

# ETHICS IN CLINICAL RESEARCH A HISTORY OF HUMAN SUBJECT PROTECTIONS AND PRACTICAL IMPLEMENTATION OF ETHICAL STANDARDS

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**Abstract:** *The current regulations for clinical research are based on a combination of ethical thought and history, some of it being very tragic. This article presents the ethical and historical underpinnings of these regulations, including the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, Title 21 Code of Federal Regulations (CFR) Parts 50 and 56, 45 CFR Part 46, and the International Conference on Harmonization Good Clinical Practices. In addition, the article highlights the role of the therapeutic misconception, which occurs when patients enrolling as research subjects misinterpret and perhaps even distort information about the research because they believe that aspects of the research will directly benefit them.*

The current regulations for clinical research are based on a combination of ethical thought and history, some of it being very tragic. The word 'ethics' derives from the Greek, *ethos*, which means custom or character. Ethics is contrasted with morality, which frequently relates to how you were raised and what values you learned from parents, religion, culture, and other influences. Ethics is more systematic, as the following conception suggests: ethics is the systematic study of values by which a determination of what is the right and wrong thing to do is made.

Ethics is also different from law and regulation, both of which mandate a certain way of acting. The United States regulations for the protection of human subjects provide baseline minimums with which everyone must comply in operating an institutional review board (IRB), obtaining informed consent from research subjects, and conducting research in an ethical manner.

Ethical thought has helped shape the regulations. But ethics goes beyond what the regulations require to include for what we ought to do. Ethics asks, "What ought I to do?" and "What is the right thing to do?"

Throughout the 4,000 year history of ethics there have been many interesting theories about what ethics ought to be and what principles should be at the forefront of our thinking. In examining and using these ethical theories, we are trying to justify particular rules, procedures, or outlooks on ethics and what we ought to do. The challenge, especially in a practical environment such as clinical research, is to translate the theoretical concepts from ethics into action. The regulations help us accomplish this task.

## **ETHICAL PRINCIPLES FOR CLINICAL RESEARCH**

A variety of codes and reports

form the bedrock or foundation for the ethical conduct of clinical research (Table 1). These codes and reports have been translated into particular practices, guidelines, and requirements in our current regulations. However, ethical principles must be discussed within their historical context. There have been many tragedies throughout the history of research involving human subjects, and many people were harmed as a result of their unwitting participation in research. From an ethical perspective, it does an injustice to them to abstract thinking regarding the regulations away from its historical and ethical context.

### The Nuremberg Code

The modern history of human subject protections begins with the discovery of the atrocities committed by Nazi physicians. For example, such atrocities included twin experiments, where one twin was exposed to a pathogen and then autopsied to determine the natural progression of the disease. The other uninfected “control” twin was then “sacrificed” to see what the differences were. It may constitute a very interesting comparison from a scientific perspective, but such an experiment was wholly unethical and inhumane.

The judges at the trial had no basis in law by which to judge the Nazi physicians. They developed 10 principles for this purpose, and these principles formed the basis of what came to be known as the Nuremberg Code for research involving human subjects. Highlights of the Nuremberg Code include:

- Voluntary consent is essential. This requirement is at the heart of what the Nazis did wrong. They did not ask any of the people who were subject to their experiments if they wanted to participate.

**TABLE 1**  
**The Foundation for the Ethical Conduct of Clinical Research**

- The Nuremberg Code
  - The Declaration of Helsinki
  - The Belmont Report
  - 21 CFR Parts 50 and 56
  - 45 CFR Part 46
  - International Conference on Harmonization Good Clinical Practices
- Research risks must be minimized and relative to the anticipated benefits of the research.
  - The research must benefit society. It is unethical to needlessly endanger the well being of human volunteers if other methods of investigation exist. Poorly designed human subject research is unethical from its inception. If you do not have the statistical power to answer your research question, no IRB should approve the research. If you have a flaw in the research design, or if you can improve the research design to have a better risk/benefit profile, you must do it.
  - Research must be based on pre-clinical studies in animals and knowledge of the condition under study. Many of the Nazi experiments were performed just because the physicians found them interesting.
  - Subjects have the right to end their participation in research.

Unfortunately, the Nuremberg Code did not have much impact in the United States outside of the scholarly community.

### The Declaration of Helsinki

The Declaration of Helsinki is a “living” document that attempts to take into account the evolving

nature of scientific research. It was first adopted by the World Medical Assembly in 1964, and revised in 1975, 1983, 1996, and 2000. Highlights of the Declaration of Helsinki include:

- In research, the well being of subjects should take precedence over the interests of science and society.
- Several ethical standards are articulated: respect for persons and protection of subjects’ health and rights.
- Some populations are vulnerable (e.g., the physically or mentally handicapped) and require special protections.
- Experimental procedures must be detailed in a protocol, which is submitted to an ethical review committee. This statement represents one of the first articulations of the requirement for a protocol, which includes the scientific reasons for and the purpose of the study, and what questions the researchers hope to answer by conducting the study.
- Investigators must submit information regarding the research (especially monitoring information such as serious adverse events) to the ethical review committee.
- Assessment of risks and benefits to subjects or others is required before conducting the research.
- Subjects must be informed volunteers. If they cannot consent for themselves, then legally authorized representatives must consent on their behalf.
- Subjects have the right to safeguard their own integrity (another application of the principle of respect for persons).
- Informed consent must be documented.
- The context of obtaining informed consent is as important as the information presented in the informed consent document itself. If the researcher is also the

subject's physician, a physician not connected with the research or the subject's medical care should obtain informed consent to minimize undue influence.

### Research Abuses

In 1966, Henry Beecher, a Harvard anesthesiologist, authored an exposé of numerous unethical experiments that had been published in prominent medical journals. Beecher did not furnish names or references to the research. His goal was not to encourage prosecution but rather to increase awareness of broader ethical problems in human experimentation. He wanted to heighten awareness that unethical activities in the United States were very similar to what happened in Nazi Germany. His article had a major impact on the development of the regulations. His conclusions included:

- Unethical treatment of human subjects was not confined to the barbarism of the Nazis.
- Informed consent is a goal. It is something we may never be able to achieve, but we should strive for it.
- It is not enough to mention that consent was obtained; subjects must be informed and understand the risks.
- There should be a second safeguard: "an intelligent, informed, conscientious, compassionate, responsible investigator."
- Experiments are ethical or not ethical at their inception, experiments do not become ethical or unethical afterwards. If you design the research properly, you should have an ethically conducted protocol as long as adequate protections are built into the protocol to protect human subjects.

Beecher was correct. The saddest example in our country of a research abuse was the so-called

Tuskegee Syphilis Study (1932-1972). In 1972, *The New York Times* published articles exposing ethical atrocities associated with a Public Health Service study on the natural progression of syphilis in poor and largely uneducated African-American men in rural Tuskegee, Alabama. The study was only supposed to last about six months but the researchers were getting "good data" and decided to continue it. In the 1940s, when penicillin became widely available, researchers withheld treatment from the men.

These revelations spurred Congressional hearings. The resulting National Research Act in 1974 authorized the formation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission's charge included examination of the conduct of all federally sponsored human subject research in the United States and development of the philosophical and ethical principles that should govern scientific research with human beings as the test subjects. The Commission produced many reports, the most influential of which is the Belmont Report.

### The Belmont Report

The Belmont Report articulates three core ethical principles:

- **Respect for persons:** This principle concerns the ability of a person to direct his/her own actions. The requirement to obtain informed consent from prospective subjects is the practical translation of this ethical principle. Capacity to consent is also important. You must ensure that the person you are asking to undergo a clinical trial has the capacity to freely authorize his/her participation.
- **Beneficence:** This principle

requires a balance between minimizing harms by good study design and maximizing any benefits that might accrue to study participants.

- **Justice:** This principle asks us to take a broader view of the research. There should be an equitable distribution of benefits and burdens, with equitable subject selection. Sometimes implementing this principle can be daunting due to entrenched social inequalities and disparities that exist in our country and in the world.

Each of these principles is translated into specific requirements in all current regulations of the Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), and the International Conference on Harmonization (ICH).

Respect for persons is translated into the requirement to obtain informed consent from subjects before they participate in research. There are three components of a valid informed consent process: information, comprehension, and willful volunteering. There are several questions related to these components. How much information should be disclosed? We all know how long and complicated consent forms can be. Most are supposed to be written between a sixth- and eighth-grade level; I have seen few informed consent documents written at that level. How should complex medical information regarding risks be presented to subjects? The manner and context in which information is conveyed influences comprehension and can be as important as the information itself. The subject must make a free and uncoerced decision to participate (e.g., not to be pushed by family members, by the prospect of receiving reimbursement for participation, by free access to

investigational drugs, or by offers of free medical care).

The principle of beneficence asks us to balance the risks and benefits. Everyone needs to be involved in this—the investigator, the IRB, and subjects.

- The investigator must determine whether the research design is sound, and whether there are other ways to achieve the benefits of the research. Such determinations require thinking “outside of the clinical research box.” The IRB can often be a good source of information because it has seen so many protocols.
- The IRB must determine whether the risks are justified.
- The subjects have a responsibility to decide whether to risk any of the possible harms that are mentioned in the information presented to them.

The determination must be a “favorable” risk/benefit assessment. There is no one formula for conducting a risk/benefit assessment, and determining the balance is frequently difficult. In addition, investigators and subjects may confuse the severity of harm with the possibility of harm. There are five factors to consider in making a risk/benefit assessment:

1. Brutal/inhumane treatment is never justified.
2. Risks must be minimized. Ask whether human subjects are even needed. Technology might allow the use of in vitro models, computer software modeling, or tissue samples instead of human subjects.
3. A high probability of harm must be justified.
4. Involvement of vulnerable populations must be justified.
5. The relevant risks and benefits must be presented in the informed consent document.

Justice requires fair and equitable procedures in the selection of research subjects. Achieving justice in clinical research is sometimes difficult. Investigators should not offer beneficial research only to some individuals and select “undesirable” subjects for more risky research. To society, adults are preferred as subjects before children, and some classes of subjects (e.g., the mentally ill, people who are institutionalized, and prisoners) may not participate unless certain conditions pertain. The Belmont Report notes that we may not be able to eliminate deeply entrenched societal injustices, but efforts should be made to target as wide an audience as possible.

#### **TRANSLATION OF ETHICAL PRINCIPLES INTO REGULATIONS**

Sections 111 of both the FDA and DHHS regulations for the protection of human subjects outline criteria that the IRB must consider when determining whether research can be approved (Table 2):

1. Risks are minimized through a sound research design. The IRB can frequently help with research design. Investigators should respond to IRB research design suggestions as part of the IRB’s mission to ensure protection of human volunteers, not as interference in the science. Having someone who is familiar with research design to help craft the protocol is also a good idea; sponsors are generally good at designing their protocols. In addition, IRBs should have at least one member with research design expertise.
2. Risks are reasonable relative to anticipated benefits (the principle of beneficence).
3. Selection of subjects is equitable (the principle of justice).
4. Informed consent will be obtained and documented. Who will obtain informed consent? How will it be documented?

What sort of safeguards will be put into place so that people know the tests for which they are volunteering?

5. Data safety monitoring is adequate.
6. Privacy and confidentiality provisions are adequate.
7. Appropriate safeguards are included for vulnerable subjects.

In the background of each of these considerations are principles from the Belmont Report, the Declaration of Helsinki, or the Nuremberg Code. Since the IRB’s focus is to protect human subjects, including information about each of these required elements in a bulleted list within a protocol should make the IRB’s job easier.

**TABLE 2**  
**Translation of Ethical Principles into Regulations**

- Risks are minimized through a sound research design
- Risks are reasonable relative to the anticipated benefits
- Selection of subjects is equitable
- Informed consent will be obtained and documented
- Data safety monitoring is adequate
- Privacy and confidentiality provisions are adequate
- Appropriate safeguards are included for vulnerable subjects

#### **Informed Consent Requirements**

- Legally effective informed consent
- No coercion or undue influence
- Language understandable to the subject
- No exculpatory language where subjects waive or appear to waive legal rights

The principle of respect for persons is translated into requirements for informed consent (Table 2). “Legally effective informed consent” means ensuring that subjects have the legal right to consent for themselves or that an appropriate legally-authorized representative is used when the subject cannot consent for himself/herself. In recruitment, investigators and study coordinators must ensure that they introduce no coercion or undue influence in their presentation of the informed consent information. Language must be understandable to the subject and must not include exculpatory language where a subject either waives or appears to waive a legal right to which they would otherwise be entitled.

A written consent document is required. It must be in language understandable to the subject or the subject’s legally-authorized representative and signed by the subject (or the legally-authorized representative). A copy of the informed consent document must be given to the subject, who must have an opportunity to read the document before signing it.

**THE THERAPEUTIC MISCONCEPTION**

The therapeutic misconception can be a vexing ethical issue for obtaining valid informed consent (Table 3). The therapeutic misconception occurs when patients enrolling as research subjects misinterpret and perhaps even distort information about the research, such that they believe that aspects of the research will directly benefit them, or that there is a benefit at all. The term first appeared in the literature in 1987, when Paul Appelbaum and colleagues published “False Hopes and Best Data: Consent to Research and the Therapeutic Misconception” in the *Hastings Center Report*. The information in this article is based on that publication.

The therapeutic misconception is very common in Phase 1 oncology trials. It is rare for people to benefit from a dose-escalation trial. When you ask research subjects, even in Phase 1 studies, why they are enrolling, the literature on therapeutic misconception indicates that they frequently misconstrue the difference between research and treatment and wrongly believe that they will directly benefit from their participation in the Phase 1 study.

The therapeutic misconception is caused by a variety of factors.

- **Human nature (we hear only what we want to hear):** For example, people only hear “access to cutting-edge interventions” and “free medical care,” not “scientific research study.”

**TABLE 3  
The Therapeutic Misconception**

**Definition:**

- The therapeutic misconception occurs when patients enrolling as research subjects misinterpret and perhaps even distort information about the research, such that they believe that aspects of the research will directly benefit them

**Causes:**

- Human nature: we hear only what we want to hear
- The trenchant notion of “personal care” in clinical medicine: confusion of roles of physician as clinician and as researcher
- The confusing methods of science (randomization, use of a study protocol, use of placebos, blinding, and control groups)

- **The trenchant notion of “personal care” in clinical medicine (confusion of roles of physician as clinician and as researcher):** Any clinician who conducts a clinical trial must follow the protocol, in which the notion of personal care must usually be abandoned in order to properly follow the dictates of the scientific protocol.

- **The methods of science (randomization, use of a study protocol, use of placebos, blinding, and control groups):**

These concepts can be very confusing to subjects if they are not explained adequately. The notion of personal care is the physician’s first obligation. The physician makes decisions, with the patient’s input, that will benefit the patient most. The application of this shared decision-making model is not necessarily the case in a clinical trial. Moreover, the methods of human experimentation listed above may inhibit the application of personal care in clinical research in the following ways:

- There is always a chance that the subject’s interests may become secondary to the investigator’s scientific interests; and
- Randomizing subjects for the sake of good science negates the concept of “personal care” — the physician cannot determine which treatment a subject receives. Subjects who will be randomized often think they will get the treatment, not the placebo.

Appelbaum and his colleagues observed informed consent transactions on several psychiatry protocols. They found that research subjects systematically misinterpreted the risk/benefit ratio