THE ESTABLISHMENT OF INSTITUTIONAL REVIEW BOARDS IN THE U.S. BACKGROUND HISTORY

William H. Schneider
History Department, IUPUI
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Prior to the twentieth century, research ethics were primarily governed by individual conscience and professional codes of conduct. Whether and how humans might be investigated, however, has always been subject to the laws and customs of the society and government at the time. For many reasons, in the second half of the twentieth century, an elaborate set of rules and regulations about research were established by the American government to protect individual and public interests. What follows is a discussion of why federal rules and regulations were established, including the Institutional Review Boards.

Background

There are many examples of professional and governmental regulation of medical practice in ancient times. Hammurabi's Code (18th century b.c.) gave detailed and explicit penalties for what we would call malpractice, and to this day Western doctors swear an oath attributed to the 5th century b.c.physician Hippocrates which includes an affirmation, "to abstain from all intentional wrong-doing and harm, especially from abusing the bodies of man or woman, bound or free." There is also early evidence that ethical problems of research on humans were recognized, as in the case of the Roman physician Celsus (1st century a.d.) who wrote that using criminals as subjects for dangerous experiments was justified if it would benefit many other innocents.

Sometimes laws or customs which aimed at protecting human subjects have restricted new discoveries, as in medieval Europe where governments and the Catholic church outlawed autopsies. But there are also historical examples of reactions to researchers who unduly risked harm to human subjects. When attempts to use sheep's and calve's blood in the first human transfusions in the late 1660s produced questionable and some harmful results, the practice was banned in France for over 100 years.

Take Home Point:

Restrictions on research involving humans are not something new. Governments and the professions as well as religion and the public have long acted to protect individual and community interests.

Modern Science, Experimentation, and early codes of conduct

Several historical developments prior to the twentieth century shaped the conduct of research and the regulations in America today.

The scientific revolution (beginning in the17 c) developed a method of investigation which included controlled observation and the reporting of results for verification. This expanded the number of people doing research, and the method was soon applied to experiments involving humans. At first, the numbers of people involved were small and most often included the researchers themselves or their families.

The most famous examples were the most successful ones, such as Edward Jenner who demonstrated the value of innoculation against smallpox at the end of the 18th century. After observing milkmaids in rural England who acquired immunity after exposure to an animal form of the disease, Jenner tested the practice first on his own son then a child in his town.

By the end of the nineteenth century, thanks to the growth of universities and potential commercial applications of discoveries, the amount of research on humans grew and prompted the proposal of some codes to protect the subjects of research.

> One of the earliest and most famous was written by **William Beaumont**, a U.S. army doctor stationed on the Northwest frontier in the 1820s. Beaumont treated a patient with a unique stomach gunshot wound that permitted him to do pathbreaking experiments. His published account, Physiology of Digestion (1833) included a document of indenture (not exactly consent) signed by the patient wherein he agreed,"to assist and promote by all means in his power such philosophical or medical experiments as the said William Beaumont shall direct or cause to be made on or in the stomach of him." In exchange the patient received lodging, and payment of $150 a year.
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> Other researchers and physicians recognizing the potential ethical dilemmas of research involving human subjects included the French physiologist **Claude Bernard**. In his 1865 text, Introduction to the Study of Experimental Medicine, Bernard declared it not just the researcher's right but a duty "to perform an experiment on man whenever it can save his life, cure him or gain him some personal benefit." But Bernard saw it as wrong to "perform on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e., to the health of others."
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> **William Osler**, who gained fame as a professor at the new Johns Hopkins Medical School, gave an address in 1907 which echoed Bernard's sentiments that any experiment must likely benefit the patient, and that "the final test of every new procedure, medical or surgical, must be made on man, but never before it has been tried on animals." He also added that "full consent" must be obtained from the patients, based on "full knowledge of the circumstances."

With the discovery of the germ theory at the end of the nineteenth century, both the successes and the number of experiments increased dramatically. There were also failures which prompted action by governments to protect human subjects.

> In 1900 the Prussian state government promulgated a law prompted by a scandal in1892 where Albert Neisser a Prof. Of Dermatology at Univ. of Breslau, conducted experiments aimed at immunizing healthy subjects against syphilis. Serum was taken from patients

with syphilis and used to inoculate 4 healthy children and three adolescent prostitutes. All contracted syphilis, but consent had not been obtained from any of the subjects or their parents or guardians.

Inflamed by the press, the scandal eventually prompted action by the Prussian Minister of Religious and Medical Affairs which promulgated "Instructions to the Directors of Clinics, Out-patient Clinics and Other Medical Facilities."

It prohibited "absolutely" medical intervention other than diagnosis, therapy and immunization if,

> "the person in question is a minor or not fully competent on other grounds;"
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> "the person concerned has not declared unequivocally that he consents to the intervention;"
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> "the declaration has not been made on the basis of a proper explanation of the adverse consequences that may result from the intervention."

Take Home Point:

By the beginning of the twentieth century, there was ample experience with ethical problems involving humans in scientific experimentation to produce codes of conduct and government regulations. These included the notions of risk versus benefit as well as informed consent, but the codes were not yet widespread or broadly binding

Research Ethics in the Twentieth Century

The final developments that produced our current method of protecting human research subjects were the result of historical events in the twentieth century. Some of these were long building and gradual, such as the rise of the mass press and public opinion, the spread of democratic governments, and the increasing involvement of government support for research. Other influences grew out of the changing nature of scientific knowledge and research which required more subjects for study, and promised more successful applications of findings.

There were also some unpredictable accidents of history, such as the Second World War which accelerated some developments and was a dramatic turning point in many of these trends. For example, the war produced unprecedented government spending on all kinds of scientific research, including medical. It also produced unprecedented horrors of the callous disregard of human life in the name of scientific research, most notoriously by the Nazi medical experiments in concentration camps.

NUREMBERG CODE

On December 9, 1946, 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. During World War II, German physicians conducted medical experiments on thousands of concentration camp prisoners without their consent. They shot concentration camp prisoners to test blood clotting. They infected groups of inmates with viruses, then only treated part with the test vaccines, while they observed he course of the disease in the untreated inmates. They tested poison bullets to find more effective ways of killing; they tested prisoners to see how long they could remain alive under high altitude conditions of low air pressure and lack of oxygen.

Several German doctors had argued in their own defense that their experiments differed little from previous American or German ones. In fact, American government experiments during the war had tilted the risk/benefit balance in favor of anticipated benefits to soldiers fighting the war by accepting increased risks of experiments on subject populations such as children or asylum patients who could hardly be informed or give their consent. But these were not widely known, and paled in comparison to the actions of the German doctors which the indictment described as "murder, torture, and other atrocities committed in the name of science." In the verdict issued on August 19, 1947, seven defendants were found guilty and sentenced to death, eight defendants were sentenced to imprisonment from ten years to life, and seven were found not guilty.

But that was not enough for the American doctors Andrew Ivy and Leo Alexander who had worked with the prosecution team. They submitted a memorandum outlining legitimate research to the Counsel for War Crimes, which was the basis for a section of the final verdict entitled "Permissible Medical Experiments." The ten points of the section have been subsequently referred to as "The Nuremberg Code."

They were remarkably complete and sophisticated, revealing Ivy and Alexander's research on the history of writing and practice of human experimentation. [see A. C. Ivy, "The History and Ethics of Use of Human Subjects in Medical Experiments," Science 108 (July 2, 1948),1-5]. Of note is the following:

Quality of experiments and experimenters

(2) must be "for the good of society" and results "unproduceable by other means;"

(3) must be based on results of animal experimentation;

(8) should be conducted by "scientifically qualified persons."

Safeguards

(5) No experiment should risk death or disabling injury, "except, perhaps, in those experiments where the experimental physicians also serve as subjects;"

(6) risk should never exceed the importance of the problem to be solved;

(9, 10) experiment should be designed to be stopped at any point by: a) scientists if continuation is judged "liable to result in bringing disability or death to experimental subject; or b) by the human subject.

The first point, however, was the requirement that "the voluntary consent of the human subject is absolutely essential." This included "sufficient knowledge and comprehension" by subjects, "to make an understanding and enlightened decision."

In hindsight, the biggest problem with the code was compliance and enforcement. In fact, the Nuremberg Code explicitly left this up to the experimenter. The final paragraph of the first point said, "The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity."

Take Home Point:

Although it did not carry the force of law, the Nuremberg Code was a very complete statement about the use of humans in experiments which came at a moment in history which made it internationally visible. The code was very naïve, however, in its assumptions about enforcement.

Related Internet Links (from the U.S. Holocaust Museum)**:**

The Doctor's Trial https://www.ushmm.org/information/exhibitions/online-exhibitions/special-focus/doctors-trial

The Nuremberg Code https://www.ushmm.org/information/exhibitions/online-exhibitions/special-focus/doctors-trial/nuremberg-code

THALIDOMIDE TRAGEDY

In the late 1950s, thalidomide was approved as a sedative in Europe before it was approved in the United States by the FDA. The drug was originally taken because it was believed to control sleep and nausea throughout pregnancy, but by 1961 there were reports that taking this drug during pregnancy caused severe deformities in the fetus, and it was banned in 1962. Although not approved in the U.S., it was given in “clinical trials” which at the time meant distributing more than two and a half million tablets to approximately 20,000 patients across the nation, including approximately 3,760 women of childbearing age, at least 207 of whom were pregnant. Many patients did not know they were taking an experimental drug, nor did they give informed consent. The FDA found that 17 babies in the U.S. were born with deformities from thalidomide, but it is estimated that thousands of babies in West Germany, Great Britain, and Canda 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. The amendments were passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to FDA the effectiveness of their products before marketing them.

Take Home Point:

The thalidomide tragedy led to some of the FDA regulations that are in existence today.

Internet References (from *The Smithsonian Magazine*)**:**

The Woman Who Stood Between America and a Generation of 'Thalidomide Babies.' How the United States escaped a national tragedy in the 1960s https://www.smithsonianmag.com/science-nature/woman-who-stood-between-america-and-epidemic-birth-defects-180963165/

DECLARATION OF HELSINKI

In 1964, the World Medical Association established recommendations guiding medical doctors in biomedical research involving human subjects. 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 include:

- Research with humans should be based on laboratory and animal experimentation
- Research protocols should be reviewed by an independent committee
- Informed consent is necessary
- Research should be conducted by medically/scientifically qualified individuals
- Risks should not exceed benefits

Take Home Point:

The Declaration of Helsinki built on the Nuremberg code by insisting that research with human subjects is justified only when the degree of risk to subjects does not exceed the humanitarian importance of the knowledge to be gained. It also increased international awareness of the problems and proposed a mechanism for outside review of protocols. Like the Nuremburg Code, it is not a legally binding instrument under the international law, but instead draws its authority from the degree to which it has been codified in, or influenced, national or regional legislation and regulations.

Related Internet Links (from the World Medical Association)**:**

Declaration of Helsinki https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/doh-jun1964/

Henry Beecher article in *New England Journal of Medicine* 1966

The memorandum establishing Institutional review Boards IRBs was the direct result of an exposé, very threatening to the medical establishment. It began as a talk in 1965, later published in the NEJM by Henry Beecher, a Harvard Medical School anesthesiologist. His subject was the conduct of experiments since 1945 in the U.S. involving human subjects.

> Beecher examined 50 published examples (refined to 22 for purposes of reference in the article) which he called, "examples of unethical or questionable ethical studies." Though he softened his critique by calling these more the result of "thoughtlessness and carelessness" rather than "willful disregard of the patients' rights," his examples included experimentation with new methods of heart catheterization that had little therapeutic value to patients, and trials of new drugs as cures which obviously were done without patients' consent.

Beecher was both naïve and overly optimistic in his suggested remedy for the problem: requiring publishers to exercise judgement about whether researchers obtained informed consent and properly weighed the risks and gains, before deciding to publish results. Of course, Beecher's greatest importance was the immediate stir his earlier talks as well as this publication added to an increasingly wary public. Even before publication of the article, NIH announced in Dec. 1965 it would have guidelines requiring approval of protocols for research on human subjects before a study could begin. The following February 1966 the new policy was issued.

Beecher's article: "Special Article: Ethics and Clinical Research," NEJM 274 (1966), 1354-60 http://wayback.archive-it.org/4657/20150930181806/http:/www.hhs.gov/ohrp/archive/documents/BeecherArticle.pdf

About Henry Beecher https://www.harvardmagazine.com/2017/03/henry-knowles-beecher

"Ethics and Clinical Research" — The 50th Anniversary of Beecher's Bombshell http://www.bvs.hn/Honduras/CEIB/Ethics.and.Clinical.Research_NEJM_June.2016.pdf

USPHS memo on review boards 1966

Memorandum issued by the Research Grants Division of USPHS on Feb. 8, 1966

Excerpt from the policy

> No new, renewal, or continuation research or research training grant in support of clinical research and investigation involving human beings shall be awarded by the Public Health Service unless the grantee has indicated in the application the manner in which the grantee institution will provide prior review of the judgement of the principal investigator or program director by a committee of his institutional associates. This review should assure an independent determination: (1) of the rights and welfare of the individual or individuals involved, (2) of the appropriateness of the methods used to secure informed consent, and (3) of the risks and potential medical benefits of the investigation. A description of the committee associates who will provide the review shall be included in the application.

Of note:

-tie to funding for enforcement; reflection of government support for medical research

-involvement of institution

-involvement of committee of "associates" for independent judgement

-safeguard of individual rights

-beyond informed consent, requirement of description of method

-determination of risks v/s benefits

In 1969 the committees were expanded to include non-scientific members.

In 1971 the use of community standards was added to judge proposals.

Take Home Point:

From the historical perspective, the most important new features of the institutional review boards created by the 1996 USPHS memo were the involvement of outside reviewers and a mechanism of enforcement which tied compliance to funding.

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https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwi50uvWk9zyAhXidM0KHTtaAEMQFnoECAMQAQ&url=https%3A%2F%2Fhistory.nih.gov%2Fdownload%2Fattachments%2F1016866%2FSurgeongeneraldirective1966.pdf%3Fapi%3Dv2&usg=AOvVaw1xEuPMPgCPlajRasR2WzpB

for the full directive, "Surgeon General's Directive on Human Experimentation," July 1, 1966

TUSKEGEE SYPHILIS STUDY (1932-1972)

During a research study conducted by the US Public Health Service beginning in 1932, hundreds low-income African-American males from rural Alabama with a high incidence of syphilis infection, were periodically examined for 40 years to determine whether the course of their disease was different from syphilis in whites. Subjects were given free medical examinations, but they were not told about their disease. Even though a proven cure (salvarsan) existed at the time and a much more effective on (penicillin) became available in the 1950s, the study continued until 1972 with participants and their families being denied treatment.

In some cases, when subjects were diagnosed as having syphilis by other physicians, researchers intervened to prevent treatment. The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare only after its existence was exposed in a newspaper story, and it became a political embarrassment. In 1997, President Clinton apologized to the study subjects and their families.

Take Home Point:

The study used disadvantaged, rural black men to study the course of an untreated and contagious disease after recognized treatments were available. Participants were not informed of the purpose of the study which did not minimize risks to human subjects. In fact, it increased their risks. The issues involved in the Tuskegee syphilis study heightened awareness of the need to protect human subjects and to assure their informed voluntary consent to participate in human subjects research.

The Tuskegee study also increased suspicion in the African-American community about participation in medical research and the racism of researchers.

Related Internet Links:

The Tuskegee Timeline (from the CDC) https://www.cdc.gov/tuskegee/timeline.htm

About the USPHS Syphilis Study (from Tuskegee University) https://www.tuskegee.edu/about-us/centers-of-excellence/bioethics-center/about-the-usphs-syphilis-study

Presidential apology
https://clintonwhitehouse4.archives.gov/textonly/New/Remarks/Fri/19970516-898.html

For video, click here https://www.youtube.com/watch?v=l1A-YP24QwA