Chapter 1
Ethical and Regulatory Mandate for Protecting Research Participants

1. ETHICAL FOUNDATION: THE NUREMBURG CODE

The history of human subject protection in research can be traced back to the post World War II identification of the war-related research experiments conducted by Nazi physicians. The judgement rendered in this trial included a set of standards to become known as *The Nuremburg Code*. This Code was the "ethical yardstick" by which the defendants in these trials had been measured and their guilt determined. The Nuremburg Military Tribunal developed 10 principles as a means of judging their research practices known as *The Nuremburg Code* (see Table 1.1). The Code is significant because it established the necessity for requiring the voluntary consent of the human subject and assigns responsibility for the quality of the consent process on any individual "who initiates, directs, or engages in the experiment".

a) The Nuremburg Code Summarized
   i. The voluntary consent of the human subject is essential.
   ii. The experiment should yield fruitful results for the good of society, unprocurable by other means.
   iii. The experiment should be designed and based on previous animal experimentation and knowledge of the disease such that anticipated results will justify its performance.
   iv. The experiment should avoid all unnecessary physical and mental suffering and injury.
   v. No experiment should be conducted where there is a prior reason to believe that death or disabling injury will occur.
   vi. The degree of risk should never exceed the humanitarian importance of the problem.
   vii. The subject should be protected against even remote possibilities of injury, disability, or death.
   viii. The experiment should be conducted only by scientifically qualified persons.
   ix. The human subject should be at liberty to end his/ her participation in an experiment if the subject has reached the physical or mental state where continuation of the experiment seems to the subject to be impossible.

b) The scientist in charge must be prepared to terminate the experiment if there is probable cause to believe that continuation of the experiment is like to result in injury, disability, or death to the experimental subject.

2. ETHICAL FOUNDATION: DECLARATION OF HELSINKI

The Nuremberg Code's principles were later expanded to further protect subjects. *The World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects* (1964, last revision 2000) calls for prior approval and ongoing monitoring by independent ethical review committees.

a) Introduction

i. Research involving human subjects includes research on identifiable materials or identifiable data.
ii. Considerations related to the well-being of the subject should take precedence over the interest of science and society.
iii. Even the best medical methods must be challenged continuously through research on effectiveness, efficiency, accessibility, and quality.

iv. Vulnerable research populations need special protections, particularly those who are economically and medically disadvantaged as well as those who cannot consent for themselves, those who may be subject to duress, those who have no potential of benefiting personally from the research, and those for whom the research is combined with care.

b) Basic Principles for All Medical Research

i. The life, health, privacy, confidentiality, physical and mental integrity, and dignity of the human subject must be protected.
ii. Caution must be exercised in research, which may affect the environment. Additionally, the welfare of animals used for research must be respected.
iii. Research must conform with scientific principles, be formulated in an experimental protocol that is publicly available and be submitted for ethical review independent of the investigator or the sponsor.
iv. Research should be preceded by assessment of predictable risks, burdens, and benefits and should be conducted only if its importance outweighs the inherent risks and burdens to the subject.
v. Any investigation should cease if risks are found to outweigh potential benefits or if there is not conclusive proof of beneficial results.
vi. Research is only justified if there is a reasonable likelihood that the populations in which the research is conducted stand to benefit from it.
vii. Research subjects must be volunteers informed about the research aims, methods, funding sources, possible conflicts of interest, institutional affiliations, anticipated benefits, potential risks and discomforts, and the right to abstain or withdraw without reprisal. If written consent cannot be obtained, a non-written consent must be formally documented and witnessed.
viii. If the subject is in a dependent relationship with the physician or may be under duress, informed consent must be obtained from a qualified research team member, who is not engaged in the investigation and is completely independent of this relationship.
ix. Informed consent must be obtained from a legally authorized representative if the subject is a minor or is physically or mentally unable to consent. Assent of the subject must also be obtained. These groups should be included only if the research promotes the health of the population they represent and cannot otherwise be carried out.
x. Research should be conducted on individuals from whom it is not possible to obtain consent only if the condition preventing consent is a necessary characteristic of the research population. Consent to remain in the research should be obtained from the individual or legally authorized representative as soon as possible.
xi. Authors and publishers have an obligation to publish only research that is in accord with the Declaration of Helsinki's ethical principles.

c) Additional Principles for Reseach Combined with Medical Care

i. The benefits, risks, burdens, and effectiveness of a new method should be tested against the best current methods.
ii. At the conclusion of the study, every subject should be assured of access to the best methods identified by the study.
iii. Patients should be fully informed about which aspects of care are related to the research.
iv. When proven methods do not exist or have been ineffective in treating a patient, and with the patient's informed consent, the physician may use unproven measures believed to offer hope of saving life, re-establishing health, or alleviating suffering.

3. ETHICAL FOUDNATION: BELMONT REPORT

The identification of ethically questionable research resulted in legislation in 1974 (The National Research Act) calling for regulations to protect human subjects and the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to examine ethical issues related to human subject research. The Commission's final report, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (79 FR 12065, April 17, 1979), defines the ethical principles and guidelines for the protection of human subjects. The Belmont Report's most important contribution is its elucidation of three basic ethical principles.

a) Respect for Persons

Respect for Persons incorporates two ethical principles: first, individuals should be treated as autonomous agents and second, steps should be taken to protect individuals with diminished autonomy.

The principle of respect is applied in the consent process, assuring that individuals have the information required to make an informed determination about participation in research.

Vulnerable populations include individuals who have limited autonomy such that they cannot fully participate in the consent process or may be vulnerable to coercion in some situations. Regulations make provisions for specific populations such as prisoners, children, students, subordinate individuals and the decisionally-impaired; however, others may be determined vulnerable based on socio-economic circumstances or diagnosis.

The Prisma Health Institutional Review Board, as a function of its assessment of each study, will review circumstances and make determinations as required to the vulnerability of specific study populations.

b) Beneficence

According to the Belmont Report, "Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also making efforts to secure their wellbeing". Expression of beneficent actions include, do not harm, maximize possible benefits, and minimize potential harms. The principle of beneficence is reflected in regulations as a requirement to perform risk/benefit assessment.

c) Justice

Justice requires fairness in distribution. This implies that an injustice occurs when benefit to which a person is entitled is denied without good reason or some burden is unduly imposed. Justice is relevant to the selection of research participants at two levels, the social and the individual. It requires fairness in inclusion and exclusion criteria.

The Belmont Report also provides important guidance regarding the boundaries between biomedical research and the practice of medicine. The Prisma Health Human Research and Protection Program and the Prisma Health Institutional Review Board are guided in human subject research by the ethical principles set forth in the Belmont Report. All IRB members, IRB professionals, investigators, and research and support staff should be thoroughly familiar with and apply these most basic ethical principles in the approval and conduct of human subjects research.

4. DEPARTMENT OF HEALTH AND HUMAN SERVICES (DHHS) REGULATIONS

The federal regulations were directly derived from the ethical principles discussed above. In 1971, 17 federal departments and agencies adopted a common set of regulations called "The Common Rule", which governs human subjects research sponsored by the federal government. In May 1974, the Department of Health, Education, and Welfare (later divided to form the Department of Health and Human Services (DHHS) and the Department of Education) codified its basic human subjects protection regulations at 45CFR Part 46, Subpart A.

The equivalent FDA human subjects protection regulations govern drugs, biologics, and devices regardless of study sponsorship. The Common Rule has established three main protective mechanisms to include review of research by an institutional review board, required informed consent of participants, and institutional assurances of compliance.

Department/Agency	**CFR Citation**
Department of Agriculture	7 CFR, Part 1C
Department of Energy	10 CFR, Part 745
National Aeronautics and Space Administration	14 CFR, Part 1230
Department of Commerce	15 CFR, Part 27
Consumer Product Safety Commission	16 CFR, Part 1028
International Development Cooperation Agency, Agency for International Development	22 CFR, Part 225
Department of Housing and Urban Development	24 CFR, Part 60
Department of Justice	28 CFR, Part 46
Department of Defense	32 CFR, Part 219
Department of Education	34 CFR, Part 97
Department of Veterans Affairs	38 CFR, Part 16
Environmental Protection Agency	40 CFR, Part 26
Department of Health and Human Services	45 CFR, Part 46
National Science Foundation	45 CFR, Part 690
Department of Transportation	49 CFR, Part 11
Central Intelligence Agency	Executive Order
Social Security Administration	Authorizing Statute
Nuclear Regulatory Commission	10 CFR 35.6
Department of Homeland Security	Public Law No: 108-458.8306

5. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS

The FDA has codified informed consent (21 CFR Part 50), IRB (21 CFR Part 56), and child protection (21 CFR Part 50, Subpart D) regulations that are similar to the DHHS regulations. Additional FDA regulations relevant to the protection of human subjects addresses Investigational New Drug Applications (21CFR Part 312), Biological Products (21CFR Part 600), and Investigational Device Exemptions (21 CFR Part 812).

In general, FDA human subjects protection regulations apply to investigational and other research involving products regulated by the FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.

Prospective IRB review and approval is required for all clinical investigations and all other research involving products regulated by the FDA for human use, even when an Investigational New Drug (IND) or Investigational Device Exemption (IDE) is not required.