

The Ethical Foundations of the Federal Regulations Governing Human Subjects Research in the United States

I. The Evolution of Human Subjects Protection

Three documents addressing the ethical conduct of research with human beings have provided the ethical foundation for the evolution of federal regulations for the respect and protection of human subjects in the United States. Two of these documents are international codes of conduct; the other document, the Belmont Report, provides an ethical framework to guide the preparation, analysis, and evaluation of biomedical and behavioral research proposals that are conducted within the United States.

A. International Developments

1. The Nuremberg Code

The Nuremberg Code was developed in 1947, following the Nuremberg trials of physicians and scientists who had performed horrifying experiments on prisoners during the Nazi era. It was the first internationally recognized ethical code for the conduct of human research. The thrust of this document is manifest in its first principle:

“1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.” (Nuremberg Military Tribunal, from *U.S. v. Karl Brandt*, et al., The Nuremberg Code, 1947)

Interestingly, prior to the rise of the Nazi regime, Germany had adopted a strong federal law in 1931 that set forth the obligations of physicians and the rights of human research subjects. Among other things, this law required special protections for groups of persons who were unable to protect their own interests as research participants. Physicians and scientists of the Third Reich set aside this law, performing experiments on human subjects with no regard for their autonomous consent or their wellbeing. Those who were conscripted as research subjects in Nazi experiments were treated as less than

full persons and as expendable in the pursuit of information that might benefit the Nazi regime.

In response to the abject disregard of the humanity, autonomy and interests of vulnerable persons and groups by the Nazis, the Nuremberg Code essentially ruled out the involvement of such populations in future research, including sick patients. As a result, the ten principles of the Nuremberg Code essentially read as rules for the conduct of research on “healthy volunteers.” Unfortunately, this provides no guidance on the questions of whether and how to involve persons who may be vulnerable, that is, compromised in terms of their ability to represent their own interests in deciding whether to participate in research.

2. The Declaration of Helsinki

In 1964, the World Medical Association issued the Declaration of Helsinki. This international code specifically focuses on medical research, acknowledges the multiple sources of vulnerability that must be taken into account in protecting research subjects, issues principles for the protection for the vulnerable who must sometimes be involved in such research, and prioritizes the duties of physician-researchers “to protect the life, health, privacy, and dignity of the human subject.” The Declaration of Helsinki is a living document: it has been amended five times, most recently in 2000. A much more complex code than the Nuremberg Code, the flavor of the Declaration of Helsinki is captured in one of its nine introductory principles:

“Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and in need of protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.” (World Medical Association, Declaration of Helsinki: Ethical Principles for Medical research Involving Human Subjects (Edinburgh: October 2000))

B. Research Ethics Developments in the United States

1. Continuing research abuses in the U.S.

Despite worldwide attention to the abuses of human research subjects following World War II, the development of the Nuremberg Code and the Declaration of Helsinki, and a 1964 policy change by the National Institutes of Health that all research funded by the United States Public Health Service be reviewed by an ethics committee, inadequate attention to the rights and interests of human subjects remained. In 1966, a landmark article appeared in the *New England Journal of Medicine* describing 22 examples of

unethical experimental medicine in the United States. In this article, Dr. Henry K. Beecher of the Harvard Medical School described instances of “experimentation on a patient not for his benefit but for that, at least in theory, of patients in general” in which consent was not obtained and/or patients were put at unacceptable risk. These experiments were hardly secrets buried deep in the past: Beecher had gathered them from recently published articles by leading researchers in U.S. medical journals. About them, he wrote:

“Human experimentation since World War II has created some difficult problems with the increasing employment of patients as experimental subjects when it must be apparent that they would not have been available if they had been truly aware of the uses that would be made of them....An experiment is ethical or not at its inception; it does not become ethical *post hoc* – ends do not justify means. There is no ethical distinction between ends and means.” (Henry K. Beecher, “Ethics and Clinical Research,” *New England Journal of Medicine* 274 (1966): 1354-60)

2. Steps toward regulation in the U.S.

In 1973, Senator Edward Kennedy led congressional hearings on the problem of unethical medical research in response to ongoing disclosures of the abuse of research subjects’ rights in both medical and behavioral research. These abuses violated a number of agreed upon ethical principles for the conduct of human research. For example, some experiments unjustifiably selected and failed to protect highly vulnerable groups of subjects (both institutionalized and non-institutionalized); some involved the deception of subjects or the violation a subjects’ privacy; and some even withheld known effective treatment from sick patients. Most seriously, one of the most egregious violations of respect, protection, and fairness to human subjects was a project of the U.S. Public Health Service from 1932-1972, the Tuskegee Syphilis Study. This project continued for 6 years after the National Institutes of Health had issued its policy requiring ethics review reflecting the principles of the two extant international codes discussed above.

The Congressional response came in 1974 with the passage of the National Research Act, which significantly changed the U.S. approach to regulating human subjects research in two ways. First, it established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (henceforth, the ‘National Commission’) to develop the ethical standards and regulatory principles and rules that would govern human research. Second, the National Research Act founded our current Institutional Review Board (IRB) system. The central requirement of this system is that research funded by the Department of Health, Education, and Welfare (DHEW) (now by the Department of Health and Human Services (HHS)) must be reviewed and approved for their adherence to regulations for the respect and protection of human subjects. This review and approval is to be conducted by a research review board constituted according to federal regulations within institutions doing research. These two creations of the National Research Act (the National Commission and the IRB structure) of course go hand in hand: a regulatory structure requires clear regulations if it is to function effectively and consistently.

3. The work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

a. Addressing the respect and protection of vulnerable populations

The National Commission began its work in 1975, immediately focusing on the identification of vulnerable populations of special concern (children, pregnant women, prisoners, and persons with dementia), and the development of ethical frameworks for the use of such populations to shape the federal regulations and guidelines applicable to each population.

b. Generating an ethical framework for human subjects research: *The Belmont Report*

From 1975-1978, the National Commission focused on frameworks protective of vulnerable subject populations. In 1978, The National Commission issued the Belmont Report - a modest 8-page document containing the foundational ethical framework for all federal regulations and guidelines concerning research involving the use of human subjects in the U.S.

The Belmont Report has not only provided the ethical cornerstone for human subjects research since then, it has shaped the field of bioethics' defining attention to patient autonomy. The significance of this document is hard to overstate. As an ethical framework, it models a strategy characteristic of the fields of bioethics and research ethics: that one reasons from a framework of ethical principles considered necessary and sufficient to ground a thorough analysis of a problem, and justification for a position, on an ethically-challenging situation or policy question in health care practice and human research. Because the Belmont Report is the ethical foundation for the U.S. regulations concerning human research, let us look closely at its three ethical principles, along with the rules and applications associated with each of them in the Report.

The authors of the Belmont Report intended to provide more general ethical principles, indeed, and adequate ethical framework, to use as the basis for the ethical analysis of questions arising in the conduct of human research. The previous codes (Nuremberg and Helsinki) consisted of specific guidelines or rules. The Belmont Report attempted to lay out the ethical grounding of those guidelines and rules. It did so in the form of three basic ethical principles: respect for persons, beneficence, and justice. Respectively, they derive from the ethical theories of Kantian ethics, utilitarianism, and theories of justice oriented to individual rights rather than social justice. The status and role of the three principles is explained in this way in the Report:

“These three [ethical principles] are comprehensive...and stated at a level of generalization that should assist scientists, subjects, reviewers, and interested citizens to understand the issues inherent in research involving human subjects. These principles cannot always be applied so as to resolve beyond dispute particular ethical problems. The objective is to provide an analytical framework that will guide the resolution of ethical problems arising from research involving human subjects.” (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the protection of Human Subjects of Research* (Washington, D.C.: Department of Health, Education, and Welfare, 1979).

4. The Common Rule

In 1981, the Department of Health and Human Services (HHS) promulgated the federal regulations for the respect and protection of human subjects Title 45, Part 46 of the *Code of Federal Regulations* (45 CFR 46). These regulations guide researchers in the development of their research proposals, and IRBs in their evaluation of them. On occasion, revisions are made to these regulations. There are many ethically contested issues in human subjects research – some of these issues were hinted at in the brief discussion of the Belmont Report above. In 1991, the regulations at 45 CFR 46 were adopted by 17 federal agencies. Because so many federal agencies now subscribe to 45 CFR 46, it is referred to as the Common Rule. Any institution engaged in human subjects research that is funded from a federal source is obligated to have an infrastructure in place for the evaluation of that research (an IRB infrastructure), and to adhere to the Common Rule in the evaluation, approval, and ongoing scrutiny of that research as it is being conducted. Most institutions choose to apply the Common Rule to all of the research done within their walls. Since some of the research done at St. Olaf College is funded from federal sources, St. Olaf’s compliance with 45 CFR 46 (in terms of its IRB infrastructure and its application of the Common Rule) is federally mandated. In addition, St. Olaf is strongly committed to the ethical review of all research done under the auspices of St. Olaf College.

II. *The Belmont Report: Principles for the Respect and Protection of Human Research Subjects*

A. Respect for persons

The first of the Belmont Report principles, respect for persons, requires in the main that we identify and honor the capacity for self-determination of anyone who is approached to participate, or who is participating, in human research. To do so, we must (i) treat individuals as autonomous agents, and (ii) protect persons of diminished autonomy.

Applying the principle of respect for persons, then, we must provide for informed consent to participation in the research project (either by the prospective subject herself

or a qualified surrogate). The duty to obtain informed consent to participation in research carries with it three requirements: information, comprehension, and voluntariness. For the present purpose, that of summarizing the requirements of the Belmont Report, it will suffice to say that in relation to every individual research proposal, special issues may arise in relation to any or all of these elements of informed consent. The crucial framing principle is the focus on enabling the individual to make an autonomous choice: what counts as sufficient information may vary from one person to another; assuring comprehension may require the conveying of information in multiple, and perhaps unique ways; and conditions that may compromise the voluntariness of consent must be addressed.

In recruiting subjects incapable of autonomous choice, the Belmont Report allows for the use of surrogate decision-makers. Of course, the same high standards of informed consent obtain. The task of such surrogates becomes that of either representing the presumed values and wishes of the potential subject (if that is possible), or representing their best interests.

B. Beneficence

The ethical principle of beneficence imposes two obligations: “(1) do not harm and (2) maximize possible benefits and minimize possible harms.” One of the primary commitments of this principle is to not harm an individual, even when the potential benefits to others might seem to be of overwhelming, overriding importance.

The other commitment of the principle of beneficence is a “favorable risk/benefit assessment.” Applying this principle, that is, performing the risk/benefit calculations required by it, is a complex and demanding task.

One of the problems with performing this calculation is the multi-factorial nature of benefit. Benefit from research participation may accrue to the subjects themselves, to others, or to “society.” How much risk (i.e., possibility of harm) is it ethically acceptable to invite potential subjects to assume, in exchange for what positive returns or benefits (either to themselves, to others, or to society)? What risk/benefit equation should we use to determine when it is ethical to offer participation in research as an option to a person? And, should that equation differ depending on the subject population in question?

To complicate matters more, risk is a matter of both probability and magnitude. How should the magnitude of harm and the probability of harm be factored into the determination that benefits have been maximized and risks have been minimized? The risk/benefit assessment the Belmont Report requires is that the *probabilities and magnitudes of possible harms* be weighed against the *anticipated benefits* of the research. The multi-factorial nature of benefit must somehow be calculated, and the types or risks must be considered. Risks may include risks of physical and psychological harm, legal, economic, and social harm; and of course the benefits in these categories must be identified and weighed as well.

C. Justice

The third principle in the Belmont Report's ethical framework is the principle of justice. Clearly, many of the abuses of research subjects both during and after WWII had not only dishonored individual autonomy and ignored the elements of beneficence, but also exploited vulnerable or marginalized individuals, groups or populations. The Tuskegee Syphilis Study is a prime example, among many others.

With the addition of the principle of justice to the ethical framework, it was clear that it was not only ethically required to identify and assess the favorability of the risk/benefit ratio in relation to research, it was equally important to assure that the distribution of the burdens (risks) and benefits of the research be fair. The burdens and benefits of research should be equally distributed so that those who bear the burdens of research also stand to receive its benefits, that potentially beneficial research be fairly accessible, and that risky research not be inequitably imposed. This required attention to the selection of subjects on both the individual and social levels: the Belmont Report called for fairness to individual subjects and social justice to classes of subjects in subject selection.

When this principle of justice was articulated in the Belmont Report, it stood against the exploitation of individuals and groups for the sake of others – it was more about eliminating the custom of unfairly distributing research burdens among those who lacked personal, economic, and social power than it was about assuring that research in the interests of marginalized or underrepresented groups be pursued. So the principle of justice, as articulated in the Belmont Report, was primarily about protecting the rights of some not to be used to benefit others only; not about rethinking the research agenda to address the needs and interests of groups/populations with less economic and social power.