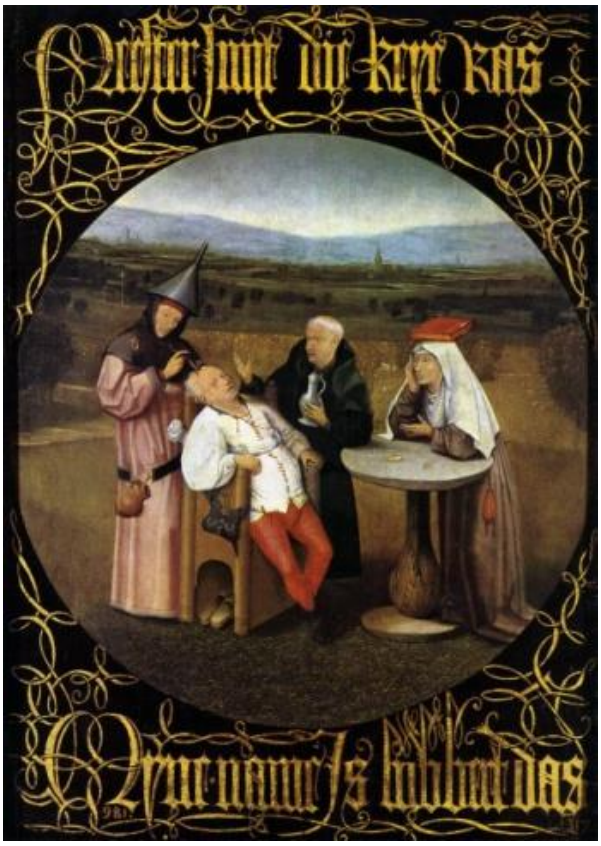
USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Human Subjects Research



Office for the Protection of Research Subjects (OPRS)

Dalar Shahnazarian, MSW Candidate, IRB Student Mentor;
Susan L. Rose, Ph.D.; Jennifer Hagemann, MS; Monica Aburto

This series of booklets is adapted from the Collaborative Institutional Training Initiative (CITI) Responsible Conduct of Research online course available at www.citiprogram.org

Also available in the RCR Series:

Using Animal Subjects in Research

Collaborative Research

Peer Review

Data Management and Acquisition

Conflicts of Interest and Commitment

Mentoring Student Researchers

Research Misconduct

Responsible Authorship and Publication

About the Source Material

The Collaborative Institutional Training Initiative (CITI) web based education program, developed by the University of Miami and the Fred Hutchinson Cancer Research Center, offers training in Human Subjects Research, the Responsible Conduct of Research, and Good Clinical Practice. CITI is currently used by over 1130 participating institutions and facilities from around the world and offers online course material in more than seven different languages. CITI RCR was developed with public funds and thus allowed access to material used to create these booklets.

Introduction to Human Subjects Research

This booklet is intended to offer information and generate discussion about the responsible conduct of research associated with human subjects research whether biomedical or social and behavioral. Key human subjects research definitions are provided as well as a concise historical overview of how the federal regulations came about. The Informed Consent process and Institutional Review Boards are also discussed. Case studies and reference lists are provided.

What is Human Subjects Research?

Federal Regulation “The Common Rule”

In 1991, the US Department of Health and Human Services codified into regulation the Policy for the Protection of Human Subjects (Title 45, Part 46). These regulations, called the “Common Rule” (Subpart A), provide the basic foundation for the human subjects protection program in use today. This Federal Policy has been codified by all federal agencies that conduct, support, or otherwise regulate human subjects research, hence the title “Common Rule.” The Policy in Subparts B, C, D, provides specific protections to “vulnerable populations” such as pregnant women, fetuses, and neonates (Subpart B), prisoners (Subpart C), and children (Subpart D) involved in human subjects research.

To determine whether a research project is considered human subjects research one must consider the definitions provided in the Common Rule, to which numerous federal agencies are signatory. Studies not meeting the definitions are ***not*** considered human subjects research.

For more information on the Common Rule visit:
http://www.nsf.gov/bfa/dias/policy/docs/45cfr690.pdf

Defining "Human Subjects Research"

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains (45CFR46.102(d)):

1. Data through intervention or interaction with the individual, or
2. Identifiable private information.

Defining Research

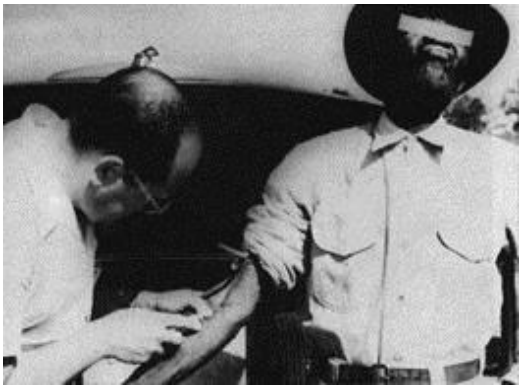
Federal Regulations define research as **“**a **systematic investigation,** including development, testing, and evaluation, designed to develop or contribute to **generalizable knowledge**” (45CFR46.102(d)). **"**Generalizable knowledge**"** is information where the intended use of the research findings can be applied to populations or situations beyond that studied.

All researchers need to be aware of whether they are conducting human subjects research in part because ethical, institutional, and legal guidelines apply to such research.

Historical Overview: Subjects Research

The current ethical and legal framework for conducting human subjects research largely stems from the Nuremberg Code, a set of guidelines articulated after World War II. It was created in response to the atrocities undertaken by Nazi researchers. The Nuremberg Code expresses the notion that human beings must voluntarily consent before they participate in research.

The World Medical Association (WMA) is an international organization representing physicians. It developed and ratified the first version of the Declaration of Helsinki in 1964, which was created in order to help articulate ethical principles that should be followed when conducting human subjects research. A primary intention behind the Declaration of Helsinki was to address ethical complexities associated with conducting human subjects research in foreign countries. According to the document, “No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration."



Because of public outrage that followed widespread disclosure that poor, black Southern males were left untreated in a government funded research project, the U.S. government in 1974 ratified the National Research Act (discussed below). This study, causing the outrage, was called the Tuskegee experiment and took place from 1932 until 1972. It involved monitoring several hundred African American males who suffered from syphilis, but were not treated for their disease. This was done so that the natural history of the disease could be observed. Among the ethical shortcomings in the study were that subjects were not told that they suffered from syphilis. An effective treatment for the disease was not available when the study began, but when penicillin was found to be a cure, it was not administered to the research subjects. The repercussions from this study have lead directly to the Belmont Report and the Federal Regulations for the Protection of Human Subjects.

The Belmont Report

In 1974, the National Research Act led to the development of the Belmont Report. The Belmont Report emphasizes three ethical principles: respect for persons, beneficence, and justice. Researchers must conduct research that adheres to these principles.

The Belmont Report can be found at http://www.hhs.gov/ohrp/belmontArchive.html

- **Respect for persons**

Respect for persons refers in part to the ethical obligation to uphold autonomy. Autonomy is defined as the right of competent individuals to make decisions about their own participation in research or medicine. According to the Belmont Report, "To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others." Respecting autonomy requires that a researcher honor the decision of a potential subject about participation in a research protocol and provide sufficient information on benefits and risks to make an “informed decision”. Federal regulations provide additional guidance for researchers if they are seeking to enroll subjects, such as children, with diminished autonomy.

- **Beneficence**

Beneficence refers to the ethical obligation to protect and uphold the well-being of individuals. According to the Belmont Report, beneficence requires one to "do no harm" and "maximize possible benefits and minimize possible harms". With regard to upholding this principle, researchers are responsible for weighing the risks of a protocol against its potential benefits. Researchers have an ethical obligation to design protocols that expose subjects to the least amount of risk possible. Being beneficent may entail that a researcher stop research for a specific subject or halt an entire protocol if harm results.

- **Justice**

Justice typically refers to the ethical obligation to distribute benefits and burdens fairly. Applying this concept to research, justice requires researchers to develop a strategy for ensuring that subjects, or perhaps the population from which research subjects were drawn, receive a fair share of the benefits stemming from the research. According to the Belmont Report, "An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly." For example, merely because it is easy to recruit a particular subset of the population for a protocol, that probably does not justify the practice of excluding other potential groups.

Beyond setting a basis for the three ethical principles, the **Belmont Report** provides a conceptual foundation for the Common Rule, which regulates how federally-funded human subjects research should be conducted.

The Informed Consent Process

Conducting human subjects research in a responsible manner requires **informed consent be** obtained from potential subjects.

Three of the fundamental components of informed consent are:

1. Subjects must be adequately informed about the research protocol in which they are being asked to enroll, including being told the potential benefits and risks that may be associated with participation.

2. The decision of each subject to enroll must be voluntary. In other words, the subject should not be unduly influenced or coerced into making a decision about participation. Undue influence or coercion includes but it is not limited to offering potential subjects an exorbitant amount of money for enrolling. It can also involve compelling a vulnerable person such as a prisoner to enroll by offering the condition of a shortened prison sentence in exchange for participation in the research protocol. Or it may be something as simple as requiring one's student or employee to be a research subject as a condition for a job or grade.

3. A subject must be competent to voice a decision about participation. The subject must be capable of understanding the information presented about the research and of appreciating the consequences of enrolling or of declining to enroll. However, there are circumstances where a non-competent individual, or a child, could participate if the parent or legally authorized representative determines participation is in the subject's best interest.

Consent Forms

Obtaining consent usually, but not always, occurs through a process where potential subjects are asked to review and sign a consent form before the research begins. When researchers develop a consent form, the following are some of the key elements that need to be described:

- The purpose of the research
- Possible benefits and risks associated with the research
- Any alternatives that are available
- The rights that each research subject has, which includes the ability to discontinue participation at any time without penalty
- How a subject's privacy and confidentiality will be protected
- Whether there is compensation for participating in the research and if so, what that compensation is
- A list of names and contact information for individuals who are responsible for answering questions or concerns about the research

The form should describe adequately the risks associated with participation and not be overly technical and confusing. Because subjects in research can be vulnerable or harmed, it is of the utmost importance that **researchers clearly and thoroughly explain key information about the research before a consent form is signed.** The forms must be written in the subjects' native language. Researchers need to

pay specific attention to making sure that consent forms are at an appropriate reading level for potential subjects so that they can understand what they are being asked to examine and sign.

It can be difficult to determine whether obtaining written consent is necessary. In general, if the research involves human participants and can pose some form of non-trivial risk to those participants, it is highly likely that consent is required. It is crucially important that researchers consult the Institutional Review Board if informed consent, and other requirements apply.

It should be emphasized that merely complying with the law does not necessarily satisfy a researcher's professional obligations when conducting research with human beings. The law provides a threshold that researchers should not fall below. However, the law or even codes of ethics cannot capture every ethical obligation that a researcher has. Thus, it is incumbent on researchers that they keep in mind that their foremost responsibility when conducting human subjects research is to the volunteering participants. Besides the potential of harm to individuals and expense to subjects or to society, research misconduct can profoundly erode public trust.

Who oversees the Human Subjects Research Process?

Institutional Review Boards (IRB)

All institutions that conduct human subjects research are required to have their own Institutional Review Board (IRB) or be named on the Federalwide Assurance (FWA) of an established IRB. The IRB's role is to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the institution or with which it is affiliated.

Academic institutions, medical centers, and private entities support and maintain federally assured IRBs to review and approve human subjects research. (USC has four IRBs, three on the Health Sciences Campus that review biomedical studies, and one on the University Park Campus that reviews social and behavioral research.)

An Institutional Review Board (IRB) seeks to ensure that only ethically and legally appropriate research involving human subjects is allowed to proceed.

Composition

In accordance with federal regulations or IRB mandate:

- IRBs are required to review human subjects research that is supported by federal funds. Yet many institutions (including USC) chose to have their IRBs examine all human subjects research protocols even if those not federally funded.

- The IRB must have at least five members, one of which must be a non-scientist and one of which must be from the outside community and not affiliated with the institution.

Role

An IRB must ensure that a research protocol fulfills certain criteria before it can be approved. An IRB must review whether researchers have created a consent process that will enable potential subjects to understand the research clearly. Further, an IRB must assess whether researchers have developed adequate safeguards for study risks and maintain privacy of data.

Faculty, staff, and students may consult with an IRB if their research involves human participants in order to determine whether IRB review is required. The use of surveys, for example, to collect data <u>about</u> students' attitudes and behaviors requires some form of IRB review.

Types of Review

The “Common Rule” (45 CFR 46) provides for three levels of review for human subjects research. They are exempt, expedited and full board:

1. **Exempt review:** exempt protocols commonly involve less than minimal risk* (e.g. anonymous survey) to subjects and fall within at least one of the six federally defined categories. These projects are reviewed by one designated reviewer or IRB member. This level of review has no continuing IRB oversight requirements.
2. **Expedited review**: expedited protocols involve minimal risk* (e.g. blood draw, longitudinal study on grades and success) and fall within one of nine federally defined categories. These projects are reviewed by one designated, well trained IRB member. This level of review has ongoing IRB oversight requirements.
3. **Full board review**: full board protocols involve greater than minimal risk* (e.g. drug, device, biologics, and collecting/recording sensitive, private information). These projects are reviewed by a fully convened IRB. This level of review is thorough, must meet all approval criteria, and has continuing IRB oversight requirements.

   *__Minimal risk__ is when the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those

ordinarily encountered in the participant's daily life or during the performance of routine physical or psychological examinations or test.

Not Human Subjects Research (NHSR)

Not all research using human subjects requires IRB review. The IRB must be involved in determining applicability when humans are involved but studies that do not meet the regulatory definitions of “human subject” or “research” are relegated to a category USC calls Not Human Subjects Research (NHSR). (See https://oprs.usc.edu/review/typesofirb/).

An additional regulatory exclusion refers to research projects that use coded (not identified) specimens or information. See the Office for Human Research Protections (OHRP) “Guidance on Research Involving Coded Private Information or Biological Specimens” for more information http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm).

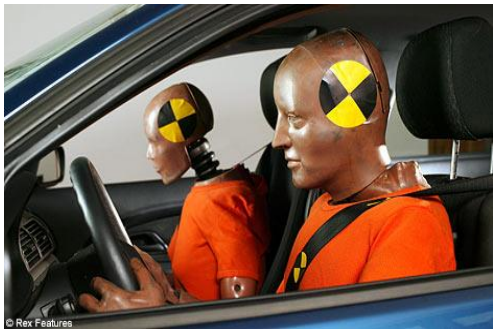
Conclusion

The definition and scope of human subjects research guidelines and regulations can and do apply to a broad range of fields. Even if researchers are not testing a drug or a medical device, they may be conducting human subjects research. Depending on the methodology, a protocol involving a computer program, medical device, survey, or a piece of exercise equipment can be human subjects research and can pose risks to human beings.

As investigators recruit human participants into research protocols with more frequency, IRBs will have a more significant role examining the safety and the welfare of the participants in new, untried research technologies. Thus, all researchers must be familiar with the process guiding how research protocols are developed and submitted to an IRB. Conducting research requires that researchers become familiar with and adhere to relevant ethical, legal, and institutional guidelines.

Case Studies

I. Don't Be a Dummy…



Dr. James Smith, an engineering researcher, is seeking to evaluate a new structural material for automobiles. Once the material is integrated into an automobile, it is designed to lessen the impact that a rear-end collision would have on passengers. Dr. Smith intends to ask for volunteers at his university to participate in his research, which would involve placing the volunteers in an automobile that is hit from behind at a low speed.

Susan, a graduate student, asks Dr. Smith about whether a protocol describing the research needs to be submitted to the university's IRB because Dr. Smith is seeking to recruit human participants. Dr. Smith replies that since the primary aim of the research is to assess the new material, the project is privately funded, and that his tests will only be conducted at a low speed, it is not the sort of research that needs to be reviewed by an IRB. Susan is concerned about Dr. Smith's response but trusts that he has more experience regarding the subject matter.

Questions for Consideration:

1. Is the research described in the scenario considered human subjects research in accordance with the federal definition?
2. Who should Susan contact someone at her university to ask for advice about what to do?
3. What are the possible professional consequences for Susan if she decides to ask for advice or do any follow-up action?
4. What are the possible professional consequences for Susan if she decides not to ask for advice or do any follow-up action?

II. A Hair Raising Experiment

Dr. Ann Johnson, a biomedical engineer, and her research team, with the assistance of funding from NIH, just recently finished designing a prototype of a biosensor. The biosensor was constructed to detect whether vital signs, such as blood pressure, sharply increase or decrease. One of its intended applications is to monitor the health of soldiers in the field. Dr. Johnson consults with one of her graduate students, Charlie, about the project and suggests that it will provide some good experience for him to work on the biosensor development and testing. Further, it might help him earn a job in the future because Dr. Johnson knows of a company that is interested in seeking a patent on the device. Dr. Johnson and Charlie meet on several occasions to determine which kinds of scenarios might be the best in order to evaluate the biosensor. Dr. Johnson and Charlie plan to recruit human volunteers and place them in moderately stressful circumstances. The testing will include having volunteers perform vigorous exercise and having them watch violent movies. Since these are the sorts of activities that humans ordinarily perform in daily life, they believe that their research methods are consistent with the aims of testing the biosensor.

Questions for Consideration:

1. Should Dr. Johnson and Charlie submit a research protocol to their IRB?

2. What kinds of risks, if any, can the research pose to human volunteers?

3. If there are risks associated with the research, how should the risks be described in a consent form?

4. Are there any other ethical issues that are raised by the case?

Resources

USC Office for the Protection of Research Subjects (OPRS):
https://oprs.usc.edu/

CITI Program:
www.citiprogram.org

USC Health Sciences IRB:
https://oprs.usc.edu/hsirb/

USC University Park IRB:
https://oprs.usc.edu/upirb/

Office of Research Integrity (ORI):
http://ori.dhhs.gov/

USC Contacts

Office for the Protection of Research Subjects
3720 South Flower Street, Third Floor
Los Angeles, CA 90089-0706
Tel (213) 821-1154
Fax (213) 740-9299
E-mail: oprs@usc.edu
https://oprs.usc.edu/

Health Sciences Institutional Review Board
General Hospital, Suite 4700
1200 North State Street
Los Angeles, CA 90033
Tel (323) 223-2340
Fax (323) 224-8389
E-mail: irb@usc.edu
https://oprs.usc.edu/hsirb/

University Park Institutional Review Board
Credit Union Building (CUB), Suite 301
3720 S. Flower Street
Los Angeles, CA 90089
Tel (213) 821-5272
Fax (213) 821-5276
E-mail: upirb@usc.edu
https://oprs.usc.edu/upirb/

Office of Research
Credit Union Building, Suite 325
3720 S. Flower Street
University of Southern California
Los Angeles CA 90089-4019
Tel (213) 740-6709
Fax (213) 740-8919
E-mail: vice.president.research@usc.edu
http://www.usc.edu/research/

CITI Helpdesk
Tel (213) 821-5272
E-mail: citi@usc.edu
https://oprs.usc.edu/education/citi/

iStar Technical Help
Tel (323) 276-2238
E-mail: istar@usc.edu
Web: http://istar-chla.usc.edu

Office of Compliance
3500 Figueroa Street
University Gardens Building, Room 105
Los Angeles, CA 90089-8007
Tel: (323) 740-8258
Fax: (213) 740-9657
E-mail: complian@usc.edu
http://www.usc.edu/admin/compliance/

USC Stevens Institute for Innovation
3740 McClintock Ave. Hughes EEB 131
Los Angeles CA 90089
Tel: (213) 821-5000
Fax:(213) 821-5001
http://stevens.usc.edu/

Health Research Association (HRA)
1640 Marengo Street, 7th Floor
Los Angeles, CA 90033
Tel (323) 223-4091
Fax (323) 342-0947
Web: http://www.health-research.org/

IRB Student Mentor
Tel (213) 821-1154
E-mail: irbgara@usc.edu
https://oprs.usc.edu/education/mentor/

Office of Contracts and Grants-UP
Credit Union Building (CUB), Suite 303
3720 S. Flower Street
Los Angeles, CA 90089
Tel: (213) 740-7762
Fax: (213) 720-6070
http://www.usc.edu/research/dcg/

Office of Contracts and Grants-HSC
1540 Alcazar Street, CHP 100
Los Angeles, CA 90033-9002
Tel: (323) 442-2396
Fax: (323) 442-2835
http://www.usc.edu/research/dcg/