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Declaration of Helsinki: The ethical cornerstone of human clinical research

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The Declaration of Helsinki was adopted in June 1964 in Finland. What is this document and why was it adopted by the World Medical Association (WMA)?[1]

EVENTS LEADING TO THE DECLARATION OF HELSINKI

During the Second World War, vulnerable populations and inmates of concentration camps[2] were subjected to a range of vile and lethal procedures in the guise of medical research. Leading academicians and scientists were responsible for legitimizing the devaluation of human life and setting the stage for medical crimes.[3] These heinous war crimes culminated in the landmark Nuremberg trial in Germany in 1946.[2] The name was derived from its aptly chosen locale, Nuremberg, that housed Hitler's Palace of Justice, including large courtrooms and an adjoining prison.

During this trial, the essential obligation of the physician to the human subject of research was defined for the first time. Ten directives for human experimentation were issued which came to be known as the Nuremberg code. It was the first international standard to outline the basic principles governing the ethical conduct of research on humans and has had a profound impact on human experimentation.[4] The Nuremberg code sowed the seeds for the Helsinki Declaration.[3]

FORMATION OF THE WORLD MEDICAL ASSOCIATION

While this storm of medical crimes raged, the need to form a world body that would define and promulgate medical ethics throughout the world was acutely felt. Thus was conceived the World Medical Association (WMA) around the year 1947. All the internationally accepted ethical declarations that guide the medical profession worldwide, including the Declaration of Helsinki, stem from the WMA.[5] The intention of the WMA is to ensure that not only are the ethical declarations taught at medical schools and discussed by practicing doctors all over the world, but that they are in daily use.

ESSENCE AND KEY FEATURES OF THE DECLARATION OF HELSINKI

This document has become the ethical cornerstone of biomedical research in humans over the past 40 years.[6] Its main focus is on protecting a patient's interest and well being, and spells out detailed guidelines to ensure the same. It places the entire responsibility of safeguarding the patient's health, privacy and dignity on the physician. Thus, in a sense, it rewrites the Oath of Hippocrates, in the spirit, "of causing no harm to patients". Key elements of the Declaration of Helsinki are discussed below.

Patient safeguard before advancement of science

In human research, the interest of science and society should never take precedence over considerations related to the well being of the subject. The interests and safeguard of patients come first. It categorically disallows the liberty to investigators for asking patients/volunteers to make sacrifices for the greater good of

mankind.[7] This is at odds with the theory of utilitarianism which states that any action is justified if it benefits the majority.

Informed consent – the pivotal element in the Helsinki declaration

A healthy volunteer or patient must not be led into a study unawares. He should be equipped with enough and appropriate information so that he is in a position to volunteer for study of his own free will. It is the duty of the investigator to share and explain thoroughly the details of the drug being used, the possible risks involved, his right to withdraw from the trial and his right to compensation in case of adversities.

A patient's rights must be spelt out clearly in the informed consent form, which must be provided to him in a language he best understands. Endless questions may be raised about what counts as full consent or sufficiently informed consent. Patients may find it difficult to grasp the concept of randomization and other clinical research parlance. This quandary can be minimized by tactful and sympathetic dialogue with potential subjects, not forgetting the moral dictum of preventing patient exploitation.[8]

The patient is required to give his informed consent voluntarily, without duress, before enrollment into a trial, i.e. before any trial-related investigation is conducted to test his eligibility for the trial, in the presence of an independent witness. Informed consent should not be regarded as just a signature at the bottom of a form. It is about the dignity and empowerment of trial subjects and the genuine participation of patients in research, a partnership.[8]

The Declaration permits the use of children as subjects, provided the permission of the subject's legal guardian is obtained.[4] Even in cases of critically ill patients and mentally incapable individuals, consent by proxy should be sought.[9] It clearly specifies that people who cannot give informed consent should be included in research only under exceptional conditions.[14] A let out clause allows physicians to do without informed consent,[10] but the specific reasons must be stated in the protocol for transmission to the Ethics Committee for review.

The onus of clinical research and patient safeguard rests solely on the investigator

Research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of research, even though the subject has consented.[11] The investigator must be adequately equipped to handle any side effects.

The protocol should be reviewed by the Institutional Review Board (IRB)

The Declaration of Helsinki stresses that the design and performance of the study should be clearly formulated in an experimental protocol. This protocol must be scrutinized by a specially appointed independent committee of experts (Ethics Committee) or Institutional Review Board (IRB). The Committee should be provided with information regarding funding, sponsors and other potential conflicts of interests and incentives for the subject. The committee also has the right to monitor ongoing trials. It is the duty of the investigator to furnish them with all details.

Placebo-controlled studies - generally not allowed, permitted only under specific circumstances

Consolidating on the tenet of safeguarding patient interest further, the declaration explicitly forbids use of a placebo group if an accepted treatment exists. It is mandatory to compare the drug under study to the best available treatment. In any medical study, all patients, including those of a control group, should be assured of the best-proven diagnostic and therapeutic methods.

It, however, does not rule out the use of a placebo where no satisfactory treatment is available. Also, a

clarification of the Declaration of Helsinki issued in October 2001 states that a placebo control may be ethically acceptable when there is a scientifically sound methodological reason or the study involves a minor condition with no additional risk of serious harm.[12] This is in contrast to the US FDA regulatory requirements, which actually encourage placebo comparisons. This clause against indiscriminate placebo use is relevant from the practical sense too. When a new treatment comes along, clinicians want to know whether it is better than the old one.[7] No scientific mind would be content in knowing whether the new treatment is more or less effective than nothing.[13]

Guidelines with regard to publication

In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results.[1] A journal editor may reject all studies that do not include informed consent[9] or are not in accordance with the principles laid down in this declaration.

REVISIONS OF THE DECLARATION OF HELSINKI

The Declaration of Helsinki has been revised time and again since new technologies present new ethical challenges not traditionally covered by medical ethics. The fifth revision, in October 2000, emphasizes in much clearer terms than ever before, the duty that doctors owe to the participant in medical research. It adds that every patient entered into a study should have access to the best treatment identified by the study, after the study is completed. Further, it is obligatory on the part of the investigator to declare any financial or potential conflict of interest.[14]

In fact, a recent Washington Post investigation into research in developing countries revealed "a booming, poorly regulated, testing system that is dominated by private interests, and that far too often betrays its promises to patients and consumers".[15] The fifth revision takes cognizance of this fact and tries to preempt the potential for "exploitation" of this largely illiterate and vulnerable population.

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This is the first in a series of guest articles that introduce our readers to various aspects of research methodology. Appropriate ethical evaluation is a pre-requisite for any research. Hence, we begin this series with an article on the Declaration of Helsinki, which is the guiding document for researchers all over the world. If you wish to contribute an article on any aspect of research methodology, please send an e-mail to editor@ijdvl.com