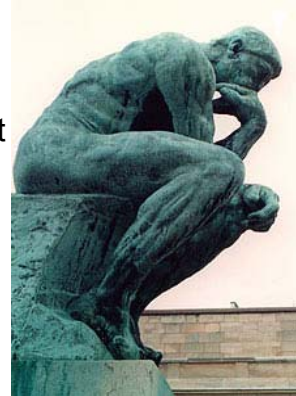

Why Ethics is Important

We are concerned here with normative ethics that tell us how things ought to be, not what is. These are the rules that we use to make decisions and to assess or justify actions and behavior. In research, these rules answer the questions: How should researchers behave? How should researchers not behave? How should we determine what research should be conducted? How should we determine what research should not be conducted?



There are many advantages to understanding research ethics. Ethical principles:

- ▶ Provide us with a structure for analysis and decision-making.
- ▶ Support and remind researchers to protect human subjects.

Historical Development

The events that led up to the development of current thinking on human research protections and the regulatory system now in place occurred in both biomedical and social/behavioral research.

Events in Biomedical Research

Nuremberg Code

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. It became clear during the trial that no accepted standards existed regarding the conduct of human research. The court found that it could not convict the defendants of violating the rights of research subjects. However, the court did convict 15 of the 23 defendants of murder. The court condemned 7 to death by hanging, sentenced 8 to prison from 10 years to life, and acquitted 8. [[Mitscherlich & Mielke](#)] To fill the void in the absence of a legal standard for research the court included in the legal judgment 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.

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 after the conviction of the Nazi doctors, and it applied to only non-therapeutic human subjects research.

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](#)]

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).

The Public Health Service Syphilis Study (1932-1971)

One of the seminal events in the development of the current regulatory environment was the Public Health Service (PHS) Syphilis Study (1932 – 1972), the so-called "Tuskegee 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 initially to make treatment available to African-American men with syphilis, although at the time the study began there was no known effective treatment. After funding to make drugs available was cut, the study became a natural history study. Hundreds of men with syphilis and hundreds of men without syphilis (serving as controls) were enrolled into the study. The men were recruited without their 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. To prevent them 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 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.

Recent Events

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.

Events in Social & Behavioral Research

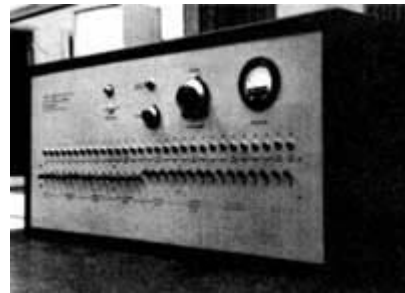
Wichita Jury Case (1953)

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

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

Milgram "Obedience to Authority Study" (1963)

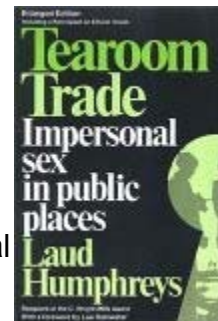
The purpose of this study was to learn more about how humans respond to instructions from people in positions of authority. The researchers informed volunteers that the purpose of the research was to study learning and memory. Each subject was told to teach a "student" and to punish the students' errors 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 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.

Humphrey "Tea Room Trade Study" (1970)

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 and collected data about their sexual orientation, and marital and family status.



Ethical problems: invasion of privacy, use of a vulnerable population, lack of informed consent. [[Warwick](#)]



Zimbardo "Simulated Prison" (1973)

This landmark psychological study of the human response to captivity and, in particular, prison life, involved assigning roles to male student volunteers as "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, failed to

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, neutrality of researcher.

Restaurant Letter Study (2001)

Not all the events that raise concerns about research ethics occurred in the past. Recently, a faculty member from the Business School of a major university designed and implemented a study to elicit responses from restaurants 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 and employees suffered severe emotional distress before learning that it was a hoax. The researcher later admitted the falsehood in a letter of apology. He explained that "the letter was fabricated to help collect data for a research study that I designed concerning vendor response to customer complaints." This 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

In the aftermath of the events through the 1970s, 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 IRBs 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 conduct of human research.
- ▶ Develop guidelines to ensure that human research is conducted in accordance with those principles, which, in turn, led to the current federal regulations.

In 1974 the Department of Health, Education and Welfare issued 45 CFR 46 "Regulations for the Protection of Human Subjects of Biomedical and Behavioral Research". Based on the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978), the Department of Health and Human Services (HHS) revised and expanded its regulations for the protection of human subjects 45 CFR 46 in the late 1970's and early 1980's. In 1991 sixteen other federal agencies and departments agreed to apply the basic requirement in 45 CFR 46 to the research they fund or conduct, and in 2005, the Department of Homeland Security adopted the regulations. The basic regulations are referred to as the "Common Rule."

Ethical Principles

The Belmont Report

In 1979, after several years of deliberations, the National Commission published the Belmont Report. The Report is a summary of the basic ethical principles identified by the National Commission in the course of its deliberations in February 1976 supplemented by the monthly deliberations of the Commission that were held over a period of nearly four years. It is a statement of the basic ethical principles and guidelines that should be used to resolve the ethical problems that surround the conduct of research with human subjects.

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.

All individuals involved in the conduct of human research should read the **Belmont Report**. The conduct of ethical research is not intuitive – being a good

person is no more sufficient for the conduct of ethical research than being brilliant is sufficient for the conduct of good science. One must know and understand the basic principles of science and know how to apply them to the design and conduct of research in order to do good science. So, too, must one know and understand the basic ethical principles in the Belmont Report and know how to apply them in order to conduct ethical research.



Respect for Persons

This principle requires researchers to treat individuals as autonomous human beings, capable of making their own decision/choices, 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 the control or influence of others)

Subjects have full 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.

Rules derived from the principle of respect for persons include:

- ▶ The requirement to obtain and document informed consent.
- ▶ The requirement to respect the privacy interests of research subjects.
- ▶ The requirement to consider additional protections when conducting research on individuals with limited autonomy

Beneficence

This principle requires researchers to minimize the risks of harm and maximize the potential benefits of their work. 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 humanity as a whole. In general, the risks and benefits to the individual subjects carry more

weight than benefits to others. As The Belmont Report states, "Beneficence thus requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research."

The rules derived from the principle of beneficence include:

- ▶ The requirement to use procedures that present the least risk to subjects consistent with answering the scientific question.
- ▶ The requirement to gather data from procedures or activities that are already being performed for non-research reasons.
- ▶ The requirement that risks to subjects be reasonable in relation to both the potential benefits to the subjects and the importance of the knowledge expected to results.
- ▶ The requirement to maintain promises of confidentiality.
- ▶ For research that involves more than minimal risk of harm, the requirement to monitor the data to ensure the safety of subjects.

Justice

The principle of justice requires us to treat people fairly and to design research so that its burdens and benefits are shared equitably. 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, cannot say "no" or do not know that they can say "no". In order to avoid exploitation the selection of subjects should solely based on scientific justification.



The rules derived from justice include:

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

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 in light of all three principles.

Applying the Belmont Principles

The need for protecting human subjects through research ethics and regulations is as relevant 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.

Review by an Institutional Review Board (IRB)

In addition to providing ethical guidance for the conduct of research involving human subjects, the Belmont Principles form the basis for many of the requirements found in the federal regulations. In fact, the specific criteria for IRB approval spelled out in 45 CFR 46.111 of the regulations are drawn directly from



the three basic Belmont Principles. Therefore, the Belmont Principles also serve as a guide to compliance with the federal regulations.

According to Section 111, in order to approve research the IRB must determine that all of the criteria in the section are satisfied. The following summarizes the criteria, along with the relevant principles from the Belmont Report:

- Risks to subjects are minimized [Beneficence]
- Risks are reasonable in relation to anticipated benefits [Beneficence] .
- Selection of subjects is equitable [Justice] .
- Informed consent is sought from each subject [Respect for Persons] .
- Informed consent is appropriately documented [Respect for Persons] .

And when appropriate:

- Data collection is monitored to ensure subject safety [Beneficence] .
- Privacy and confidentiality of subjects is protected [Respect for Persons & Beneficence] .
- Additional safeguards are included for vulnerable populations [Respect for Persons] .

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

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.

The Need for Independent, Objective Review of Research

Since the Belmont Report and the other professional ethics codes provide guidance on the ethical conduct of research, the question arises as to why we need IRB review. Why not just obtain a commitment from the researchers that they will follow the ethical principles in the conduct of their research? The answer is found in some basic principles of human nature.

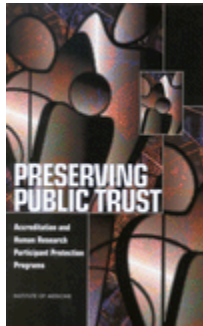
First, highly motivated people tend to focus on their goals and may unintentionally overlook other implications or aspects of their work. Take, for example, driving on the highway. When one is late for an appointment, one tends to drive faster and may be tempted to break the speed limit. It is not that the person does not care about safety; rather, at that moment they are focusing on the goal of getting to their appointment and not considering the safety implications of what they are doing. What keeps most people from driving at excessive speeds is that there is a system in place that results in consequences for people who drive at unsafe speeds. Researchers are highly motivated people who tend to focus on their scientific goals, just as drivers focus on getting to an appointment on time. As a result, they may overlook the ethical implications of what they are doing. The purpose of IRB review is to provide a system that requires researchers to take ethics into account when designing and conducting their research or there will be consequences.



The second principle of human nature that drives the need for IRB review is that no one can be totally objective about his or her own work. One way that this affects the conduct of research is that people underestimate the risks resulting from projects with which they are very familiar. For example, cars had seat belts for years, but people rarely wore them until there were laws requiring seat belt use. Most people understood that seat belts saved lives and prevented injury, so why didn't they use them? In part, people underestimated the risk of having an accident while driving because they drove on a daily basis. Similarly, researchers tend to underestimate the risks of their research, not because they are callous, but because the procedures are so familiar to them. In addition to underestimating risks, researchers have an inherent conflict of interest when judging their own research. They have a stake in getting the research done as quickly and efficiently as possible. As a result of both of these principles, every research activity needs an independent, objective review. This is one important function of the IRB review process.

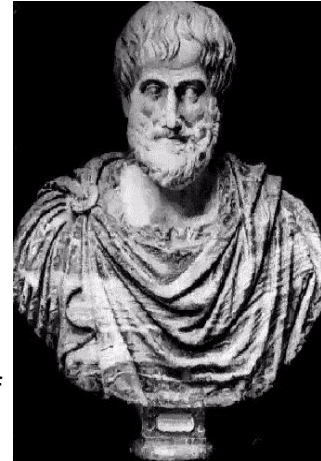
Even if researchers were well versed in the ethical principles and committed to the ethical conduct of research, IRB review is necessary to ensure that ethical

concerns are not overlooked.



Public Trust

In addition to ethical principles, the regulations also reflect the need to maintain the public trust in research. Researchers do not have the right to conduct research, especially research involving human subjects. Society grants researchers the privilege of conducting research. The granting of that privilege is based on the public's trust that research will be conducted responsibly. Erosion of that trust can result in the withdrawal of this privilege.



The federal regulations that currently govern human subjects research evolved as a response to the erosion of public trust that resulted from the scandals described above. Without regulations, these events caused the public to question the ethics of researchers conducting human subjects research. Congress, responding to public concern, directed that federal agencies to adopt regulations for research funded or conducted with federal funds and for research using products regulated by the U.S. Food and Drug Administration (FDA). Should additional events erode the public trust, Congress will order additional restrictions and could even ban some types of research altogether.

Public trust is maintained through accountability – the ability of researchers to demonstrate to others that they are conducting research responsibly. Accountability is accomplished through documentation. It is not sufficient for researchers to conduct ethical research. They need to be able to document that they have done so. Therefore, in addition to setting standards for the ethical conduct of research involving human subjects, the federal regulations include requirements for the necessary documentation of that ethical conduct. The purpose of the documentation requirements in the regulations is not to satisfy the regulators, but to preserve the public trust in research.

Summary

To quote from the publication "Preserving the Public Trust" prepared by the Institute of Medicine, "The complex system that sustains research is ultimately premised on trust – trust in the people and organizations that conduct research. In the wake of revelations about lapses in research ethics, such trust must be earned..."

The evolution of the currently regulatory process governing human subjects

research is based on preservation of the public trust by establishing standards for the ethical conduct of human subjects research and requirements to ensure the accountability of researchers engaged in such research.

The IRB review system is designed to provide an independent, objective review of research involving human subjects so that the privilege of conducting human subjects research may be maintained.

Revised 8-22-05