

**EXHIBIT J**

---

# *Institutional Review Board Guidebook*

## \* INTRODUCTION \*

---

A. History of the Human Subjects Protection System  
B. The Belmont Report || C. Suggestions for Further Reading

---

### **A. THE HISTORY OF THE HUMAN SUBJECTS PROTECTION SYSTEM**

The modern story of human subjects protections begins 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. Similar recommendations were made by the World Medical Association in its *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*, first adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964, and subsequently revised by the 29th World Medical Assembly, Tokyo, Japan, 1975, and by the 41st World Medical Assembly, Hong Kong, 1989. The Declaration of Helsinki further distinguishes therapeutic from nontherapeutic research.

In the United States, regulations protecting human subjects first became effective on May 30, 1974. Promulgated by the Department of Health, Education and Welfare (DHEW), those regulations raised to regulatory status NIH's Policies for the Protection of Human Subjects, which were first issued in 1966. The regulations established the IRB as one mechanism through which human subjects would be protected.

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 met from 1974 to 1978. In keeping with its charge, the Commission issued reports and recommendations identifying the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and recommending guidelines to ensure that research is conducted in accordance with those principles. The Commission also recommended DHEW administrative action to require that the guidelines apply to research conducted or supported by DHEW. References for the Commission's reports are listed in Appendix 1 (General Bibliography). The Commission's report setting forth the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects is titled *The Belmont Report*, and is discussed in depth below.

In 1981, in response to the Commission's reports and recommendations, both the Department of Health and Human Services (DHHS, formerly DHEW) and the FDA promulgated significant revisions of their human subjects regulations. As Levine (1986) points out, these revisions "do not alter the general principles of IRB review as they had evolved over the preceding three decades. Rather, they are concerned with some of the details of what the IRB is expected to accomplish and some of the procedures it must follow" [p. 324].

The DHHS regulations are codified at Title 45 Part 46 of the Code of Federal Regulations. Those "basic" regulations became final on January 16, 1981, and were revised effective March 4, 1983, and June 18, 1991. The June 18, 1991, revision involved the adoption of the Federal Policy for the Protection of Human Subjects. The Federal Policy (or "Common Rule," as

it is sometimes called) was promulgated by the sixteen federal agencies that conduct, support, or otherwise regulate human subjects research; the FDA also adopted certain of its provisions. As is implied by its title, the Federal Policy is designed to make uniform the human subjects protection system in all relevant federal agencies and departments. The Federal Policy is discussed in depth in Chapter 2, Section A(i).

Additional protections for various vulnerable populations have been adopted by DHHS, as follows:

Subpart B, "Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women and Human in Vitro Fertilization" became final on August 8, 1975, and was revised effective January 11, 1978, and November 3, 1978.

Subpart C, "Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects" became final on November 16, 1978.

Subpart D, "Additional Protections for Children Involved as Subjects in Research" became final on March 8, 1983, and was revised for a technical amendment on June 18, 1991.

FDA regulations on the protection of human subjects are codified at Title 21 Parts 50 and 56 of the Code of Federal Regulations. Part 50, which sets forth the requirements for informed consent, became final on May 30, 1980, and was revised effective January 27, 1981, March 3, 1989, and June 18, 1991. Subpart C, which provides special protections for prisoners, was adopted on July 7, 1981; the effective date of Subpart C has been stayed until further notice. Part 56, which sets forth the provisions for institutional review boards, was adopted on January 27, 1981, with revisions to some sections effective February 27, 1981, March 3, 1989, and June 18, 1991.

Additional FDA regulations that are relevant to IRB review of research are Parts 312 (Investigational New Drug Application), 812 (Investigational Device Exemptions) and 860 (Medical Device Classification Procedures).

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, which met from 1980 to 1983, produced numerous reports on various aspects of medical ethics and biomedical and behavioral research. Its mandate with respect to the protection of human subjects was, first, to review the federal rules and policies governing human subjects research, and second, to determine how well those rules were being implemented or enforced. References for the President's Commission's reports are listed in Appendix 1 (General Bibliography).

Several excellent sources trace the history of human subjects research and the development of the IRB system as a mechanism for the protection of human subjects. An account of the history of human subjects research and the human subjects protection system in the United States can be found in David J. Rothman's *Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision Making* (Chapters 1-5 and Epilogue) and in Dennis Maloney's *Protection of Human Research Subjects*. Rothman details the abuses to which human subjects were exposed, culminating in Henry Beecher's 1966 article, "Ethics and Clinical Research," published in the *New England Journal of Medicine*, and ultimately contributing to the impetus for the first NIH and FDA regulations. Other equally useful sources include Robert J. Levine's *Ethics and Regulation of Clinical Research* (Chapter 14), Joan E. Sieber's *Planning Ethically Responsible Research*, Robert M. Veatch's "Human Experimentation Committees: Professional or Representative?," and William J. Curran's "Government Regulation of the Use of Human Subjects in Medical Research: The Approaches of Two Federal Agencies."

[Return to Top of Page](#)

## B. THE BELMONT REPORT

On September 30, 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research submitted its report entitled "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research." The Report, named after the Belmont Conference Center at the Smithsonian Institution where the discussions which resulted in its formulation were begun, 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 quintessential requirements for the ethical conduct of research involving human subjects.

*Respect for persons* involves a recognition of the personal dignity and autonomy of individuals, and special protection of those persons with diminished autonomy.

*Beneficence* entails an obligation to protect persons from harm by maximizing anticipated benefits and minimizing possible risks of harm.

*Justice* requires that the benefits and burdens of research be distributed fairly.

The Report also describes how these principles apply to the conduct of research. Specifically, the principle of *respect for persons* underlies the need to obtain informed consent; the principle of *beneficence* underlies the need to engage in a risk/benefit analysis and to minimize risks; and the principle of *justice* requires that subjects be fairly selected. As was mandated by the congressional charge to the Commission, the Report also provides a distinction between "practice" and "research." The text of the *Belmont Report* is thus divided into two sections: (1) boundaries between practice and research; and (2) basic ethical principles. The full text of the *Belmont Report*, which describes each of the three principles and its application, is provided in the Guidebook in Appendix 6; a summary follows.

### 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 designat[ing] an activity designed to test an 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" 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."

### Applying the Ethical Principles

**Respect for Persons.** Required by the moral principle of respect for persons (*see* definition, above), **informed consent** 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), their 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. Responding to the question of what constitutes adequate information, the Report suggests that a "reasonable volunteer" standard be used: "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. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation." Incomplete disclosure is justified only if it is clear that: (1) the goals of the research cannot be accomplished if full disclosure is made; (2) the undisclosed risks are minimal; and (3) when appropriate, subjects will be debriefed and provided the research results.

Second, subjects must be able to comprehend the information that is given to them. The presentation of information must be adapted to the subject's capacity to understand it; testing to ensure that subjects have understood may be warranted. 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. [*See* discussions on this issue in other sections of the Guidebook, including Chapter 6, "Special Classes of Subjects."] Each such class of persons should be considered on its own terms (*e.g.*, minors, persons with impaired mental capacities, the terminally ill, and the comatose). Respect for persons requires that the permission of third persons also be given in order to further protect them 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 (*see* definition, above), **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 not only the benefits for the individual,

but also the societal benefits that might be gained from the research.

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 presuppositions of the 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 inhumane 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" (e.g., 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 (e.g., involving "undesirable" persons in risky research). Further, "social justice" indicates an "order of preference in the selection of classes of subjects (e.g., adults before children) and that some classes of potential subjects (e.g., 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." Nontherapeutic research that involves risk should use other, less burdened populations, unless the research "directly relate[s] to the specific conditions of the class involved."

[Return to Top of Page](#)

## SUGGESTIONS FOR FURTHER READING

- **Beauchamp**, Tom L., and Childress, James F. *Principles of Biomedical Ethics*, 3d ed. New York: Oxford University Press, 1989.
- **Beecher**, Henry K. "Ethics and Clinical Research." *New England Journal of Medicine* 274 (1966): 1354-1360.
- **Curran**, William J. "Government Regulation of the Use of Human Subjects in Medical Research: The Approaches of Two Federal Agencies." In *Experimentation with Human Subjects*, edited by Paul A. Freund, pp. 402-454. New York: George Braziller, 1970.
- **Fried**, Charles. *Medical Experimentation: Personal Integrity and Social Policy*. New York: American Elsevier Company, 1974.
- **Levine**, Robert J. *Ethics and Regulation of Clinical Research*. 2d ed. Baltimore: Urban and Schwarzenberg, 1986. See especially Chapter 14, "The Institutional Review Board."
- **Maloney**, Dennis M. *Protection of Human Research Subjects: A Practical Guide to Federal Laws and Regulations*. New York: Plenum Press, 1984.
- **McCarthy**, Charles R. "Experience with Boards and Commissions Concerned with Research Ethics in the United States." In *Research Ethics*, edited by Kare Berg and Knut Erik Tranoy, pp. 111-122. New York: Alan R. Liss, 1983.
- **McCarthy**, Charles R. "Current Regulations for the Protection of Human Subjects." In *Alzheimer's Dementia: Dilemmas in Clinical Research*, edited by Vijaya L. Melnick and Nancy N. Dubler, pp. 13-18. Clifton, NJ: Humana

Press, 1985.

- **Marshall**, Ernest. "Does the Moral Philosophy of the Belmont Report Rest on a Mistake?" *IRB* 8 (No. 6, November/December 1986): 5-6.
- **Rothman**, David J. *Strangers at the Bedside: A History of How Law and Bioethics Transformed Medical Decision Making*. New York: Basic Books, 1991.
- **Rothman**, David J. "Ethics and Human Experimentation: Henry Beecher Revisited." *New England Journal of Medicine* 317 (No. 19, November 5, 1987): 1195-1199.
- **Sieber**, Joan E. *Planning Ethically Responsible Research: A Guide for Students and Internal Review Boards*. Applied Social Research Methods Series, vol. 31. Newbury Park, CA: Sage Publications, 1992.
- **Twenty Years After: The Legacy of the Tuskegee Syphilis Study**. *The Hastings Center Report* 22 (No. 6, November/December 1992): 29-40. Includes articles by Arthur L. Caplan, Harold Edgar, Patricia A. King, and James H. Jones.
- **U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research**. A complete list of the National Commission's reports and recommendations is provided in Appendix 1.
- **U.S. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research**. A complete list of the President's Commission's reports is provided in Appendix 1.
- **Veatch**, Robert M. "Human Experimentation Committees: Professional or Representative?" *Hastings Center Report* 5 (No. 5, October 1975): 31-40.

[Return to Top of Page](#)

[Return to Index Page](#)

---

Introduction