Basic ethical considerations and principles in the development of Biomedical research and Gastroenterology

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Include in your current choice, as an object of your will, the future integrity of man
Hans Jonas

Abstract
This article attempts an overview of ethics in research. It emphasizes principles and philosophical foundations of research and stresses the importance of recognizing them in the process of clinical research so that they will be taken into account by those who do research in gastroenterology and digestive endoscopy. The article is based on the legal regulations of Colombia and especially highlights the importance and validity of the subjects who participate in research.

Key words
Ethical principles, clinical research, research in Gastroenterology and Digestive Endoscopy.

INTRODUCTION

The following article aims to create awareness among those who conduct research in gastroenterology and digestive endoscopy about the enormous importance and responsibility of observance of rules and ethical principles that govern human research. Scientific and clinical research, which becomes more important everyday in the areas of gastroenterology and digestive endoscopy, have made undeniable contributions to medical science and humanity, but they have also raised sometimes entailed forgetfulness, carelessness or, at least, inadvertence in regard to the rules and principles of ethics in human research (1).

The risk may be greater when we are treating patients at the same time we are doing scientific and investigative research. This is particularly the case when drugs or new techniques or endoscopic procedures are tested.

We thought it would be appropriate to share and refresh our knowledge of ethical principles that should be kept in mind whenever we conduct research. We present them here in a concise way which especially highlights those that seem basic because our main goal should always be the patient's health, in other words the, "primacy of the human person," as the center of research (2).

PURPOSE AND RELEVANCE OF RESEARCH IN MEDICAL ETHICS

The practice of medicine has been governed by the Hippocratic Oath since the fifteenth century BC. For many years this has been the oath which supports a physician's moral ideal, which emphasizes healing attention and which takes care of the relationships with disciples and relatives of patients. Currently medical interventions such as surgery,

including the possibility of abortion, are being questioned. This oath has been maintained for many centuries. It was in the twentieth century when were initial changes were made to update this oath and provide guidance to how to be a medical doctor in the current world's society. Then came the oath proposed by the World Medical Association which is a commitment of the doctor once admitted to be a member of the profession (3):

- "I promise solemnly to consecrate my life to the service of humanity,
- "To give to my teachers the respect and gratitude they deserve,
- "To practice my profession with conscience and dignity,
- "To always ensure the health of my patient,
- "To save and respect the secrets confided in me, even after the death of the patient,
- "To keep intact, by every means in my power, the honor and the noble traditions of the medical profession,
- "To consider as brothers and sisters to my colleagues,
- "I will not permit considerations of political affiliation, class, creed, age, illness or disability, nationality, ethnicity, race, sex or sexual orientation to intervene between my duty and my patient,
- "To ensure the maximum respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity,
- "I make these promises solemnly, freely and upon my honor."

This promise to comply with ethical and moral duty has been extended with the responsibility principle of Hans Jonas. Jonas' thought arises from the knowledge of our high level of technical-scientific development which allows us to intervene in different times of life and which makes us capable of influencing the environment and modifying life on the planet. Initially ethics was recognized as related to man with himself and therefore constituted anthropocentric ethics. The responsibility principle makes us reflect and engage with the vulnerability of nature that is subject to human intervention (4). This concept integrates ethics in a global way. This subject has been extended by the Global Bioethics of Potter in which medical ethicist consider the original meaning of bioethics and extend their thoughts and activities to public health issues worldwide. As doctors we are forced to consider not only the everyday clinical decisions but also the long-term consequences of the recommended actions and of consequences that we failed to consider (5). This is critical in research because to comply with it we must recognize that it is in principle beneficial to both the subjects enrolled in the research and the society in the long term, and at the same time it must allow for definition of therapeutic or diagnostic proposals.

Law 23 of 1981 is legal framework in Colombia which establishes the rules of medical ethics. Chapter 1, Article 1 of the Declaration of Principles refers to research. It states,"... the physician will adjust to the methodological and ethical principles that protect the interests of science and the rights of the person, protecting her or him from suffering while fully maintaining his or her integrity." The legal framework for research in Colombia is Law 8430 of 1983 which allows for the creation of Research Committees and Research Ethics Committees through which the recommendations of the World Health Organization WHO for the fulfillment of Good Clinical Practices (GCP) are applied.

GCPs are international rules of quality and scientific ethics for designing, implementing and reporting clinical trials which involve human beings in research. Their aim is to provide public assurance about the validity of data and rights. The integrity and confidentiality of the participants have been protected. Similarly, they note the responsibilities of the different people involved in each of the planning and implementation phases of a clinical trial (6).

GENERAL ETHICAL PRINCIPLES FOR BIOMEDICAL RESEARCH INVOLVING HUMANS

Since ancient times man has done research based on clinical observations, for example that described by Thomas Sydeham (1624 - 1689) in relation to epidemic diseases in London. Sydeham recognized that the behavior of diseases could be due to possible factors specific to the individual or to external influences of different orders. There has been evolution inside medical research in different methodologies, epidemiological assessments that give weight to this research. We have answers in etiological, diagnostic and therapeutic accuracy supported by technical and scientific development. This becomes especially true in the twentieth century when we find the medicalization of medicine. Here we see how the impact of interventional capacity to modify the course of disease, intervene into the ends of life, and replace organ functions requires evaluation of its effectiveness and of the weight of these procedures precisely through the validity of research that respects methodological rigor.

The historic the impact of the Second World War (1939 - 1945) and the ethical questions which arose after the world learned of what was done in the concentration camps is well known. This gave rise to the Nuremberg Code of 1947 which initiated regulations to include and give recognition to the subject recruited for research. Other events that reaffirm these ethical questions were the research supported by the National Institute of Health in the United States, particularly the Tuskegee Study 1932 - 1972 which violated all the rights of an individual to obtain health. A population

of black prisoners who had been diagnosed with syphilis was taken in order to observe the patterns of the disease without providing treatment which was already known. The study violated the participants' right to decide willingly. The participants were deprived of knowledge of the implications of the disease in relation to their partners and children, and the possibility of treatment was hidden. The investigation lasted 40 years until the atrocity created by physicians and its health consequences for those enrolled in the investigation and their families was discovered. The American government, recognizing the serious consequences of the investigation, compensated and apologized to African-American population during President Bill Clinton's administration. These and other situations gave rise to the Helsinki Declaration of 1964 and the Belmont Report 1979. Each reflects the principles of research. They were developed in the twentieth century when there was greater enactment of the rights and duties of humanity in terms of the defense of life and the preservation of human dignity.

The 1964 Declaration of Helsinki, Finland of the World Medical Association (7) promulgated the rights and principles of research. Numerous revisions have been made, most recently in 2008. The declaration emphasizes research principles, recognition of the need to protect and benefit the individual who is the subject of research, better examination of disease conditions with high interest in public health, and recommendations about modifications of phases of research. It discusses placebos and recognizes the impact of technological scientific development. Therefore, the 1964 Declaration of Helsinki not only reviews the fundamental principles of research, but also seeks recognition of scientific validity. It amplifies the concept that autonomy validates human dignity and the idea that informed consent forms are documents which increases trust in medical activities in by recognizing the researcher as valid representative the individual who is the subject of research.

The medical community performing research recognizes scientific validity when it complies with scientific rigor, objectivity, integrity, independence, truth and transparency in a context in which the relevance and value of research for the benefit of the community can be visualized thus fulfilling bio-ethical principles of research.

The **Belmont Report** attempts to provide an opportunity to scientists, individuals who are subjects of research, evaluators and supporters of the research whether scientific or citizens to understand the ethical framework for the conduct of research. The report is based on three principles that are given in a general context under conditions that require deepening and individual assessments. It is an exercise that takes place within the ethics committee investigation. It also aims at recognizing the differences between clinical practice and research. These principles are:

1. Respect for Persons. This principle refers to recognition of individual autonomy and implies autonomy with responsibility and the capacity to participate and contribute. Similarly, it recognizes those whose autonomy has been violated or diminished in order to protect them. Recognition of this principle allows the individual to enter voluntarily into research and requires great respect and responsibility on the part of the researcher.
2. Beneficence. This principle refers to the ability to maximize benefits and minimize harm. This should be taken into account both in the short and long term. The researcher should assess the relevance of the research and whether benefits outweigh risks. The researcher should distance herself or himself from patient care and from recruitment of individuals for research.
3. Justice: In relation to research this principle emphasizes the opportunity to participate in an investigation, but a balance must be found with who the individual who is subject to research is, what benefits that person receives, and what is the weight of that person's participation. Similarly, populations that may be linked to an investigation, but whose free will may be violated must be identified. Examples of such populations include people deprived of freedom, pregnant women and children. The aim of the investigation will clarify what is the benefit that will result from development of the research. To understand the benefits and burdens of the investigation, it is important to recognize:
    - To each person an equal share.
    - To each person according to her/his individual need.
    - To each person according to his/her individual effort.
    - To each person according to her/his social contribution.
    - To each person according to his/her merits.

These principles must be evaluated within the research protocol which must take into account the characteristics of the population which will be studied by the investigation. The protocol must recognize the ethical and legal framework of the country in which the research will be carried out (8).

SOME SPECIAL CONSIDERATIONS IN THE CASE OF BIOMEDICAL RESEARCH IN GASTROENTEROLOGY AND DIGESTIVE ENDOSCOPY

The increased number of controlled clinical studies involving endoscopic procedures whose evaluation also involves assessment of endoscopic findings is striking. In addition, it is remarkable how fast new endoscopic techniques have become routine in clinical practice. This of course requires the participation of healthy individuals or patients in these studies. It is clear that such research activity under no cir-

cumstances is exempt from compliance with ethical and legal standards for each fact and country (1, 9, 10).

On the other hand, the difficulty in developing guidelines, consensus or even specific laws about them raises problems of different orders. First, the initial experiences of new therapeutic or endoscopic techniques are derived from common sense or personal experience or from some groups. Few initial experiences are obtained from evidence based medicine although this can vary considerably from country to country depending on the degree of development. In addition, new technologies are generally more advanced than the legal structures that regulate them, and in each country there is significant variability. All of this has weakened attempts to adopt universal, legal and economic standards (1).

We recommend with particular interest the reading of the publication (1) of the European Society of Gastrointestinal Endoscopy from the Workshop on Research Ethics based on Endoscopy in 2003. Most of the issues discussed there are summarized below:

Suitable design of studies: Because studies based on endoscopy usually involve patients, the fundamental concept from the ethical point of view (as we have mentioned before) for the design of the study should focus clearly and primarily on the health of patients and not on the procedure itself thereby emphasizing the primacy of the human being (9).

Consideration of the risks and benefits for the individual and for society: In research work in which a method of intervention for patients with a disease is included; the distinction between practice and research can be unclear. Therefore, it is very important for the researcher to be fully empowered in the aim of the research to prioritize the benefit the individual, in this case the patient, will receive. In practice, the physician doing the research seeks to provide a diagnosis or therapy for the patient, but the physician must also clearly see benefit for the patient during the procedure. If the research seeks to demonstrate a hypothesis and arrive at conclusions, then it should be demonstrated that the research has value to the patient and society. This should be evident in the objectives (as mentioned earlier), justification and purpose of the whole research project.

The handbook of medical ethics of the World Medical Association, states:

> "Although such participation in research is valuable experience for physicians, there are potential problems that must be recognized and avoided. In the first place, the physician's role in the physician-patient relationship is different from the researcher's role in the researcher-research subject relationship, even if the physician and the researcher are the same person. The physician's primary responsibility is the health and wellbeing of the patient, whereas the researcher's primary responsibility is the generation of knowledge, which may or may not contribute to the research subject's health and wellbeing. Thus, there is a potential for conflict between the two roles. When this occurs, the physician role must take precedence over the researcher." (11)

All research protocols must comply with scientific rigor, as has been stated, and follow epidemiological methodology. In parallel they should comply with ethical considerations within which are evaluated inclusion and exclusion criteria, study population of the research project, timing, and reporting of serious and not serious adverse events. The requirement for signed Informed Consent forms, as documents attesting to the intention of the investigation, as we have already specified, should have clear information about the content and the language to be used, should have complete and accurate information about the purpose of research, interventions that will take place, potential risks and about what results are expected from the research. In addition, research protocols should define what will be done with the results and information that the subject will receive during and after the investigation as well as the consequences and treatment alternative therapies after the study. The Nuremberg Code was the first to require informed consent and to give them validity. It states in its first paragraph: "The voluntary consent of the human being is absolutely essential" (11).

This research will be approved or rejected by the Research Ethics Committee (REC) of the institution in which the research will take place. If the institution does not have a Research Ethics Committee it should request a review from another facility that is able comply with this request. The REC must comply with Good Clinical Practices which is certified by INVIMA (*Instituto Nacional de Vigilancia de Medicamentos y Alimentos* – National Institute for Vigilance of Medicines and Foods) in Colombia. The REC will evaluate the research, the investigator, the sponsor, the institution in which the research will be carried out and the different steps in the research project. Its primary objective will be protection of individuals enrolled in the research. Follow-up reports will be evaluated, and adverse event reports will be evaluated with great zeal.

Among the responsibilities of the investigator and the sponsor of the research project is recognition of the confidentiality of the data collected for research. Therefore, from the same demographic data, any data that can generate identification of the individual must be masked. Login

codes must be used for research in order to avoid the risk of identification or association. Randomization of individuals depends on design of the research project but should be formally established. The data used for the research project will permanently be saved with secrecy and confidentiality. Custody of information must be maintained for at least 5 years after completion of an investigation. There are deeper discussions about biopsy and endoscopic samples because of the occasional risk of complications as well as the need for care of samples and sample banks requirements for storage of biopsies, genetic material, and other biological samples. These vary according to international recommendations and from country to country (1).

Whether research work requires the inclusion of healthy volunteers depends on the study design. However, use of healthy volunteers must be limited to non-therapeutic endoscopic procedures and every precaution should always be taken to avoid any injury. Nevertheless, indications for inclusion of healthy volunteers in non-therapeutic endoscopic studies are still very limited. The consensus of the European Society of Gastrointestinal Endoscopy (ESGE) recommends that when healthy volunteers need to be included, medical students and staff members should not be used, given their relationships of dependency on the institution. Instead, healthy volunteers may be recruited through public notices. If required, volunteers should be paid but not excessively (1,22). Informed consent forms, as we have already said, will be independent for each patient. They will fully discuss risks in particular and in detail. With all of this, researchers must make a proper risk-benefit assessment and do everything to preserve the health and privacy of healthy volunteers. If patients are included as controls all the legal and ethical standards mentioned above should obviously be maintained (1,22) and certainly the primary mission is to treat the disease and avoid harming these patients (1,22).

Research studies for implementation of new therapeutic endoscopic techniques, such as submucosal dissection techniques, endoscopic anti reflux procedures, bariatric surgery, and endoscopic myotomies, as has already been mentioned, have ethical considerations that must be addressed. In the first place, patients included in a study should be fully informed about the benefits, risks and alternatives that they have. (1, 23) Limitations of financial resources should be considered in developing countries like ours, given the high costs of these techniques, so that the most prevalent health problems are prioritized. These techniques should be evaluated in the context of clinically controlled and randomized experiments in specialized centers conducted by professionals with certified training and high standards of patient safety (1, 23).

Clinical research has inherent conflicts of interest, especially research sponsored by the pharmaceutical industry. These conflicts of interest arise in all clinical research efforts as a result of the tension between the responsibilities of professionals for research and their responsibilities for patients, and as the result of academic and financial incentives provided for research sponsored by the pharmaceutical industry. (12) Any conflict of interest must be declared by researchers, both to the individuals involved in the research and in the published results.

Conflicts of interest are also found within sponsoring companies due to their commercial interest in their own products that they are investigating. These products can include medicines, new technologies, procedures, tools or endoscopic equipment, and even vaccines. There have also been conflicts of interest among individuals who are the subjects of research because of the opportunity to receive compensation or incentives for participation, the opportunity for improved health and access to laboratory studies or costly interventions. The impact of conflicts of interest on researchers may also be related to the stages of research, as is the case in Phase III or IV when advances in research have already been made and the scientific impact decreases (13).

Conflicts of interest related to funding sources affect all levels of the research process from researchers conducting meta-analyses of pharmaceuticals and procedures all the way to the publishing process where it affects editors and members of the editorial boards of scientific journals. Conflicts of interest even affect experts who develop guidelines and clinical consensuses. (13, 17-21).

Chapter II of Article 6 of Resolution 3823, "By which is created the Advisory Commission on Science and Technology of the Ministry of Health and in which the rules regulating the activities of scientific development in the health sector are established," the Colombian law governing pharmaceutical research, states: "Pharmaceutical research projects will be evaluated by the National Institute for Vigilance of Medicines and Foods INVIMA (*Instituto Nacional de Vigilancia de Medicamentos y Alimentos*) which will report quarterly to the Department of Scientific and Technological Development, using a form designed for that purpose. In addition, it will send a copy of the results of these studies, once these have been completed."

Resolution 8430 of 1993 of the Ministry of Health established the scientific, technical and administrative rules for health research. It includes the legal guidelines for implementation of research in Colombia and provides recognition of the different factors that may be involved in the

investigation. It recognizes payment for investigation to the researcher taking into account that this should not create a conflict of interest. It also regulates the use of drugs, medical devices and equipment in various stages of research, establishes rules for protection of research subjects, considerations against including subjects from vulnerable populations, and emphasizes informed consent.

CONCLUSION

We have tried to generate information that stimulates knowledge and ethical processes for consideration in research, especially within our academic environment and for the professionals in the various areas of Gastroenterology. We have highlighted principles and foundations that recognize the value of every human being who may be a subject of a research project but who above all else is our patient.

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