Chapter 14 Ethics of Clinical Research

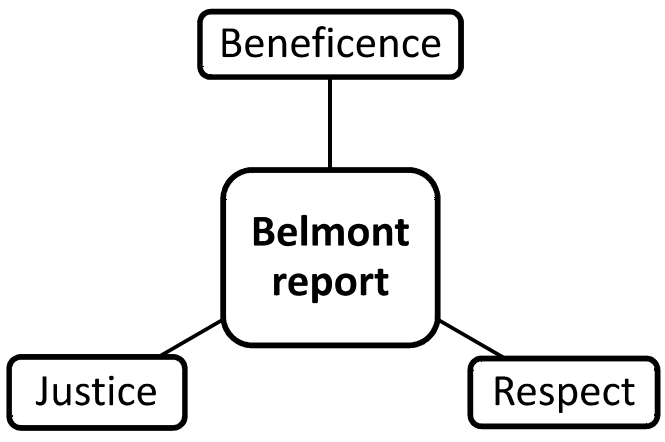
Historical Overview

Nuremberg Code of ethics (1947)

During the 2nd world war, Nazi doctors had done several crimes during human experiments on concentration camp prisoners. As a response of these Nuremberg Trials, the Nuremberg code of ethics was introduced in 1947 as a landmark document in the history of medical research ethics.

Belmont report (1976)[7]

The Belmont report was written by the national commission for the protection of human subjects of biomedical and behavioral research. It outlines three key ethical principles for conducting research with human subjects: respect for persons, beneficence, and justice.



Declaration of Helsinki

The declaration of Helsinki was adopted by the 18th general assembly of the world medical association in Helsinki, Finland, June 1964. It was amended several times in 1975, 83, 89, 96, 2000, 2002, 2004, 2008, and 2013. The declaration of Helsinki is currently the cornerstone of human research ethics in the world.

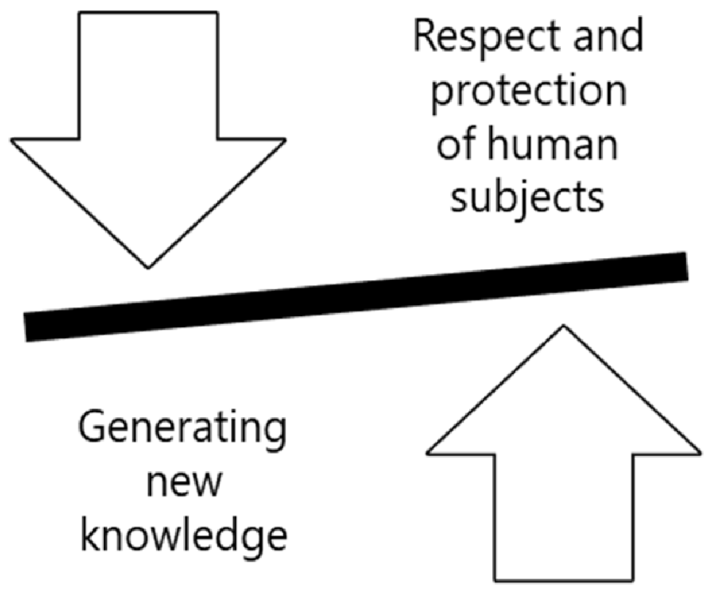
The key principals in the declaration of Helsinki

- DOH states the ethical principles of medical research involving human participants, human material, and human data.
- DOH is mainly directed to physicians and anyone who is involved in medical research on human subjects.
- Physicians main responsibility is the health of their patients, which comes in the first consideration. The International Code of Medical Ethics confirms that "A physician shall act in the patient's best interest when providing medical care."

[7] https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

- The purpose of medical research is to understand the causes, development, and effects of diseases and improve the preventive, diagnostic, and therapeutic interventions.
- All interventions must be evaluated continuously through research studies in order to ensure their safety and efficacy.
- Physicians are responsible for protecting the life, health, dignity, integrity, right of self-determination, privacy, and confidentiality of personal information of the research participants.
- Researchers should consider the ethical, legal, and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal, or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this declaration.
- Researchers who participate in medical research should be qualified ethically, educationally, and scientifically to do research. Research on healthy volunteers must be monitored by an approved and qualified physician.
- Underrepresented groups in the population should receive appropriate chances to participate in research.
- Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
- Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.
- In medical research, investigators should reduce the risk to a minimum.
- Benefits should outweigh the harm.
- Research must be preceded by careful evaluation of predictable risks to patients, or healthy volunteers enrolled in the study.
- During the study, risks must be monitored and documented by the researcher.

- If risks are found to outweigh potential benefits, investigators should modify or stop the study
- Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.



- Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
- All vulnerable groups and individuals should receive specifically considered protection.
- Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group, and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices, or interventions that result from the research.
- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
- The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
- The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
- In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.
- The research protocol must be submitted for consideration, comment, guidance, and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the

researcher, the sponsor, and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards, but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

- The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.
- Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.
- Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
- In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.
- After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
- All medical research subjects should be given the option of being informed about the general outcome and results of the study.
- When seeking informed consent for participation in a research study, the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations, the informed

consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

- For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.
- When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
- Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances, the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with the condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.
- The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
- For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage, and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations, the research may be done only after consideration and approval of a research ethics committee.
- The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best-proven intervention(s), except in the following circumstances:

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
- And the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best-proven intervention.
- Extreme care must be taken to avoid abuse of this option.
- In advance of a clinical trial, sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.
- Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
- Researchers, authors, sponsors, editors, and publishers all have ethical obligations about the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results, must be published or otherwise made publicly available. Sources of funding, institutional affiliations, and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.
- In the treatment of an individual patient, where proven interventions do not exist, or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, reestablishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Patient rights

- Autonomy
- Informed consent
- Beneficence
- Non-maleficence
- Justice
- Confidentiality

Informed Consent

Consent involves the procedure by which an individual may choose whether to participate in a research study or NOT.

Direct Consent	Substitute (Third Party) Consent
• Agreement obtained directly from the person involved in the study • Most preferred	• Given by someone other than the person involved in the study • When? A person not having the capacity to make decisions or is dependent on others for his welfare. • Who? Children People with cognitive or emotional disabilities.

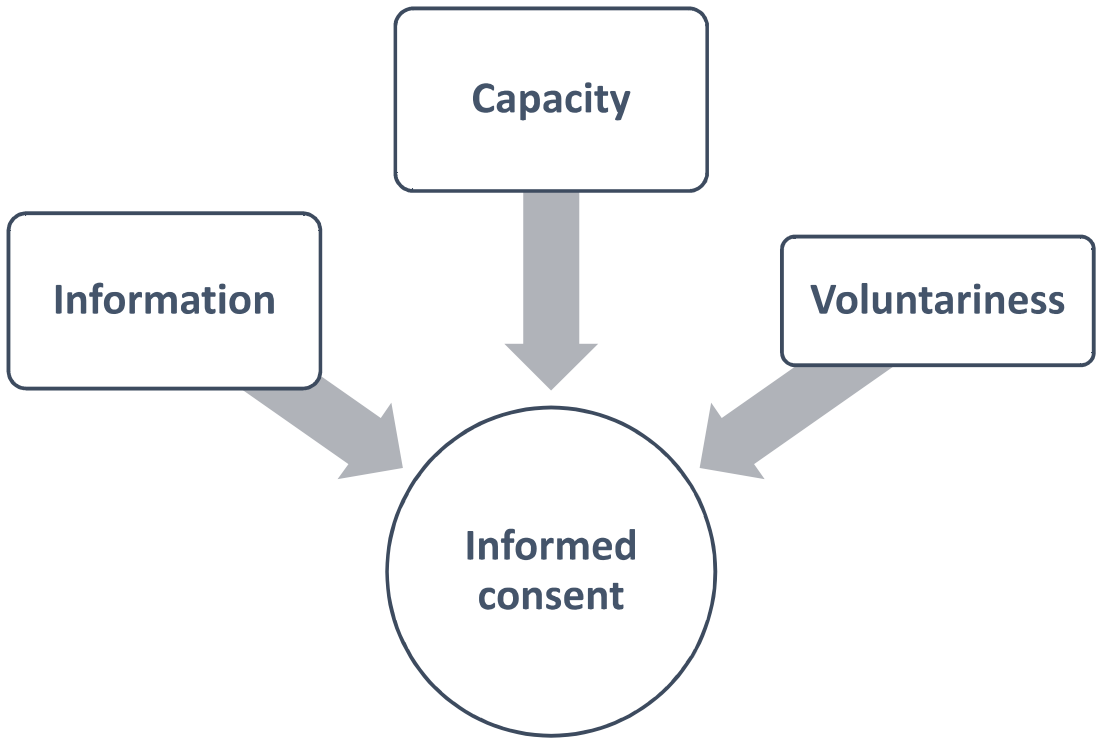
Elements of the informed consent

[1] Capacity

The patient/ person involved should have the capacity to evaluate the information received and make his own choice based on his evaluation

Is the person competent or incompetent?

This is based on his ability to acquire, retain and evaluate information



Incompetent Persons

- Children
- Patients with cognitive or emotional disabilities
- Incarcerated patients

Rights are legally protected by obtaining permission from parents or legal guardians

[2] Information

- What is the information given?
- How was it presented?

The information must be planned and presented by the researcher in a way, making it fully understandable by the participant.

[3] Voluntariness

The free power of choice without intervention of force or threat