



The Declaration of Helsinki - The cornerstone of research ethics

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The modern era of oncology is dominated by data arising from cancer clinical trials. Research ethics guidelines are needed to help investigators to protect the rights and welfare of human participants involved in research, to promote the adherence to the ethical and scientific principles underlying research and to allay public concerns about the responsible conduct of medical research. Three fundamental ethical principles underlying research that involves humans are respect for persons, beneficence and justice. The Declaration of Helsinki (DoH), developed by the World Medical Association (1964), is the most widely accepted code of research ethics. The DoH has been revised five times, the last time by the 52nd WMA General Assembly in Edinburg, Scotland (October, 2000). The distinction between therapeutic ("clinical") and non-therapeutic research, the standards of care ethically required when research is combined with medical care and the ethics of placebo-controlled trials were three major points of discussion. In the revised version of the DoH, the WMA holds its main position to serve and protect human participants from potentially harmful research projects, while at the same time encouraging their involvement in ethical and scientifically valid research aiming to challenge and improve the understanding and treatment of disease.

KEY WORDS: *Clinical trials; Research; Helsinki Declaration; Ethics, Medical*

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INTRODUCTION

Clinical trials are the most widely accepted tools in the search for more effective prophylactic, diagnostic or therapeutic procedures in oncology. A clinical trial is defined as an experiment on humans, being carried out in order to answer a precisely defined scientific question (s) and to find better ways to prevent, diagnose, or treat cancer (1,2). The research involving human participants must be conducted in accordance with the standards of research ethics that promote and protect their rights and welfare.

Fundamental ethical principles

Three fundamental ethical principles underlying research involving human participants are respect for persons, *beneficence and justice* (3).

The principle of *respect for persons* ("respect a person's wishes") incorporates two ethical convictions: a) respect for autonomy: potential participants should be treated as autonomous beings, capable of making an informed decision whether to participate in a research and b) persons with diminished autonomy are entitled to additional protection. The implementation of this general principle is the requirement for informed consent of each potential participant.

The principle of *beneficence* ("do the most positive good") obligates the investigator to maximize benefits and minimize harm that might occur from the research. The principle finds expression in the requirement for risk/benefit assessment and balance before and during the research.

The principle of beneficence relies on Hippocratic principle of *non-maleficence* ("do no harm") which, applied to the field of medical research, means that one should not injure one person regardless of the benefits that might come to others.

The physician's fundamental duty is to do his best to protect rights and welfare of people in their research projects. In other words, the goals of research should always be secondary to the welfare of research participants. In the Declaration of Geneva of the World Medical Association (WMA) it is written: "The health of my patient

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will be my first consideration" (4). The International Code of Medical Ethics states that "a physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient" (4).

The principle of *justice* ("be fair") requires that we select participants fairly and without bias. Individual participants or communities should be selected in such a way that the risks of the research are equally distributed and benefits will be equally enjoyed. The principle finds its application in fairness in the selection of individual research participants and in the protection of vulnerable communities / groups.

The Declaration of Helsinki

The Declaration of Helsinki (DoH) is the cornerstone statement of ethical principles in biomedical research (5). The full title of the DoH is "Ethical Principles for Medical Research Involving Human Subjects". It was adopted by the 18th WMA General Assembly in Helsinki (1964) as a set of principles to guide physicians and others engaged in medical research to protect human participants and conduct their research in an ethical manner.

Historically, the DoH stems from the Nuremberg code (6), which was written as a reaction to the horror of the Nazi experiments during the Second World War. In 1946, 23 Nazi physicians and administrators were indicted before the Nuremberg war crimes Tribunal for their willing participation in the systematic torture, mutilation, and killing of the concentration camp prisoners in biomedical experiments. During the Trial, the Nuremberg code was drafted as a set of standards for judging physicians and scientists about ethics of their experiments. Despite the arguments that experiments were medically justified, the Nuremberg Tribunal condemned them as "crimes against humanity"; the physicians were found guilty and imprisoned or were sentenced to death. In the 1947 verdict, the judges included a section called "Permissible Medical Experiments", with a set of ten conditions to be met before research could be deemed ethically possible. This section became known as the Nuremberg code of 1947 (6). The Nuremberg code was the first international standard of human experimentation ethics.

The DoH (5) was developed by medical community in response to the Nuremberg code to refocus the physicians on their fundamental duty to safeguard the welfare of people in their research projects:

"It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty" (paragraph 2), and to affirm the WMA position that responsible conduct of ethical human research is the basis for medical progress:

"Medical progress is based on research which ultimately must

rest in part on experimentation involving human subjects. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society" (paragraph 5)

Since it was drawn up in 1964, the DoH has been revised five times, the last time by the 52nd WMA General Assembly in Edinburgh, Scotland (October, 2000). Last revision of the DoH caused one of the most thorny debate and polarization in the medical community (7-11). The need for the distinction between therapeutic ("clinical") and non-therapeutic research, the standards of care ethically required when research is combined with medical care and the ethics of placebo-controlled trials were three major points of discussion (9).

The revised DoH (5) consists of 32 paragraphs arranged in introduction (part A), basic principles for all medical research (part B) and additional principles for medical research combined with medical care (part C). Previous distinction between therapeutic ("clinical") and non-therapeutic research is rejected (see arguments for in ref. 8).

The goal of this paper is not to retell the paragraphs of the DoH; the reader must refer to the original document. Important ethical principles and procedures will, however be highlighted and interpreted. To achieve this objective other international research ethics guidelines (2,3,12,13), as well as two recently published reports (9,14) on the revision, interpretation and implementation of the revised DoH were used as a reference.

BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH (paragraphs 10-27)

"It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject" (paragraph 10).

The importance of good research design formulated in an experimental protocol (paragraphs 11-14). Medical research involving human participants should be scientifically sound and properly designed to permit valid conclusions (1,2). Scientifically unsound research exposes participants to risk to no purpose. The research question should be formulated after detailed review of all existing scientific data, other relevant literature and results of preliminary testing. All aspects of a research (the rationale, the objective and procedures designed to reach the objective) should be prospectively described in an experimental protocol. The research protocol should always contain a statement of the ethical considerations involved and should indicate that it is compliant with the principles of the DoH (5).

Qualifications/competence of the research investigator (paragraph 15). The investigator should be medically qualified and trained in research methods and principles of research ethics to assume responsibility for proper conduct of the research, medical

care and protection of human participants (2,13).

Risk/benefit assessment and balance (paragraphs 16-18). The principle of *beneficence* forbids the imposition of unwarranted risks on human research participants.

"Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject" (paragraph 18).

It obligates the researcher to perform a careful assessment of predictable risks and foreseeable benefits before and to monitor risk/benefit balance during the research (3). The term "risk" refers to the possible harm (its nature, probability and magnitude); the "benefit" could be individual (something that could improve individual health or well-being) or societal (the acquisition and the improvement of medical knowledge). Every research must be preceded by sufficient preliminary testing (laboratory, animal or human experiments) and the researcher must decide when it is justifiable to perform a research seeking for certain benefits despite the involved risks and burdens. The researcher should terminate the ongoing investigation if the risks outweigh the potential benefits or if positive and beneficial result has been identified. The principle of *beneficence* requires that we protect human participants against risk of harm to but also that we should be concerned about the loss of the societal benefits that might be gained from research (3). However, in the interest of securing benefits for science and society no individual shall be intentionally injured.

Informed consent of prospective participants (paragraphs 22, 23). "The subjects must be volunteers and informed participants in the research project" (paragraph 20).

The requirement for informed consent is the application of general principle of respect for persons (3). Potential participants should be given the opportunity to choose, to the extent they are capable, whether or not to participate in a proposed research. A potential participant commit and consent to participate after he/she has been adequately informed about the research, has understood the information and the right to refuse to participate or to withdraw from the research at any time without penalty and loss of any entitlement (12). Preferably, the consent should be given in writing. A participant's signature on the written consent document indicates that he/she has voluntarily decided to participate in the research having read and discussed the information presented.

The process of obtaining informed consent of subjects is, thus, based on three elements: information, comprehension and voluntariness (12,13). The DoH (5) has established essential items of information for potential participants to ensure that they are adequately informed about the research. The information should be presented in non-technical language, consistent with maturity, educational level and cultural views of the potential participants.

The investigator is responsible for ascertaining that the information has been understood. Also, the investigator should ensure that the consent is truly voluntarily given, free of coercion or undue influence.

Protection of a legally incompetent participant or a participant incapable of giving consent (paragraphs 24 - 26). Although the informed consent is a central requirement for ethical research, there are situations when the participant is incompetent or incapable of giving consent (12). Children, for example, are legally incompetent of giving consent. The capacity could also be limited by some physical or mental conditions (i.e. mentally disabled patients, the terminally ill, the comatose patients). In such situations, the DoH (5) allows for surrogate consent from a legally authorized representative. When a participant is legally incompetent but able to give assent to decisions about participation in research, the principle of *respect for persons* requires that investigator must obtain that assent in addition to the consent of a legally authorized representative.

The research participants unable to give valid informed consent are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.

The DoH (5) further states (in accordance with the principle of *justice*) that research on legally incompetent participants should only be conducted when the research is necessary to promote the health of the population represented, and when this research cannot be performed on legally competent persons. Similarly, research on participants with physical / mental condition that renders them unable to give informed consent is allowed only if the condition is a necessary characteristic of the research population.

The role of an independent ethical review committee (paragraph 13). Together with the investigator's responsibility to protect research participants and the requirement for informed consent, an independent ethical review committee (ERC) provides an additional assurance that participants are protected. The ERC is responsible for reviewing the scientific and ethical justification for proposed research, the informed consent process, and the qualifications / competence of the investigator / research team (13). After the review the ERC gives its guidance and, where appropriate, approval. Before initiation, each research project must be approved by the ERC. The ERC has also the right to monitor the ethics of ongoing projects. The investigator has the obligation to communicate with the ERC and to submit all documents and information necessary for the review.

Safeguarding privacy of research participants and confidentiality of research data (paragraph 21). Patients have the right to expect that their physicians will hold all information about them in strict confidence unless they have given consent to a disclosure of such information. Also, the research may involve the col-

lection and storage of data that, if disclosed to third parties, could cause harm or distress. Investigators should maintain the privacy of research subjects including their personal identity and all personal medical information. The investigator should also prevent the disclosure of research data to other than authorized individuals. Informed consent should contain a statement describing to what extent medical and research records will be kept confidential, including examples of those who may have access to the records.

Ethical obligations of authors and journal editors (paragraph 27). In publication of the research results, both authors (investigators) and journal editors have ethical obligations: "Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication" (paragraph 27).

Request for public scrutiny and transparency regarding economic incentives involved in research (paragraphs 13 and 16). The DoH (5) requires that the design of all studies should be made publicly available and calls for absolute transparency regarding economic incentives involved in research.

ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE (paragraphs 28 - 32)

"The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects"

The DoH (5) contains additional ethical principles for protection of patients who are participants in medical research combined with medical care (when, for example, the goal is to evaluate the safety and efficacy of a new treatment) (7-9). This kind of research (frequently called "clinical") is justified by the expected direct (prophylactic, diagnostic or therapeutic) benefit to the individual patient.

The standard of care ethically required in the control group and the use of a placebo (paragraph 29). Paragraph 29 of the DoH (5) addresses the standard of care ethically required in the control group and the use of a placebo in randomized clinical trials. The DoH states that any (prophylactic, diagnostic or therapeutic) method being tested should be compared with "the best current method". The use of placebo (or no-treatment) control group is

ethical only when there is no established (standard) method available. The use of placebo or no-treatment control is prohibited in a setting where proven, effective method already exists.

The paragraph 29 is in accordance with an essential ethical requirement for a randomized clinical trial- a state of equipoise (15). A state of equipoise is a state of "genuine uncertainty" which of two methods to be compared is superior. Usually, a researcher expects the new method to be better, but there should be no *solid scientific* evidence for its superiority. If a proven, effective method already exists (which by definition is superior to placebo) the equipoise is only possible when the new method is compared with the established one. Besides, the essential question of importance for a physician is how the new method compares with the established one, not with nothing (16).

The paragraph 29 of the DoH (5) runs counter to traditional thinking that a placebo-controlled trial is a "gold standard" for rapidly obtaining clear data about safety and efficacy of a new method (8). Comparison with active control requires larger and longer studies with more complicated design and less reliable results. Drug-approval agencies (especially Food and Drug Administration) and sponsors of clinical research argue that the DoH is too restrictive: rapidly obtaining a reliable result to an important research question is the primary ethical obligation. Longer and larger studies would increase human participants risk and delay patient access to new potentially beneficial methods (17,18).

However, the ethical standards should not be lowered due to the sense of urgency. Scientific considerations should not take precedence over ethical ones and they must not weaken the basic principle of *beneficence*.

Above mentioned arguments are more in accordance with marketing principles and less with the basic principle of researcher's commitment to an individual patient (7,10,16) and may represent a shift to an efficiency-based standard of research.

The best international standard of care and not the local one should be taken as a reference when deciding what is the best current method. This is important, especially with the internalization of medical research. If, for example, a trial is conducted in developing country, should the standard of sponsoring country (Western standard) or existing local standard be used (19, 20)? If the local standard is no treatment (and this, unfortunately, is frequent in poor communities) this would give the investigator the opportunity to conduct a placebo-controlled study in country A which perhaps could not be conducted in country B. In other words, it could mean that a research that is unethical in country B can be ethical in country A and, unfortunately, lead to exploitation of population in country A for research projects that could not

be carried out in country B.

The use of local standard as a reference is advocated with the explanation that, unfortunately, poor nations could not afford all the health care available to industrialized nations and must therefore be allowed to develop the treatments they could afford. In addition, the research undertaken in a particular country should be relevant to the local health care needs and conditions (see controversy over the ethics of HIV-trials in Africa: 19,21,22). The position of the WMA, however, is that the "standard of care" should be universal and that the same ethical guidelines should apply wherever research is being conducted (23) (see also below).

Protection of research participants in developing countries (paragraphs 19, 29 and 30). The pressing need for new drugs and the internalization of research has brought the ethics of research in developing countries into focus (19,20,24-27). In the revised DoH (5), the issue of protection of human participants in developing countries was given particular attention.

The population in these countries is disadvantaged in various ways (medically, politically, economically, socially, technologically, etc.) and is considered vulnerable. The WMA was particularly concerned about protecting developing countries from being exploited for research sponsored by companies from developed countries (19,21,22). Dr. Anders Milton, chairman of the WMA, said: "Research should not be carried out in countries in development just because it is cheaper and the laws are more lax. The same ethical rules should apply wherever research is being conducted" (28).

In the revised version of the DoH, research participants from developing countries are protected by requirement for comparing of any new method against the best international standard (paragraph 29). This will ensure that they would get access to the best current prophylactic, diagnostic or therapeutic method if they agreed to take part in a research. The concept is further extended by the requirement for researchers and sponsors to ensure access to the best proven method identified by the study to the research participants at the study conclusion (paragraph 30).

The WMA encourage the internalization of research but also guard against the exploitation of people in developing countries for research that would only improve the practice of developed countries (paragraph 19). This is in accordance with the general principle of *justice*.

The dual responsibility of a physician-investigator (paragraph 31). In a research combined with medical care the physician and a patient have additional roles of investigator and research subject. The physician's fundamental responsibility is to act as a healer and safeguard the rights and welfare of the patients partic-

ipating in his/her research project. Additional role of research scientist must never interfere with the therapeutic patient-physician relationship.

CONCLUSION

In conclusion, medical progress is inevitably based on experimentation on human beings. Research ethics guidelines are needed to help investigators to protect the rights and welfare of human participants involved in research, to promote the adherence to the ethical and scientific principles underlying research and to allay public concerns about the responsible conduct of medical research.

The DoH is the most widely accepted statement of ethical principles for medical research involving human subjects. Due to significant changes in the field of medical research (the growth of research conducted by for-profit organizations, the introduction of efficiency-based marketing principles and the internationalization of research) the WMA has revised the 1996 version of the DoH (9,14,29). In the revised version the WMA holds its main position to serve and protect human participants from potentially harmful research projects, while at the same time encouraging their involvement in ethical and scientifically valid research aiming to challenge and improve the understanding and treatment of disease.

"In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published" (paragraph 32).

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