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Ethics and regulatory aspects in medical research

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The article describes the development of ethical and regulatory principles in medical research. A brief historical compendium of the evolution of guidelines and regulatory specification is presented. Any scientists need to be familiar with the content and the intention of such guidelines and regulations.

Keywords: Ethics in research and science, code of Nuremberg, declaration of Geneva, declaration of Helsinki, international conference on harmonization, good clinical practice, medical research

Introduction

Research, in its general meaning, is the process of perceiving and collecting data in order to enhance knowledge. However, in science, research needs to be defined more precisely. A systematic and organized approach based on a clearly formulated problem is mandatory. Proceeding in a methodical manner is essential because only well-defined processes guarantee acceptable and valid results. Prepared and controlled research projects are in contrast to spontaneous observations, which are needed in order to create new ideas as foundations of novel hypotheses. The primary goal is to answer a research question stated a priori. A well-defined and clearly postulated question is the key element of a scientific project. Without a clearly formulated question any answer is worthless, even if the results are negative, unexpected or undesirable.

Research is one of the pivotal ethical topics in medicine. Human subjects participating in research need to be especially alert. One of the points of focus of the Nuremberg Trial [1946–1947], (known as the Doctor's Trial), was medical experimentation in human beings during World War II. The arguments of the accused to the effect that the incriminated experiments had been similar to those of pre-war testing highlighted the need for comprehensible definitions of legal and illegal experiments. The *Code of Nuremberg (CoN)* (Tab. 1) was published as early as in 1947 and incorporated into medical research [3]. A key element of the CoN is the voluntary contribution of any participant, based on informed consent. Although not implemented into local laws, the CoN still serves as a cornerstone of human research ethics.

In the year 1948 the World Medical Association (WMA) formulated the *Declaration of Geneva (DoG)* (Tab. 2) as a physician's dedication to the humanitarian aims of medicine [5]. The DoG is a revised formulation of the Oath of Hippocrates.

A further instance of unethical research was the Tuskegee Syphilis Study (1932–1972), which has become a symbol of racism and abuse of vulnerable subjects in medicine [9] (Tab. 3). The political consequence of the study was the *Belmont Report* released in 1979 by the National Commission for the Protection of Human subjects of Biomedical and Behavioural Research. The report identifies three guiding principles for research: respect for persons, beneficence, and justice [8]. A recently published review demonstrated the current validity of ethical issues in medical research [7]. Familiarity with the Syphilis Study at Tuskegee does not automatically ensure accurate knowledge of it and awareness of it does not necessarily imply willingness to participate in biomedical research. In addition to awareness and knowledge of the Syphilis Study at Tuskegee, many published studies suggest that a wide array of structural and sociocultural factors influence the willingness of minorities to participate in biomedical studies [7].

Declaration of Helsinki

In 1964 the WMA developed a set of ethical principles for the conduct of medical experiments, named the *Declaration of Helsinki (DoH)* [6]. The DoH is considered one of the most influential documents in research ethics (Tab. 4). The purpose of the DoH was to create a guideline for physicians committed to medical research projects. It focused on the researchers' responsibility to protect research subjects. However, the strict rule of voluntary contribution as mentioned in the CoN, and the personal informed consent of each participant, were modified. A legal representative, or a responsible relative could now provide consent if the participant was unable to provide his autonomous consent. Consequently, research involving children (especially for vaccines) and

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research on incompetent or captive populations became permissible.

Since its approval the DoH has undergone six revisions. In the first revision, published in 1975, the concept of supervision and control was implemented. Independent committees such as institutional review boards and research ethics committees were defined and positioned. One of the principles was that, in therapy studies, the comparator had to be the best available care. The participant's right to obtain such care was emphasized. Additionally, each research protocol had to clearly state that the DoH had been accepted and fulfilled.

Significant extensions were implemented in the fourth revision of 1996. For one thing, the placebo-controlled trial was affiliated and the following phrase added to Article II.3: "*This does not exclude the use of inert placebo in studies when no proven diagnostic or therapeutic method exists*".

The fifth revision issued in 2000 provided additional modifications apart from changes in the structure and assem-

Tab. 1: Code of Nuremberg (Source: http://ohsr.od.nih.gov/guidelines/nuremberg.html [Dec. 5th 2008])

1. The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.
2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3. The experiment should be so designed and based on the results of animal experimentation and knowledge of the natural history of the disease or other problems under study that the anticipated results will justify the performance of the experiment.
4. The experiment should be conducted so as to avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except perhaps, in those experiments where the experimental physicians also serve as subjects.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems impossible for him to be possible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

Tab. 2: Declaration of Geneva (source: http://www.wma.net/e/policy/c8.htm [Dec. 28th 2008])

AT THE TIME OF BEING ADMITTED AS A MEMBER OF THE MEDICAL PROFESSION:

- I SOLEMNLY PLEDGE to consecrate my life to the service of humanity;
- I WILL GIVE to my teachers the respect and gratitude that is their due;
- I WILL PRACTISE my profession with conscience and dignity;
- THE HEALTH OF MY PATIENT will be my first consideration;
- I WILL RESPECT the secrets that are confided in me, even after the patient has died;
- I WILL MAINTAIN by all the means in my power, the honor and the noble traditions of the medical profession;
- MY COLLEAGUES will be my sisters and brothers;
- I WILL NOT PERMIT considerations of age, disease or disability, creed, ethnic origin, gender, nationality, political affiliation, race, sexual orientation, social standing or any other factor to intervene between my duty and my patient;
- I WILL MAINTAIN the utmost respect for human life;
- I WILL NOT USE my medical knowledge contrary to the laws of humanity, even under threat;
- I MAKE THESE PROMISES solemnly, freely and upon my honor

Tab. 3: The chronology of the US Public Health Service Syphilis Study at Tuskegee

1932	600 African American men (399 diseased with Syphilis, 201 not diseased) were enrolled in the study, told to be treated for "bad blood"
	The study was designed to observe the study subjects until death
1936	Local physicians refused to give treatment to study participants due to pressure from the researchers
1940–1945	Adequate treatment was not provided, although available (Penicillin) and required by the US military
1968	The first concern about the study was raised
1969	The American Medical Association and other Organizations approved their support for the study
1972–1973	The public was informed by a report in a local newspaper. The study was stopped. Congressional hearings began. A class action law suit was filed.
1979	The Belmont Report was published
1997	The President of the US formally apologized on behalf of the nation

Tab. 4: Declaration of Helsinki Amendment 2008 (Source: http://www.wma.net/e/policy/b3.htm [Dec. 15th 2008])

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care".
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians 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.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. 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.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described 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, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. 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 change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

(Continued)

Tab. 4: (*continued*)

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

24. In medical research involving competent human subjects, 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, 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.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should 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 should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, 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 population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent 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.
29. 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 population. In such circumstances the physician should 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 a 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 should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors 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. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research 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.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the 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 interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

bly of the DoH. First, the well-being of the individual is superior to the interests of the community: "*In medical research on human subjects, considerations related to the well-being of the human subject should take preference over the interests of science and society* (*paragraph 5*)". This statement does not, however, suggest an uncritical attitude towards current methods in medical and dental care. It would be unethical not to challenge the existing medical practice. Research projects should not be ends in themselves. The needs of public health, important as may be, must not override the rights of individuals who take part in medical research [10].

The term "non-therapeutic" research, used in previous versions on the DoH, was omitted in the fifth revision. Instead it refers to the "healthy volunteer" who participates in a research project and obtains no personal benefit from the research. Vulnerable persons are explicitly mentioned in paragraph 8: "*Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence*". The use of placebos in clinical trials has been redefined: "*The benefits, risks, burdens and effectiveness of a new*

method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists".

One notices a significant shift in the 2008 version of the DoH, resulting in a limitation of benefit for research participants. The purpose of research is the advancement of knowledge for the benefit of future patients. It is not solely focused on the benefit of the current research participant. Blinded studies, especially double-blinded clinical trials demonstrate this intention (paragraph 32) [6].

Epidemiological studies are now included. Such studies, by their nature, aim at improving public health and health systems and are not focused on the individual subject. Furthermore, the last version of the DoH encourages research for populations that have previously been under-represented, such as children and pregnant women. Risks and burdens in research projects have to be assessed not only in matters of the individual; the impact on the community also must be taken into account [11].

The DoH was supplemented by the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* in 1993 [1]. The World Health Organization (WHO) instructed the Council for International Organizations of Medical Sciences (CIOMS) to produce a document that would protect research participants particularly in Third World countries.

The International Conference on Harmonization

In 1990, the *International Conference on Harmonization (ICH)* of Technical Requirements for Registration of Pharmaceuticals for Human Use was founded by the FDA (Food and Drug Administration), the EC (European Commission), and the MHLW (Japanese Ministry of Health, Labour and Social Affairs) in alliance with the pharmaceutical industry. In Europe the EMEA (European Medicines Agency) was established by the EC. It is concerned with technical and scientific support for ICH activities. The WHO, the European Free Trade Association (EFTA), and Canada (represented by Health Canada) have been accorded the status of observers. The goal of the conference is to standardize and harmonize marketing approval for pharmaceutical products in order to reduce duplicate testing and minimize delay. ICH guidelines are implemented in Europe, US, and Japan only. Several guidelines have been developed, such as Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP). These guidelines are obligatory and stringent. Non-adherence to ICH guidelines is only permitted in justified and reasonable cases.

The topics of the ICH are arranged in four major categories [4]: Quality, Safety, Efficacy and Multidisciplinary. Quality relates to chemical and pharmaceutical quality assurance, such as stability and impurity testing. Safety encompasses in vitro and in vivo pre-clinical studies such as those focusing on carcinogenicity and toxicity. Clinical studies involving dosing and response evaluation are efficacy issues. All other subjects not explicitly covered by the other categories are integrated into the multidisciplinary section, such as the Medical Dictionary for Regulatory Activities (MedDra) and the Common Technical Document (CTD).

In clinical research, the ICH GCP Guidelines define the roles and responsibilities of the investigator and the sponsor. All relevant aspects of the conduct of a clinical trial are stated and can be used as a reference for any clinical research situation. The trial protocol, the investigators' brochure and essential documents for the conduct of a clinical trial are also incorporated in the ICH GCP. Although developed for clinical trials, these guidelines are also relevant for other types of research projects involving humans. The regulatory bodies in the ICH member states refer to the ICH GCP Guidelines in their directives. The EU Directive 2001/20/EC and 2005/28/EC lay down principles and detailed guidelines for good clinical practice [2]. The WHO published guidelines for GCP in 1995 [12].

Conclusion

A variety of ethical issues may arise from a research project and must be considered from the first stage of planning. As outlined in this paper, a number of resources are now available for guidance in ethical matters. One is often required to follow several different codes or guidelines, and the researcher needs to be familiar with their contents and differences.

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