Chapter 2
Ethics

This chapter examines the history and development of current human research subjects protections in the US by summarizing the significant ethical and regulatory documents: Nuremberg Code, Declaration of Helsinki, National Institute of Health's Policies for the Protection of Human Subjects, National Research Act, and the Belmont Report. This chapter further describes the boundaries between 'medical practice' and research and the basic principles for conducting ethical human subjects research.

2.1 Nuremberg Code

Modern human subjects protections began in 1948 with the Nuremberg Code developed for the Nuremberg Military Tribunal as standards by which to judge the human experimentation conducted by the Nazis. The Code captures many of what are now taken to be the basic principles governing the ethical conduct of research involving human subjects. The first provision of the Code states that "the voluntary consent of the human subject is absolutely essential." Freely given consent to participation in research is thus the cornerstone of ethical experimentation involving human subjects. The Code goes on to provide the details implied by such a requirement: capacity to consent, freedom from coercion, and comprehension of the risks and benefits involved. Other provisions require the minimization of risk and harm, a favorable risk/benefit ratio, qualified investigators using appropriate research designs, and freedom for the subject to withdraw at any time.

2.2 Declaration of Helsinki

Recommendations similar to the Nuremberg Code were made by the World Medical Association in its initial Declaration of Helsinki 1965. The current Declaration of Helsinki 2013 further distinguishes therapeutic from non-therapeutic research and restrict use of placebos in clinical trials, a position not accepted by the US.

2.3 National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

In July of 1974, the passage of the National Research Act established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission (established partly in response to outrage over the Tuskegee study funded by the U.S. Public Health Service) met from 1974 to 1978. In keeping with its charge, the Commission issued reports and recommendations identifying the basic ethical principles that underlie the conduct of biomedical and behavioral research involving human subjects and recommended guidelines to ensure that research is conducted in accordance with those principles. The Commission also recommended Department of Health, Education, and Welfare (DHEW) administrative action to require that the guidelines apply to research conducted or supported by DHEW. The Commission's report set forth the basic ethical principles that underlie the conduct of biomedical and behavioral research involving human subjects which is titled The Belmont Report.

Boundaries between Practice and Research

While recognizing that the distinction between research and therapy is often blurred, practice is described as "interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment, or therapy to particular individuals."

The Commission distinguishes research as "designating an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective."

The Report recognizes that "experimental" or innovative procedures do not necessarily constitute research, and that research and practice may occur simultaneously. It suggests that the safety and effectiveness of such "experimental" procedures should be investigated early, and that Institutional oversight mechanisms, such as medical practice

committees, can ensure that this need is met by requiring that "major innovation(s) be incorporated into a formal research project."

2.4 Belmont Report

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted its report titled *The Belmont Report: Ethical Principles and Guidelines for the Human Subjects of Research*. The Report sets forth the basic ethical principles underlying the acceptable conduct of research involving human subjects. Those principles, respect for persons, beneficence, and justice, are now accepted as the three essential requirements for the ethical conduct of research involving human subjects.

Respect for Persons

Informed consent, required by the moral principle of respect for persons contains three elements: **information, comprehension, and voluntariness**. First, subjects must be given sufficient **information** on which to decide whether or not to participate, including the research procedure(s), purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research.

Where persons with limited ability to comprehend are involved, they should be given the opportunity to choose whether or not to participate (to the extent they are able to do so), and their objections should not be overridden, unless the research entails providing them a therapy unavailable outside of the context of research. Each such class of persons should be considered on its own terms (minors, persons with impaired mental capacities, the terminally ill, and the comatose). Respect for such persons may require that the permission of third parties also be given in order to further protect these persons from harm.

Finally, consent to participate must be **voluntarily** given. The conditions under which an agreement to participate is made must be free from coercion and undue influence. IRBs should be especially sensitive to these factors when particularly vulnerable subjects are involved.

Beneficence

Closely related to the principle of beneficence, risk/benefit assessments "are concerned with the probabilities and magnitudes of possible harms and anticipated benefits." The Report breaks consideration of these issues down into defining the nature and scope of the risks and benefits, and systematically assessing the risks and benefits. All possible harms, not just physical or psychological pain or injury, should be considered. The principle of beneficence requires both protecting individual subjects against risk of harm and consideration of the benefits for the individual, as well as reasonably achievable societal benefits.

In determining whether the balance of risks and benefits results in a favorable ratio, the decision should be based on thorough assessment of information with respect to all aspects of the research and systematic consideration of alternatives. The Report recommends close communication between the IRB and the investigator and IRB insistence upon precise answers to direct questions. The IRB should: (1) determine the validity of the theory underpinning the proposed research; (2) distinguish the "nature, probability and magnitude of risk…with as much clarity as possible;" and (3) "determine whether the investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies."

Five basic principles or rules apply when making the risk/benefit assessment: (1) "brutal or inhuman treatment of human subjects is never morally justified;" (2) "risks should be minimized, including the avoidance of using human subjects if at all possible;" (3) IRBs must be scrupulous in insisting upon sufficient justification for research involving "significant risk of serious impairment" (direct benefit to the subject or "manifest voluntariness of the participation"), (4) the appropriateness of involving vulnerable populations must be demonstrated; and (5) the proposed informed consent process must thoroughly and completely disclose relevant risks and benefits.

Justice

The principle of justice mandates that the selection of research subjects must be the result of fair selection procedures and must also result in fair selection outcomes. The "justness" of subject selection relates both to the subject as an individual and to the subject as a member of social, racial, sexual, or ethnic groups.

With respect to their status as individuals, subjects should not be selected either because they are favored by the researcher or because they are held in disdain (involving "undesirable" persons in risky research). Further, "social justice" indicates an "order of preference in the selection of classes of subjects (adults before children) and that some classes of potential subjects (the institutionalized mentally infirm or prisoners) may be involved as research subjects, if at all, only on certain conditions."

Investigators, Institutions, or IRBs may consider principles of distributive justice relevant to determining the appropriateness of proposed methods of selecting research subjects that may result in unjust distributions of the burdens and benefits of research. Such considerations may be appropriate to avoid the injustice that "arises from social, racial, sexual, and cultural biases institutionalized in society."

Subjects should not be selected simply because they are readily available in settings where research is conducted, or because they are "easy to manipulate as a result of their illness or socioeconomic condition." Care should be taken to avoid overburdening institutionalized persons who "are already burdened in many ways by their infirmities and environments." Non-therapeutic research that involves risk should use other, less burdened populations, unless the research "directly relate(s) to the specific conditions of the class involved."

Chapter 3:

Federal Regulations and State Laws

Chapter Contents

3.1 – Department of Health and Human Services (DHHS)

3.2 – Department of Defense (DOD) / Department of the Navy (DON)

3.3 – Department of Justice (DOJ)

3.4 – Department of Energy (DOE)

3.5 – Department of Education (ED)

3.6 – State Laws that Apply to Human Subjects Research