Chapter III

ETHICS OF RESEARCH INVOLVING HUMAN BEINGS

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Researchers and sponsors must bear in mind the ethical issues that any research involving human beings is likely to raise. It is therefore their responsibility to anticipate these questions even before drafting the protocol. An independent Research Ethics Board (REB) will review the protocol before it is authorized and implemented. It may request amendments to the initial protocol. He will also be kept informed of the progress of the study by the principal investigator. This chapter presents the fundamental principles of ethics to which research involving human beings must refer. The objective is not to go into the details of the constitution and operation of an ethics committee, nor to comment on the regulations on clinical research currently in force, but to raise the questions that any researcher will have to ask before conducting a search.

APPLICATION OF FUNDAMENTAL ETHICAL PRINCIPLES TO RESEARCH

Any research involving human beings (healthy or sick), whether clinical trials, epidemiological research, studies in psychology or in the social sciences, can raise ethical questions. These should always be considered by the researcher and research sponsor from the initial phase of protocol development. In most countries, there are regulations (legislation, guidelines, etc.) that govern these research activities; there are also international standards and codes of professional ethics (see annexes). The investigator must be aware of them and respect them; training in research ethics is therefore desirable for professionals involved in this type of work. The principal researcher must also refer to a REB (Research Ethics Committee) for a prior evaluation of the research protocol, in each of the countries where it is to be implemented. The ethical evaluation of research protocols and international and national normative frameworks is based on fundamental ethical principles, formulated after the Second World War in the Nuremberg Code and then the Declaration of Helsinki, as well as numerous guidelines such as those Councils of International Organizations of Medical Sciences or the World Health Organization (see appendix).

A - MAXIMIZING THE BENEFITS OF RESEARCH

The research is justified by the hypothesis of a benefit for the health of the population; it may be new scientific data, new diagnostic strategies, new treatments, new vaccines, etc. The research protocol is designed to provide scientifically valid and generalizable data. The expected benefit must be compared with the risks incurred by the subjects involved in the study and for the community to which they belong (risk/benefit ratio).

In cases where the benefit is essentially expected for the community (e.g. phase I clinical trials, see chapter 7), the risk for the participants should be all the lower as the individual benefit is close to zero. In other cases, one can hope for a benefit for the participants of the study, it will be weighed against the potential risks. In all cases, the expected benefit of the

research must be clearly explained to all participants (see **free and informed consent process**). It happens that the benefit of a new treatment appears before the end of the trial, this one will then have to be stopped to allow all the participants including those of the control group to benefit of this new treatment.

B - MINIMIZE THE RISKS INHERENT IN ANY RESEARCH

The risks involved are of different types:

- physical damage, due to the complications of a new pharmaceutical product or a new technology,
- psychological damage, such as stress, invasion of privacy by breach of confidentiality and the social discrimination that may ensue.

Risks must be distinguished from constraints and inconveniences, such as having to undergo a blood sample or giving time to answer a questionnaire. The damages suffered by a participant are the responsibility of the research promoter who will have to compensate for them. It is the role of the "Data Safety Monitoring Boards" (DSMB) (see appendices) to detect adverse effects of new drugs as quickly as possible on the basis of information provided by the principal investigators, so that they are corrected as soon as possible. In some cases, the clinical trial will be interrupted for safety reasons.

The inconveniences are most often foreseeable and may be the subject of compensation for the participants (e.g. payment of transport costs and compensation for time spent). Under no circumstances will compensation be considered as a benefit of the research for the participant.

Risks and inconveniences are the subject of clear information, transmitted to potential participants before their inclusion in the study.

It is therefore a question of optimizing the risk/benefit ratio for the participants in the research and the population to which they belong. Particular attention will be paid to people who find themselves in a situation of vulnerability due to their age (minors or elderly people), their health condition (people affected by mental or conscience disorders), their social situation (people deprived of their freedom, marginalized, illiterate or living in extreme poverty); more generally, special protection must be provided for people whose decision-making autonomy is insufficient to ensure the validity of the free and informed consent process.

The ethical evaluation of a research protocol begins with the verification of its scientific relevance. According to the adage "what is not scientific is not ethical", we will avoid exposing participants to the risks of research whose scientific relevance is not proven; we will also avoid devoting human and financial resources to research that is futile or whose probable impact on health is negligible.

C - RESPECT THE DIGNITY OF PEOPLE

Respect for decision-making autonomy: free and informed consent process

The process of free and informed consent must be both dynamic and interactive, it must allow a decision free from any coercion, based on complete, transparent, understandable information and adapted to the person to whom it is addressed. This process and the means of support used (written document, visual support, etc.) must be described and evaluated by the

REB (see appendix). The decision is usually authenticated by a written document, signed by the participant; in any case the consent must be 'express' (expressed in a formal manner).

When the research participant is a minor, her/his consent will be sought on the basis of appropriate information; parental or legal guardian consent is required. In the case of illiterate people, recourse to a third party will be necessary. Of course the information and the decision of the person to participate or not will be expressed in a language that this one masters.

The free and informed consent process must take into account the particular socio-cultural context in which the research takes place. For example, in certain cases, the information and the opinion of the community will have to precede the decision of the individual. The time required for this process is variable, it must be sufficient to allow a good understanding:

- potential risks and benefits,
- the terms and conditions for covering any damages due to the study,
- the duration, procedures, constraints and possible compensation,
- the objectives of the research and treatment alternatives,
- the methodology (randomization, double blind, use of placebo, etc.),
- the possibility for the participant to modify his decision and withdraw his consent at any time without prejudice to him,
- measures guaranteeing the confidentiality of personal data,
- the possibility of further research, for example the use of samples and the creation of biobanks,
- and sources of research funding.

Respect for privacy: confidentiality of personal data

The confidentiality of personal data is a principle of medical ethics already explained by the Hippocratic Oath. Personal data collected during research activities will only be shared with persons who are aware of the confidentiality measures that must be applied to them.

Different measures can be considered: anonymization, codification, limited access; identification of subjects when publishing study results should not be possible. Destruction of data after the end of the study may be required in certain cases. To maximize the benefits of research, it will sometimes be necessary to make the link between the data collected and the person concerned. This is the case, for example, of the results of HIV tests which must be communicated to people so that they can benefit from appropriate care. These measures will be evaluated by the REB and explained to potential study participants.

A breach of confidentiality can sometimes lead to serious consequences for the person, for example in certain psychiatric conditions, certain particularly discriminating infectious diseases, in certain socio-cultural contexts, such as HIV/AIDS or tuberculosis; data concerning sexual behavior or illegal activities will be collected with great caution. Care will be taken not to disclose any information concerning a person's health to an insurance company, a judicial authority, an employer or even a relative, the prior authorization of the person concerned being necessary for the sharing of this information, for example with a loved one.

D - APPLICATION TO RESEARCH OF THE PRINCIPLE OF JUSTICE

1. Develop national research priorities that respond to population health priorities

Since 2000, the attention of the international community has been drawn to the need to improve coherence between research priorities and health priorities, particularly in emerging countries. International research will be more "just" if it makes it possible to better answer the questions raised by the management of diseases affecting most vulnerable populations.

2. Promote the sharing of the benefits of international research

The number of clinical trials carried out in emerging countries follows an exponential curve. On the other hand, the impact of the benefits of this research in terms of access to new knowledge, new diagnostic or prevention strategies and new treatments remains insufficient and the distribution of these benefits is too often inequitable, favoring the countries promoting research to the detriment of host countries. Sponsors and researchers have a responsibility to seek to maximize the benefits of their research for the populations in which it is conducted.

3. Respect transparency and access to quality scientific data

This aspect of research ethics is at the origin of various initiatives such as, for example, the development of national clinical trial registers, supported by the WHO. Scientific publications have an important role in the dissemination of research results. This dissemination requires that the research be carried out in compliance with the best international ethical standards. If the research is justified and the expected results relevant, they should be published and made accessible to the scientific community and even to the public. It should be noted that negative results are rarely published although they may have significant scientific interest; this type of publication should be encouraged for the sake of transparency.

4. Ensure the participation of all the actors concerned

Patient associations and numerous non-governmental organizations contribute to better informing citizens and particularly those most concerned by research. Researchers and promoters therefore have more and more interactions with civil society, thus helping to maintain public confidence.

E- INTERNATIONAL RESEARCH

The implementation of research protocols in emerging countries and therefore in very diverse socio-economic contexts raises complex ethical questions. Thus, the process of free and informed consent prior to the implementation of the same research protocol in different countries may follow different procedures depending on the culture and social context of each country. A tension can then arise between ethical principles with a universal aim and particular cultural values. Local RECs should consider this tension and suggest practical modalities that do not run counter to universal principles.

The question of sharing the benefits of research mentioned above arises more acutely in the context of international research. The international debate has focused on this issue for a

decade, allowing advances not only in terms of international regulations but also for the establishment of prior agreement procedures between the various research actors aimed at increasing the benefits of this and their sustainability for the populations concerned.

Many voices have been raised to denounce a double ethical standard, sparking a lively controversy, particularly around the use of the placebo. In fact, some populations find themselves in a situation of vulnerability. For this, many initiatives aim to strengthen local RECs and harmonize national regulations; the World Health Organization, in collaboration with other international organizations, whether governmental or not, is working in many developing countries to set up research ethics review systems that ensure the promotion of the fundamental rights of individuals.

CONCLUSIONS AND PERSPECTIVES

Ethical questioning must be proactive, aiming to improve the quality and impact of research on the health of populations. One of the difficulties comes from the diversity of the actors concerned: researchers, promoters, participants, political decision-makers, research institutions and regulatory bodies. The diversity of contexts in which research takes place makes it even more complex. It is therefore difficult to find points of consensus on issues such as the conditions of use of the placebo or the equitable sharing of the benefits of research.

However, a better approach to these questions is facilitated by the training of research actors. The consolidation of the RECs, their interaction with the research teams and the research regulatory authorities should make it possible to improve the quality of the evaluation and ethical monitoring of protocols. The establishment of international networks contributes to the harmonization of ethical standards and working methods of RECs, proposals are being made in a growing number of countries to set up a mechanism for accrediting ethics committees. International organizations of the UN family such as the World Health Organization or UNESCO, regional organizations such as the Council of Europe work together to support countries in this task. All of these efforts would be in vain without the competence and integrity of the research teams. Training in scientific research and in particular in research ethics must be offered to all researchers to guarantee the scientific rigor and ethical quality of health research.

Appendices

1. Reference texts in France

When a research project includes tests or experiments carried out on human beings (medicine, material, instrument, technique), the law defines the conditions under which these research projects are authorized, to guarantee the quality and safety of their course, and in particular to protect the people taking part in the tests.

The reference law is Law No. 88-1138 of December 20, 1988, known as the Huriet Law (revised in 2009). For other laws, decrees and circulars, refer to the site http://www.legifrance.gouv.fr '*Protection of persons undergoing biomedical research and related provisions'*.

Some institutions have also adopted conventions, for example: ANRS, Institut Pasteur.

2. International standards (binding or not)

- Declaration of Helsinki (2008)
- CIOMS (research including humans 2002 and epidemiological research 2009)
- Additional Protocol to the Oviedo Convention (Council of Europe),
- UNESCO Universal Declaration on Bioethics and Human Rights
- WHO and UNAIDS guidelines

See also the WHO website: http://www.who.int/ethics/research/en/index.html

3. The seven ethical conditions for research involving the participation of human subjects

(ref: Ezekiel J. Emanuel, David Wendler & Christine Grady, "What Makes Clinical Research Ethical?" JAMA 283 (2000): 2701-11)

- The social, scientific or clinical value.
- Scientific validity.
- A fair selection of subjects.
- A favorable risk-benefit ratio.
- An independent evaluation.
- Informed consent.
- Respect for recruited subjects.

4. Some definitions

(ref: Networking for Ethics on Biomedical Research in Africa, Sixth Framework Program (2002 – 2006), Science and Society)

Autonomy: ability to consider alternatives, make choices, and act without undue influence or interference from others.

Charity: ethical principle relating to the obligation to maximize benefits and minimize harm.

Research Ethics Board (REB): a group intended to protect the rights, dignity, and well-being of research participants in deciding whether to approve, reject, or make changes to a research protocol.

Data and Safety Monitoring Board (DSMB): a committee of scientists, physicians, statisticians, and others who collect and analyze data during a clinical trial to monitor for possible adverse effects and other trends. DSMBs have the authority to require the modification or termination of a study or the disclosure of additional information to study participants.

Fair: just. In the context of research, this term is often used to indicate that the benefit and burden of research are equitably distributed among different groups in society.

Independence: applied to ethics review committees, this term refers to the ability of the committee to make its own decisions. A committee is not independent if its conduct is dictated by government officials or if it includes too many members with ties to particular stakeholders such as research sponsors.

Justice: ethical principle requiring equitable distribution of burdens and benefits, often expressed as treating similarly people with similar circumstances or characteristics.

Informed consent process: process by which a person decides whether or not to participate in a research protocol. This process typically includes the transmission of written information and a face-to-face interview, in order to ensure that potential participants are duly informed and fully understand the risks, benefits and possible alternatives.

Sponsor (of a drug trial): any person or entity initiating clinical research on a medicine – usually the manufacturer of the medicine or the research institute that developed the medicine. The promoter does not carry out the research but distributes the new drug to researchers and doctors in charge of the clinical trial.

Protocol: document which defines the objective, the conditions of realization and the progress of the test.

Risk: likelihood and extent of harm or injury (physical, psychological, social or economic) arising from participating or having participated in a research project. The likelihood and possible extent of harm can vary from negligible to significant.

Research subject: a person whose physical or behavioral characteristics and reactions are studied as part of a research project.

Transparency: ethical principle encouraging decision-making bodies to make the decision-making process available and accessible to the public, through clear and frequent communication of information about how decisions are made and for what reasons.

Voluntary: without coercion, threat or undue coercion. Term used in the context of research to describe the decision that a person makes to participate (or continue to participate) in a research project.