
- How many studies are from Central Campus?
  600
  233 in 2010

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Why Do We Do Research?

Darkness in El Dorado: How Scientists and Journalists Devastated the Amazon
By Patrick Tierney
What is Human Subjects Research?

**Research:** A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

**Human subject:** Living individual(s) about whom investigator (prof or student) conducting research obtains (1) data through intervention or interaction with individual, or (2) identifiable private information.

**Benefit:** A valued or desired outcome; an advantage.

**Risk:** The probability of harm or injury (physical, psychological, social, or economic) occurring as a result of participation in research study. Probability and magnitude of harm may vary from minimal to significant. Federal regulations define only "minimal risk."

**IRB** To protect rights and welfare of research subjects. Functions as a compliance committee focusing on shared values members who serve as advocates for protection of human subjects involved in research.
Some Events that Led to Regulations

Nazi Experiments

Milgram Experiment

Tuskegee Study 1932-1972

NEED FOR AN ETHICS CODE
Geneva Conventions

First Geneva Convention (1864)
- centered on care for wounded soldiers
- …and then adapted for maritime war and prisoners of war
- significantly updated in 1906, 1929, and 1949.

The Conventions were expanded in 1949:
- 1st: wounded soldiers on battlefield (chapter II, article 12)
  - “They shall be treated humanely and cared for by the Party to the conflict in whose power they may be, without any adverse distinction founded on sex, race, nationality, religion, political opinions, or any other similar criteria. Any attempts upon their lives, or violence to their persons, shall be strictly prohibited; in particular, they shall not be murdered or exterminated, subjected to torture or to biological experiments;.”
- 2nd: Wounded and shipwrecked at sea
- 3rd: Prisoners of war
- 4th: Civilians under enemy control

Additional Protocols were added in 1977:
- 1st Protocol: International conflicts
- 2nd Protocol: Non international conflicts

To date, over 190 countries have signed
**Nuremburg Code**

Benchmark document for medical ethics created after WWII in 1949. Document outlines 10 Points as follows:

1. Voluntary consent of human subject is essential
2. Experimentation should yield fruitful results for benefit of society
3. Experiments should be based on the results of animal studies
4. Experimentation should be conducted to avoid all unnecessary physical and mental suffering, injury
5. No experiment should be conducted when there is reason death or disabling injury will occur
6. Degree of risk taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment
7. Proper preparations should be made, adequate facilities provided to protect experimental subject
8. Experiment should be conducted only by scientifically qualified persons
9. During experiment the human subject should be at liberty to bring the experiment to an end
10. During experiment the scientist in charge must be prepared to terminate the experiment at any stage
IRB - History

• 1940s: Nazi Prisoner Experimentation

The Nuremburg Code
• Informed consent without coercion
• Human experiments should be based on animal experimentation
• Anticipated results should justify the experiment
• Only qualified scientists should conduct medical research
• Physical and mental suffering should be avoided
• No expectation of death or disabling injury

What Impact Did the Nuremburg Code Have on Mid-20th Century Research?
..... Tuskegee Study

The Tuskegee Study of “Untreated Syphilis in the Negro Male” (also known as the Tuskegee Experiment) was a clinical study, conducted between 1932 and 1972 in Tuskegee, Alabama by the U.S. Public Health Service.
The Tuskegee Study

- 600 low-income African-American males, Recruited 399 poor, mostly illiterate African American sharecroppers with syphilis to study the natural progression of the disease if left untreated.
- Lasted 40 years.
- Free medical examinations were given but participants were not told about their disease.
- When penicillin became available in the 1950s, the study continued and participants were denied treatment.
- Many participants died of syphilis.
- The study was stopped in 1972 by the U.S. DHEW only after its existence was publicized.
Stanley Milgram experiments on obedience to authority which he conducted at Yale University in 1961-1962.

- His experiment in its standard form included a fake shock machine, a "teacher," a "student" and an experimenter in a laboratory setting.
- The participant was told that he or she had to teach the student to memorize a pair of words, and the punishment for a wrong answer was a shock from the machine.
- The teacher sat in front of the shock machine, which had 30 levers, each corresponding to an additional 15 volts. With each mistake the student made, the teacher had to pull the next lever to deliver a more painful punishment.
- While the machine didn't generate shocks and a recorded voice track simulated painful reactions, the teacher was led to believe that he or she was shocking a student, who screamed and asked to leave at higher voltages, and eventually fell silent.

- If the teacher questioned continuing as instructed, the experimenter simply said, "The experiment requires that you go on," said Thomas Blass, author of the biography "The Man Who Shocked The World: The Life and Legacy of Stanley Milgram"
- "What the experiment shows is that the person whose authority I consider to be legitimate, that he has a right to tell me what to do and therefore I have obligation to follow his orders, that person could make me, make most people, act contrary to their conscience," Blass said.
H: DO circumstances drive immoral behavior?

- In this study, designed by Prof Zimbardo, 24 male college students were randomly designated as either prison guards or prisoners, and lived in the basement of the university's psychology building playing these roles in their respective uniforms.
- Within 3 days, participants had extreme stress reactions, Zimbardo said. The guards became abusive to the prisoners -- clean toilet bowls with bare hands, sexually taunting them, asking them to strip naked, etc, 5 prisoners had to be released before the study was over.

- Zimbardo's own role illustrated his point:
  - in the role of prison administrator, he became so engrossed in the jail system that he didn't stop the experiment as soon as this cruelty began.
  - "If I were simply the principal experimenter I would have ended it after the second kid broke down," he said. "We all did bad things in this study, including me, but it's diagnostic of the power situation."
1971: STANFORD “PRISONER STUDY”

“Our planned two-week investigation into the psychology of prison life had to be ended prematurely after only six days because of what the situation was doing to the college students who participated. In only a few days, our guards became sadistic and our prisoners became depressed and showed signs of extreme stress.” [http://www.prisonexp.org/](http://www.prisonexp.org/)

Ethical concerns surrounding the famous experiment often draw comparisons to the [Milgram experiment](http://www.prisonexp.org/), which was conducted in 1961 at [Yale University](http://www.prisonexp.org/) by [Stanley Milgram](http://www.prisonexp.org/), Philip Zimbardo’s former high school friend.
### Summary

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<th>Document</th>
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<th>Emphasis</th>
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<td>Geneva Conventions</td>
<td>1949 and 1977</td>
<td>Customary laws to protect non combatants of war</td>
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<td>Nuremberg Code</td>
<td>1949</td>
<td>Laws developed from WWII medical experimentation of humans</td>
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<td>Helsinki Declaration</td>
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<td>Ethical guidance for those conducting medical research on humans</td>
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<td>Belmont Report</td>
<td>1979</td>
<td>Major ethical statement guiding human research in U.S.</td>
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- Prompted by the **Tuskegee Syphilis Study** (1932-1972) and these others the **National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research** (1974-1978), with HEW, revised and expanded regulations for the protection of human subjects regulations **45 CFR part 46** in the late 1970's.
- In 1979, the Commission’s report “Ethical Principles and Guidelines for the Protection of Human Subjects of Research” was published nicknamed the **Belmont Report**, for the Belmont Conference Center, where the National Commission met when first drafting the report.
I. Respect for Persons (Autonomy)
Belmont Report 1979

• Treat individuals as autonomous agents
• Do not use people as a means to an end
  – Participants voluntarily consent to participate in research
• Give extra protection to those with compromised autonomy
• Allow people to choose for themselves
  – Obtain truly informed consent
  – Privacy and confidentiality are protected
II. Beneficence (“Do no harm”)

Belmont Report

- Acts of kindness or charity that go beyond duty
- Obligations derived from beneficence: Do no harm; Prevent harm; Promote good outcomes.
  - The risks of research are justified by potential benefits to the individual or society
  - The study is designed so risks are minimized
III. Justice (Share the Burden)

Belmont Report

• Fair sharing of burdens and benefits of research
• Don’t use populations out of convenience
• People who are likely to benefit from participating in research are not systematically excluded
Rules and Regulations

Office for Human Research Protections (OHRP)

The **OHRP** is a division of the U.S. Department of Health and Human Services. The homepage contains news, information, and links relevant to the IRB policies and procedures, including an IRB member guidebook.

Food and Drug Administration (FDA)

**FDA's Guidance on Protection of Human Subjects.** The FDA's information sheets regarding the projection of human participants for IRBs and investigators; includes a guide on informed consent.
Rules and Regulations

- **21CFRparts =** Title 21, CFR, Parts 50, 54, 56,
- **FDA312 =** U.S. Food and Drug Administration Information Sheets for the “Guidance for Institutional Review Boards and Clinical Investigators.”
Levels of IRB Review

• **Full Board** – greater than minimal risk, vulnerable populations require full committee review; 2 primary reviewers

• **Expedited** – minimal risk (1-2 reviewers)

• **Exempt** – less than minimal risk (1-2 reviewers)

• **Not Human Subjects Research** (1 reviewer, staff)

• **Modifications & amendments** - may require Full or Expedited review depending on risk - When anything in approved study is changed; need approval prior to implementation or carrying on with study.

• **Continuing Review or Renewals**- may require Full or Expedited review depending on risk – PI submits **progress report 45 days prior** to expiration; approval must be granted prior to continuing study into another year or cycle.
IRB Review

To approve research the IRB must determine that:

– Risk to subjects are minimized

– Risks to subjects are reasonable in relation to subject benefit

– Subject selection is equitable

– Informed consent obtained

– Provisions are adequate for monitoring safety

– Provisions to protect subject privacy and data confidentiality are adequate

– When subjects are likely vulnerable to coercion or undue influence additional safeguards to protect subject rights and welfare have been included
Full Board Review

- Vulnerable Populations (Children, prisoners, pregnant women, fetuses, cognitively impaired)
- Investigational drugs, devices, biologics
- Most Invasive Procedures
- Sensitive questions related to criminal/sexual behavior, drug/alcohol use
Expedited Review
(Categories 1-7)

1) Clinical Studies: IND/IDE NOT required
2) Blood Sample collection (routine methods-small amounts)
3) Prospective Collection of biological samples-noninvasive means
4) Data collected through noninvasive means (routinely practiced in clinical settings)
5) Materials (data documents, specimens etc.) have been collected or will be collected for non-research purposes
6) Collection of voice, video or digital data for research purposes
7) Individual or group behavior, surveys, interviews, oral histories

Investigational New Drug (IND) Application Process
Investigational Device Exemption (IDE)
Expedited Review
(Categories 8-9)

8) Continuing Review of research previously approved by the convened IRB with no further direct subject participation

9) Continuing review of research (not under an IND or IDE) where the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified

Investigational New Drug (IND) Application Process
Investigational Device Exemption (IDE)
Exempt Review
(6 categories)

1) Research conducted in commonly accepted educational settings involving normal educational practices

2) Educational tests, surveys, interviews, or observation of public behavior unless subjects can be identified and disclosure of data could place subject at risk

3) Educational tests, surveys, interviews, or observation of public behavior that involve elected/appointed public officials/candidates for public office or research conducted under federal statute

4) Collection/study of existing data, documents, records, specimens, if put available or if the information is not identifiable

5) Research and demonstration projects conducted/approved by Department/Agency heads designed to study/evaluate public benefit or programs

6) Taste and food quality evaluation and consumer acceptance studies

(refer to 45 CFR46.101(b) for all categories and full descriptions)
Not Human Subjects Research

• Analysis of de-identified data (no link betw data & subject)
• Survey about a product or service
• Course-related activities designed specifically for educational/teaching purposes (e.g. res methods class)
• Information-gathering interviews where questions focus on things, products, or policies

ALSO Important “part” of any protocol ----

• **Closures** –
  – study closed when project is over or when data analysis continues on de-identified data only.
  – PI submits closure report prior to study expiration

• **Reactivation** –
  – expired or closed studies can be reactivated within 6 mos;
  – studies closed longer than 6 mos must follow the New Study procedures.
Informed Consent

• What is the ethical principle? Respect for Persons - Autonomy

• Legally informed consent. Subject must:
  – Understand the facts
  – Appreciate the implications of decision
  – Have the ability to decide
  – Have the ability to communicate a decision

• Circumstances of consent
  – Provide sufficient opportunity to consider participation
  – Minimize the possibility of coercion
  – Minimize the possibility of undue influence
Informed Consent Process – Mandatory Elements

– study involves research
– purpose of the research
– description of procedures, identifying those that are experimental
– description of risk
– description of benefit
– disclosure of alternatives
– extent confidentiality will be maintained
– if compensation and treatment from injury are available
– contact for research, subjects’ rights and adverse event issues
– participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
Up to IRB Whether Consent Process is altered in any way (waivers)

- Minimal risk
- Rights and welfare not adversely affected
- Not practical without waiver
- Provide information after participation
- Procedures do not require written consent outside of research
Privacy and Confidentiality: Terms to Know

What is the difference between privacy and confidentiality?

– Privacy is about **people and setting**
  * Having control over the extent, timing, and circumstances of sharing oneself with others.
  * Privacy is an individual right.

– Confidentiality is about **data**
  * Disclosed private information, given in a relationship of trust, will not be divulged to others in ways not originally agreed upon.
  * **It is the obligation of the researcher to keep collected private information from being shared with others.**
Vulnerable Populations
(45 CFR 46 Subparts B, C, D)

Extra Protections for Vulnerable Subjects:

- Subpart B
  - Pregnant Women
  - Fetuses
  - Neonates

- Subpart C
  - Prisoners

- Subpart D
  - Children

Vulnerability is a power differential (can be situational and individual) and subjects MUST receive extra protections

- Comatose patients
- Elderly
- Employees
- Mentally disabled
- Students
HIPAA

• Health Insurance Portability and Accountability Act (HIPAA)
  – protect the confidentiality of personal health care information effective April 14, 2003
  - demographic information; medical history; information relating to the past, present or future physical or mental health or condition of an individual that is identifiable; the provision of health care to an individual or the payment for the provision of health care; physical examinations, blood tests, x-rays; and other diagnostic and medical procedures
  - must develop and submit a HIPAA Authorization form that contains core elements in the HIPAA Privacy Rule
  - A template for a valid HIPAA Authorization form for use by Main Campus investigators is available at the IRB website for Research Compliance Services: [http://research.unm.edu/rcs/](http://research.unm.edu/rcs/).
CITI (Online Human Subjects Education)

- CITI—Collaborative Institutional Training Initiative
  - Required for all “Key Personnel” listed in Protocol
  - Two tracks—Biomedical and Social & Behavioral
  - Available 24/7 from any computer, login from anywhere, asynchronous
  - Accepted by the National Institute of Health (NIH). Replaces the HRRC Web-based training or other UNM IRB training materials. Certificate valid for two years, print and provide with new protocol submissions

- BUT! Are there problems?
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<tr>
<th>Name</th>
<th>Email</th>
<th>Phone</th>
<th>Role</th>
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<tbody>
<tr>
<td>Kevin Ferrell</td>
<td><a href="mailto:ferrell@unm.edu">ferrell@unm.edu</a></td>
<td>505.277.2644</td>
<td>Interim IRB Manager</td>
</tr>
<tr>
<td>Kathleen Schmidt</td>
<td><a href="mailto:kaschmid@unm.edu">kaschmid@unm.edu</a></td>
<td>505.277.2644</td>
<td>Admin Assist III</td>
</tr>
<tr>
<td>Cecilia Brooke Cholka</td>
<td><a href="mailto:cbcholka@unm.edu">cbcholka@unm.edu</a></td>
<td>505.277.4944</td>
<td>IRB Analyst</td>
</tr>
<tr>
<td>Vanessa Tan</td>
<td><a href="mailto:vtan@unm.edu">vtan@unm.edu</a></td>
<td>505.277.0547</td>
<td>IRB Analyst</td>
</tr>
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Follow the submission guidelines below.
Main Campus IRB Office - 1805 Sigma Chi NE,
505.277.2644  Website: research.unm.edu/IRBmaincampus
Skype: unmoirb  Twitter: @UNMOIRB  Facebook: www.facebook.com/unmoirb

The IRB Committee reviews and approves protocol applications submitted by investigators in the fields of social, behavioral, and educational research.

How To Submit Your Applications

- The IRB Office will accept email submissions in the interim. Instructions for e-mail submissions:
  - **Download** the most current version from the IRB Library
  - **Complete** all sections of the form and relevant attachments(s); Signature is REQUIRED
  - **Submit** forms & relevant attachment(s) to: IRBmaincampus@unm.edu

  **NOTE:** Incomplete submissions and combined PDF packets will not be accepted. NO CLICK-IRB APPS ACCEPTED!
Is Compliance Enough?

Jesse Gelsinger (1999)
Died in a gene therapy trial at UPenn. Researchers were later cited for violations of safety standards and informed consent requirements.

Ellen Roche (2001)
Healthy lab tech who volunteered and died after inhaling hexamethonium during an asthma study at Johns Hopkins. She developed a cough and flu-like symptoms which led to organ failure.

Jolee Mohr, age 36 (2007)
Died during a clinical trial using gene therapy to treat rheumatoid arthritis. The photograph was taken on July 1, the day before she received the injection. A sudden infection (histoplasmosis) raged through her body and caused her organs to fail just after the experimental treatment was injected into her right knee, which has raised suspicion that her death was linked to the therapy. It was theorized that the virus spread beyond the injection site and combined with other immunosuppressant drugs already taken by Mohr, leaving her vulnerable to a lethal fungal infection. *Photo: Courtesy of the Mohr family, from Wired 8-30-07 & 11-12-07*