Ethical Framework and Operational Guidelines for the Conduct of Human Subjects Research

Nuremberg Code - 1947

The Nuremberg Code was one of the results of the Nuremberg Trials, brought on by the inhumane and unethical experiments conducted in Nazi concentration camps. Although the code did not carry the force of law, it was the first international document which advocated for voluntary participation and informed consent.

Ten points:

1. Voluntary consent of the human subject is absolutely essential
2. Must yield fruitful (meaningful) results and not be unnecessary
3. Human experiments should be based on prior animal experimentation and knowledge of natural history of the disease
4. Avoid all unnecessary physical and mental suffering and injury
5. No expectation of death or disabling injury from the experiment
6. Risk must not exceed benefit
7. Proper facilities must be provided
8. Only qualified scientists should conduct medical research
9. Must allow voluntary withdrawal
10. The scientist must be prepared to termination the experiment if continuing is likely to result in injury, disability, or death to the subject.

Declaration of Helsinki - 1964

The Declaration of Helsinki was developed by the World Medical Association as a set of ethical principles built off the Nuremberg Code. It is morally binding on physicians and made the first major impact on the research community.

The Declaration laid out 5 basic principles with additional operational procedures to assist in ethical research.

Basic Principles:

1. Respect for the individual
2. Right to make informed consent
3. Investigator's duty is solely to the patient/volunteer
4. Participant's welfare must always take precedence over the interests of science and society
5. Ethical considerations must always take precedence over laws and regulations.

Belmont Report - 1979

Following public outcry after the discovery of the Tuskegee Syphilis Study and complaints that the Nuremberg Code and Helsinki were difficult to interpret and inadequate to cover complex situations, the US Government drafted the National Research Act of 1974. This act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. They created the Belmont Report, which remains the basis for the US Department of Health and Human Services human subject protection regulations.

<u>3 Core Principles:</u>

1. Respect for Persons
    - Individuals should be treated as autonomous agents and vulnerable individuals should be protected
    - Autonomy through informed consent, voluntariness, and understanding
2. Beneficence
    - Maximize benefits and minimize risks
    - Do no harm
3. Justice
    - Individuals should receive fair and equal distribution of clinical research burdens
    - Selection of subjects is equitable

45 CFR 46 – "The Common Rule" - 1981

U.S. Department of Health and Human Services (DHHS) regulations based off the Belmont Report. The Office for Human Research Protections (OHRP) is responsible for the implementation of 45 CRF 46.

- Subpart A – The Common Rule – Fundamental guidelines for ethics of all human research; Governed IRBs
- Subpart B – Additional protections for research with pregnant women and fetuses
- Subpart C – Additional protections for research with prisoners
- Subpart D – Additional protections for research with children
- Subpart E – Requirements for IRB registration

ICH Good Clinical Practice – 1997

International Conference on Harmonization Good Clinical Practice (ICH-GCP) was developed as an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involved the participation of human subjects. The goal was to facilitate the mutual acceptance of credible and ethical clinical trial data on an international level so that applications for marketing to various regulatory agencies around the work can occur without redundant testing.

Endorsed by the FDA in 1997, ICH guidelines have been adopted into law in several countries. Although ICH guidelines are not law in the US, they are used as guidance in the form of Good Clinical Practice (GCP) and should be strictly followed.

<u>GCP training is required for all persons participating in NIH-funded or FDA regulated clinical trials.</u>