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History and Ethics of Human Subjects Research

University of Virginia - IRB-HSR RESEARCHER BASIC COURSE

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History and Ethics of Human Subjects Research

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Introduction

Concerns about the ethics of research involving human subjects have a long history. As a society, we have learned difficult lessons on how to ensure the ethical conduct of research while continuing in the advancement of scientific knowledge for the benefit of humanity. The ethical principles and regulations that have been developed over the years are designed to help ensure that the rights and welfare of human subjects in research are protected and maintain the public trust in the research enterprise. This module describes the history of concern about ethical research involving human

subjects, the ethical principles developed to guide the conduct and review of such research, and the development of the regulations governing it. It also describes the current ethical and regulatory concerns in human subjects research.

Learning Objectives

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

- Discuss the historical basis for regulations governing human subjects research.
- Identify the ethical principles underlying research involving human subjects.
- Explain how the U.S. federal regulations are designed to implement those ethical principles and preserve the public trust.
- Discuss the current regulatory environment for human subjects research.

History

Throughout the history of scientific research there have been ethical concerns regarding the use of humans as research subjects. Early medical researchers struggled with ethical concerns, such as:

- Edward Jenner (1789) who tested smallpox vaccine
- Claude Bernard (1865) who developed ethical maxims regarding human research
- Louis Pasteur (1885) who tested the rabies vaccine
- Walter Reed (1900) who studied yellow fever

Nuremberg

Modern concern regarding the ethics of research involving human subjects developed as the result of the Nazi regime's atrocities during World War II. During the Nuremberg War Crimes Trials following the war, 23 Nazi doctors were charged with crimes against

humanity.

As stated in the trial's transcript, the defendants were charged with "perform[ing] medical experiments upon concentration camp inmates and other living human subjects, without their consent, in the course of which experiments the defendants

committed the murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts [described in the indictment]" (Trials of War Criminals 1949a).

The Nuremberg Code (1947)

As part of the verdict, the court enumerated rules for "Permissible Medical Experiments," now known as the "Nuremberg Code." These rules include, among other ethical principles:

- A requirement for voluntary consent
- That the research have scientific merit
- That the benefits of the research outweigh risks
- That the subjects have the ability to terminate participation in the research at anytime

The Nuremberg Code had little direct effect on human research following the war partly

The Nuremberg Code had little direct effect on human research following the war partly because of its origin in concern about Nazi atrocities. The Nuremberg Code has not been adopted as law or as part of any professional ethical code. Still, its influence as a source document on the ethics of human subjects research has been significant. **Read more about the Ten Points of the Nuremburg Code**.

Henry K. Beecher Article

Beecher's (1966, 1354-60) article entitled, "Ethics and clinical research," detailed 22 published medical studies presenting risk to subjects without their knowledge or approval. These articles were published in some of the most prestigious journals and outlined research on human subjects conducted at some of the most prestigious organizations in the country. Beecher's article clearly demonstrated that unethical research was not confined to Nazi atrocities.

U.S. Public Health Service (PHS) Study of Untreated Syphilis

The PHS Study of Untreated Syphilis was a medical research project conducted by the PHS from 1932 to 1972 (commonly known as the "Tuskegee Syphilis Study" or the "PHS Syphilis Study") that examined the natural course of untreated syphilis in Black American men (CDC 2013). According to the Centers for Disease Control and Prevention (CDC), the subjects, all impoverished sharecroppers from Macon County, Alabama, were unknowing subjects in the study; they were not told that they had syphilis, nor were they

offered effective treatment when it became available in the late 1940s with the availability of penicillin. The study concluded in 1972 when stories about the study appeared in the public press and caused a public outcry.

Other Abuses

Two of the other publicized examples of ethical abuses in research are the Willowbrook studies (1956-1970), where children with intellectual disabilities were deliberately infected with the hepatitis virus, and the Jewish Chronic Disease Hospital study (1963), where live cancer cells were injected into 22 cognitively impaired patients. These and other cases of abuse, including publicity about extensive medical research conducted on prisoners in correction facilities, contributed to the public concern over medical research.

National Research Act

In response to the public concern about the ethics of the PHS Syphilis Study, prisoner research, Willowbrook, and other abuses in human research, hearings on "Quality of Health Care - Human Experimentation" were held before the Subcommittee on Health of the U.S. Senate Committee on Labor and Public Welfare (commonly referred to as the "Kennedy Hearings") in 1973. Because of these hearings, Congress passed the 1974 National Research Act. The National Research Act has two major provisions relevant to human subjects research.

1. It established the "National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research" (The National Commission) to identify the basic ethical principles underlying human subjects research and develop guidelines for ensuring that human subjects research is conducted according to those guidelines.
2. It required the establishment of Institutional Review Boards (IRBs) at organizations

receiving PHS support for human subjects research.

The National Commission

The National Commission met from 1975 through 1978 and issued a series of reports on vulnerable populations (such as, fetuses, children, prisoners, and the "mentally infirm"), psychosurgery, IRBs, and other topics that included recommendations for regulating human subjects research. These recommendations had significant influence on the development of the federal regulations governing human subjects research. The results of the National Commission's deliberations regarding basic ethical principles were summarized in its final report, published in 1979, which was entitled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research" (commonly referred to as the *Belmont Report*).

Ethical Principles

There are three ethical principles that provide the framework for human subjects research that were identified by the Belmont Report.

The Belmont Report

The *Belmont Report* is based on the deliberations of the National Commission, including an intensive four-day period of discussions that were held in February 1976 at the Smithsonian Institution's Belmont Conference Center.

The *Belmont Report* identified three basic principles relevant to the ethical conduct of research involving human subjects:

- Respect for Persons
- Beneficence
- Justice

These three principles "provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects" (The National Commission 1979).

Respect for Persons

The principle of Respect for Persons is based on the ethical concept that individuals should be treated as autonomous agents. "To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others" (The National Commission 1979). Some individuals do not have full autonomy based on their condition (such as their age, health, cognitive ability) or their circumstances (such as poverty, lack of education or social status). Under the principle of Respect for Persons, individuals with diminished autonomy need additional protections. "The extent of

protection afforded should depend upon the risk of harm and the likelihood of benefit. The judgment that any individual lacks autonomy should be periodically reevaluated and will vary in different situations" (The National Commission 1979).

Application of Respect for Persons	
Informed Consent	"Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied" (The National Commission 1979). These standards include: • **Information**: In deciding how much information to provide to potential subjects, the *Belmont Report* states, "the extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge" (The National Commission 1979). That is, the information should be sufficient so that a "reasonable volunteer" can decide whether to participate. • **Comprehension**: Information should be provided to potential subjects in such a way that they could understand what is being conveyed. "Because the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible

	for ascertaining that the subject has comprehended the information" (The National Commission 1979). • **Voluntariness**: As stated in the *Belmont Report*, "An agreement to participate in research constitutes a valid consent only if voluntarily given" (The National Commission 1979). While research participation is rarely coerced, undue influence can be part of the consent process when there is inequitable social pressure or there are inappropriate rewards to participate. In the PHS Syphilis Study, subjects were not informed that they were in a research study; in the Nazi experiments, subjects were not free to decline to participate. Full knowledge about the nature of the research and voluntary participation are both essential components of informed consent; so, in neither case was informed consent obtained. In addition, as Beecher showed, failure to obtain consent is not limited to such notorious research studies.
Privacy	While not directly addressed in the *Belmont Report*, respect for persons also involves respecting an individual's right to privacy, the right to control access to one's self and information, and protecting the confidentiality of private, identifiable information about individuals. Research should be evaluated to ensure that the subject's right of privacy is not violated and the confidentiality of information is protected.

Beneficence

The principle of beneficence includes the obligation of researchers to strive to do no harm and to maximize benefits and minimize harms. "Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being" (The National Commission 1979). The obligation "to do no harm" does not mean that it is never justified to expose subjects to risk. "The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone

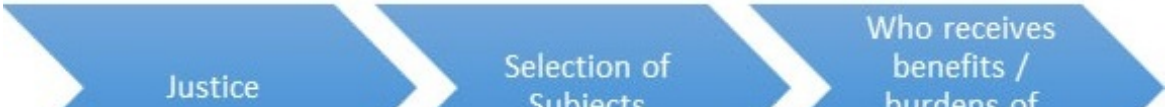
certain benefits despite the risks involved, and when the benefits should be foregone because of the risks" (The National Commission 1979).

Application of Beneficence	
Systematic Assessment of Risks and Benefits	In order to evaluate whether the research meets the ethical standard of beneficence, there must be a systematic assessment of the risks and benefits of the research and a determination that the risks are justified by the research's anticipated benefits. Risk is not harm, it is the possibility of harm, and an analysis of the risks must take into account both the magnitude of the possible harm and the probability that the harm may occur. The research's anticipated benefits may be to the individual research subjects or they may be to others in the form of the advancement of scientific knowledge. "In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight. On the other hand, interests other than those of the subject may on some occasions be sufficient by themselves to justify the risks involved in the research, so long as the subjects' rights have been protected" (The

	National Commission 1979). In the PHS Syphilis Study, even after effective treatment for syphilis was developed using penicillin, it was withheld from the subjects.
Minimization of Risk	In addition to determining that the risks are reasonable in relation to the anticipated benefits, the principle of beneficence requires that the risks in the research are the minimum required to achieve the research objective. To do this, researchers and IRBs should carefully consider alternative, less risky procedures or modifications to the procedures that reduce the magnitude or probability of the possible harm to subjects.

Justice

The principle of justice requires that the selection of subjects is equitable. "Who ought to receive the benefits of research and bear its burdens? ...An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly" (The National Commission 1979). In the past, much research was conducted with subject populations because of convenience (such as prisoners or institutionalized children) and these vulnerable subjects bore the burdens of the research, but not the benefits. The principle of justice requires a fair sharing of the burdens and benefits of research and that groups are not exploited because of their circumstances.



Application of Justice	
Selection of Subjects	As stated in the *Belmont Report*, "the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied" (The National Commission 1979). The selection of subjects must be based on the research's scientific needs, not on convenience in recruitment. Researchers should be able to scientifically justify the inclusion or exclusion of subjects. Subjects should not be denied access to potential benefits of participating in the research because of considerations such as whether they speak English. Also included in this analysis is the requirement to avoid undue influence in the recruitment of subjects. Undue influences are real or perceived pressures to participate and can arise from financial incentives, inequitable power relationships, and implied benefits from participating. The selection of subjects in the Nazi experiments and the research involving prisoners in the U.S. clearly was not equitable. Both involved captive individuals with limited freedom to refuse. In the U.S. prisoner studies, prisoners were used as subjects in research designed to advance medical knowledge, not to benefit the prisoners. In the Willowbrook studies, vulnerable, institutionalized children were used as research subjects. Although parents gave consent, it is not clear that it was truly informed consent. In addition, for some of the studies, the only way parents could get treatment for their children was to enroll them

	in the study.

General Considerations

In identifying and discussing the three basic ethical principles, the *Belmont Report* does not indicate any order of their importance. The three principles provide an "analytical framework" for making decisions regarding ethical research. All three principles have to be considered equally when making ethical decisions about research and deciding how to apply them often requires difficult ethical decision-making. At times, the principles might come in conflict with each other. Procedures to ensure beneficence might come in conflict with the principle of justice. For example, the need to protect children from risk might come in conflict with the need to include children for scientific validity. The goal of ensuring that research meets these ethical principles requires careful analysis and consideration by researchers and IRBs.

Development of U.S. Regulations

Federal regulations governing human subjects research in the U.S. are designed to implement the *Belmont Report's* principles and restore the public trust in research. The public outcry over ethical abuses in research reflects an erosion of public trust in research and Congress enacted legislation to restore this trust.

Read about early U.S. regulatory requirements on research involving human subjects...

In 1966, concern over abuses in research led the PHS to issue the policy "Clinical Research and Investigation Involving Human Beings." According to the policy, grantees were required:

> To indicate the manner in which the grantee institution will provide prior review by a committee of...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 (Surgeon General 1966).

In 1974, in anticipation of the National Research Act, the PHS policy was raised to regulatory status in 45 CFR 46, the "Regulations for the Protection of Human Subjects of Biomedical and Behavioral Research."

> 45 CFR 46 was the first set of federal regulations to detail specific requirements and procedures for organizational assurances, IRB review, informed consent, and the ethical conduct of research.

Based on the National Commission's recommendations, additional protections for targeted vulnerable populations were added to 45 CFR 46 in the following years. These include:

- **Subpart B** - Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research (1975; revised in 2001).
- **Subpart C** - Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects (1978).
- **Subpart D** - Additional Protections for Children Involved as Subjects in Research (1983). In 2001, FDA added a slightly revised version of Subpart D to 21 CFR 50. It was revised in 2013.

In response to the National Commission's reports and recommendations, both the U.S. Department of Health and Human Services (HHS [formerly the Department of Health, Education, and Welfare]) and the FDA promulgated significant revisions of their human

Education, and Welfare]) and the FDA promulgated significant revisions of their human subjects regulations between 1980 and 1981.

- 45 CFR 46 was revised in 1981.
- FDA adopted 21 CFR 50 on informed consent in 1980 and 21 CFR 56 on IRBs in 1981.

- The HHS and FDA regulations were developed to be congruent with differences reflecting the different types of research covered by the two agencies. Subsequently, the FDA adopted regulations on investigational medical devices (21 CFR 812) in 1980 and investigational drugs and biologics (21 CFR 312) in 1981.

In 1991, 17 federal agencies that conduct, support, or otherwise regulate human subjects research issued uniform regulations based on 45 CFR 46, Subpart A entitled "The Federal Policy for the Protection of Human Subjects." Because this set of regulations, for the most part, contains the same requirements, it is often referred to as the "Common Rule." The Common Rule remained almost unchanged until 2017.

In 2017, HHS and 15 other federal agencies issued a Final Rule to update the regulations. The revisions were designed to strengthen protections for human subjects, as well as reduce administrative burdens and add flexibility for the modern research environment (HHS 2017). Major changes were made to requirements for IRB operations, informed consent, definitions, and exemptions. The revised rule is referred to as the 2018 Requirements of the Common Rule, with a general compliance date of 21 January 2019.

International Regulations

Since the Nuremberg Trials, various international codes and standards have been adopted to apply to the ethical conduct of human subjects research.

- Declaration of Helsinki: In 1964, the 18th World Medical Assembly meeting in

Helsinki, Finland, adopted "Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects." This document, commonly referred to as the Declaration of Helsinki, has been revised multiple times (1975, 1983, 1989, 1996, 2000, 2008, and 2013).

- CIOMS guidelines: In 1982, the Council for International Organizations of Medical Sciences (CIOMS) adopted the "International Ethical Guidelines for Biomedical Research Involving Human Subjects," which were revised in 1993, 2002, and 2016.
- WHO guidelines: In 2001, the World Health Organization (WHO) adopted "Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants." These documents are designed to serve as international guidelines for the review and conduct of research involving human subjects.
- ICH guidelines: In 1996, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), an organization that brings together the drug regulatory authorities and the pharmaceutical industry of Europe, Japan, and the U.S., adopted standards on Good Clinical Practice (ICH E6). ICH E6 details the responsibilities and expectations of all individuals involved in the conduct of clinical trials, including researchers, monitors, sponsors, and IRBs. ICH E6 standards, while not part of any country's regulations, provide international standards for transnational pharmaceutical research. ICH renamed itself “International Council for Harmonisation” in 2015, added members, and in 2016 released a revised E6(R2) guideline. The FDA adopted the revised E6(R2) guideline as guidance.

Other Country Regulations/Codes

There are human subjects research regulations that are in effect in other countries. The Office for Human Research Protections (OHRP) provides a curated list. Some examples include:

- **European Union:** Clinical Trials Directive (Officially Directive 2001/20/EC of 4 April 2001)
- **Canada:** Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans
- **Indian Council of Medical Research:** Ethical Guidelines for Biomedical Research on Human Participants
- **Office for Human Research Protections (OHRP):** International Compilation of Human Research Standards; lists human research standards around the world

Recent History

During the period from 1974 through the mid-1990s, it seemed as if the concerns regarding ethical research had been addressed by the federal regulations. Most organizations had established IRBs, and IRB review and approval was required for federally funded research and research conducted under FDA regulations.

However, things were not as good as they seemed. There were concerns that researchers and IRBs were not fully complying with the federal regulations on human subjects research and complaints continued. In 1983, as a follow up to the National Commission, a Presidential Commission report on the IRB process raised concerns about the adequacy of the IRB review process. During this period, the Office for the Protection from Research Risks (OPRR) (the predecessor to OHRP) at the National Institutes of Health (NIH) conducted multiple investigations of allegations of non-compliance with the regulations.

Independent Reviews

General Accounting Office - March 1996

"Scientific Research: Continued Vigilance Critical to Protecting Human Subjects"

In response to the concerns noted above, the U.S. General Accounting Office (GAO 1996) was asked by Congress to investigate the system for protecting human subjects. The GAO found that the oversight procedures were impaired by IRBs' heavy workloads and competing demands, limited funds for on-site inspections, the complexity and volume of

research under review, and reliance on researchers' self-assurances that they were complying with requirements. GAO also found limited direct oversight by the federal agencies charged with the responsibility of enforcing the regulations.

HHS Inspector General - June 1998

"Institutional Review Boards: A Time for Reform"

Following the GAO report, the HHS Inspector General conducted an independent investigation of the IRB review process (Office of Inspector General 1998). This investigation also raised serious concerns about the effectiveness of the IRB process including:

- IRBs reviewed too much, too quickly with too little expertise.
- IRBs conducted minimal continuing review of approved research.
- IRBs provided little training for researchers and board members.
- IRBs faced conflicts resulting from the prestige and revenue brought to their organizations by research. These conflicts threatened the IRB's independence.
- Neither IRBs nor the HHS devoted much attention to evaluating IRB effectiveness.

Increased Vigilance

These two reports raised the level of concern regarding the effectiveness of the IRB system. One direct result was increased vigilance by the FDA and OPRR. OPRR began a series of both "for cause" and "not for cause" investigations of IRBs.

These investigations resulted in several organizations losing the ability to conduct federally funded human research ("shut down"). These organizations included some of the most prestigious research organizations in the country.

While the result of these investigations did produce changes in the oversight of human subjects research, public attention became focused on the problem because of the highly publicized death of Jesse Gelsinger, who was a subject in a research study.

Read about the impact of a subject's death and the effect on human subjects research.

Responding to the outcry over Jesse's death, HHS Secretary, Donna Shalala, published an article entitled, "Protecting Research Subjects - What Must Be Done." Shalala's (2000, 808-10) article called for a revision of the IRB system, increased oversight by federal agencies, and increased education of IRB members and researchers. Her article also announced that the human protections functions of OPRR were being transferred to the newly created OHRP, which was being placed under the Secretary's Office.

Current Situation

The main conclusion reached after these events is that IRBs are not enough to protect human subjects in research. Out of the discussion addressing the problems with the IRB system arose the concept of a human research protections program (HRPP). An **HRPP** is a comprehensive and organized system of shared responsibility at an organization to ensure the protection of human subjects participating in research. The objective of this system is to assist organizations in meeting ethical principles and regulatory requirements for the protection of human subjects in research. The IRB is an important component of an HRPP, but it is only one part of an overall organizational program to protect human subjects.

In addition to the development of HRPPs, recent events have resulted in:

- Higher standards for IRB review
- Increased responsibility for researchers
- Increased requirements regarding conflict of interest
- The accreditation of HRPPs

These are all designed to strengthen the protection of human subjects in research and ensure that human subjects research is conducted ethically.

History and Ethics of Human Subjects Research

Summary

Historical events and abuses have shaped the development of ethical principles and regulations governing research involving human subjects. The ethical principles in the *Belmont Report* guide the review and conduct of human subjects research. The regulations provide a framework to help ensure the ethical conduct of human subjects research. Standards continue to evolve as events in human subjects research evolve.

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Original Release: January 2004

Last Updated: January 2018

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