

Chapter 1. Ethical Considerations

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I. INTRODUCTORY REMARKS

One of many characteristics of modern society is a pronounced interest in ethical questions. Medicine, especially research on humans, is expectedly, at the top of the list. Why is that so? In spite of the fact that many patients receive therapeutic benefits from participating in clinical trials, benefits that may even be greater than those of standard medical care, randomized clinical trials differ from standard medical treatment in their purpose, characteristics, justification of risks and allocations of interventions according to chance. The research based on various interventions potentially poses risks to the participants that are not always compensated for by medical benefits but that are justified by the potential scientific value of the knowledge which will be got from the trial.

The history of international instruments on ethics is not long. Already before World War II, use of controlled clinical trials was proposed and accepted as the scientific, reliable way of proving efficacy and safety of new therapeutic agents. The atrocious experiments performed by nazi physicians during World War II led, almost immediately (1947) after the war, to the preparation of the Nuremberg Code on ethics of medical research. The Helsinki Declaration followed in 1964 and is now (sixth revision in 2000) taken as the gold standard for research ethics, intending to provide a universal set of principles, which direct the ethical conduct of clinical medical research involving human subjects throughout the world. This is still true in spite of several weaknesses which are at the moment of writing these lines intensively discussed. Other instruments must be mentioned, such as the UN General Assembly Universal Declaration of Human Rights in 1948 and the International Covenant on Civil and Political Rights in 1966. The Belmont Report, elaborated in the US in 1979, is in this country very important for developing new drugs. The Belmont report is, in the US, almost better known than the Helsinki Declaration, and, with its legislative revisions performed later, it is still a very comprehensive instrument.

Recent and very important instruments are the documents issued by the 1990 founded International Conferences of Harmonization (ICH) founded in 1990. Originally the basic aim of ICH was to harmonize the requirements for new drugs in the three biggest drug developers, namely US, European Union and Japan. Later, its guidelines and consensus documents have been accepted by the «rest of the world» most probably because of the importance of the pharmaceutical markets in these countries rather than because of other less materialistic reasons.

The first principle of ICH (taken from WHO GCP in 1995) states: "Clinical trials should be conducted in accordance with the ethical principles that have the origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirement(s)".

The booklet prepared by the Council of International Organizations of Medical Sciences (CIOMS) in 1982, in 1993 and in 2002 is today the most informative and comprehensive source of information for ethical research, trying to correct the inconsistencies of the latest revisions of the Helsinki Declaration. These inconsistencies perhaps explain why »studies that breach the provisions of the Helsinki Declaration are still commonly conducted, with the full knowledge of regulatory agencies and institutional review boards«.

Of the realistic and justified aspects of the Helsinki Declaration, the most important is the respect for the person's rights e.g. personhood of subjects, followed by investigators beneficence for subjects participating in the trial and distributive justice in distribution of risk and benefit associated with medical research. The growing importance of persons rights (patients and healthy volunteers) is illustrated by the special attention given to trials in vulnerable and socially unprivileged patients.

Issues of conflict of interest, of transparency and of publishing negative trials are closely linked with ethics as well.

II. THE ETHICS COMMITTEE

The guarantee for the ethical conduct of the study should be a multidisciplinary ethical body called in various countries the Ethics committee, institutional review board, independent ethical committee (EC/IRB). Its size is according to many documents of “at least five” members. This important detail is not mentioned in the Helsinki Declaration. With a small number of members it cannot be expected that an institutional review board will be independent when it decides about resources brought by the sponsor to the institution and its investigators. The number of members must be large enough to ensure that besides the layman, the nurse, the ethicist, and the statistician (who are often named as useful non-scientific members of EC/IRB), at least some members must be experts in the medical and scientific aspects of the clinical trial. Scientific and ethical review cannot be separated. How can someone discuss the ethics of a clinical trial without knowing in detail all facts about the disease in question and its standard treatment? Only medically and scientifically competent members of the ethical committee can safeguard the rights, safety and well-being of the research subjects.

Is it optimal that the same ethics committee, and this is often the case, evaluates research projects and other relevant ethical questions which are constantly present in a health institution, such as artificial prolongation of life of irreversibly sick patients, abortions, unethical behaviour of medical staff, to name only a few.

The EC/IRB should be an independent body, either regional or (for smaller countries) central-national and should discuss research projects only. Such development goes in the described direction and many (even bigger) countries already have central ethics research committees or institutions (US Office for Human Research Protection, U.K. Central Office for Research Ethics Committees, Canada National Council on Ethics in Human Research). In the EU for multicentre trials one member country must give one opinion. This is achieved in various ways one of them being that the central committee delegates the decision to a regional one.

II.1. Informed Consent Document (ICD)

How does the EC/IRB functions and what are the foci of their activity? The most important ethical aspect of the clinical trial is the Informed Consent Document (ICD). The already mentioned International Covenant accepted by the United Nations Assembly in 1966 stresses that « no one shall be subjected without his free consent to medical or scientific experimentation ». A number of documents, meetings and discussions have been written and organized about the optimal format of this important ethical aspect of the clinical trial documents.

It is of the utmost importance that the subject participating in a scientific research project, for instance a clinical trial, understands all details of the planned experiment. To reach this aim the investigator must ensure that the prospective subject has got all the necessary information on the basis of which he reaches at the decision to take part in the trial without having been subjected to coercion, undue influence or inducement, or intimidation. The ICD should contain a statement indicating that the study involves research, should describe the purpose of the research, the expected duration of the subject’s participation, should contain the description of the procedures to be followed (with the indication of which are experimental), of the study treatments, and, if applicable, the nature of random assignment. Moreover the ICD should contain a description of the foreseeable risks or discomforts, of the benefits that may be expected for the subject or for others and disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. In addition the ICD will include a statement

describing the extent to which confidentiality and privacy (of records identifying the subject) will be maintained, a statement that participation is voluntary and that the refusal to participate involves no penalty or loss of benefits. It must describe the actions foreseen in the case of injuries (compensation, medical treatment), explanation on whom to contact for additional questions, and, if applicable, any other necessary detail which ensures complete comprehension of above mentioned points by the participant.

Whenever it is not possible to obtain the written ICD, the non-written consent should be documented and witnessed. The problems of obtaining a written ICD for trials in patients with decisional (cognitive) impairment such as patients who are mentally ill, those with Alzheimer's disease, acutely ill subjects (head trauma, cardiopulmonary arrest, and stroke) or children (no uniform criteria for assent and dissent exist) are considerable. In these cases a legally authorised representative, a proxy or an advanced ICD (in the case of anaesthesia for example) should be used.

In addition, financial details of the trial should be disclosed. Transparency of financial arrangements encourages people to do the right thing. The individual investigator should not stand to benefit personally in financial terms from their involvement in the study.

II.2. Analysis of Details

Another function of the EC/IRB is to conduct a careful analysis of all details, which could influence the reliability of the trial results. The new sentence in the latest revision of the Helsinki declaration must be mentioned here (articles 19 and 20): "Medical research is only justified if there is a reasonable likelihood that populations in which research is carried out stand to benefit from the results of the research".

The analysis should begin with the investigator and their team, their potential to recruit subjects without aggressive behaviour, the likelihood of a conflict of interest when trying to serve both the best interests of the patients and the best interests of the research. The analysis should also consider the remuneration and other advantages for both the investigator and their institution. The patient selection, the planned measurements (frequency, justified invasiveness), concomitant and rescue therapy, monitoring of adverse events (especially those which will indicate the need to stop the trial) and comparator therapy must be analyzed.

II.3. Placebo

The function of the EC/IRB is to analyze the need to use placebo. The use of placebo has been considered by many as non-realistic and unjustified. The most controversial item of the last two revisions of the Helsinki declaration (article 29) states: "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". Strictly interpreted, this article would rule out the use of placebo controlled clinical trials e.g. a dummy treatment administered to the control group in a controlled clinical trial in order that the specific and non-specific effects of the experimental treatment be distinguished whenever licensed therapeutic method already exists. Active controls (which the investigators are keen for) cannot, in many circumstances, provide reliable evidence of efficacy and safety of the new drug, except by showing the non-inferiority of the new drug. There are many groups of therapeutic agents where placebo controls are justified or even mandatory: analgesics, many psychopharmacologicals, antihypertensives, antianginals, antiarrhythmics and drugs used in primary prevention to name only a few. It is essential that the use of placebo does not pose a risk of serious discomfort, irreversible harm or death or that existing therapy improves survival or decreases serious morbidity.

The sixth revised version of the Helsinki Declaration raised a number of discussions, many more than after the fifth version in which the same proposal was already present, with the result that the World Medical Association prepared a special footnote which states: “The WMA hereby reaffirms its position that extreme care must be taken in making use of placebo-controlled trials and that in general this methodology should only be used in the absence of existing proven therapy. However placebo-controlled trials may be ethically acceptable, even when proven therapy is available, under the following circumstances:

- where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy and safety of prophylactic, diagnostic or therapeutic method; or
- where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious irreversible harm”.

Beside WMA, many meetings in various international organizations like the European Medicines Evaluation Agency (EMA), the Food and Drug Administration (FDA), the Pharmaceutical Research and Manufacturers of America (PhRMA), the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) and the European Forum for Good Clinical Practice (EFGCP) have discussed the need for a new revision of the Helsinki declaration because of the presence of other conflicting articles. For example, article 30 states that “every patient should be assured of access to the best proven method identified by the study”. This is not acceptable because of the widely known fact that one study cannot identify “the best proven method”.

Therefore, a new version of the Declaration of Helsinki is to be expected. In September 2003 the General Assembly of WMA founded a Working group (its deadline is May 2004) with this goal.

II.4. Payment

Payment in the form of money, gifts, and privileges can only be offered as a recruitment incentive not as a benefit for participation. In clinical trials the prospects of benefit from an experimental treatment and the provision of free ancillary care are viewed as compensation for participation. Healthy volunteers do not need treatment and care. So payment is justified as an incentive for participation.

There are many other ethically sensible areas of clinical research. The examples are, beside those already mentioned, the need to withhold treatment, wash out periods, research involving foetuses and in vitro fertilization, involving pregnant women, children, college students and prisoners. In each of these cases the local EC/IRB has to adapt its decisions according to the local legislation, uses and environment.

In conclusion, clinical trials have numerous ethical aspects. A scientifically and medically well planned clinical trial is ethical and represents the only way for obtaining reliable results which will help in better treatment of a wide circle of patients. Local EC/IRBs have to define what is methodologically essential and ethically appropriate and these aspects are still the subject of intense debate. Ethical committees structured as proposed in this chapter guarantee that ethical principles, accepted to day as appropriate, are observed.

III. SUGGESTED READINGS

1. Council of International Organizations of Medical Sciences, International Ethical Guidelines for Biomedical Research Involving Human Subjects, Geneva 2002.
2. Amdur RJ, Bankert EA, Institutional Review Board, Management and Function, Jones and Bartlett Pubs, Boston 2002.
3. Vrhovac B, Placebo and Helsinki Declaration, What to Do? Sci Engen Ethics (in press 2003).

4. Miller, FG, Rosenstein DL, The Therapeutic Orientation to Clinical Trials, N Engl J Med. 2003;348:1383-86.
5. World Medical Association Declaration of Helsinki: Ethical principles for Medical Research Involving Human Subjects, Edinburgh Scotland, World Medical Association, October 2000: Accessed Aug 10,2003 at <http://www.wma.net/e/policy/b3.htm>
6. Diamant JC, The revised Declaration of Helsinki-Is Justice Served? Int J Clin Pharmacol Ther 2002;40:76-83.
7. European Union's Clinical Trials Directive, Accessed Aug 10, 2003 at http://www.barnettinternational.com/RSC_PDFUploads/nda%20eu%20toc.rtb
8. Good Clinical Practice Consolidated Guideline, Accessed Aug 10, 2003 at http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/goodclin_main_e.html
9. European Forum for Good Clinical Practice, European Guidelines for Auditing Independent Ethics Committees, Geneva 2002.
10. World Health Organization (TDR/CDS/WHO) Operational Guidelines for Ethics Committees That Review Biomedical Research, WHO, Geneva 2000.
11. The European Agency for Evaluation of Medicinal Products: EMEA/CPMP, Position Statement on the USE of Placebo in Clinical Trials with regard to the revised Declaration of Helsinki, EMEA/17424/01.
12. International Conference on Harmonization (ICH) Good Clinical Practice Guidelines Accessed Aug 10, 2003 at <http://www.ifpma.org/ich5e.html>
13. National Council on ethics in human research-Canada Accessed Aug 19, 2003 at http://www.ncehr-cnerh.org/english/mstr_frm.html