

## The Historical, Ethical, and Legal Background of Human-Subjects Research

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**The current system of human-subject-research oversight and protections has developed over the last 5 decades. The principles of conducting human research were first developed as the Nuremberg code to try Nazi war criminals. The 3 basic elements of the Nuremberg Code (voluntary informed consent, favorable risk/benefit analysis, and right to withdraw without repercussions) became the foundation for subsequent ethical codes and research regulations. In 1964 the World Medical Association released the Declaration of Helsinki, which built on the principles of the Nuremberg Code. Numerous research improprieties between 1950 and 1974 in the United States prompted Congressional deliberations about human-subject-research oversight. Congress's first legislation to protect the rights and welfare of human subjects was the National Research Act of 1974, which created the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research, which issued the Belmont Report. The Belmont Report stated 3 fundamental principles for conducting human-subjects research: respect for persons, beneficence, and justice. The Office of Human Research Protections oversees Title 45, Part 46 of the Code for Federal Regulations, which pertains to human-subjects research. That office indirectly oversees human-subjects research through local institutional review boards (IRB). Since their inception, the principles of conducting human research, IRBs, and the Code for Federal Regulations have all advanced substantially. This paper describes the history and current status of human-subjects-research regulations. *Key words:* research, institutional review board, IRB, human-subjects research. [Respir Care 2008;53(10):1325–1329. © 2008 Daedalus Enterprises]**

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Dr Rice presented a version of this paper at the RESPIRATORY CARE Journal Symposium at the 53rd International Respiratory Congress of the American Association for Respiratory Care, held December 1-4, 2007, in Orlando, Florida.

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The author reports no conflict of interest related to the content of this paper.

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## Introduction

The institutional review board (IRB) is predominantly an American configuration, designed to evaluate the ethical aspects of human-subjects research. Other countries have similar organizations, termed, for instance, research ethics committee or ethical review board. The following description details the history and research events behind the legislation that established IRBs and the current United States regulations and guidelines for research with human subjects.

### Brief History of Research Ethics and Regulation

In the last half century the level of oversight on human-subjects research has exploded from almost none to what is now an exhaustive system of protections (Fig. 1). After World War II the Nuremberg trials were conducted to prosecute Nazi leaders for crimes against humanity. A substantial proportion of the trials involved Nazi physicians who had forced prisoners to undergo appalling, inhumane procedures in the name of clinical research. For example, Nazi physicians subjected prisoners to freezing, injection of typhus into the blood, and direct ophthalmic injection of toxic substances, all in the name of "research." At the time of the Nuremberg court there were no laws, regulations, codes, or formal documents that stated ethical standards for human-subjects research, so the trial proceedings resulted in the development of a document, the Nuremberg Code, that articulated the basic requirements for conducting research in a manner that respects the fundamental rights of human subjects. The 3 basic elements of the Nuremberg Code (voluntary and informed consent, a favorable risk-to-benefit analysis, and the right to withdraw without repercussions) became the foundation for subsequent ethics codes and federal research regulations. Thus, every person involved in human-subjects research should read the Nuremberg Code (<http://www.hhs.gov/ohrp/references/nurcode.htm>).

Despite playing an integral role in the creation of the Nuremberg code, the United States federal government still had only a very minor role in regulating research, until as recently as 1950. At that time no federal regulations required IRB approval in most research settings. Between 1950 and 1974, however, several controversies in human research were highly publicized, especially those that involved perceived abuses of the rights of vulnerable people. In 1955, University of Chicago researchers audiotaped jury deliberations of criminal trials in Wichita, Kansas, to study juries' decision-making process and whether showmanship by trial lawyers influences jury decisions. To avoid influencing their behavior, the jurors were not told that they were being recorded or that they were part of a research project. After publication of the study's findings,

discussions focused on the unethical nature of deceiving people for research purposes in a setting where privacy and confidentiality were expected. Shortly thereafter, Congress passed a federal law that prohibits recording jury deliberations; this was the first legislation related to human-subjects research.

The use of ethics committee review of research began in the late 1950s. The National Institutes of Health created a Clinical Research Center to oversee the conduct of clinical research. The Clinical Research Center's policy required review of all research by an ethics committee before it could be initiated. A similar process, although less formal, was occurring at most public and private institutions across the United States. This culminated in 1964, when James Shannon, Director of the National Institutes of Health, established a policy that required ethics committee review of all research funded by the Public Health Service.

Furthermore, 3 events during the 1960s heralded a change in the ethical oversight of human-subjects research. In the late 1950s the investigational drug thalidomide was used to treat discomforts associated with pregnancy, including morning sickness and insomnia. At the time it was neither a requirement nor standard practice to inform patients of the investigational nature of pharmaceuticals being tested. In 1962, however, it became apparent that thalidomide caused birth deformities. Public outrage about these fetal deformities resulted in an amendment to the Food, Drug, and Cosmetic Act; investigators were required to obtain informed consent from subjects before administering investigational medications. This was the first instance of a federal agency establishing and enforcing specific ethical standards for the conduct of human-subjects research.

In 1964 the World Medical Association met in Helsinki, Finland, to draft a document that describes the ethical standards of human-subjects research. In addition to the 3 central principles of the Nuremberg Code, the Declaration of Helsinki (<http://www.fda.gov/oc/health/helsinki89.html>) added 2 novel elements:

- The interests of the subject should always be placed above the interests of society.
- Every subject should get the best known treatment.<sup>1</sup>

The association has met many times since that initial meeting in 1964 to review, reaffirm, and revise the Declaration. In 1966 researchers began using the Declaration of Helsinki to police their own conduct in human research and focus attention on the need to improve ethical conduct in human-subjects research.

In 1966 *The New England Journal of Medicine* published the article "Ethics of Clinical Research,"<sup>2</sup> by Henry Beecher, a senior member of the anesthesiology faculty at Harvard Medical School. Beecher detailed unethical practices in 22 studies conducted by respected investigators

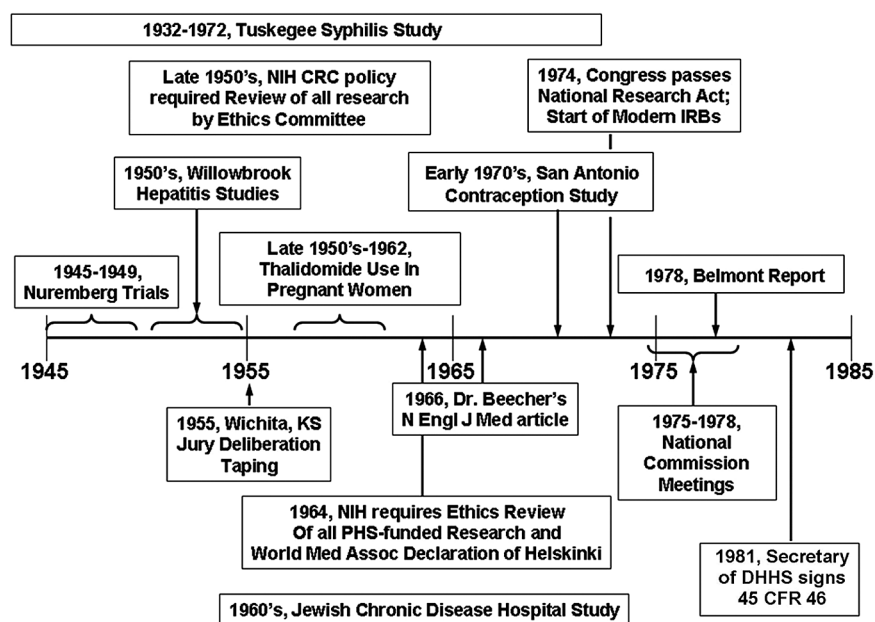


Fig. 1. Timeline in the development of regulations on human-subjects research protections and institutional review boards (IRBs). NIH = National Institutes of Health. CRC = Clinical Research Center. PHS = Public Health Service. DHHS = Department of Health and Human Services. CFR = Code of Federal Regulations.

and published in prestigious medical journals. The unethical practices ranged from lack of informed consent to increased risk for participants. He also proposed that the decision of whether a study is ethical should be determined at its inception, not after the results are known. This article was a milestone in the history of human-subjects research, in that a member of the research community (as opposed to an outside observer) focused attention on the need to improve ethical conduct in human-subjects research.

Four infamous studies in the 1950s and 1960s received unprecedented national media attention that raised public outrage, although none of the studies individually resulted in federal regulation. In the 1950s, studies of hepatitis transmission were performed in Willowbrook State School, an extended-care facility for mentally-challenged children, in New York. Because many of the Willowbrook residents contracted hepatitis at the facility, the importance of understanding hepatitis transmission was never questioned. However, there was intense debate in professional journals and the national media over the design of these studies, which involved intentionally infecting healthy children with hepatitis by feeding them a solution made from the feces of those with active hepatitis.

The Jewish Chronic Disease Hospital study generated similar debate in the 1960s. In that study, live cancer cells were injected into the bloodstream of chronically ill, mostly demented, elderly patients in this New York City hospital. All of the subjects had illnesses that compromised the immune system, and this study was designed to determine

the influence of a weakened immune system on the spread of cancer.

In the early 1970s a contraception clinic that served mostly indigent patients in San Antonio, Texas, evaluated the efficacy of various types of oral contraceptive pills, in a randomized, blinded, placebo-controlled study. The patients' indigence rendered them unable to seek contraceptive advice or medication elsewhere. Unfortunately, none of the participants were informed that they were participating in this type of research or that they might be receiving placebo, and many had unplanned pregnancies.

The most infamous study, the Tuskegee syphilis study, is well known to most investigators. The study was funded by the United States Public Health Service to investigate the natural history of untreated syphilis in humans. Participants with known syphilis were observed without treatment and subjected to tests and procedures, including spinal taps, done solely for research purposes, to follow the course of their illness. When this study was developed in 1932, it was considered ethically sound because there was no effective treatment for syphilis. However, the subjects were from one of the most vulnerable populations: uneducated, poor, African-American sharecroppers from Macon County, Alabama, who were known to have syphilis. These subjects had no meaningful understanding of the research or their condition. In fact, most participants thought they were receiving medical care and did not understand that they were participating in research designed merely to follow the course of their illness. During the study the antibiotic penicillin, known to be highly effective against

syphilis, became available, but the investigators decided to continue to follow the subjects for several years without treatment, so as not to interrupt the study. The study was finally halted in 1972, after national media attention generated public outrage. The Tuskegee syphilis study stained the integrity of the research enterprise because it was funded by the federal government, for a long period, and it exploited vulnerable people who believed they were receiving beneficial medical care for their disease. Numerous articles and books have been written about the ethical implications of the study, and it will continue to affect our thinking about human-subject-research ethics for years to come.

### **The National Research Act of 1974 and the National Commission**

All of this national debate, and especially the heated debate about the federally funded Tuskegee syphilis study, culminated in congressional hearings about human-subjects research, directed by Massachusetts Senator Edward Kennedy, in 1973. From these hearings a consensus was reached that federal oversight was required to protect the rights and welfare of research subjects in both biomedical and social-sciences research. This consensus led to the development and passage of the National Research Act in 1974, which initiated the federal oversight of human-subjects research. The National Research Act accomplished 2 things that played a major role in shaping research regulation today. First, it established the modern IRB system for oversight of human-subjects research. Second, the highly contested debate and hearings made many people realize the complexity of establishing ethical standards for human-subjects research. The legislators recognized that ethics questions and situations are complex and it is often difficult to decide what is ethical, so the legislation created the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research (commonly known as the National Commission), which was composed of experts in ethics, religion, law, industry, and medicine. They met numerous times between the years 1975–1978 and defined problems and issued recommendations on human-subjects research, and published numerous reports about the classes of vulnerable subjects (eg, children, pregnant women, prisoners, and persons with impaired decision-making ability), which established the ethical framework for considering and approving research with vulnerable populations.

### **The Belmont Report**

In 1979 the National Commission detailed the fundamental ethical principles that guide the conduct of human-subjects research<sup>3</sup> in the Belmont Report ([http://www.hhs.](http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm)

<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm>), named for the Belmont Conference Center at the Smithsonian Institution, where the core meetings took place. The Belmont Report is an approximately 5,500-word document that describes the 3 fundamental principles that are now accepted as the minimum requirements for ethical human-subjects research: respect for persons, beneficence, and justice.

The principle of respect for persons incorporates 2 components related to individual autonomy: that each individual has the right to self-determination, and that persons with diminished autonomy (“vulnerable” people who lack the capability of self-determination) are entitled to additional protection to prevent exploitation. Four ethical research requirements follow directly from the principle of respect for persons:

1. Participants must voluntarily consent to participate in research.
2. The consent must be informed consent.
3. Participants’ privacy and confidentiality must be protected.
4. Participants have the right to withdraw from research participation without penalty or repercussions.

The principle of beneficence requires that research be designed to maximize benefit and minimize harm. In other words, the risks of the research must be justified by the potential benefits to the individual and/or society. The founders of the Belmont Report acknowledged that comparing the risk to the individual and the benefit to society is often difficult, and they recommended that determinations be made on a case-by-case basis.

The third principle is justice. The concept of justice relates to the distribution of risk across society. The Belmont Report directs that members of society who are likely to benefit from the research bear the potential risks of such research equally. In other words, the research should not systematically select specific classes of individuals simply because they are readily available where research is conducted or because they are “easy to manipulate as a result of their illness or socioeconomic condition.” Instead, enrollment should focus on individuals for reasons directly related to the research. Recent years have seen debate over whether the principle of justice also extends to protect persons from systematic exclusion from research that may apply to them. The implication is that research should not systematically exclude a specific type of person (eg, children or pregnant women) who might benefit from participation or to whom the research results are likely to apply.

### **The Institutional Review Board**

The National Research Act of 1974 also paved the way for the modern IRB system of regulating human-subjects

research. Federal regulations in the act required IRB approval for most human-subjects research, defined the policies and procedures IRBs must follow when considering research, and established the criteria for IRB approval of research proposals. After the National Commission disbanded, responsibility for implementing its recommendations was delegated to the Office for Human Research Protections, a division of the Department of Health and Human Services. IRBs function under the power of the Office for Human Research Protections, whose job is to develop and oversee compliance with regulations for the protection of human subjects. In 1981 the Secretary of the Department of Health and Human Services signed a revised Code of Federal Regulations for the Protection of Human Subjects, as put forth by the Office for Human Research Protections, in Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>). In 1991 these regulations were adopted by the 16 federal agencies that conduct, support, or otherwise regulate human-subjects research, including the National Institutes of Health. These regulations are commonly known as the Common Rule, and they guide IRB decision making/approvals. The regulations continue to be reviewed and revised (as recently as November 2001) in response to changes in thinking and scientific advances. Of note, the Food and Drug Administration also adopted certain provisions of the Common Rule, but has its own set of regulations for the protection of human subjects, codified at Title 21, Parts 50 and 56 of the Code of Federal Regulations.

### **Modern Day Institutional Review Boards and Human-Subject Protections**

The human-subjects-research legislation and regulations continue to evolve. The Common Rule is intermittently reviewed and revised to adapt to changing thoughts, evolving science, and ethical concerns. For example, the ethics

of genetic research and emergency research without consent are relatively new ethical considerations. The ethics and regulations concerning these specialized research areas could not even be considered prior to the advancement of science into these areas. Although legislation and regulations have adapted with the science, the resulting modern-day institutional review process has become quite complex and laborious. In fact, the process at many institutions has become so rigid and laborious that it may obscure the ultimate goal of such oversight, namely to protect the rights and welfare of human subjects.

### **Summary**

Numerous research incidents led to tighter oversight of human-subjects research. The Nuremberg Code and Declaration of Helsinki are the international ethical standards for human-subjects research. In the United States, IRBs were established by federal legislation in response to growing concerns over ethics in human-subjects research, especially with vulnerable subjects. The main role of IRBs is to protect the rights and welfare of human subjects. The complexity of providing such protection has rendered the make-up and modern-day functioning of IRBs complex. The ultimate goal of the IRB, however, parallels that of the researcher; both are charged with ensuring that human-subjects research is conducted ethically, with sound scientific rationale, to maximize benefits and minimize risks.

### **REFERENCES**

1. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 1997;277(11):925-926.
2. Beecher HK. Ethics of clinical research. *N Engl J Med* 1966;274(24):1354-1360.
3. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission). Belmont Report: Ethical principles and guidelines for the protection of human subjects of research. Washington, DC: Federal Register Document; April 18, 1978:79-12065.