History & Ethical Principles

This module discusses the evolution of the ethical principles that guide research design and the development of the federal regulations that govern the conduct of research in the United States.

Introduction

The first century physician Celsus justified experiments on condemned criminals in Egypt using wording that became a classic defense for hazardous experimentation: "It is not cruel to inflict on a few criminals sufferings which may benefit multitudes of innocent people through all centuries." [Brady and Jonsen]. Both the ethics and regulation of human subjects research have changed considerably since Celsus' time.

A brief synopsis of the history behind the current regulatory structure for research with human subjects reads as follows:

Highly publicized abuses in research led to congressional hearings in 1974. Congress commissioned the preparation of a set of ethical principles, known as the Belmont Report. The Federal Regulations for Protecting Research Subjects were subsequently revised and expanded, based in large part on the Belmont Report. These ethical principles and regulations govern the practice of research with human subjects in the United States.

Researchers in the social and behavioral sciences and humanities attest, correctly, that the development of the regulations was driven by abuses in biomedical research. However, the current regulations reflect and embody the ethical principles described in the Belmont Report and these principles have broad applicability. For example, the principle of respect for persons requires appropriate informed consent, and a portion of the regulations covers the informed consent process.

This module will discuss examples of research abuses in biomedical research and examples of research in the social and behavioral sciences that raised ethical issues. Some of these studies, such as the Tuskegee study, the Milgram Obedience to Authority Study, and the Stanford Prison Experiment will be familiar to many readers.

While it is possible to conduct ethical research without knowing the history described in this module, knowing the history helps to understand the regulations and their intended impact on the practice of research with human subjects.

(For a description of the flexibility provided in the regulations that are useful for researchers in the social and behavioral sciences in the humanities, such as exemptions and waivers of documentation of consent, see the module in this series called The Regulations: An Overview.)

By the end of this module you should be able to:

- Describe major historical events that have influenced how research involving human subjects is conducted today.
- IDiscuss selected studies that have violated ethical standards.
- List the Belmont principles.
- Discuss the relationship between the Belmont principles and the federal regulations.

Events in Biomedical Research

Nuremberg Code

At the end of World War II, 23 Nazi doctors and scientists were put on trial for the inhumane treatment and murder of concentration camp inmates who were used as research subjects. In the absence of a legal standard for the conduct of research, the court wrote a standard into its legal judgment. This new standard included ten points describing required elements for conducting research with humans. These points became known as the Nuremberg Code.

In summary, the Nuremberg Code includes the following guidance for researchers:

- Informed consent is essential.
- Research on human subjects should be based on prior animal work.
- The risks should be justified by the anticipated benefits.
- Only qualified scientists should be allowed to conduct research with human subjects.
- Physical and mental suffering must be avoided.
- Research in which death or disabling injury is expected should not be conducted.

Despite the historical importance of the Code, and the undeniable value of its general intent, it did not consider issues relevant for research in social and behavioral sciences. For example, the Code prohibits waivers of informed consent, often needed to obtain scientific validity in research in the social and behavioral sciences.

After the Nuremburg trials ethical principles for conducting biomedical research have been reinterpreted and refined. For example, the World Medical Association developed a code of research ethics, known as the Declaration of Helsinki, published in 1964 and subsequently revised.

Researchers in the social and behavioral sciences and the humanities are guided by their professional associations, such as the American Anthropological Association and the American Psychological Association, which published ethical guidelines for research with human subjects in the 1950s, with updates at intervals. Even though these guidelines and those of the Declaration of Helsinki are available, they have not always been followed in practice.

Beecher Article

In 1966 Dr. Henry K. Beecher, an anesthesiologist, wrote an article (Beecher HK. "Ethics and Clinical Research" NEJM June 16, 1966) describing 22 examples of research studies with controversial ethics. These studies were conducted by reputable medical researchers and published in major journals. Beecher wrote, "medicine is sound, and most progress is soundly attained;" However, if unethical research is allowed to proceed it will "do great harm to medicine." Beecher provides estimates of the number of unethical studies and concluded, "unethical or questionably ethical procedures are not uncommon." [Beecher] Beecher's article played an important role in heightening the awareness of researchers, the public, and the press to the problem of unethical human subjects research. *"Until this article we assumed that unethical research could only occur in a depraved regime like the Nazis."*- Robert J. Levine, MD (personal communication).

The Public Health Service Syphilis Study (1932-1972)

One of the seminal events in the development of the current regulatory environment was the Public Health Service (PHS) Syphilis Study (1932 - 1972), frequently referred to as the "Tuskeegee Syphilis Study" [see "Bad Blood: The Tuskegee Syphilis Experiment", Revised Edition by James H. Jones] . Initiated and funded by the PHS, this study was designed as a natural study of the course of syphilis in African-Americans. At the time the study began there was no known safe and effective treatment. Hundreds of men who did not know they had syphilis and hundreds of men without syphilis (serving as controls) were enrolled into the study. The men were recruited without their fully informed consent. They were deliberately misinformed about the need for some of the procedures. For example, spinal taps were described as necessary and special "free treatment" for "bad" blood.

More importantly, even after penicillin was found to be a safe and effective treatment for syphilis in the 1940s, the men with syphilis were denied antibiotics. In addition, the researchers continued to protect the status of the study as a "natural history." To prevent the

subjects from being treated by the military or by local physicians, the investigators arranged with the local draft board to prevent the men from being drafted, arranged with local physicians to withhold treatment, and told the men that if they volunteered for the military, they would no longer receive financial compensation for taking part in the study. The study continued to track these men sporadically until 1972 when the first public accounts of the study appeared in the national press. Not providing penicillin once it was deemed safe and effective may have been responsible for 28 deaths, 100 cases of disability, and 19 cases of congenital syphilis. [Levine]

Ethical problems: lack of informed consent, deception, withholding information, withholding available treatment, putting men and their families at risk, exploitation of a vulnerable group of subjects who would not benefit from participation.

More Recent Events

Death of a Normal Volunteer

On March 31, 1996, a 19-year-old Asian -American student at the University of Rochester responded to an advertisement for study subjects to undergo bronchoscopy for the harvest of alveolar macrophages. The bronchoscopy was difficult and required numerous doses of topical lidocaine. The investigators repeatedly asked the subject if she wanted to continue and the subject nodded her head "yes." The study was completed, but the subject returned to the hospital in cardiac arrest from an overdose of lidocaine and died April 2, 1996. An investigation into this death revealed that the protocol did not specify the number of lidocaine doses, that the doses were not documented, that the subject was not observed after the bronchoscopy, and that the concentrations of lidocaine were increased without IRB approval.

*Ethical problems:*Exploitation of a vulnerable population (student volunteers), inadequate informed consent

Death on Gene Transfer Trial

In the fall of 1999, 18-year-old Jesse Gelsinger died as a result of his participation in a gene transfer trial. Jesse had a rare metabolic disorder that was being controlled by medication and a strict diet. Shortly after the gene transfer attempt Jesse experienced multiple organ failure and subsequently died. This case catapulted gene transfer research into the national news. Serious concerns related to conflict of interest, data safety monitoring, and informed consent made the Gelsinger case a contemporary illustration of continued doubts about the ethical integrity of research with human subjects.

*Ethical problems:*Institutional and researcher conflict of interest, inadequate informed consent

Events in Social and Behavioral Sciences

The following are examples of research studies in the social and behavioral sciences that raise ethical issues.

Wichita Jury Case (1953)

In this study researchers tape-recorded jurors' private deliberations in six courtroom trials to measure the influence that attorney comments have on subsequent jury decision making. The judge and attorneys knew the research was being conducted, but the jurors did not, so as not to bias their behavior. The tapes were played at a law conference and the study was reported in a local newspaper. The resulting concern that the possibility of future taping could have a repressive effect on future juror deliberations resulted in a 1956 federal law banning all recording of jury proceedings.

Ethical problems: Compromising the integrity of important social institutions, lack of informed consent, invasion of privacy.

Milgram's "Obedience to Authority Study" (1963)

The purpose of this study was to learn more about how humans respond when given instructions from people in positions of authority. The researchers informed study volunteers that the purpose of the research

was to study learning and memory. Each subject was told to teach a "student" and to punish the students' errors by administering increasing levels of electric shock. The "students" were confederates of the researcher and were never actually harmed. The "students" pretended to be poor learners. They mimicked pain and even unconsciousness as the subjects increased the levels of electric shock. Sixty-three percent of the subjects administered what they thought were lethal shocks; some did so even after the "student" claimed to have heart disease. Some of the subjects, after being "debriefed" from the study, experienced serious emotional crises.
Ethical Problems: Deception, unanticipated psychological harms.

Allen's "Nazi Seizure of Power Study" (1965)

In his study "The Nazi Seizure of Power; the Experience of a Single German Town, 1922-1945,",first published in 1965, William Sheridan Allen interviewed residents of a town in Germany about their lives during Hitler's rise to power. He made a commitment of confidentiality with regard to the names of his informants and of the town and used pseudonyms for the town and individuals when writing a book based on the interviews. After the book was subsequently translated into German, based on the information provided and additional investigative journalism, a German magazine was able to determine the real name of the town and the identities of many of Allen's narrators and published the information in an article.
Ethical Problems: Failure to maintain adequate confidentiality to protect against deductive disclosure of identity by others with additional information.

Humphreys' "Tea Room Trade" (1970)

In this study the researcher observed homosexual practices in public restrooms. The researcher went undercover as a homosexual and gained the confidence of the men by acting as a "look out." The researcher identified 100 active subjects by tracing their car license numbers. A year after he completed the observational portion of his study, the researcher disguised his appearance and in the communities where he knew the subjects lived interviewed some of the "tearoom regulars" in their own homes. He used a social health survey collecting data about their sexual orientation and marital status. Interviews were sometimes conducted in the presence of wives and children. At no time did he tell them anything about the relationship of the interview to the prior observational work.
Though the publication of the book based on the dissertation may have been helpful in dispelling some stereotypes, the report had sufficient detail that the identities of some of the participants were obvious to them and their families.
Ethical problems: Invasion of privacy, use of a vulnerable population, lack of informed consent, failure to protect against deductive disclosure of identity.

Zimbardo "Simulated Prison" (1973)

This landmark psychological study of the human response to captivity and, in particular, prison life, involved assigning roles to normal male student volunteers to create groups of "prisoners" and "guards." The research became so intense, as physical and psychological abuse of "prisoners" by "guards" escalated, that several of the subjects experienced distress less than 36 hours after the study began. Dr. Philip Zimbardo, the researcher, did not stop the experiment/simulation until six days had passed. See Dr. Zimbardo's web site for more details on this study.
Ethical problems: Harm to subjects, lack of neutrality of researcher.

Restaurant Letter Study (2001)

It is important to note that not all the events that raise concerns about research ethics in both biomedical and social and behavioral research occurred before the 1974 congressional hearings. In 2001, a faculty member from the business school of a major university designed a study to see how restaurants would respond to complaints from putative customers. As part of

the project, the researcher sent letters to restaurants falsely claiming that he and/or his wife had suffered food poisoning that ruined their anniversary celebration. The letters disclaimed any intention of contacting regulatory agencies and stated that the only intent was to convey to the owner what had occurred "in anticipation that you will respond accordingly." Restaurant owners were understandably upset and some employees lost their jobs before it was revealed that the letter was a hoax. The researcher later admitted the falsehood in a letter of apology to each restaurant. The study had not been submitted to an IRB for review. An investigation by the Federal Office for Human Research Protections (OHRP) followed. In addition, the restaurants filed a lawsuit against the university.

Ethical problems: Deception, lack of informed consent, infliction of emotional distress.

Development of the Regulatory Process

As noted earlier, responding to public concerns over research abuses, primarily the Public Health Service Syphilis Study, the US Congress held hearings on"Quality of Health Care - Human Experimentation" in 1973. The hearings led to the National Research Act of 1974 which:

- Established the "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research"
- Required the establishment of Institutional Review Boards at institutions receiving US Department of Health, Education and Welfare (now the Department of Health and Human Services) support for human subjects research.

The charge of the National Commission was to:

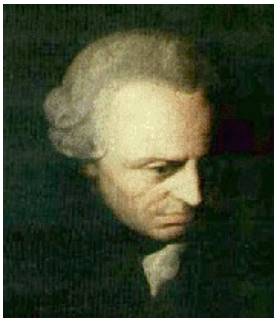
- Identify the basic ethical principles that underlie the proper conduct of human research
- Develop guidelines to ensure that human research is conducted in accordance with those principles.

Based on the work of the National Commission, the Department of Health and Human Services (HHS) revised and expanded its regulations for the protection of human subjects in the late 1970s and early 1980s. In 1991 sixteen other federal agencies and departments agreed to apply the regulations to the research they fund or conduct, and in 2005, the Department of Homeland Security adopted the regulations. (The adoption of the regulations by multiple federal agencies and departments is the reason the regulations are referred to as the "Common Rule.")

Ethical Principles

The Belmont Report

In 1979, motivated by the Public Health Service's syphilis study and others, and after several years of deliberations, the National Commission published the Belmont Report: a statement of the basic ethical principles and guidelines to be used to resolve the ethical problems that surround the conduct of research with human subjects.



The Belmont Report identifies three basic ethical principles for conducting research with human subjects. These principles are commonly called the Belmont Principles. The Belmont Principles are respect for persons, beneficence, and justice.

What follows is a summary of the Belmont Report. The full report (approximately seven pages long) provides the conceptual foundation for the federal regulations and the conduct of research with human subjects and is recommended reading.

Respect for Persons

This principle requires researchers to treat individuals as autonomous human beings, capable of making their own decisions, and not to use people as a means to an end. The principle also provides extra protection to those with limited autonomy.
Elements of autonomy include:

- Mental capacity (the ability to understand and process information)
- Voluntariness (freedom from undue control or influence of others)

Subjects have autonomy when they have the capacity to understand and process information, and the freedom to volunteer for or withdraw from research without coercion or undue influence from others.
In practice, the principle of respect for persons involves creating a meaningful consent process. This means providing prospective subjects with all the information they need to make a decision to participate in research and allowing subjects to withdraw from research without any adverse consequences if they change their minds.

Beneficence

This principle requires researchers to minimize the risks of harm and to maximize the potential benefits of their research. This principle demands that researchers and IRBs conduct a careful assessment of the risks of harm and the potential benefits of the research and ensure that the potential benefits justify the risks of harm. This may include, in some cases, alternative ways of obtaining the benefits sought in the research.
The term "risk" refers to a possibility that harm may occur. However, the assessment of risk requires evaluating both the magnitude of the possible harm and the likelihood that the harm will occur. The types of harms to be assessed include not only physical harms but also psychological, legal, social, and economic harms. The term "benefit" is used in the research context to refer to something of positive value related to health or welfare. Those benefits can accrue to individual subjects or to others, such as a community, or people in general.

Justice

According to the Belmont Report, "Just as the principle of respect for persons finds expression in the requirements for consent, and the principle of beneficence in the risk/benefit assessment, the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects."
The principle of justice requires us to design research so that its burdens and benefits are shared equitably. In principle, those who benefit from the research should share in the burden of being subjects in the research. Those who serve as subjects in the research should share in the potential benefits from the research. Individuals or groups should not be selected for research participation solely because they are available, vulnerable, or because they cannot say "no" or do not know that saying "no" is an option. To avoid exploitation, the selection of subjects should be based solely on scientific justification.

Balancing the Three Principles

It was the Commission's intention that each of the three principles should have equal moral force. This means that in some situations, the three principles might be in conflict with one another. For example, we might derive from the principle of respect for persons that we should limit the involvement of children in research because children are unable to choose for

themselves. But, we might derive from the principle of justice that we must involve children in studies so that children will have the opportunity to benefit from the research. The *Belmont Report* states that one principle does not always outweigh another. Rather, we are required to consider each case separately and on its own merits while seeking to uphold all three principles.

Review by an Institutional Review Board (IRB)

The regulations list criteria for IRB approval of a research protocol that are directly related to the three Belmont principles as follows:

Beneficence

Risks to participants are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose participants to risk.

Risks to participants are reasonable in relation to anticipated benefits, if any, to participants, and the importance of the knowledge that may reasonably be expected to result.

Risks to participants are minimized whenever appropriate, by using procedures already being performed on the participants for other purposes.

When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of participants.

When appropriate, there are adequate provisions to maintain the confidentiality of data.

Justice

Selection of participants is equitable.

Respect for Persons

Informed consent will be sought from each prospective participant or the participant's legally authorized representative, in accordance with, and to the extent required by the regulations.

Informed consent will be appropriately documented in accordance with, and to the extent required by the regulations.

When appropriate, there are adequate provisions to protect the privacy of participants.

When some or all of the participants are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these participants.

Other Ethical Guidelines

Professional associations of social and behavioral sciences have adopted ethical guidelines for the conduct of human subjects research, including the American Psychological Association, the American Sociological Association, the American Anthropological Association, the Oral History Association, and others. These guidelines provide discipline-specific ethical guidelines, which help inform IRBs and researchers.

Summary

Historical events and contemporary abuses inform the development of ethics related to the protection of human research subjects. IRBs use guidance from The Belmont Report, the Declaration of Helsinki, and professional codes of ethics in their reviews to provide the highest levels of protection.

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