

## Use of Human Subjects

### Background

Advances in human health and welfare ultimately depend on research with human subjects. Properly controlled studies with human subjects are essential to verify any conclusions about normal physiology, mechanisms of disease, effectiveness of treatment, learning, or behavior. Unfortunately, not all human studies have been justifiable and useful. Human cruelty can be perpetrated in the name of research. Some of the best known examples occurred in Nazi Germany. Investigations following the war uncovered many atrocities, such as studies in which subjects were immersed in very cold water to gauge how long it would take to die of hypothermia. The discoveries of these abuses were the basis for the Nuremberg trials and development of the Nuremberg Code (1949), the first international codification of minimal expectations for the conduct of research involving human subjects. Some of the most important provisions of the Code were that experiments with human subjects should occur only in the context of a clear scientific rationale and only with subjects who have freely chosen to participate.

Harm to unwilling subjects under the guise of research has not been unique to the Nazis. During World War II, the U.S. conducted medical experiments on people not competent to consent and on subjects without their knowledge (Vanderpool, 1996). In 1932, prior to the start of World War II, 400 African American males with syphilis had been entered into a study at Tuskegee, Alabama with the intended purpose of documenting the natural course of their disease (Rivers et al., 1953; Jones, 1993). Although treatments of presumed efficacy were available, these were withheld while the study participants were led to believe that experimental procedures (such as spinal taps to examine cerebrospinal fluid) were for the purpose of therapy. By the 1950's, penicillin was available and known to be highly effective against syphilis, but it also was withheld. The surviving participants were only given treatment in 1972, after the nature of the study became publicly known, and 23 years after publication of the Nuremberg Code. Recognition of problematic studies published in the medical and social science literature resulted in the appointment of a federal commission to identify fundamental principles that should govern human subjects studies. The final product of this commission was the Belmont Report (1979). It defined the three ethical principles (listed below) that now guide studies with human subjects in the U.S.

1. **Respect for persons**

'Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection.'

2. **Beneficence**

'Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.'

3. **Justice**

'An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly...'

At least three important premises underlie these principles. The first is that studies with human subjects are necessary for improvements in health and welfare. Second, to conduct such research is a privilege, not a right, extended to researchers by society, institutions, and the research subjects themselves. Finally, neither the risks nor the costs of any research study should outweigh the likely benefits.

## **Regulations and Guidelines**

Seventeen federal agencies have regulations governing the conduct of research involving human subjects. Examples of agencies with human subject requirements include the Department of Health and Human Services (DHHS), the Food and Drug Administration (FDA), the National Science Foundation, and the Departments of Defense, Education, Justice, and Veterans Affairs.

Different agencies define 'human subject' in different ways, but it includes (at minimum) any living person who is involved in research either as an experimental subject or as a control. The scope of activities included under the definition of 'research' is broad. One federal regulation defines research as any 'systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.' (Code of Federal Regulations for Department of Health and Human Services 45CFR46.102(d)).

Human subject protections are a shared responsibility of principal investigators, other personnel involved in studies with human subjects, and the Institutional Review Board (IRB). The IRB is a primary mechanism for federally-mandated institutional protection of human subjects. An IRB is designed to be an advocate for potential and actual research subjects. Under both DHHS and FDA regulations, the IRB is responsible for approving or disapproving all covered research activity, requiring for instance that subjects are given enough information to be able to provide informed consent. The IRB must conduct periodic reviews of research to ensure continued protection of the welfare of human subjects and compliance with relevant regulations.

In addition to the above regulatory oversight, because of concerns about protection of human subjects, the Department of Health and Human Services also requires education of all key personnel working on PHS-funded studies with human subjects (NIH, 2000).

## **Considerations**

### **Regulations**

Research that involves humans is subject to regulation. No procedure or study should be performed that is not explicitly exempted or a part of an approved protocol. Applicable regulations include requirements for adherence to IRB-approved research protocols, maintenance of documentation and records, obtaining approval prior to initiation of changes, and reporting of adverse events. Investigators are responsible for identifying all applicable regulations and complying with them.

### **Responsible conduct**

Responsible conduct of research involving human subjects requires much more than complying with regulations. The spirit of the regulations and of good science both require that researchers critically review what is known and give thoughtful consideration to what defines an acceptable study. This consideration is necessarily an ongoing process. Factors to be considered include changes in our best understanding of the science, of the risks and potential benefits, of alternative methods for study, and so on. The decision to conduct a study with human subjects carries both ethical and regulatory responsibilities to protect the welfare and interests of those subjects, to design the study so as to minimize risks to subjects, and to obtain adequate training for protecting the interests and welfare of the research subjects.

### Justification and necessity

A prerequisite for the responsible research involving humans is a realistic examination of the probability and magnitude of both the risks and the benefits of the research. Investigators must assess whether the risks are reasonable in relationship to the benefits to the individual subjects and the knowledge to be gained.

### Informed Consent

Investigators conducting a research study with human subjects have an absolute responsibility to ensure that consent to participate has been given freely and is based on an understanding of the risks and benefits. Informed consent is often needed even for studies in the social sciences that impose little or no inconvenience, but still present the risk of a loss of privacy or confidentiality. Although some costs or risks may be more injurious than others, it must be up to the potential research subject, not the research investigator, to decide whether such costs or risks are outweighed by the benefits of participation.

### Informed Consent as a Process

The most visible indication of 'informed consent' is a document to be signed by the research subject. This document is important because it provides a consistent body of information that the investigator and the IRB have agreed is necessary for individuals to provide their informed consent. Unfortunately, subjects may sign such forms without understanding them and, even if those forms were initially understood, changing circumstances may mean that the subjects are no longer truly informed. Therefore, informed consent is not a single event, but an ongoing process.

### Diminished Capacity to Consent

Not all subjects are able to give truly informed consent. In some cases, it is difficult to ensure that consent is given freely, such as in prison populations. In other cases, it may be difficult to convey the necessary information or to verify an understanding in people with reduced decision-making capacity, such as some subjects with developmental disabilities, psychiatric disorders, or advanced dementia. In these cases, research investigators have an additional burden to meet ethical and regulatory obligations for protecting the right of self-determination for prospective or current research subject.

## Summary

- **Comply with regulations**  
No research study of human subjects should be performed that is not explicitly part of an approved protocol.
- **Critically evaluate the use of humans**  
The spirit of the regulations and good science both require that individuals give

thoughtful consideration not only to compliance with regulations, but to what defines an acceptable use of human subjects.

- [Protect individual rights to self-determination](#)  
The decision to participate in research should be based on truly informed consent. This means that researchers have an ongoing obligation to ensure that subjects understand the risks and benefits of participation, which should continue only if the subjects (or their surrogates) freely agree to remain in the study.
- [Promote responsible use of human subjects](#)  
If you are responsible for training others or if you observe indifference to considerations for human volunteers for research studies, you should make attempts to initiate discussion, to identify relevant regulations, and to promote responsibility in studies involving human subjects. If violations of regulations are observed, then those observations should be reported to the appropriate people in the institution.

## Discussion questions

Answer all questions in your own words and submit your responses to Andrekia Branch ([aebbranch@vcu.edu](mailto:aebbranch@vcu.edu)) in the Office of Postdoctoral Services:

1. Describe at least one historical example of unethical studies involving human subjects. Identify federal regulations that are apparent responses to such abuses.
2. List and explain the three ethical principles of the Belmont Report for research involving human subjects.
3. What are the responsibilities of an Institutional Review Board (IRB)?

## Suggested reading(s)

[Columbia University](#)

[North Carolina State University](#)

[University of Montana \(posted by the Office of Research Integrity\)](#)

[Responsible Conduct of Research: Human Subjects \(UCLA\)](#)

## Resources

### Works cited

- Belmont Report (1979)

<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>

- DHHS (2005): Protection of Human Subjects, Title 45 Part 46  
[http://www.access.gpo.gov/nara/cfr/waisidx\\_05/45cfr46\\_05.html](http://www.access.gpo.gov/nara/cfr/waisidx_05/45cfr46_05.html)
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<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>
- Nuremberg code (1949)  
<http://www.hhs.gov/ohrp/references/nurcode.htm>
- Rivers E, Schumann SH, Simpson L, Olansky S (1953): Twenty years of followup experience in a long-range medical study. Public Health Reports 68(4): 391-395.
- Vanderpool HY (1996): The Ethics of Research Involving Human Subjects: Facing the 21st Century. University Publishing Group, Frederick, Maryland.

### **Guidelines for Research with Human Subjects**

- Helsinki declaration (1964-2004) The World Medical Association's statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Revised October 2000  
<http://www.wma.net/e/policy/b3.htm>
- Shuster E (1997): Fifty years later: The significance of the Nuremberg Code. New Engl J Med 20(337): 1436-1440.

### **Human Subjects Research Regulations and Oversight**

- FDA (2006): Institutional Review Boards, Title 21 Part 56  
[http://www.access.gpo.gov/nara/cfr/waisidx\\_06/21cfr56\\_06.html](http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfr56_06.html)
- FDA (2006): Protection of Human Subjects, Title 21 Part 50  
[http://www.access.gpo.gov/nara/cfr/waisidx\\_06/21cfr50\\_06.html](http://www.access.gpo.gov/nara/cfr/waisidx_06/21cfr50_06.html)
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<http://www.hhs.gov/ohrp>
- Office for Protection from Research Risks (OPRR) (1993): Protecting Human Research Subjects: Institutional Review Board Guidebook. US Government Printing Office, Washington, DC.

[http://www.hhs.gov/ohrp/irb/irb\\_guidebook.htm](http://www.hhs.gov/ohrp/irb/irb_guidebook.htm)

## Ethics and Human Research

- Beecher HK (1966): Ethics and clinical research. *New Engl J Med* 274: 1354-1360.
- Emanuel EJ, Wendler D, Grady C (2000): What Makes Clinical Research Ethical? *Journal of the American Medical Association* 283(20): 2701-2711.
- Levine RJ (1988): *Ethics and Regulation of Clinical Research*. 2nd Edition, Yale University Press, New Haven, CT.
- Milgram S (1983): *Obedience to Authority*. Harper Collins, New York.
- Sieber JE (1993): Ethical considerations in planning and conducting research on human subjects. *Academic Medicine* 68(9)(suppl.): S9-S1.

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