Use of Human Subjects in Research

November 3, 2011

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Reading material

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- **Instructions for taking CITI Training:**
  [http://tulane.edu/asvpr/responsible-conduct-in-research-training.cfm](http://tulane.edu/asvpr/responsible-conduct-in-research-training.cfm)
Research on human subjects

- Biomedical and Public Health research often involves working with or on human subjects or human tissues
- Can result in dilemma for the investigators
- When goals of study are expected to make a major contribution to the field, the study results can become more important than protection of the study subjects – appearance of bias/conflict
- Investigators and members of their institutions are obliged to give forethought to the maximization of benefits and the reduction of risk that might occur from the research investigation
Ethical consideration

- Unethical to consider or use human subjects as a means to an end (applies to animal use in general)
- Demonstrating respect for research participants is fundamentally bound by ethical principles of conducting studies to fulfill research objectives
- Regulations, policies, and guidance for implementation of principles used to define ethical research are regularly reviewed
- Significant historical events have typically influenced current ethical guidelines and HHS regulations
Historical events

- Nazi Medical War Crimes (1939–1945)
- Experiments conducted by Nazi physicians during World War II subjected human beings to unprecedented degree of harm and suffering
- “Medical experiments” were performed on thousands of concentration camp prisoners
  - Treatment for malaria, mustard gas, jaundice, etc.
  - Effects of freezing, altitude, sea water, drugs, etc.
  - Mass sterilization
Historical events

- In December 1946, the War Crimes Tribunal at Nuremberg indicted 20 physicians and 3 administrators for their willing participation in the systematic torture, mutilation, and killing of prisoners in experiments. The Nuremberg Military Tribunals found that the defendants had:
  - Corrupted the ethics of the medical and scientific professions
  - Repeatedly and deliberately violated the rights of the subjects
  - The actions of these defendants were condemned as crimes against humanity. Sixteen of the twenty-three physicians/administrators were found guilty and imprisoned, and seven were sentenced to death.
Nuremberg Code - 1947

http://ohsr.od.nih.gov/guidelines/nuremberg.html

A set of ten Directives establishing moral, ethical, and legal concepts in the conduct of research with human subjects. The Code has been the model for many professional and governmental codes since the 1950s and has served as the first international standard for the conduct of research.

1. Voluntary consent of the human subject is absolutely essential
2. The experiment must yield generalizable knowledge that could not be obtained in any other way and is not random and unnecessary in nature
3. Animal experimentation should precede human experimentation
4. All unnecessary physical and mental suffering and injury should be avoided
5. No experiment should be conducted if there is reason to believe that death or disabling injury will occur
6. The degree of risk to subjects should never exceed the humanitarian importance of the problem
7. Risks to the subjects should be minimized through proper preparations
8. Experiments should only be conducted by scientifically qualified investigators
9. Subjects should always be at liberty to withdraw from experiments
10. Investigators must be ready to end the experiment at any stage if there is cause to believe that continuing the experiment is likely to result in injury, disability or death to the subject
The Syphilis Study at Tuskegee (1932-1972)

Involved approximately 600 African-American men: about 400 with syphilis (cases) and about 200 without syphilis (controls)

Recruited without informed consent and, in fact, were led to believe that some of the procedures done in the interest of research (e.g., spinal taps) were actually “special free treatment.”

By 1936, it was apparent that many more infected men than controls had developed complications

10 years later, reports indicated that the death rate among those with syphilis was about twice as high as it was among the controls.

In the 1940s, penicillin was found to be effective in the treatment of syphilis

The Syphilis Study at Tuskegee continued, however, and the men were neither informed about nor treated with the antibiotic
Historical events

- The first accounts of this study appeared in the national press in 1972.
- Evoked public outrage and appointment of an ad hoc advisory panel by the US Govt. to review the study and develop recommendations to ensure that such experiments would never again be conducted.
- Outcomes included:
  - National Research Act of 1974 - Govt mandate for HS protection
  - Basic HHS Policy for Protection of Human Research Subjects - Code of Federal Regulations TITLE 45, PUBLIC WELFARE; DEPARTMENT OF HEALTH AND HUMAN SERVICES PART 46, PROTECTION OF HUMAN SUBJECTS
  - National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research - Belmont report
Belmont Report - 1979

- The Belmont Report identified three principles essential to the ethical conduct of research with humans.

- These three basic principles serve as the foundation of the current HHS regulations and guidelines for the ethical conduct of human subjects research supported by HHS (http://ohsr.od.nih.gov/guidelines/belmont.html).

- Respect for persons
  - Prospective research participants must be given the information they need to determine whether or not they want to participate in research.

  - There should be no pressure to participate and ample time to decide.

  - Respect for persons demands that participants enter into the research voluntarily and with adequate information. This is called informed consent.
- Special provisions may need to be made when an individual’s comprehension is severely limited or when a class of research participants is considered incapable of informed decision making (e.g. children, people with severe developmental disorders, or individuals suffering from dementias). Even for these persons, however, respect for persons requires giving them the opportunity to choose, to the extent they are able, whether or not they wish to participate in research activities. In some cases, respect for persons may require seeking the permission of other parties, such as a parent or legal guardian.

- **Beneficence**
  - Do no harm; obligated to Maximize possible benefits and minimize possible harms

- **Justice**
  - Requires that individuals and groups be treated fairly and equitably in terms of bearing the burdens and receiving the benefits of research.
  - The principle of justice may arise in decisions about inclusion and exclusion criteria for participation in research and requires investigators to question whether groups are considered for inclusion simply because of their availability, their compromised position, or their vulnerability — rather than for reasons directly related to the problem being studied.
Belmont Report

The challenges in applying the Belmont principle of respect for persons are in:

- Making sure that potential participants comprehend the risks and potential benefits of participating in research
- Avoiding influencing potential participants’ decisions either through explicit or implied threats (coercion) or through excessive compensation (undue influence) Influencing an individual's decision about whether or not to do something by using explicit or implied threats (loss of good standing in a job, poor grades, etc.).

The challenge inherent in applying the Belmont principle of beneficence is how to determine when potential benefits outweigh considerations of risks and vice versa.

The challenge of applying the Belmont principle of justice is how to decide which criteria should be used to ensure that harms and benefits of research are equitably distributed to individuals and populations.
● OHRP definition of “Investigator” includes anyone involved in conducting the research.

● The act of solely providing coded private information or specimens (for example, by a tissue repository) to does not constitute involvement in the conduct of the research.

● However, if the provider also collaborates on other activities related to the conduct of the research, such additional activities does constitute involvement in the conduct of the research.

● Examples of such additional activities include, but are not limited to: (1) the study, interpretation, or analysis of the data resulting from the coded information or specimens; and (2) authorship of presentations or manuscripts related to the research.

Human Subjects Research

- A living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual or obtains identifiable private information. Regulations governing the use of human subjects in research extend to use of human organs, tissues, and body fluids from identifiable individuals as human subjects and to graphic, written, or recorded information derived from such individuals. (See section 4.1.14 Human Subjects Protections in the NIHGPS and the OER Research Involving Human Subjects Webpage.)

- Human Subjects Assurance: A document filed by an institution conducting research on human subjects with the Office for Human Research Protections--HHS which formalizes its commitment to protect the human subjects prior to receiving any HHS grant funding. The document assurance number will be required for grant applications prior to federal funding.
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<tr>
<th>Is NOT Human Subjects Research</th>
<th>Is Human Subjects Research</th>
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<td>◆ Specimens/data NOT obtained from living individuals</td>
<td>◆ Specimens/data IS obtained from living individuals</td>
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<tr>
<td>◆ Human cell lines from commercial provider</td>
<td>◆ Specimens/data collected from any provider specifically for the proposed research and can be linked to individual by recipient or provider</td>
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<td>◆ Human cells about which all information has been published</td>
<td>◆ Provider is an investigator per OHRP definition</td>
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<td>◆ Unidentifiable specimens/data from a commercial provider</td>
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Is it human subjects research?

- You are an investigator proposing to use data from a colleague’s database to conduct secondary analyses. You want to examine the behavior and attitudes in male spouses of female business executives. Your colleague will provide coded data for your proposed studies, and you and he enter into an agreement by which he will keep the key to the code and will have no other involvement in the research. Therefore, your colleague is not an investigator in your research.

- Is this human subject research?
Is it human subjects research?

- The correct answer is No.
- The study does not involve human subjects because both criteria are met:
  - The private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
  - The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain
- The use of anonymized data means that the investigator cannot identify the individuals to whom the data pertain, and obtaining the data from a colleague with whom the investigator is not collaborating means that the colleague will not be able to link any research results to identifiable individuals.
Is this human subjects research?

Another way to assess:

- It depends upon the facts and whether the person is engaged in an activity that represents a systematic investigation that intends to develop or contribute to generalizable knowledge for the field, will publish the results.

- A “systematic investigation” is an activity that involves a prospective research plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a research question.

- “Generalizable knowledge” involves studies that are designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside the specific study population), inform policy, or generalize findings.

- Federal regulations do not provide a definition for either systematic investigation or generalizable knowledge, guidance on who is to make that determination. Such decisions are made on a case by case basis depending upon the facts.

- If activity is part of a class project, the activity usually does not meet the generalizable knowledge test.
Is it human subjects research?

- Study comparing cognitive behavior therapy to medication in treating depression?
  - Yes, this is research, unless investigator is not doing anything with the data.

- Focus group study of parenting practices?
  - Maybe. What is the planned use of the data? If it is a systematic investigation and designed for generalizable knowledge, then yes. If presented solely in class, then no. If conducted for quality improvement within group, then no.

- Research in historic archives to learn about what the pioneers ate?
  - No, as this would not involve living human subjects. However, if the archives contained data on living people, the research may fall under exempt category. Look to what the proposed use of the data.

- Study that counts the number of Hispanic surnames in the Nashville telephone directory?
  - No. Counting names in the phone directory is not a “systematic investigation”, i.e., an activity that involves a prospective research plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a research question.
Informed Consent

- A legally-effective, voluntary agreement that is given by a prospective research participant following comprehension and consideration of all relevant information pertinent to the decision to participate in a study.

- Voluntariness: Individuals’ decisions about participation in research should not be influenced by anyone involved in conducting the research: “…consent must be freely given or truly voluntary.”

- Comprehension: Individuals must have the mental or decisional capacity to understand the information presented to them in order to make an informed decision about participation in research.
Informed consent

Disclosure HHS regulations (45 CFR 46.116(a)) require that researchers disclose:

- The purpose of the study
- Any reasonably foreseeable risks to the individual
- Potential benefits to the individual or others
- Alternatives to the research protocol
- The extent of confidentiality protections for the individual
- Compensation in case of injury due to the protocol
- Contact information for questions regarding the study, participants’ rights, and in case of injury
- The conditions of participation, including right to refuse or withdraw without penalty
- This disclosure must be made in such a way that it provides a reasonable person the information she or he would need in order to make an informed decision
- Should be understood as an on-going process rather than a level of legal protection for an institution. It is not intended to be a one-time act of having a participant sign a form
- Informed consent is designed to inform research subjects about the purpose, risks, potential benefits and alternatives to the research that allows people to make a decision about whether or not to participate based on their own goals and values. This exchange of such information should occur at enrollment and throughout the study.
Waiver of informed consent

HHS regulations (45 CFR 46.116(d)) allow informed consent to be waived only if:

- A legally-effective, voluntary agreement that is given by a prospective research participant following comprehension and consideration of all relevant information pertinent to the decision to participate in a study.
- Participation in the research involves no more than minimal risk “The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”
- The waiver must not adversely affect the rights and welfare of research participants
- Incomplete disclosure or deception must be essential to the ability to carry out the research Withholding some information in order to conduct an unbiased study, with the understanding that the information could be material to a decision by prospective participants about whether or not to participate in the study.
- Misleading research participants about the research purpose or procedures.
- Whenever appropriate, research participants will be given additional pertinent information after they have participated in such a study (debriefing)
Clinical Trial

- A prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

- Biomedical clinical trials of an experimental drug, treatment, device, or behavioral intervention may proceed through four phases:
  - Phase I. Tests a new biomedical intervention in a small group of people (e.g. 20-80) for the first time to determine efficacy and evaluate safety (e.g., determine a safe dosage range and identify side effects).
  - Phase II. Study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and further evaluate safety.
  - Phase III. Study to determine efficacy of the biomedical or behavioral intervention in large groups of people (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the interventions to be used safely.
  - Phase IV. Studies conducted after the intervention has been marketed. These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
Clinical Research

Research with human subjects that is:

- **Patient-oriented research.** Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. It includes:
  - mechanisms of human disease
  - therapeutic interventions
  - clinical trials
  - development of new technologies

- **Epidemiological and behavioral studies**

- **Outcomes research and health services research**

- **Studies falling under 45 CFR part 46.101(b) (4) (Exemption 4) are not considered clinical research by this definition**
Human Research Protection at Tulane

- Tulane’s Human Research Protection Program (“HRPP”) includes SOPs that incorporate state and federal regulations, including the DHHS regulations located at 45 CRR 46 (known as “The Common Rule”) and FDA human subjects regulations.

- Tulane HRPP SOPs are published at: [http://tulane.edu/asvpr/irb/policies.cfm](http://tulane.edu/asvpr/irb/policies.cfm)

- The IRB is the decision making body of Tulane’s HRPP.

- The Tulane Human Research Protection Office (“HRPO”) administers the HRPP
Contact Information

❖ Tulane’s Human Research Protection Office (HRPO): 504.988.2665; irbmain@tulane.edu; http://tulane.edu/asvpr/irb/index.cfm
❖ Tulane human subjects protection policies: http://tulane.edu/asvpr/irb/policies.cfm
❖ Research Compliance (Brian Weimer): 504.988.1147; bweimer@tulane.edu; Room 2425 of Tidewater Bldg.; http://tulane.edu/asvpr/research-compliance.cfm
❖ Instructions for taking CITI Training: http://tulane.edu/asvpr/responsible-conduct-in-research-training.cfm