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Research Ethics: advances and challenges

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Abstract
The topic of research ethics is part of the scientific agenda in distinct areas of knowledge. The diversity of the aspects involved shows the complexity of the dilemmas that emerge in this scenario. This paper pays special attention to four points that deserve reflexion, be they in the international or in a Brazilian context: the existing link between method and research ethics, the process of training and strengthening young scientists, the defense of *a single standard* for international collaborative studies, and the proposal to revise the current text of the Helsinki Declaration. The analysis of these points permits to verify that significant advances in this field have occurred; however, the constant attempts to loosen the ethical requirements used to guide scientific practice could cause a backslide that would bring serious consequences for research participants. Brazil is a privileged country because the Brazilian system for ethical review of researches (the System CEP/Conep – Research Ethics Committees and Brazilian National Commission on Research Ethics) is linked to democratic control, which guarantees the originality and legitimacy the system needs in order to defend the interests and rights of subjects who participate in research.

Keywords
research ethics; science; training; research; Helsinki Declaration

The topic of research ethics, in its different facets and nuances, is part of the scientific agenda in different areas of knowledge and reveals the complexity of the questions that emerge in this scenario. Bringing science and ethics close is not an easy job and the process of developing ethical sensitivity represents a current challenge. The incorporation of ethical requirements in the context of scientific practice intends to guarantee the protection required for research participants and strengthen behaviors and values that favor the exercise of equity, responsibility, and respect for human rights.

Brazil is a country in which the discussion about ethical principles which should guide how research is conducted has advanced rapidly, and this has allowed the creation and consolidation of the Brazilian system for ethical review of researches. This system was instituted by Resolution CNS 196/1996, which was elaborated and disseminated by the National Health Council (Conselho

Nacional de Saúde 1996). It is called the CEP/Conep System and is composed of a National Research Ethics Commission and 581 research ethics committees that operate inside the country in universities, research centers, and hospitals (Conselho Nacional de Saúde 2008a). Since 1996 additional resolutions for studies included in the so-called special topics areas (international cooperation, human reproduction, indigenous populations, human genetics, multicentric projects, and the storage of biological material) have been elaborated as a way of dealing with the scientific advances and the new dilemmas that have arisen during this period (Conselho Nacional de Saúde 2008b).

Considering the international and Brazilian context regarding research ethics, I chose four topics that deserve our attention: the existing link between method and research ethics, the process of training and strengthening young scientists, the defense of *a single standard* for international collaborative studies, and the proposal to revise the current text of the Helsinki Declaration.

The development of studies involving human beings has one main goal: producing generalizable knowledge which can be incorporated into public health policies, which reveals its social and scientific importance (Emanuel 2000; Emanuel et al. 2004). As such, the evidence produced could contribute to: improving the quality of life of people, groups, and communities; to the understanding of the social determinants of the process of health/illness; as well as to the proposal of strategic solutions capable of transposing barriers and improving care in public health intended for the general population. If we follow this argument, it is possible to understand that ethical reflection should accompany the different phases of a study's development: its conception, the definition of the research question, the choice of the study design, entry in the work field, execution of the investigation, data analysis, and dissemination of the results (Guilhem & Zicker 2007).

Different from what one would think, the link between method and ethics is present in all of the international ethical guidelines used as a reference to subsidize the execution of studies. The Nuremburg Code (1947) was elaborated in the post World War II period and is considered to be the first international document to incorporate ethical requirements for the execution of studies. The protective safeguards include the procurement of informed consent[a] and the voluntariness of participation as a way of minimizing the risks to which the participants could be exposed. Parallel to this, the document dedicates six of its ten paragraphs to showing the importance of the scientific and social validity of research involving human beings.

The Helsinki Declaration, elaborated by the World Medical Association (WMA), is a document that was initially intended for the medical class and has the goal of repairing society's image of medical scientists (World Medical Association 1964). In fact, "the document is an unfolding of some of the ethical norms of the Nuremburg Code but with more concrete goals for intervention in biomedical research" (Guilhem & Diniz 2008: 21). In its first revision, elaborated during the Association's 29th Reunion in Tokyo in 1975, the concept of reviewing the research protocol by an independent committee, specialized in research ethics, as stated in Article 1.2 was introduced:

> "The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance" (World Medical Association 1975).

The perceived importance of the review and ethical reflection of the experimental protocol led the WMA to introduce this point in the Helsinki Declaration. This became the first guideline to propose this as a fundamental requirement for the execution of studies including human participants.

Another document that deserves to be mentioned is the Belmont Report since it is widely used as a reference for the ethical review of studies as well as a base for the formulation of other international and national guidelines. Three ethical principles were defined as fundamental requirements for guiding the execution of studies: respect for people, beneficence, and justice. Each one of these assumes practical correspondence: informed consent, evaluation of the risk/benefit ratio, and the equitable selection of research subjects, fundamental elements that indicate the importance of the tie between science and ethics, which is expressed in this text:

> "(…) the assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research. *For the investigator, it is a means to examine whether the proposed research is properly designed.* For a review committee, it is a method for determining whether the risks that will be presented to subjects are justified. For prospective subjects, the assessment will assist the determination whether or not to participate" (Diniz 2008: 198).

All subsequent guidelines used these three documents as a reference for the elaboration and incorporation of their principles and guidance. This also occurred with Resolution CNS 196/1996, which highlights the need to do an ethical evaluation of the research's methodological approach (Conselho Nacional de Saúde 1996). Chapter 3, titled Ethical Aspects of Research Involving Human Beings, delimits the requirements that should be analyzed for proving the ethical approach of a study. This conception is important since it is necessary to understand that the chosen methodology could include various procedures that could have ethical implications for the participants.

Nonetheless, it is not up to the research ethics committee to judge the researcher's methodological selection. This is an activity that should be conducted by one's peers since the scientific referential is determined by the different fields of knowledge. However, it is the committee's responsibility to evaluate the consistency of the procedures and techniques used for the analysis of

the indicated data to verify if: the proposed objectives can be reached, the research question can be answered, and if there is a guarantee for the protection of the participants. This process is of fundamental importance since a questionable scientific study with inconsistent procedures would reveal an ethical shortcoming and could put the study's subjects at risk, besides wasting time and human and financial resources, with results that may not be taken advantage of (Loue 2002).

These considerations permit to initiate the second topic: the process of ethical training for young scientists. Once again, all of the international documents and Brazilian regulations indicate the need for the technical training of researchers, which should be documented in their *Curriculum Vitae*. Yet, this preparation is not always accompanied by the reflection upon and the actual learning of the values and behaviors that permit the development of ethical sensitivity. This understanding assumes special relevance since the ethicity required for conducting research involving human beings "(…) goes beyond the process of reviewing the protocols written by the research ethics committees" and implies in the adoption of responsible postures on the part of the investigators (Zicker 2006: 2).

There is a consensus that the ethical principles used to direct the practice of research be considered universal. However, depending on the place where the studies are conducted (i.e. developing countries), there could be many questions as well as possible deviations in executing these studies. Among these questions we can cite: the lack of access or limited access to health services and education; the standard of care offered by the local health services, which are far from being the same as those practiced in developed countries; the lack of access to consumer goods; and even gaps in the researchers' training. It is evident, therefore, that the "(…) existence of international documents and domestic regimentation represent the initial step for the adoption of ethical principles in the practice of research" (Zicker 2006: 1).

This is a reflection that needs to be broadened when we are faced with embarrassing situations in relation to behaviors adopted by researchers while they are conducting investigations. The *Nature* recently published articles that revealed the questionable posture of American researchers while conducting studies. Under the title *Scientists behaving badly*, the authors presented the results of a study done with 3,247 researchers — 1,479 young scientists and 1,768 in the middle of their carriers (Martison 2005). Around 35% of those interviewed mentioned having adopted, in the last three years, some type of improper conduct in their activity. Among these the most cited behaviors were: falsification, fabrication, hiding data, plagiarism, breaking confidentiality, disregarding the participants' well-being, using other people's ideas without asking permission, and modifying the methodological design or the results due to pressure from financial sponsors. One aspect which presented significant statistical difference was the fact that researchers in the beginning of their carriers adopted fewer abusive behaviors than colleagues in an intermediate phase of their carrier. These results show the fundamental importance of early exposure to topics related to the ethical aspects necessary for conducting research.

In the American context, another study showed that many incidents of improper conduct in research are not communicated to the competent authorities (Titus 2008). Even though authors recognize the study's limitations, the main behaviors reported were data falsification or fabrication, and plagiarism. Yet again the senior researchers or those in the middle of their carriers were the ones who adopted this type of behavior more frequently. These studies show that this practice exists, but it is not considered to be the predominant behavior. Even so, we must be cautious since "(…) scientific fraud has been growing in function of the large quantity of money involved in research", the need to secure resources for the institutions where scientists work, the existing competitivity between researchers, and even the fear of losing one's job (Goliszek 2004: 44).

This is not only the prerogative of scientists in developed countries. Just for example, in the study coordinated by David M. Kent, the authors presented a hypothetical study with therapy for HIV/Aids (Kent 2003). They verified that 68% of those interviewed would accept conducting a study in which the "…therapy tested had potential local benefit, even when this therapy was recognized as being inferior to that used in the country that sponsored the study…". That is, the adoption of a *double standard* in developing studies is one of the possibilities in such a context, independent of where the researcher is located. These results are regrettable, mainly because the researchers interviewed had all received some type of training related to research ethics.

The incorporation of values and the acquisition of ethical competence is a process that demands reflection and should be initiated in the first stages of academic training. The use of active methodologies for the teaching-learning process can contribute to the training of future researchers and prepare them to face and minimize possible conflicts of interest that could arise in their daily scientific practice.

These examples allow us to begin talking about the third topic: the challenge to maintain *single standard* for the development of international collaborative researches, also called international multicentric studies (Meinert 1996). This type of study is done in different contexts that are marked by extreme inequality and their execution raises serious questions.

Traditionally, international multicentric studies have obeyed the following logic: a) they are supported by institutions (universities, pharmaceutical industries, governmental agencies, or international organizations) located in developed countries (i.e. the sponsoring countries) and are conducted in developing countries (i.e. the host countries) (Guilhem & Diniz 2008); b) these institutions are responsible for designing the study, choosing the procedures and the process for random-

izing the sample in the different arms of the study, that is, defining who will be the participants that will be included in the experimental group(s) or in the control group, besides selecting the researchers and the research centers where the study will be conducted; c) all of the research centers follow the same research protocol in all of the participating centers, independent of where they are located; d) The sponsoring institutions are also the owners of the data collected, which will be systematized in the countries where the study originated (usually the country where the sponsor of the study is located); e) The dissemination of the results is done by the sponsor and any publication utilizing any part of the data collected by one of the team members must have obtained formal authorization from the sponsor (Guilhem 2003). There is, therefore, a prioritization in this process and it is necessary to consider who will be the most benefited by the use of the obtained results.

What characterizes a *double standard* is the adoption of two different standards of care during the process of conducting the study, chosen in function of the country where the study is done and the study's participants. This is not the position in the current version of the Helsinki Declaration, which in Paragraph 29 defines that a study can only be done if it abides by the following criteria:

> "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" (World Medical Association 2000: 4).

For those who defend the *double standard*, nevertheless, the execution of studies controlled by placebo, even in the presence of internationally consolidated treatments, would be acceptable if this treatment were not available in the host country. That is, global inequality, which permits the adoption of different standards of care in different countries, would be a completely justifiable situation for the use of a *double standard*.

According to Macklin's (2004) argument, part of the discussion on this topic began when ethicists tried to answer the following questions: a) Should biomedical studies be conducted in Third World countries when they could just as well be done in the United States or Europe?; b) Is it acceptable that the ethical standards adopted in industrialized countries be modified or loosened when developed countries conduct studies in developing or poor countries? A possible answer to the first question is that there is a large number of multicentric studies being conducted in developed countries, which can be observed by simply accessing a platform which lists clinical trials and verifying the location of the studies (US National Institutes of Health 2008). But it is necessary to consider that in these countries there are very rigid criteria for conducting studies and protection organizations for research participants have been formalized. The answer to the second question is the one that raises greater controversy since the modification of the standards adopted in rich countries is what is responsible for generating the *double standard* in research, an ethically unacceptable situation.

The defense of a *single standard* in research begins with the Helsinki Declaration and the existing correlation with articles from other international guidelines and national regulations, especially those destined for the execution of researches in developing countries. However, the presence of these documents is not always capable of transcending the circuit of fragilities that countries and people are exposed to in a context that is economically and socially unequal. Still referring to Macklin's (2004) conception, it is possible to conduct multinational investigations and at the same time respect and protect the dignity of the participants included in the studies. But, for this to happen, is would be necessary to adopt a culture of human rights, using it as a reference and putting it above existing documents, which should be considered *de facto* for countries, communities, and, why not, for the businesses and institutions that retain the economic power to conduct research.

In the last two revisions of the Helsinki Declaration, the Brazilian posture was to oppose any change in the declaration that would permit the emergence of a *double standard*, defending the use of universal values and ethical principles while conducting studies. This represents the unconditional defense of a *single standard* and the fight to maintain the guarantees and rights of the participants.

This debate brings us to the last point: the proposal to revise the current Helsinki Declaration. This process began in May 2007, when national medical associations and the different actors involved in conducting medical studies were invited to: identify paragraphs from the Declaration that they would like to revise, submit specific proposals for clarification, or even, set forth new topics that should be included in the document. As a result, two initial proposals were elaborated, presented to the scientific community, and exhibited for public consultation. The final version will be voted on at the next assembly of the WMA, which will be held in Seoul, South Korea, in October 2008. It is important to analyze, then, some of the points that were approved, such as how we can adapt the participants' guarantees and protections.

Among innumerous questionings, there are three points that cause the greatest controversy in the proposed text. The first of these is about the use of placebos. An explanation was included in Paragraph 32, which states:

> "When for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of a method and the patients who receive placebo or no treatment will not be subject to any a additional risk of serious or irreversible harm" (World Medical Association 2008: 2).

This passage opens way for the use of placebos even when there is an internationally consolidated treatment. It is necessary that we question in which conditions it would be ethically acceptable to keep study participants only on placebos, depriving them of medications that

have been proven to be effective for their condition. The defense here is that the treatment that is being studied should be compared with the existing therapy.

Another relevant aspect is related to the participants' access to the medications and treatments considered by the study to be successful. Several questions emerge in this context: Up to what point should the medications be supplied after the end of the study? Who should assume the ethical and legal responsibility of supplying the medications after the study? What should be done if the medication is not commercially available or is not included in the treatments furnished by the Brazilian Unified Health System? Except for the last one, the answer to these questions was included in Paragraph 14:

> "(…) 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 methods identified as beneficial in the study or access to other appropriate care of benefits" (World Medical Association 2008: 1).

In truth, this is a delicate semantic modification, which adjusts the access that was previously conceded in Paragraph 30 of the current version of the resolution, where it is indicated that: "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study" (World Medical Association 2000: 5). That is, guaranteeing post-study access to something less than the best existing methods is considered ethically questionable.

One last point is in relation to the inclusion of children and adolescents as participants in studies. Despite being considered vulnerable groups, there are drugs and treatments that could be beneficial for these groups, but for whom simply no specific protocol has been developed. Studies with vulnerable populations should consider the benefits and knowledge that could be produced and applied to improve the quality of life of these groups. As such, it is important that these studies be conducted, certifying that they obey the scientific and ethical criteria so that children and adolescents are protected. Besides this, an additional point specifies that the youngster's own decisions in relation to the study should be respected.

It is interesting to highlight that the Helsinki Declaration has been incorporated by the scientific community of different fields of knowledge as a reference document for the development of studies; yet, it was a document that was originally written specifically for doctors. Nevertheless, we can verify that in this new version, the inclusion of Paragraph 2, in which "(…) the World Medical Association invites other participants in medical research involving human subjects to adopt these principles" (World Medical Association 2008: 2). The recognition that multidiciplinarity in the context of health research can be considered an advance and the invitation for a plurality of opinions, which widens the scope of the discussions, will contribute to guaranteeing the protection of the research participants.

To end, the analysis of these four points allows us to verify that there have been significant advances in the dialog about the great dilemmas that permeate the development of research. Among these we can cite: the delimitation of universal ethical principles to be used in this setting, the elaboration of international and national regulations and legislation, and the preoccupation of scientists and the society in general that the control of scientific practice should not be restricted to scientists. In this aspect, Brazil has advanced greatly: the CEP/Conep System is located in the National Health Council, an example of democratic control of health policies, which demonstrates the originality of the Brazilian system for the ethical review of studies and its legitimacy to defend the interests and rights of the people included in research and obviously the defense of a *single standard* in research.

Note

1. The term *informed consent* is used in the international context to indicate the process of obtaining the voluntary acceptance of the participant who will be included in the study. In Brazil the adopted term is *Free and Informed Consent*. I chose to maintain the first denomination for all of the international documents cited in this text.

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