History of Ethics

Prior to 1906, when the Pure Food and Drug Act was passed, there were no regulations regarding the ethical use of human participants in research. There were no consumer regulations, no Food and Drug Administration (FDA), no Common Rule, and no Institutional Review Boards (IRBs). What follows is a brief discussion of why federal rules and regulations were established and why IRBs became a necessity.

Nuremberg Code: The most dramatic and well-known chapter in the history of research with human participants opened on December 9, 1946, when an American military tribunal opened criminal proceedings against 23 leading German physicians and administrators for their willing participation in war crimes and crimes against humanity. Among the charges were that German Physicians conducted medical experiments on thousands of concentration camp prisoners without their consent. Most of the participants of these experiments died or were permanently crippled as a result.

As a direct result of the trial, the Nuremberg Code was established in 1948, stating that "The voluntary consent of the human participant is absolutely essential," making it clear that participants should give consent and that the benefits of research must outweigh the risks.

Although it did not carry the force of law, the Nuremberg Code was the first international document which advocated voluntary participation and informed consent.

Thalidomide: In the late 1950s, thalidomide was approved as a sedative in Europe; it was *not* approved in the United States by the FDA. The drug was prescribed to control sleep and nausea throughout pregnancy, but it was soon found that taking this drug during pregnancy caused severe deformities in the fetus. Many patients did not know they were taking a drug that was not approved for use by the FDA, nor did they give informed consent. Some 12,000 babies were born with severe deformities due to thalidomide.

U.S. Senate hearings followed and in 1962 the so-called "Kefauver Amendments" to the Food, Drug and Cosmetic Act were passed into law to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to the FDA the effectiveness of their products before marketing them.

Declaration of Helsinki: In 1964, the World Medical Association established recommendations guiding medical doctors in biomedical research involving human participants. The Declaration governs international research ethics and defines rules for "research combined with clinical care" and "non-therapeutic research." The Declaration of Helsinki was revised in 1975, 1983, 1989 and 1996 and is the basis for Good Clinical Practices used today.

Issues addressed in the Declaration of Helsinki:

- Research with humans should be based on the results from laboratory and animal experimentation

- Research protocols should be reviewed by an independent committee prior to initiation
- Informed consent from research participants is necessary
- Research should be conducted by medically/scientifically qualified individuals
- Risks should not exceed benefits

Tuskegee Syphilis Study (1932-1972): During a research project conducted by the U.S. Public Health Service, 600 low-income African-American males, 400 of whom were infected with syphilis, were monitored for 40 years. Free medical examinations were given; however, participants were not told about their disease. Even though a proven cure (penicillin) became available in the 1950s, the study continued until 1972 with participants being denied treatment. In some cases, when participants were diagnosed as having syphilis by other physicians, researchers intervened to prevent treatment. Many participants died of syphilis during the study. The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare only after its existence was publicized and it became a political embarrassment. In 1997, under mounting pressure, President Clinton apologized to the study participants and their families.

National Research Act (1974): due to the publicity from the Tuskegee Syphilis Study, the National Research Act of 1974 was passed. The National Research Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was charged to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human participants and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles.

The Commission drafted the **Belmont Report,** a foundational document for the ethics of human participants' research in the United States.

Radiation Experimentation and Human Participant Abuses: Another example of abuses of human participants occurred during World War II and the early cold war when U.S. officials studied the effects of radiation through experiments on hospital patients, pregnant women, retarded children, and enlisted military personnel. Few of the participants of the experiments gave informed consent; most had no knowledge that they were being subjected to radioactive materials. Manhattan Project officials authorized the wartime experiments to establish health and safety standards for the thousands of workers in atomic bomb plants. After the war, as the cold war deepened, officials justified expanded study of the effects of radiation on the grounds of national security. Following congressional investigations, numerous official reports, scholarly studies, and lawsuits, the government in the 1990s offered apologies and financial compensation to some of the human radiation testing victims.

Important Points:

- Nazi atrocities in World War II drew attention to the lack of international standards on research with human participants and led to the formulation of the Nuremburg Code.

- The thalidomide disaster led to the adoption of the "Kefauver Amendments" to the Food, Drug and Cosmetic Act, requiring drug manufacturers to prove to the FDA the effectiveness of their products before making them.
- The Declaration of Helsinki is the basis for Good Clinical Practices used today.
- The Tuskegee Syphilis Study is probably the worst case of unethical human participants' research in the history of the United States.
- The National Research Act codified the requirement that human participants in research must be protected and set the stage for the issuance of the Belmont Report.

The Belmont Report:

Carrying out its charge, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research prepared the Belmont Report in 1979. The Belmont Report attempts to summarize the basic ethical principles identified by the Commission in the course of its deliberations. The Report is a statement of basic ethical principles and guidelines that should assist in resolving the ethical problems that surround the conduct of research with human participants. The three basic principles and their corresponding applications are:

Principal	Application
Respect for Persons • Individuals should be treated as autonomous agents • Persons with diminished autonomy are entitled to protection.	**Informed Consent** • Participants, to the degree that they are capable, must be given the opportunity to choose what shall or shall not happen to them • The consent process must include three elements: o Information, o Comprehension, and o Voluntary participation
Beneficence • Human participants should not be harmed • Research should maximize possible benefits and minimize possible risks	**Assessment of risks and benefits** • The nature and scope of risks and benefits must be assessed in a systematic manner
Justice • The benefits and risks of research must be distributed fairly	**Selection of participants** • There must be fair procedures and outcomes in the selection of research participants

Important Point: The Belmont Report established three basic ethical principles - autonomy/respect for persons, beneficence and justice - which are the cornerstone for regulations involving human participants.

Related Link:

http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html