Chapter 1: History and Ethical Principles

Introduction

The first century physician Celsius 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 & Jonsen].

Both the ethics regarding human subjects research and regulations for such research have changed considerably since Celsius' time. This chapter discusses the evolution of ethical review principles, and how they have influenced research involving human subjects.

By the end of this chapter you will be able to:

Discuss why ethics are necessary when conducting research involving human subjects.

Describe the major historical events that have influenced how research involving human subjects is conducted.

Identify problems with past studies that have violated ethical standards.

Describe the Belmont Principles.
Discuss the ethical standards for research that guide us today.

1.1 : Why Are Ethics Necessary

We are concerned with normative ethics, asking questions such as: What ought morality be? How should researchers behave? How should researchers not behave? What character traits should researchers cultivate as virtues? And, what character traits should researchers try to avoid?

There are many advantages to understanding research ethics. Concepts of research ethics:

Provide us with a structure for analysis and decision-making.
Support and remind researchers to protect human subjects.
Provide workable definitions of benefits and risks, along with guidelines for evaluating and balancing the benefits and risks of our studies

1.1.1: Definition of "Benefit"

A benefit is the positive value or advantage of being part of the research study. This value or advantage might be concrete for individual subjects, like a greater chance of having a good therapeutic outcome. Alternatively, it might be more intangible and general. For example, the results from a study could be crucial to understanding the underlying socioeconomic causes of drug addiction.

1.1.2: Definition of "Risk"

Risks generally are evaluated according to the probability and magnitude of any harm that might occur. Will the risk occur in almost all subjects or in only one of 10,000 subjects? We can also quantify risk according to the magnitude of harm. Will the harm consist of some minor itchiness, or will some subjects die? Risks can also be classified according to their type. In medical research we often focus on physical risk. However, risks may also be social, legal, economic or psychological in nature. In addition, risks may apply to the individual subject or may apply to a broader segment of the society.

1.1.3: Balancing Benefits and Risks

Risks to the subject or society must be weighed against potential benefits. The probability of harm relative to the probability of benefit should be determined, as well as the relative magnitude of risks and possible benefits. As an aside, payment for study participation should never be considered a benefit. One of the most difficult things that researchers and IRBs have to do is to determine that the potential benefits of the outcomes of the research outweigh the risks of conducting the research. This is difficult because:

> Neither the potential benefits or risks can be known ahead of time.
> The risks are assumed by individuals, while the benefits may accrue to society at large rather than to individuals.

1.2 : Historical Events that Have Influenced Human Research

1.2.1: First Documented Human Subject Research

The development of research ethics has evolved over time. Among the first human subject research experiments to be documented were vaccination trials in the 1700's. In these early trials physicians used themselves or their family members as test subjects. For example:

> Edward Jenner (1749-1823) first tested smallpox vaccines on his son and on neighborhood children.

Johann Jorg (1779-1856) swallowed 17 drugs in various doses to record their properties.

Louis Pasteur (1822-1895) "agonized over treating humans," even though he was confident of the results obtained through animal trials. He finally did so only when he was convinced the death of the child, the first test subject, "appeared inevitable." [Rothman]

1.2.2: The Era of Modern Science

The era of modern science started in the 1900's and the progress of medicine began to accelerate. Walter Reed's well-known experiments to develop an inoculation for yellow fever were at the forefront of these advances. These experiments, however, unlike earlier experiments with vaccinations, were carefully scrutinized.

Dialog from testimony before the Royal Commission of Vivisection (1908) follows[Brady & Jonsen]:

Commission: I understand that in the case of yellow fever the recent experiments have been on man.

Osler: Yes, definitely with the specific consent of these individuals who went into the camp voluntarily.

Commission: We were told by a witness yesterday that, in his opinion, to experiment upon man with possible ill result was immoral. Would that be your view?

Osler: It is always immoral, without a definite, specific statement from the individual himself, with a full knowledge of the circumstances. Under these circumstances, any man, I think is at liberty to submit himself to experiments.

Commission: Given voluntary consent, you think that entirely changes the question of morality or otherwise?

Osler: Entirely.

1.2.3: Nuremberg Code

Society's high regard for the medical profession, however, was not to last. At the end of World War II, 23 Nazi doctors and scientists were put on trial for the murder of concentration camp inmates who were used as research subjects. Of the 23 professionals tried at Nuremberg, 15 were convicted, 7 were condemned to death by hanging, 8 received prison sentences from 10 years to life, and 8

were acquitted. [Mitscherlich & Mielke] Included in the legal judgment and sentences handed down at the culmination of the trial were 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 should be based on prior animal work.
> The risks should be justified by the anticipated benefits.
> Only qualified scientists must conduct research.
> Physical and mental suffering must be avoided.
> Research in which death or disabling injury is expected should not be conducted.

1.2.4: Effect of the Nuremberg Code

The Code had little impact on researchers in the United States, who thought that the principles in the Code were already implicit in their work and that it was simply a document to condemn the Nazi atrocities and to convict the Nazi doctors. There were a number of problems with the Code itself. For example it did not have the strength of law, it was created post hoc, and it applied to only non-therapeutic human subjects research.

1.2.5: Declaration of Helsinki

In 1964 the World Medical Association developed a code of research ethics that came to be known as the Declaration of Helsinki. It was a reinterpretation of the Nuremberg Code, with an eye to medical research with therapeutic intent. Subsequently, journal editors required that research be performed in accordance with the Declaration. In principle, this document set the stage for the implementation of the Institutional Review Board (IRB) process. [Shamoo & Irving]

1.2.6: 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 that had been conducted by reputable researchers and published in major journals. Beecher wrote, "medicine is sound, and most progress is soundly attained;" however, if unethical research is not prohibited it will "do great harm to medicine." Beecher provides estimates of the number of unethical studies and concludes, "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).

1.3 : Ethical Problems with Past Studies

1.3.1: Ethical Problems

The Beecher article and increased public awareness brought to light problems with ethics in research such as the following:

1. Lack of informed consent
2. Coercion or undue pressure on volunteers (or on a parent to volunteer their child)
3. Use of a vulnerable population
4. Exploitation of a vulnerable population
5. Withholding information
6. Withholding available treatment
7. Withholding information about risks
8. Putting subjects at risk
9. Risks to subjects outweigh benefits
10. Deception
11. Violation of rights

1.3.2: Historic Case Studies

Each of the following exhibited one or more of the ethical problems listed above.

1.3.2.1: Willowbrook Hepatitis Study

In 1956, at an institution for mentally retarded children in Staten Island, New York, a study was initiated to determine the natural history of viral hepatitis and to test the effectiveness of gamma globulin as an agent for inoculating against hepatitis. Children were deliberately infected with a mild form of hepatitis.

The investigators defended the study by stating that most new children would become infected with hepatitis within their first 6-12 months at the institution. Although permission was obtained from parents, the parents were not fully informed of the possible hazards involved in the study. There is evidence that the parents were led to believe that the child would not be enrolled at the school unless the parents signed the consent form.

Ethical problems: exploitation of a vulnerable group of subjects, withholding information about risks, coercion or undue pressure on parents to volunteer their children. [Munson]

1.3.2.2: Jewish Chronic Disease Study

In 1963 live cancer cells were injected into senile patients without their knowledge as part of a study of immunity to cancer. Since the investigators believed that the cells would be rejected, the researchers did not inform the patients or seek consent because they did not want to frighten them.

Ethical problems: lack of informed consent, use of a vulnerable group of subjects. [Levine]

1.3.2.3: San Antonio Contraception Study

In San Antonio, Texas, a number of Mexican-American women participated in a 1971 study to determine side effects of an oral contraceptive. The women came to a clinic seeking contraceptives. Unbeknownst to them, the study was designed so that half the women would receive oral contraceptives for the first half of the study, then switched to placebo. The women initially receiving placebo were placed on the oral contraceptive for the second half of the study. 10 of the 76 subjects became pregnant while using placebo.

Ethical problems: lack of informed consent, use of a vulnerable group of subjects, risks to subjects outweighed benefits. [Levine]

1.3.2.4: Tea Room Trade Study

The study planned first to obtain information about homosexual practices in public restrooms and then to conduct further investigation on the men who took part in the acts. The researcher went undercover 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 initial study of direct observation of homosexual acts the researcher distributed a "social health survey" throughout the communities where he knew the subjects lived.

Ethical problems: use of a vulnerable population, reinforced image that social scientists use deception casually in research, lack of informed consent. [Warwick]

1.3.2.5: Obedience to Authority Study (Milgram Study)

The purpose of this study was to determine response to authority in normal humans. The researchers told recruited volunteers that the purpose 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 shocks. The "student" was a confederate of the researcher who pretended to be a poor learner and mimicked pain and even unconsciousness as the subject increased the levels of electric shock. 63% of the subjects administered lethal shocks; some 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.

1.3.2.6: The Public Health Service Syphilis Study (1932-1971)

Initiated by the Public Health Service, this study was designed to document the natural history of syphilis in African-American men.

At the time the study began there was no known treatment for syphilis. Hundreds of men with syphilis and hundreds of men without syphilis (serving as controls) were enrolled into the study. The men were recruited without truly 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."

Even after penicillin was found to be a safe and effective treatment for syphilis in the 1940's, the men were denied antibiotics. The study continued to track these men until 1972 when the first public accounts of the study appeared in the national press. The study resulted in 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.

1.4 : The Belmont Principles

1.4.1: Research Ethics since the 1970s

The Public Health Service (PHS)Syphilis Study is among the most influential in shaping public perceptions of research involving human subjects. After the press "blew the whistle" on the PHS Syphilis Study, Congress formed an Ad Hoc Panel. The Panel determined that the PHS Syphilis Study should be stopped immediately and that oversight of human research was inadequate. The Panel recommended that federal regulations be designed and implemented to protect human research subjects in the future. Subsequently, federal regulations were enacted including the National Research Act, 45 Code of Federal Regulations 46, and 21 Code of Federal Regulations 50.

1.4.2: The National Commission

In 1974 Congress authorized the formation of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, known to most people in research ethics as The National Commission. Congress charged the National Commission to identify the basic ethical principles that underlie the conduct of human research--to look at the writings and discussion that had taken place up to this time and to ask, "What are the basic ethical principles that people are using to judge the ethics of human subject research?"

Congress also asked the National Commission to develop guidelines to assure that human research is conducted in accordance with those principles.

1.4.3: The Belmont Report

The National Commission met and in 1979 published the Belmont Report. The *Belmont Report* is "required reading" for everyone involved in human subject research.

The *Belmont Report* identifies three basic ethical principles that underlie all human subject research. These principles are commonly called the Belmont Principles. The Belmont Principles are respect for persons, beneficence, and justice.

1.4.4: The Belmont Principles

1.4.4.1: Respect for Persons

This principle is found in the writings of philosopher Immanuel Kant. It requires us to treat individuals as autonomous human beings and not to use people as a means to an end. We must allow people to choose for themselves and provide extra protection to those with limited autonomy.

Elements of autonomy include:

Mental capacity, the ability to understand and process information.
Voluntariness, freedom from the control or influence of others.

Therefore, subjects have full autonomy when they have the capacity to understand and process information, and the freedom to volunteer for research without coercion or undue influence from others.

Rules derived from the principle of respect for persons include:

The requirement to obtain informed consent.
The requirement to respect the privacy of research subjects.

1.4.4.2: Beneficence

This principle reminds us to minimize harms and maximize benefits. Derived rules include:

The requirement to use the best possible research design to maximize benefits and minimize harms.
The requirements to make sure the researchers are able to perform the procedures and handle the risks.
The prohibition of research that is without a favorable risk-benefit ratio.

1.4.4.3: Justice

The principle of justice requires us to treat people fairly and to design research so that its burdens and benefits are shared equitably. Derived rules include:

The requirement to select subjects equitably.
The requirement to avoid exploitation of vulnerable populations or populations of convenience.

1.4.5: 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* says that one principle does not always outweigh another. Rather, we are required to consider each case separately and on its own merits in light of all three principles.

1.5 : Ethical Standards for Research that Guide Us Today

In the last several years reports of unethical studies including gene transfer, cancer, and psychiatric research have heightened the public awareness of these issues even further. Two recent examples follow:

-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 limit 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.

-Death on Gene Therapy Trial

In the fall of 1999, eighteen-year-old Jesse Gelsinger died as a result of his participation in a gene transfer trial. Jesse had a rare metabolic disorder, ornithine transcarbamylase deficiency syndrome (OTC) that was being controlled by medication and diet. Researchers were testing an innovative technique using adenovirus gene transfer. Shortly after treatment Jesse Gelsinger experienced multiple organ failure and subsequently died. This case catapulted research with human subjects into the national media. Serious concerns related to conflict of interest, data safety monitoring, and informed consent have made the Gelsinger case a contemporary illustration of continued doubts about the ethical integrity of research with human subjects. This case has instigated deliberations on all these controversial topics at the national level. The outcome of the discussions has yet to be determined.

1.5.1: Applying the Belmont Principles

The need for protecting human subjects through research ethics and regulations is as prevalent now as ever. Applying the Belmont principles to our studies is an important start:

> From the **principle of respect for persons** we need to conduct initial and continuing informed consent. We need to evaluate whether the research allows subjects to withdraw from the research and maintains the welfare of each subject.
>
> From the **principle of beneficence** we need to evaluate the social and scientific value of the research, the scientific validity of the research, and determine whether the research has a favorable risk benefit ratio.
>
> From the **principle of justice** we need to evaluate whether there is fair subject selection. We also need to evaluate the inclusion and exclusion criteria and the methods of recruitment.

1.5.2: Applying Research Ethics

Additional considerations in research ethics include the following:

1.5.2.1: Principal Investigator's (PI's) Relationship with Staff

A responsible PI will:

Obtain team management skills.

Encourage questions from colleagues and staff.

Listen to the concerns of the research staff, as they may be the first to point out problems with the protocol and with compliance.

Build consensus with the research team.

Eliminate intimidation by those in supervisory positions.

Authority relationships are not limited to the principal investigator and the staff, but can also include the authority of the sponsor over the principal investigator, the authority of the principal investigator over the subject, and the authority of the protocol over the principal investigator.

1.5.2.2: Investigator-Subject Relationship

The investigator must place the subject's rights, welfare, and safety above all other personal and scientific concerns. The relationship between researcher and subject is similar to a physician-patient relationship, but different in the following ways:

-Informed consent is required for participation in research.

Example: Let us suppose that a patient insists that she does not want to hear about the risks, benefits, and alternatives of a proposed medical procedure. She insists that the physician decide for her. Many would say that it is ethical for the physician to go ahead with the treatment, provided that he/she is convinced that it is in the best interest of the patient.

In research the issue is more complex and the relationship more formal. If a potential research subject is given a consent form, and the subject does not want to read the document and simply asks, "Where do I sign?" the investigator must ethically insist that the subject listen to the investigator's description of the study and other important information. The Investigator must insist that the potential subject read and understand the consent document. If the subject refuses to read the consent or hear a full disclosure of the information about the research, then the investigator has the ethical obligation to prohibit enrollment of the subject.

-Withdrawal from a study is at the discretion of the subject.

Example: A healthy research subject enrolls in a pharmacokinetic study of a drug that is known to cause anxiety and feelings of distrust. After receiving two doses, the subject declares he no longer trusts the researchers and says he will leave. The investigator says, “It’s the drug talking” and tries to continue the procedure.

An ethical researcher will permit subjects to withdraw for whatever reason or for no reason. Of course, a researcher must do what is needed for subject safety; in the example above, the investigator should ensure the subject’s emotional equilibrium returns to normal.

-Investigators should be sensitive to power relationships.

Example: It is common in basic science laboratories to obtain blood from normal volunteers, usually staff in the research lab. Some blood donors have difficult veins and may need to be stuck several times to obtain blood. Despite the increased pain of multiple sticks, staff members in an investigator’s lab may feel obliged to say, "Stick me. I don't care. I don't mind needles." Responsible investigators should recognize the problem and excuse such a person from the study. The investigator should say something to the effect that, "You are experiencing more harm than the average subject. I will find someone else to enter the study who will not experience the same anxiety and harm."

-The investigator has a moral fiduciary relationship with the subject.

Example: There are conflicts of interest that are so great that even the moral investigator will have a difficult time making the right decision. If doing what is right for the subject means losing $10 million, many of us could be susceptible to making the wrong decision. It is up to the IRB to detect and minimize these conflicts of interests. However, it is also up to the investigator to avoid entering into these untenable conflicts.

1.5.3: Research Ethics and Regulations

Federal regulations are derived from all of these ethical concerns. Federal regulations provide three basic protections to human subjects involved in research:

Institutional assurances.
Review by an Institutional Review Board.
Informed consent. – Chapter 3 of this module will review the Informed Consent process in detail.

1.5.3.1: Institutional Assurances

Institutional assurances are a mechanism to apply federal regulations to all human subject research. When institutions sign federal assurances, they may also elect to apply the Health and Human Services regulations and terms of the assurance to all research of the institution, regardless of the source of funding.

1.5.3.2: Review by an Institutional Review Board

Review by the Institutional Review Board is the glue that holds the evaluation process together. IRB review (described in detail in Chapter 2) is guided by the ethical principles described in the Belmont Report and asks the following questions when evaluating a study:

-Respect for persons

Does the consent process maximize autonomy?
Does the protocol maximize autonomy?
What additional protections have been put in place for vulnerable populations?
Does this study maximally protect subject privacy and confidentiality?

-Beneficence

Is the research design adequate? Can it be improved?
What are the risks? Have they been minimized? Is the subject informed?
What are the benefits? Have they been maximized? Is the subject informed?

-Justice

Does recruitment for the study target the population that will benefit from the research?
Does the recruitment unfairly target a population?
Are the inclusion/exclusion criteria fair?

Ethical principles and federal regulation provide a framework for IRBs to evaluate research involving human subjects. However each research study is unique and thus a comprehensive review may be a complicated process.

Credits

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