For a research ethics founded on Human Rights

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Abstract

This study aims to demonstrate that human rights should be the fundamental ethical framework of research ethics. We have divided the approach of the interrelationship between human rights framework and research ethics in three phases, the first marked by the introduction of the principles of Nüremberg, the second by the hegemony of the *Declaration of Helsinki*, and the third is characterized by the increase in international research, the decline of the *Helsinki Declaration* and the adoption of the *Universal Declaration on Bioethics and Human Rights*. Based on the tripartite methodology employed, we have concluded that, despite the unquestionable relevance of the *Declaration of Helsinki* for building a culture of respect and protection of the research subject, we can verify its loss of legitimacy, so, it must be understood that the *Universal Declaration on Bioethics and Human Rights* and the International Law of Human Rights should be the new parameters of the research ethics worldwide and in Brazil.

Key words: Research ethics. Human rights. Declarations.

Resumo

Para uma ética em pesquisa fundada nos Direitos Humanos

Este estudo visa sustentar teoricamente que os direitos humanos devem ser o referencial ético fundamental da ética em pesquisa. Para tanto, dividiu-se a abordagem da interconexão entre o referencial dos direitos humanos e a ética em pesquisa em três fases: a primeira, marcada pela instituição dos princípios de Nüremberg; a segunda, pela hegemonia da *Declaração de Helsinque* e a terceira, pelo incremento das pesquisas internacionais, pelo declínio da *Declaração de Helsinque* e adoção da *Declaração Universal sobre Bioética e Direitos Humanos*. Com fundamento na tripartição metodológica, concluiu-se que, não obstante a relevância incontestável da *Declaração de Helsinque* para a edificação da cultura de respeito e proteção do sujeito da pesquisa, assume-se o enfraquecimento de sua legitimidade, depreendendo-se que a *Declaração Universal sobre Bioética e Direitos Humanos* e o Direito Internacional dos Direitos Humanos devem ser os novos parâmetros da eticidade da pesquisa no mundo e no Brasil.

Palavras-chave: Ética em pesquisa. Direitos humanos. Declarações.

Resumen

Para una ética de la investigación basada en los Derechos Humanos

Este estudio se propone a sostener teóricamente que los derechos humanos deben ser el marco ético fundamental de la ética de la investigación. Por lo tanto, hemos dividido el enfoque de la relación entre el referencial de los derechos humanos y la ética de la investigación en tres fases: la primera marcada por la introducción de los principios de Núremberg, la segunda por la hegemonía de la *Declaración de Helsinki*, y la tercera por la expansión de las investigaciones internacionales, la debilidad de la *Declaración de Helsinki* y la adopción de la *Declaración Universal sobre Bioética y Derechos Humanos*. Basado en la metodología tripartita, se concluye que, a pesar de la importancia indiscutible de la *Declaración de Helsinki* para la construcción de una cultura de respeto y protección del sujeto de la investigación se reconoce la debilidad de su legitimidad, infiriéndose que la *Declaración Universal acerca de la Bioética y Derechos Humanos* y el Derecho Internacional de los Derechos Humanos deben ser los nuevos parámetros de la ética de investigación en todo el mundo y en Brasil.

Palabras-clave: Ética en la investigacion. Derechos humanos. Declaraciones.

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The research ethics involving humans, as considered under the perspective of international documents and the national normative framework, reflects mainly two aspects: Nuremberg ethics and the principlism theory. It is noted that in this paper Nuremberg ethics is understood as based on free and informed consent; on the calculation of risks and benefits to the research subject; on the scientific qualifications of the researcher; and on the distinction between therapeutic and non-therapeutic clinical research. Thus, it appears that, somehow, these two ethical currents are intertwined when it comes to research involving humans. However, the strength of each varies according to the historical moment.

In parallel, the human rights framework, although sharing axiological elements with the traditionally predominant ethical aspects, is clearly not accepted as a reference for research involving humans. Indeed, Beyrer and Kass[1] indicate that little attention has been given to the relationship between human rights and research ethics, and the attempts to incorporate them into codes of ethics in experiments or ethical assessment of research protocols are scarce. Taking into consideration those two identified perspectives and the conception that they are incorporated to international documents and national norms in different ways, this article aims to identify ways of interweaving the human rights framework and research ethics, as well as to check how the theme of research ethics is addressed by the International Human Rights Law.

It is appropriate to clarify that this research adopts, by assumption, the idea that since the adoption of the *Universal Declaration on Bioethics and Human Rights*, in 2005, by UNESCO[2], there was an inflection in the field of research ethics in Brazil. This inflection is embodied in extending the paradigm of research ethics, incorporating the human rights framework as a theoretical and normative framework. So it advocates the recognition that the research ethics' theme has as its central object the protection of the experiment's subject; therefore, the most appropriate normative-theoretical instrument to meet the purpose of such ethics consists of the human rights framework.

At a methodological level, the analysis focuses on major international research ethics documents – *the Nuremberg Code*[3], the *Declaration of Helsinki*[4], and the *Universal Declaration on Bioethics and Human rights* –, despite the recognition that there is currently high number of international and regional guidelines on research ethics. As for the human rights framework, we chose to address only the legally binding United Nations norms, i.e., conventions and human rights treaties.

Based on these documents, the approach of the interrelationship between the human rights framework and research ethics was divided in three phases: the first phase was marked by the introduction of principles of Nuremberg principles of Nuremberg; the second, by the hegemony of the *Declaration of Helsinki* and the third is characterized by the increase in international research, the decline of the *Helsinki Declaration* and the adoption of the *Universal Declaration on Bioethics and Human Rights*. Based on the tripartite methodology employed, this study is structured in three parts, covering each phase of research ethics.

The research has involved humans and human rights.

In this topic, it aims to expose the interconnection between research ethics involving humans and the human rights framework, from historical confluence of both and sharing of standards related to principles. First, it must be registered that the hallmarks principles of human experimentation known as the *Nuremberg Code* and the *International Human Rights Law* have surfaced in the same historical context, which is the end of World War II.

Between 1946 and 1947, twenty three Nazi doctors were tried at Nuremberg, Germany, on charges formulated by the United States of America (USA), for crimes related to scientific and medical research involving humans, framed by the Court as crimes against humanity and war. Among the crimes *on behalf of the scientific and medical progress*[5], it must be highlighted: maintaining naked victims in freezing temperatures for more than ten hours or in frozen water tanks; infection of healthy people through the bites of malaria mosquitoes; submission of victims to inhalation of mustard gas; not providing treatment to injured persons, in order to verify the process of gangrene; and the daily sterilization of victims[5].

At the trial of Nazi doctors it was found that their victims were subjected to medical and scientific experiments with absolute disregard of the volitional aspect. It was pointed out that the fact of them having signed any document or verbally acquiesced is irrelevant, because the condition of complete subjugation invalidates any formal record of consent. Still, it was found that the victims could not express, at any stage of the experiments, their

refusal to integrate them; in many cases, the experiments were conducted by disqualified persons, and all resulted in unnecessary suffering for victims and any means of preventing injuries and deaths were adopted[5].

Faced with such scenario full of atrocities, the judges realized that it was imperative to hold back to the ethics of conducts related to experiments involving humans, going beyond a mere guilty verdict for sixteen of the defendants. Indeed, they have set prescriptions concerning the permissibility of medical experimentation on ten principles, known as *Nuremberg Code* - that in response to the criminal experiments detailed during the trial intends to provide universal normative standards based on ethical principles. It was essential to demarcate the acceptable and to classify non-therapeutic human experiments, as well as the informed consent was raised to the level of a fundamental instrument to protect special populations, such as people confined in concentration camps. In this sense, *Nuremberg Code* articulates a set of principles that shall be considered in any situation in which there is the employment of people in the experiments[5].

In summary, these principles refer to the respect for the physical and mental integrity of the research subject; the experiment participant's self-determination expressed on informed consent; the risks involved; the special care for the research subject's protection; and the researcher qualification[6]. It can be seen that the *Nuremberg Code* focuses on the protection of the research subject, requiring compliance with its voluntary and pressure free, direct and/or indirect, performance. It also emphasizes that although there are risks in the course of the study, there must be balance between benefits and damage to the subject. Finally, the research conduct requires compliance to physical and mental integrity of whom it involves.

In short, the *Nuremberg Code*, the first document of medical ethics elaborated after the 2500 years mentioned by Hippocrates to informed consent[7], presents ethical and legal nature. It safeguards the physical and mental integrity of the research subjects, and, most notably, human dignity. Such protection occurs as it postulates the research subject the condition that the agent shall deliberate on his own life and actions that affects him, being conceived as an end in itself and not a mere instrument to be used for the sake of science. Thus, the *Nuremberg Code* is the principle of human dignity to the field of medicine and, more specifically, to research involving humans.

In the case of the human rights framework, similarly to Nuremberg research ethics, based on informed consent, it was obtained the international recognition consolidated at the end of World War II. The *Universal Declaration of Human Rights* adopted by the United Nations (UN) in 1948, states in its preamble the *recognition of the inherent dignity and of the equal and inalienable rights of all members of the human family*, and considers that the *disregard and contempt for human rights have resulted in barbarous acts which have outraged the conscience of mankind*[8].

As it turns out, the International Human Rights Law building rests on the sense that dignity is inseparable from the human condition, so it is not an accidental quality of certain[9]. And yet, the construction of the normative and institutional apparatus of human rights in the international arena is due to the perplexity caused by the death of thousands of innocent civilians during the Second World War and the consequent perception that ethical and legal standards should be established by international organizations. Indeed, the Commission on Human Rights, created in 1946 shortly after the beginning of the UN work, had the task of taking care of the issue of human rights and turning it into a concrete matter in the international community[10]. It was materialized, initially, under the auspices of the Commission, during the preparation of the *Universal Declaration of Human Rights*.

During this first phase of the history of correlation between research ethics and human rights, it appears the approach regarding the historical context of its emergence, their shared values and practice modes of conformation. Both, the *Nuremberg Code*, the first international document of research ethics, and the International Human Rights Law, reflect the perception of human malignancy that arises from the Second World War; as well as both bring in their bodies the principle of human dignity as the central element, and common values such as physical and mental integrity protection and personal self-determination - both the *Nuremberg Code* and the human rights have the same kind of ethical and legal standards. Both of them consist properly in prescriptive commands of conduct with the common objective of protecting the human being, especially the individual who is lying in state of heightened vulnerability, and recognition of the inherent dignity; thus opposing the Nazi conception that the value of man is determined primarily by its inherent racial virtues[10].

In summary, in this first phase there is a break with the Hippocratic ethics, which is founded on the notion that medical practice necessarily involves

the good for the patient. During the research, the researcher is often unsafe regarding the benefits and effects on the health of the participant subject. Faced with such doubt, some specific ethical commands may emerge, such as ensuring that the patient's consent is free and informed, the experiment shall not cause unnecessary suffering and damage, and risk must be acceptable.

The connection between research ethics, which is grounded in principles of Nuremberg and the human rights framework, specifically the *Universal Declaration of Human Rights*, is characterized by the common historical background and by the international community's response to the outrageous acts committed by states involved in the Great War. This connection gave rise to a propitious ambience to building international consensus on the values relating to human dignity. It shall be added that Helsinki's research ethics shares values with the human rights framework, especially the principle of human dignity. Finally, the *Nuremberg Code* and also the *Universal Declaration of Human Rights* are ethical and legal documents issued by the state, either as unilaterally, as the first, or multilaterally, as the second.

Thus, in the first phase of research ethics during the post-war, based on the adoption of principles entitled the *Nuremberg Code*, it was seen its confluence with the human rights framework. However, after this moment of historical and axiological affluence, research ethics and human rights trod different paths.

Research ethics involving humans and the human rights framework

International medical communities and medical experts proved reluctant in incorporating in their professional practice the precepts of the *Nuremberg Code*, due to establishing the absoluteness of informed consent, which was relativized in later documents published by the World Medical Association (WMA) [11]. Added to this is the fact that the *Nuremberg Code* was considered a document addressed to the Nazis, not applicable to *good researchers*[12]. Consequently, the WMA adopted a code for research and experimentation in 1954, and in 1964, on the occasion of its 18th General Assembly, established the *Declaration of Helsinki*, a statement of ethical principles addressed to medical research involving human subjects, including research on identifiable human data and materials. It is noted that the reference to the *Declaration of Helsinki* initiates from the analysis of its latest version, amended by the 59th WMA General Assembly, held in Seoul, Republic of Korea, in October 2008.

The *Declaration of Helsinki* added to the *Nuremberg Code* new elements in the ethical assessment of research as they have established the distinction between experiments involving patients and healthy subjects, as well as defended the need of a prior ethical assessment by a committee independent of research protocols[6]. In parallel, it has predicted the possibility of medical studies without informed consent (item B.29), not using, in any of its apparatus, the human rights language or the expression of human dignity.

It is only noticed a generic reference to protecting the rights of research subjects (item A.9), their right not to participate or leave the experiment (item B.24) and the duty of physicians to respect the right to self-determination (item B.11). So there are three references to the rights of research subjects and none directed to human dignity. Thus, it appears that the WMA stood apart from the human rights framework as, despite incorporating some rights of research subjects, it has not framed them as "human rights". This is partly justified by the fact that it is an ethical document addressed primarily to physicians, and not a legal instrument addressed to the states, which is a characteristic of human rights standards.

Four years after the adoption of the *Declaration of Helsinki*, Henry Beecher, a researcher at Harvard Medical School, published an article in the New England Journal of Medicine stating the occurrence of 22 apparently unethical experiments that put at risk the health of participating subjects[12]. In one article, conducted at the Willowbrook State School of New York, mentally disabled children were infected with strains of hepatitis, on the grounds they were being immunized. In 1972 there was the Tuskegee study scandal, an experiment carried out in the Southern United States, where 400 syphilitic poor African American men were left untreated, aiming to study the natural progression of the untreated disease[11].

Beecher's denunciation and the Tuskegee study disclosure showed the fragility of the *Declaration of Helsinki* and exposed the imperative need of reflection on research ethics. Due to these facts, the U.S. Senate has proposed creating a commission to address the issue of research involving humans[11]. Accepting this proposition, in 1974 the U.S. Congress established the National Commission for Protection

of Human Subjects of Biomedical and Behavioral Research, whose primary task was to identify ethical principles applicable to human experimentation. As a result, in 1978 it was created the Belmont Report, which summarized ethical principles and guidelines for research involving human subjects identified by the Commission during its deliberative process[13]. In its part B, the three basic ethical principles in the context of the research involving human subjects were established: respect for persons, beneficence and justice[13].

The Belmont Report is anchored on principlism ethical approach, not making use of the human rights framework. The principle of respect for persons focuses on the autonomy of the research subject; the principle of beneficence emphasizes the duty not to harm and to maximize possible benefits and minimize possible harms to the participant on the experiment; and the principle of justice refers to the distribution of benefits and burdens resulting from research[13]. The ethical dimension underlying the Belmont Report was subsequently systematized and further deepened in the book Principles of Biomedical Ethics, published in 1979 by Tom Beauchamp and James Childress - in which they develop the principles outlined in the Belmont Report, as general principles of research ethics and biomedical ethics in general[13].

From this report and the principlism theory, the research ethics has eminently became the principlism ethics, based on the analysis of the research subject's autonomy and the benefits and risks coming from the experiment. As a result, the analysis of research protocols involving human subjects has an apparatus of ethical norms as a parameter, such as the *Declaration of Helsinki* and the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* - formulated by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), in 1993 [14]. The ethical normative of research combine with the bioethical principles proposed by Beauchamp and Childress.

Therefore, we can assert that the second phase of research ethics rests on the ethical review of experiments involving human subjects with the following characteristics: 1) the main international norms, the *Declaration of Helsinki*, come from non-state agencies and hold ethical, not legal, nature; 2) no adoption of the human rights framework in the body. In light of the academic approach to the topic, we shall register that the four principles of Beauchamp and Childress were understood as paradigmatic for research ethics until the early 90s[15].

At this stage, within the sphere of the United Nations Human Rights Protection System there are few documents that directly address the issue of research involving humans. It is registered that in 1966, some years after the adoption of the *Declaration of Helsinki*, the *International Covenant on Civil and Political Rights* (ICCPR) [16] and the *International Covenant on Economic, Social and Cultural Rights* (ICESCR) [17] were incorporated in the International Law of Human Rights, which constitute, together with the *Universal Declaration of Human Rights*, adopted by the UN on 1948, the International Bill of Human Rights[18].

The two covenants, unlike the Declaration, have legally binding nature, forcing their adoption by states that have ratified them. The *International Covenant on Civil and Political Rights*, in its Article 7, expresses allusion to research involving humans. The apparatus determines the prohibition of torture, punishment, cruel or degrading treatments, and also, above all, the submission to medical or scientific experimentation without free consent. The General Comment 7, issued by the UN Human Rights Committee in 1982, which deals with the content of that International Covenant's article, establishes that states must create control mechanisms aiming at protecting the integrity and human dignity. It also points out that states, in their reports, present scarce information on medical or scientific experimentation.

Consequently, the Committee recommends that more attention shall be given to the means of ensuring that the free consent is observed and that the research subject is not subjected to any treatment that violates his/her dignity or integrity. Special treatment shall be dispensed to experiments involving persons not capable to consent. In General Comment 20/1992 on the same Article 7, issued by the same UN body, it is assigned to the states the obligation to adopt the measures necessary to protect the dignity and the physical and mental integrity, especially of those unable to consent, such as those found in any form of detention or imprisonment. Such people should not be subjected to scientific or medical experiment at the expense of their health.

In the sphere of the international human rights law, the *Convention on the Rights of Children*[19], from 1989, establishes in its Article 3 that all decisions concerning a child shall primarily consider the child's best interests. Its Article 12 provides

that children have the right to freely express their opinion on issues related to them, and that this opinion shall be taken into account. The Article 15 of the *International UN Convention on the Rights of Persons with Disabilities*[20], occurred in 2006, reproduces the Article 7 of ICCPR and adds that states must take all effective measures of legislative, administrative, judicial or other natures, in order to prevent persons with disabilities from being subjected to torture or to cruel, inhuman or degrading punishment.

Moreover, under the United Nations Human Rights Protection System there are examples such as the *Resolution on Human Rights and Bioethics* 1.999/63 and the Resolution 2.003/69, both issued by the then UN Commission on Human Rights[21]. These resolutions mention the recognition by the *International Covenant on Economic, Social and Cultural Rights*[17] of the right to enjoy the benefits of scientific progress and its applications, and the provision of the *International Covenant on Civil and Political Rights*[16] about experiment in humans.

The first one refers to the Principles of Medical Ethics, adopted by the General Assembly of the United Nations in Resolution 37/194 of 1982, which discusses the role of health professionals, particularly physicians, in the protection of prisoners and detainees against torture and other cruel, inhuman or degrading treatments. It points out, further, that the rapid development of life sciences opens extraordinary prospect for improving human health, but certain practices may put the individual's integrity and dignity at risk, and scientific development and its benefits shall respect fundamental human rights. In the sphere of the United Nations Human Rights Protection System, it was recommended the establishment of a special rapporteur in order to assess the guidelines for research involving humans and the guidance on ways to ensure the development and dissemination of universal *standards* to human experimentation[21].

Despite the understanding of some bioethicists that the *Declaration of Helsinki* contemplates the association between the ethics of biomedical research and human rights[22], it is clear that the human rights framework is not incorporated in the Declaration - just as it is also not incorporated in the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. From the 60s to the twenty-first century, from the perspective of bioethics, what was generated are international documents which has come from non-governmental organizations and were grounded in ethical principles, either from Nuremberg or the principlism theory, even because such entities are not competent to produce legal norms.

Corroborating this assertion, Resolution 196/96[23] , issued by the National Health Council (NHC), brings in its preamble an explicit reference to the principlism theory, as follows: *This resolution incorporates* (...) *the four basic principles of bioethics: autonomy, non-maleficence, beneficence and justice* (...). Following the model of Helsinki, there is no explicit reference to human rights in the legislative body of the NHC Resolution 196/96, despite the mention of the *Universal Declaration of Human Rights* included in its preamble.

In light of the UN Human Rights Protection System, there are solely two documents that specifically standardize scientific experiments with humans - besides these, there are statements focused on the theme, but, anyway, this matter bypasses the central concerns of human rights bodies. Notwithstanding the aforementioned gap, it is clear that many human rights can be connected with the practice of experiments, such as the right to life, health, physical and mental integrity, information, non-discrimination, access to benefits of scientific progress.

Throughout the history of the second phase of research ethics, the theme is treated primarily by health professionals and human rights have not been absorbed as a regulatory benchmark of conduct. The sense that since Nazi experiments, going through the Tuskegee study and other cases reported by Beecher, research has involved human rights violations is not commonly accepted. What has been the dominant view is that research protocols should be evaluated by ethical bodies showing no direct connection to the human rights of research subjects. Therefore, although Nuremberg's research ethics share with the referential of human rights some aspects that forge its essentiality, during the Cold War - from the 50s until the late 80s - there is no dialogical relationship between the human rights framework and research ethics.

Human rights were markedly positive in legal regulations, while research involving human beings came to be jettisoned matter of the states. Medical and scientific experiments were not in the UN Human Rights Protection System agenda as well as the WMA did not address the issue in the light of the human rights framework. Thus, the mentioned association has not considering the research subject as the holder of such rights nor obliges the State to protect him.

Human rights as an ethical and legal framework of research

In the last three decades of the twentieth century records it has been registered a staggering increase in the number of multicenter clinical research, launching a new period in the history of scientific experiments, characterized as the *internationalization of clinical research*[24]. In Brazil, the largest portion of the research relating to drugs is international - whose patronage comes from transnational companies [25].

Pharmaceutical industries based in high-income countries have shifted to low-income countries with the objective of conducting research with drugs and taking advantage of the vulnerability of their populations and the fragility of their systems of ethical review. The insertion of the pharmaceutical industry in regions of Africa, Asia and Latin America has boosted the ethical debate surrounding the adoption of different ethical standards in the research conducted in high-income countries compared to those carried out in countries of low and middle income, which may be summarized in the expression *double standard*.

This ethical argument was first placed in 1994, when a consortium of university researchers funded by the National Institutes of Health (NIH) conducted research involving humans aiming to study the prevention of transmission of HIV positive pregnant women to the fetus. During the research, it was already known that AZT provided extensive protection against transmission from mother to child, which resulted in U.S. hospitals adopting the standard of care towards the granting of AZT to HIV-positive pregnant women and newborns. However, in the midst of such medical research, researchers ministered placebo for the control group, even already existing standard of care approved in the U.S. [26].

This case was compared to the Tuskegee study by Angell[27], who also pointed the denial of treatment to women and black children. His position was supported by Sidney Wolfe and Peter Lurie, who estimated that 16 research projects, whose object was to investigate the effectiveness of a *short-course* of AZT treatment, used approximately 17,000 pregnant women in low-income countries [26].

The increased performance of the pharmaceutical industry in countries of low and middle income initiated a process aiming to loose ethical standards in order to allow the adoption of different standards of research when this was made in those countries. In this sense, researchers and bioethicists, led by Robert Levine, Yale University physician, proposed to WMA background revisions of the *Declaration of Helsinki* aiming to a more free performance by the researchers and, consequently, the adoption of less stringent ethical standards[26]. The steps being taken by researchers and bioethicists have pointed towards the power to weaken the protection of the research subject and, concomitantly, increase the income of the companies, which have as their central focus not cure AIDS, but increase their profits instead[26].

Due to the pressure performed by researchers and bioethicists, the WMA revised the *Declaration of Helsinki* in 2008, in its 59th General Assembly, in order to contemplate the flexibilities favorable to the pharmaceutical industry and contrary to the protection of research subjects, especially of those socially vulnerable[24]. The changes in the content of the *Declaration of Helsinki* with a view to accommodate it to the desires of the pharmaceutical industry can be seen as a blow to its legitimacy, which has resulted in the loss of space for the *Universal Declaration on Bioethics and Human Rights* adopted by UNESCO in 2005[2].

The *Universal Declaration on Bioethics and Human Rights* contemplates the theme of research in various devices, as in Article 4, Benefit and harm; Article 5, Autonomy and individual responsibility; and Articles 6 and 7, Consent and Persons without the capacity to consent. As an example of initiatives for the adoption of the Declaration as a substitute of the *Declaration of Helsinki*, there is the *Carta de Córdoba sobre Investigaciones con Seres Humanos* (Declaration of Córdoba on Human Research)[28] issued by the UNESCO Bioethics Network Latin America and the Caribbean (Red Bioética UNESCO América Latina y el Caribe), which rejects the version of the *Declaration of Helsinki* approved in 2008 by the WMA and proposes the adoption of the *Universal Declaration on Bioethics and Human Rights* as a normative ethical framework of reference.

The third phase of research ethics is characterized by globalization, which boosted the internationalization of clinical research and situations of research subjects' human rights violations by transnational companies. Still, at this stage, there is the interference by the pharmaceutical industry and fellow researchers in the machinery of ethical review in poor countries that are often subjected to corrupt governments, and the fragile normative research involving humans and socially vulnerable populations.

It is added to this situation the loss of academic and institutional space of the principlism theory, especially in Latin American countries[12].

Whereas in our times research involving human subjects, specifically the clinic, runs through borders, being held in low-income countries by pharmaceutical companies based in high-income countries, it is clear that the regulatory legal framework of industrial activity and the researcher must also be adopted globally. Human rights, standards of ethical-legal nature agreed by international audiences, consist of the frank language [29] shared by the states and therefore are characterized as the most appropriate ethical framework to guide the conduct of transnational companies and researchers. In this sense, the *Universal Declaration on Bioethics and Human Rights* coupled to the constituent regulations of the International Law of Human Rights should be incorporated as parameters for the evaluation of research practice of bioethicists' protocols, especially those who work in ethical review commitees[27].

In the context of research ethics in Brazil, it is important to note that although the *Universal Declaration on Bioethics and Human Rights* has been adopted in 2005, the new version of Resolution NHC 196/96 - which resulted from public consultation held between September 12 and November 10, 2011 [30] -, Resolution NHC 466 of December 12, 2012, did not incorporate the theoretical and normative framework of human rights[31].

It can be seen in the preamble of the new resolution the solely allusion to such a framework, by reference to the *Universal Declaration of Human Rights*, 1948; the ICESCR, 1966; the *International Covenant on Civil and Political Rights* , 1966; and the *Universal Declaration on Bioethics and Human Rights*. In addressing the ethics of research, Resolution NHC 466/12 ignores research subject's human rights as an ethical-legal guide for the scientific research. Then it appears that research ethics in Brazil, especially in the normative point of view, remains dissociated from human rights.

Indeed, it is advocated in this article the replacement of the principlism theory, protagonist strand of research ethics at the human rights framework, which encompasses the principles of the Declaration aforementioned and the human rights applicable to the research, such as the rights to privacy, self-determination, information, health, access to the benefits of scientific progress and physical and mental integrity. The adoption of the human rights framework as a parameter of ethical assessment is justified in cross-border activity of clinical research, as well as in the characterization of human rights as globally shared ethics, as pointed out.

It also added the fact that clinical research can give rise not only ethical violations, but violations of human rights such as the right to health when the right of access to drugs and placebo is denied. Therefore, the states, both the headquarters of the research's sponsor as its host, shall be held accountable when the research subject's human rights are violated. Thus, the incorporation of human rights framework to the research implies the assumption that the task of supervising and regulating the activities of researchers and sponsors is primarily a state duty, as it is a state obligation to prevent human rights abuses by third parties.

From the understanding that research involving humans is a matter of public nature to be regulated and supervised by the State, it appears: 1) greater protection to the research subject, mainly due to the fact that human rights are particularly sensitive to vulnerable populations: 2) increased probability that the research is intended to the public interest; 3) the possibility that state, researchers and sponsors who cause harm to the health of the research subject might be internationally blamed to the organs of the UN Human Rights Protection System and the International Criminal Court.

The proposed change of paradigm has some deployments that shall be highlighted, as not considering them may lead to changes to take place solely in the theoretical sphere. Initially, the first change concerns the categorization of situations that cause harm to the research subjects' health, such as worsening of their illness or death - moving from being a simple "ethical breach" to become "human rights violations".

Internally, as a result, the national standards, such as Resolution NHC 196/96, shall have the human rights as a landmark, giving emphasis to those directly linked to research and highlighting that violations of these shall involve national and international accountability by the Brazilian State and other violators agents. It is adduced that the *Universal Declaration on Bioethics and Human Rights* must be located at the same level of human rights standards, since, nowadays, it is a substitute for the *Declaration of Helsinki*. From the change in normative it is expected that the committees on research ethics begin to internalize human rights in their analysis, not completely replacing the ethical principles of Helsinki or the principlism theory, but amplifying the perception of their members

towards the sense pointed out above: what is at stake is the research subject's human dignity.

In the international arena, it can be noted as an implication of the concept proposed in this paper the construction of theoretical issues and policy management within international organizations and agencies assigned to observation of the international responsibility of states and transnational corporations, due to violation of research subjects' human rights.

The third phase is presented in descriptive and prescriptive bias. In the first one, it is noted the weakening of the *Declaration of Helsinki* and the rise of the *Universal Declaration on Bioethics and Human Rights*, formalizing and strengthening the interface between bioethics and human rights. In the second, it is recognized that the paradigm change in research ethics from its principlism nature to another based on human rights is still incipient, both nationally and internationally. Normative changes and concepts are necessary so that damage to research subjects is seen as a violation of human rights and not just simple ethical violations.

Final Considerations

In this study we sought to demonstrate that the interconnection between research ethics and human rights went through different moments in the history of mankind. The main objective was to maintain that in our times, because of the factors mentioned, human rights must be the fundamental ethical framework of scientific experiments.

Thus, despite the undeniable importance of the *Declaration of Helsinki* for building a culture of respect and protection of the research subject, it assumes the weakening of its legitimacy. The weakening of the document occurred since its amendment in 2008, due to pressures made by those wishing to relax its precepts and allow greater freedom of action for researchers and sponsors. However, with the increasing of international clinical research in the last decades of the twentieth century, it is imperative the existence of global normative references. Given that the *Declaration of Helsinki* no longer fulfills this role, the *Universal Declaration on Bioethics and Human Rights* and the International Human Rights Law shall be the new parameters of the research ethics worldwide and in Brazil.

This change of perspective involves reframing ethics violations within the clinical research, understanding it as a violation of human rights. Resistance of bioethicists and health professionals regarding the strong influence of the human rights framework in the sphere of scientific research, especially in the clinic, is recognized as they have no familiarity with the language of rights and many of them regard as the intrusion of the legal world. Still, it is assumed that in both, national and international spheres, states and the pharmaceutical industry are reticent about the proposal of being framed as human rights violators in situations arising from the research. Therefore, despite the contrasting positions, it is argued that research ethics founded in human rights is in an embryonic stage and the efforts for its dissemination are anchored on the idea that all human beings shall be treated with equal respect and consideration.

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