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Autonomy, consent and vulnerability of clinical research participants

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Abstract

The present study is a bibliographic review that aimed to discuss the concepts of autonomy, consent and vulnerability of clinical research participants by the qualitative approach. It also discussed autonomy *versus* paternalism, vulnerability and the double standard, and the practice of moral imperialism in peripheral countries. Reflections are offered on the points mentioned above in the light of Latin American Bioethics. Finally, the restructuring of legislation and of Research Ethics Committees represents a new perspective.
Keywords: Personal autonomy. Informed consent. Health vulnerability. Research subjects. Research-Humans.

Resumo

Autonomia, consentimento e vulnerabilidade do participante de pesquisa clínica

Esta revisão bibliográfica tem como objetivo discutir os conceitos de autonomia, consentimento e vulnerabilidade do participante de pesquisa clínica por meio de abordagem qualitativa. Discute-se ainda a relação da autonomia *versus* paternalismo; a vulnerabilidade e o *double standard*; e a prática do imperialismo moral em países periféricos. Ponderam-se os pontos mencionados sob o prisma da bioética latino-americana. Por fim, é apontada como nova perspectiva a reestruturação da legislação e dos comitês de ética em pesquisa.
Palavras-chave: Autonomia pessoal. Consentimento livre e esclarecido. Vulnerabilidade em saúde. Sujeitos da pesquisa. Pesquisa-humanos.

Resumen

Autonomía, consentimiento y vulnerabilidad del participante de investigación clínica

Este estudio de revisión bibliográfica tiene como objetivo discutir los conceptos de autonomía, consentimiento y vulnerabilidad del participante de investigación clínica, por medio de un enfoque cualitativo. Se discute también al respecto de la autonomía *versus* el paternalismo, la vulnerabilidad y el *double standard*, y la práctica del imperialismo moral en países periféricos. Se hace una reflexión sobre los puntos mencionados bajo el prisma de la bioética latinoamericana. Finalmente, se señalan como nuevas perspectivas la reestructuración de la legislación y de los comités de ética en investigación.
Palabras clave: Autonomía personal. Consentimiento informado. Vulnerabilidad en salud. Sujetos de investigación. Investigación-Humanos.

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Declara não haver conflito de interesse.

A valuable achievement in the history of bioethics has been the establishing of respect for the autonomy of research participants, who express their decisions to participate in experiments through the means of informed consent. But autonomy can be reduced due to internal or external influences, resulting in vulnerability [1]. Autonomy and vulnerability are connected, as it is important to recognize when a situation of vulnerability arises so that one can guarantee the right to autonomy of an individual, respecting their dignity [2] and guaranteeing favorable means for the granting of proper consent for the exercise of a procedure.

The present study aims to discuss the concepts of the autonomy, consent and vulnerability of the clinical research participant through a bibliographical review with a qualitative approach, considering concepts of autonomy and paternalism, vulnerability and the double standard, as well as the definition of moral imperialism in peripheral countries. The problems were analyzed from the point of view of Latin American bioethics, which is suggested as a new perspective for the restructuring of legislation and research ethics committees.

Autonomy, consent and vulnerability

Autonomy

Autonomy is related to freedom of choice, and corresponds to the ability of an individual to decide for themselves based on the alternatives presented to them, free of internal and external constraints [3]. To be autonomous, in the scope of this work, human beings must choose subjectively, taking into account their own principles, values, beliefs and perceptions. Therefore, respect for autonomy includes considering all factors that interfere with the decision-making ability of the individual.

But autonomy is not a natural characteristic of human beings; it develops from the biological, psychic and socio-cultural contributions of the environment in which they live. Temporarily or permanently, the individual can have their autonomy reduced, based on: age group, such as children; psychological state, such as people suffering from mental disorders; physical state, such as a patient in a coma, among other circumstances [3].

The *Universal Declaration on Bioethics and Human Rights* (UDBHR) [4] recognizes in Article Five that autonomy is not absolute, and that there may be situations in which it is absent. Even if a person is considered autonomous, at times they may end up acting without autonomy. Mental, emotional and physical alterations can compromise the autonomy of a subject, reducing their rational capacity [3]. However, it should be emphasized that even people affected by mental problems, or those who are confined in places of guardianship, should not be automatically considered to be without the capacity to decide. Although such an individual is declared unable to understand certain situations and make certain decisions, there are times when they can make choices about their own life.

Consent

The practical application of autonomy is consent, which is the voluntary and conscious permission to perform a procedure, treatment or experiment, based on previously clarified information. The principle of consent represented an important advance in the history of bioethics, on the basis that it is intended to curtail studies carried out without the permission of their participants. To be effective, consent must occur through a voluntary process, based on clear information, provided in a language accessible to the target audience. The purpose of the consent form is to make the choice of the participant of fundamental importance.

The UDBHR considers, however, that there are people without the capacity to consent, and in Article Seven [4] warns that special protection must be given to such individuals, and their refusal to participate in research must be respected. It is emphasized that there is a difference between having the full cognitive ability to defend one's interests and give consent, and to have reduced capacity. There are people who have their ability to give their free and informed consent reduced by restricted cognitive ability, such as people with mental disabilities. Generally, the consent of the individual responsible for this person is requested, as well as their own consent, when applicable.

Reduced ability may be due to cognitive deficits or sociocultural factors, such as low schooling or illiteracy [1], for example, which also require special attention to ensure the effectiveness of the process of free and informed consent. It should be stressed that, in addition to a low level of education, lack of familiarity with the technical terms of research may make it difficult to obtain free and informed consent. Examples of this are the words "placebo" and "randomization", which do not have a direct translation in some languages [1]. In this

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case, it is necessary for researchers to communicate appropriately, facilitating free and informed consent.

Vulnerability

The inability to make the best decision to protect one's own interests is defined as vulnerability. It is possible to classify this concept as extrinsic or intrinsic vulnerability. The first is caused by external issues such as social and cultural problems, a lack of economic resources and a low educational level. The second is due to the internal characteristics of the individual, such as mental disorders, intellectual deficits or other diseases, as well as age group, which includes children and the elderly [1].

These aspects can occur individually or simultaneously and raise ethical discussions about participation in research. This is because it is unethical to take advantage of a person's vulnerability by preventing them from deciding for themselves and including them in a procedure at the wishes of others, or by allowing them to make decisions based on information that has not been clearly communicated to them. On the contrary, for bioethics, the vulnerable individual must be protected.

Article Eight of the UDBHR [4] indicates that human vulnerability and individual integrity must be respected and protected. However, throughout history, there have been several situations in which disrespect for vulnerability has been observed, placing scientific knowledge above human values. In addition to the well-known experiments carried out in Nazi concentration camps during World War II, several other atrocities were later committed with human beings, even though ethical reflections on human participation in research already existed.

An example of this was an experiment with the mentally handicapped carried out in Sweden in the 1940s. The objective was to find out if the causes of tooth decay were related to the increase of sugar consumption. To achieve this, it was necessary to adopt an overly sweet diet and observe its influence on teeth. As they could not find volunteers, the researchers resorted to a psychiatric clinic in the city of Lund. The study was developed by the country's National Dentistry Service and was sponsored by sweet manufacturers, who argued that their candies did not contribute to the development of cavities. However, the result showed the opposite, and the teeth of the participants were ruined. It should be noted that, in this study, there was, of course, no consent from the participants or their guardians [5].

Another example of a study of vulnerable populations occurred in the 1990s in Africa, in verifying the vertical transmission of acquired immunodeficiency virus (HIV). The study consisted of testing a short-course treatment with a drug already used in developed countries, but applying a longer administration time, and employing a placebo control [6]. The study was criticized in an article published in 1997 by Lurie and Wolf [7], two US researchers linked to the Public Citizen's Health Research Group, Washington, USA, who denounced this type of research based on the fact that they exceeded the boundaries of the question of placebo use and violated informed consent, taking advantage of the vulnerability of poor and uninformed populations [7,8].

According to international regulations, such as the Helsinki Declaration, the use of a placebo is allowed when there is no proven intervention or when, for convincing and scientifically sound methodological reasons, its use is necessary to determine the effectiveness or safety of an intervention [9,10]. Brazil, however, is no longer a signatory to the Declaration of Helsinki [11] and follows the determinations of Resolution 466/2012 12 of the National Health Council (Conselho Nacional de Saúde - CNS), which governs research on human beings. In Brazil, a new therapeutic approach should be tested by comparing it with the best prophylactic, diagnostic and therapeutic methods available, and placebos can only be used when no such proven methods exist. In addition, research participants should be informed about the possibility of their inclusion in the placebo group, and what this means [12].

Problematizing concepts

Autonomy versus *paternalism*

Paternalism brings two bioethical principles into collision: beneficence and autonomy. While professionals learn in their training that they must always promote the health of patients under their care, at the same time the patients should have their autonomy respected. Paternalism can be seen as a way of reducing the autonomy of the patient. In paternalistic actions, to provide benefits or avoid harm, a professional decides for and about a patient, without the patient participating in the decision [14]. There are various

forms of paternalism. According to Beauchamp and Childress, cited by Munhoz [14], strong paternalism is when a professional makes a decision on behalf of his patient, even though the patient can decide autonomously for themselves. Weak paternalism, meanwhile, is when professionals decide on behalf of patients who are unable to decide for themselves, as well as those with temporary or permanently compromised autonomy [14].

Wulff, Pedersen and Rosenberg, cited by Segre, Silva and Schramm [15], establish other classifications of paternalism. Among these are genuine paternalism, in which the absence or significant limitation of the autonomous capacity of the patient is verified; authorized paternalism, in which there is the implicit or explicit consent of the patient; and unauthorized paternalism, in which there is no consent from the patient [15]. On the one hand, it is argued that the social, cultural, religious and emotional contexts of patients should be considered, and professionals should provide guidance so that the individuals themselves can decide on the best option. On the other hand, there are those who argue in favor of paternalism, justifying that diseases lead to the reduction of the autonomy of the patient, and that it is acceptable for professionals to act with unauthorized paternalism, as their intentions are always to promote the well-being of the patient [14].

Although it is considered that paternalism infringes the autonomy of the individual, such actions can be justified in the medical environment, especially on the basis of the principle of beneficence. For Pellegrino, cited by Rocha [16], when it comes to medical ethics, beneficence should be considered as the primary principle, since the purpose of the profession is the patient and their interests. In his work "For The Patient's Good", published in partnership with Thomasma, Pellegrino argues that beneficence is the principle that mediates the conflict between paternalism and autonomy [17]. He also advocates that the actions of the professional should be aimed at the best interests of patients, who have their own perceptions, preferences, values, and goals, which are reflected in respect for their autonomy [16]. Engelhardt, author of the book "The Foundations of Bioethics", cited by Schmidt and Tittanegro, considers autonomy to be the highest principle, as it *can serve as a basis for uniting moral strangers, which is the moral pluralism of society, because respect for the individual is the only common vision among all groups* [18].

Vulnerability and the double standard

Another practice that affects the autonomy of individuals who experience conditions of vulnerability without necessarily bringing them benefits is known as the double standard, which is the adoption of dual ethical standards for performing research in central and peripheral countries. With their bases in wealthier countries and sponsored by the pharmaceutical industry, multi-center trials seek out peripheral countries, such as the continent of Africa, to apply their research. The reason is that legislation tends to be more loosely enforced in such countries, in contrast with the host nations, where such studies would not be approved because of more rigid norms and regulations for the protection of human rights [19].

The target of these surveys are generally people with low incomes and in other situations of need. In other words, the application of clinical research is related to what is defined as social vulnerability, determined by a lack of resources, access to information, health, and public policies [20]. There may also be issues associated with gender, ethnicity and age group. It is often said that poverty is the main vector of vulnerability, but it is important to emphasize that in some cases poverty is related to gender, color and other characteristics [21]. This can also be seen in the Tuskegee case [22] and in the study on the transmission of HIV with pregnant women in Africa [6].

As a result of this practice, the question arises: is it justified to use different ethical standards for research carried out in countries that are different due to the economic, social and cultural disparities of the various nations of the world? This issue became known as "the double standards question", with some opinions against the principle, but some in favor [20]. The arguments in support of the double standard do not consider it to be an ethical deviation, for example, to use placebos in clinical trials in poor countries, even where there are proven and valid treatments for the diseases about which the studies are being conducted, provided such treatments are not accessible to the population from where the participants are recruited. Advocates argue that with clinical trials, at least a chance of treatment is given to those who were randomly selected for the test group, and that the risks of those in the control group are not increased [20].

In other words, in poor countries, where the majority of the population lacks basic health services and treatments, participation in placebo

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trials should be seen as an opportunity, as those who do not take part would not even have the chance of access to medication.[23] Another point, according to proponents of the double standard, is that such trials could bring indirect or secondary benefits to participants, such as medical care. In addition, they would be supplying health institutions in these countries with equipment and also contributing to the training of human resources[20]. Yet the double standard, while defended by some, is contested by others. Several authors criticize the use of the double standard in clinical research, such as the philosopher Ruth Macklin, cited by Guilhem[23]. In her 1976 book "Moral Problems In Medicine", she questions the carrying out of research in third world countries, instead of in the United States or Europe. She also criticizes the modification or flexibilization of the ethical parameters of research which is proposed by industrialized countries, yet carried out in poor countries, and states that the double standard is ethically unacceptable[23].

The recruitment of participants only from such countries could also lead to a bias towards external validity, as diversity is an important point for the generalization of the results. Physical, physiological, and genetic factors may affect response to treatment. Thus, the inclusion of participants from several countries is fundamental for population representation[24,25]. In addition, the use of placebos in clinical trials is related to the state of economic and social vulnerability of countries and their population, and, consequently, the scarcity or limitation of access to basic medicines[23]. But the difficulty of access to medicines should not be considered a natural inequality, but a result of the social exclusion present in poor countries as a result of political and economic conditions, in which rich countries, which today are the sponsors of research, have their share of historical responsibility[20].

Therefore, the problem of access to medicines should not be seen as a local model of treatment in order to ethically justify the reduction of protection of physical integrity and benefit-sharing to the participants of research[20]. In addition, in poor countries, the difficulties public health systems face in terms of the distribution of medicines stem partly from the prices stipulated by the pharmaceutical industry and their defense of their patents[20]. Under these conditions, the reduced research costs and the double standard permission encourage the pharmaceutical industry to maintain high prices, so that there will always be population groups without access to medicines, thus justifying the execution of clinical trials with faster execution and lower costs[20].

From a more philosophical perspective, it is not ethically acceptable that the instrumental rationality that aims at a methodological and/or economic purpose can assume a value superior to the responsibility of health professionals, whether researchers or otherwise, in the case of diseases for which treatment already exists[20]. It is important to consider that while statistical calculations of morbidity and mortality, risks, damages and research results are merely impersonal numerical data, the suffering caused by a disease that can be avoidable or treatable, and the side effects caused by a test drug, are a physical, social, mental and psychic reality experienced by individuals in their bodies and their lives[20].

As such, if a research methodology is considered unethical by developed countries, it should also be thought of as unethical when proposed for poor countries[23]. Researchers and sponsors have a moral obligation to research participants not only during the execution but also after the completion of a study. There should be a formal commitment between them so that participants who benefited from medication during the research continue to receive it until it is available or accessible through the health service of the country in question. The communities and countries that contribute to the development of the drug should benefit from it[23,26]. From an ethical point of view, at the end of the study the medicine that benefited the participants during the research should continue to be provided such individuals, as they have contributed to knowledge and taken risks, and not to provide the drug could violate their health and physical integrity.

The idea that research participants in peripheral countries should bear the consequences and take all the risks without enjoying the benefits is unfair.[23] There are arguments that judge the double standard as a form of violating human rights by breaching several principles described in the UDBHR. The double standard does not consider the vulnerability of the target population of the study or its participants, who are often vulnerated and thus not fully autonomous. Therefore, the consent process is carried out erroneously.

The double standard often also breaches the principles of benefit and harm, as in many clinical trials conducted in poor countries the participants do not benefit from the findings at the end of the study, bearing only the risks and damages

arising from their participation. This also leads to violations of the principles of equality, justice and equity, as these three elements relate to the well-being of the population in a balanced manner among peoples.

Vulnerability, peripheral countries and moral imperialism

In addition to giving rise to the double standard, the situation of poverty, related to a low level of education and added to other factors, such as the limited research capacity of some countries, gives rise to the problem of moral imperialism. An example of the indirect influence of moral imperialism is the educational actions promoted in poor countries, which through seminars and training programs are designed to convert researchers and members of ethics committees and government agencies into transmitters, in their territories, of the ideas of rich countries. Some countries have even attempted to propose amendments to the Helsinki Declaration, the main international normative document on research ethics, in order to relax the rules on the responsibilities of sponsors and multinational research groups [20,27].

The 2008 Declaration of Helsinki, a version of which Brazil is not a signatory, contained important changes, especially regarding the use of placebos and access to post-study benefits. In the previous version, it was stated that clinical research would only be justified if the population in which the research was developed benefited from the results. In addition, the use of placebo as a control was acceptable only when there was no treatment for the disorder being studied, and, at the end of the study, participants should benefit from the best methods identified therein [20].

After meetings between several countries that proposed amendments to the Declaration, the 2008 version of the document was reformulated and renumbered. The new wording states that, at the end of the study, participants should have access to interventions identified as beneficial or other appropriate care or benefits, leaving room for researchers to offer secondary benefits which are not the direct result of study [20]. The use of placebos would be allowed when it was necessary to test the safety and efficacy of the interventions, provided that the participants who received or stopped receiving some type of treatment were not subject to any risk of serious or irreversible damage, making the defense of the interests of participants fragile [20].

These changes contributed to maximizing the interests of a pharmaceutical industry which holds undisputed power, ranking among the four most profitable commercial activities in the world [20]. Most importantly, they compromised the protection of research participants, who are often from socially vulnerable communities located in peripheral countries. Poor countries are obviously more fragile than their developed counterparts, and political and economic pressures to accept these standards only tend to increase the gap between rich and poor nations in terms of development, protection and health promotion. Brazil, however, has adopted a different attitude to the Declaration. As determined by Resolution 466/2012, the use of placebos is prohibited when there is effective medication for comparison, being allowed only when there is no proven method [12,28].

Latin American bioethics in the analysis of these problems

In poor countries, where there is precarious access to various types of services, ethical regulations tend to be flawed, which allows the permitting of research that would certainly not be accepted in developed countries with stricter standards. In addition to legislation in peripheral countries, the conditions of life in such places - where there is little access to health care, medicines and basic sanitation - increases the vulnerability of the population.

However, we are dealing with a universal condition to which all are subject. This means that, as mortal beings, we are all capable of being affected by the process of vulnerability, which ceases to be a potential condition when the individual is no longer vulnerable and becomes violated [29]. The autonomy of the individual is weakened during this process, and special measures must be taken to ensure their protection, which is one of the main objectives of bioethics.

Persistent questions have arisen from the extreme economic and social inequalities present in the countries of the Southern Hemisphere, and given rise to a concept defined as "intervention bioethics". This proposes a concrete alliance with the historically more fragile parts of society and emphasizes the need to politicize the moral problems arising from the violated condition of most of the populations of Latin America and the Southern Hemisphere [30,31]. Intervention bioethics

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advocates prioritizing policies and decision-making that benefit the greatest number of people for the longest time, resulting in the best possible consequences and the search for viable and practical solutions to the conflicts that identify with the very context in which they occur [30-32].

Another concept is the so-called "bioethics of protection", which is dedicated to the population of the violated, who are not only exposed to conditions of vulnerability, but are also "wounded" by the situation. That is, those who are not fully autonomous, as they do not have the minimum resources necessary to exercise their full autonomy [33]. The objective of bioethics of protection is to promote and provide public policies capable of providing the necessary support so that individuals, despite their condition of vulnerability, can optimize their capabilities and potentials and make competent choices [29]. Its target is the population of the vulnerable and susceptible, as it aims to provide shelter for those who, in fact, are not able to deal with adverse situations through their own means.

However, the bioethics of protection does not apply to those who, while in a situation of vulnerability, can face adversities through their own means [29], as this would mean it would lose its emancipatory meaning and become paternalistic [34]. The presence of human rights in these theoretical proposals is fundamental to emphasize human dignity, as well as ensuring respect for autonomy and vulnerability and compliance with the process of free and informed consent, especially in regions where there is marked social inequality.

New perspectives from a bioethical perspective

It is important that the problems that emerge from biomedical research conducted in poor countries and sponsored by companies based in rich countries are confronted in the area of human rights, by invoking systems, both regional and within the sphere of the United Nations, to monitor these rights so that violations by the pharmaceutical industry are denounced [35]. The occurrence of a double standard in the relationships between nations represents a violation of human rights on a global scale, and should be treated as such and supported by appropriate international directives, which, in reality, protect the dignity of human beings and those who participate in scientific research [19].

It is possible to believe that there is a way in which international studies can take place in a manner that respects and protects the human dignity of the participants. To this end, the perception of human rights should override existing documents, and be a genuine part of the considerations of countries and companies that have the economic power to coordinate research [23]. For human rights-based analysis to be adopted in research, whether clinical, epidemiological or even social, it must be seen as an essential condition to enable the implementation of programs that tackle health needs in different communities around the world. Following this logic, the countries participating in studies would share in the distribution of knowledge in a fair and equitable way [23].

It is accepted that the development of international biomedical research is indispensable for scientific progress. However, it is also essential that the guidelines created at an international level to regulate the procedures of these surveys continue to evolve in the same direction, adapted to local contexts and particularities, in order to protect the participants of the research [20]. The creation of suitable guidelines requires increased rigor and technical and ethical requirements in order to balance the deficiencies that exist in the measure itself, and that are capable of intensifying existing risks or causing additional ones [20].

It is important that international rules and parameters exist to guide the planning of the scientific research developed in each country. However, the peculiarities of each nation must be taken into account so that clinical trial proposals, like globalized social operations, are carried out in a manner that respects human rights [20]. It would be appropriate for developing countries to elaborate their systems of ethical evaluation on an autonomous basis, and these national regulations could be drafted in accordance with local contexts. Instruments should also be created to foster independence, social control and transparency, which would be used democratically [20].

In Brazil, for example, protocols involving international collaboration must provide the written approval of the study in the country of origin, together with an explanation of why the study cannot be carried out in such country [36]. The creation of systems for the regulation and social control of research in peripheral countries is of paramount importance so that the present situation undergoes significant changes to

benefit the most vulnerable populations [37]. The construction of these systems is important to avoid moral imperialism and to prevent research with abusive and exploitative characteristics, as well as to encourage international research of a cooperative nature. These systems should encompass two basic designs [37]:

- Genuine formulation, which includes the elaboration of guidelines and directives adapted to the economic, social and cultural contexts of countries, based on three points of protection for bioethics, which are the proper obtaining of consent, the maximization of benefits and the minimization of risks;
- A sociopolitical program based on the elaboration of normative regulatory tools, exercised through laws and ethical directives for research involving human beings, and the mediation of democratic debates for social control, involving institutional, regional and national research ethics committees.

In this context, ethics committees are fundamental for protecting research participants. Due to their importance, factors related to their structure and functions should be considered [23]:

- The composition and training of members of committees, which should be composed of people with different backgrounds, including those who have experience in the areas of scientific and bioethical methodology. The presence of representatives of the community is also ideal, so that there is pluralism of ideas;
- That members are independent of the researchers submitting protocols for consideration, so that relationships between the two cannot affect the ethical review process;
- The ability to analyze conflicts of interest that may arise from conducting research;
- The ability to verify that the objectives outlined in the project genuinely relate to the needs of a particular community;
- The weighting of risks and benefits to protect participants from exploitation;
- The establishment of prior agreements to identify and stimulate that which is most beneficial and favorable to the participants and the countries involved after the completion of the research.

Articles that allow the checking of whether components of vulnerability are present, or if due care has been taken to avoid them, could also be included in the analysis of ethics committees. These components may be associated with social class, gender, racial aspects, sexual orientation, age group, or geopolitical location [38]. In addition to evaluating the ethical standards of research studies, ethics committees are also necessary for the process of training professionals. It is important that in the area of health this training encompasses critical ethical thinking and expands the awareness of future professionals in relation to the reality of the population, that learning is aimed at the problems of the population receiving care, and that the professional acts and interacts as a transformer of reality [13].

The protection of the vulnerable, especially those in poor countries, where people lack access to basic health and education services, has always been a concern of bioethics. In these locations, the population barely understands what it means to participate in a survey, and are unaware of the differences between medical treatment and clinical trials [23], or their risks. Consequently, the free and informed consent form is one of the main safeguards to protect participants. The need for informed consent stems from the legal foundations for any interventions involving human beings. Based on this document, the participant has access to the information necessary to understand the research, its justification, its objectives, its methodology and guarantees, as well as their own rights [23].

Another important point is that the research participant must have the time to read the form and reflect on the text, and is free to consult not only the investigator and their team, but also their family members and others to help them feel secure in making decisions. In this process, the performance of the researcher must be neutral and impartial, so that there is no influence or induction on the individual to participate in the research. In addition, the methodology of a study translates the ethics of research. By obtaining the appropriate consent of the participants, respecting their autonomy and dignity, the study recognizes their vulnerability and indicates that they must be protected.

Final considerations

The production of knowledge through scientific studies is of the utmost importance. They bring valuable achievements, and new discoveries that produce drugs and treatments, and contribute to improve the quality of life and increase the

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life expectancy of the population. However, it is necessary to reflect on the results obtained through procedures with unethical methodologies, such as the Nazi experiments that occurred during World War II. These procedures did not follow any ethical principles, as described in literature, such as the book "The Nazi Doctors and the Nuremberg Code," by George Annas and Michael Grodin, which discusses the trials of Nazi physicians [39].

The production of knowledge is valid, but the manner in which it is produced must meet ethical parameters to avoid abuses. For the development of science, it is necessary to respect limits so that no harm is suffered. It is essential to balance risks and benefits through ethical analysis, ensuring the protection of participants. In no circumstances should knowledge be placed above human values, for individuals must be an end in themselves, and not a means. Although there are international normative documents on research ethics, some practices in the scientific field persist, such as the double standard and moral imperialism, which violate various principles of human rights, such as autonomy, consent, beneficence and dignity. This is because the bioethical perception of this subject is recent and still in its early stages.

The conception of human rights should override normative documents. This idea must be adopted in developed countries, which have the economic power, coordinate research and are home the main companies in the pharmaceutical industry. Bioethics is therefore a tool for international dialogue.

Cooperation between nations, development policies aimed at combating poverty and social inequalities, and the adequate training of professionals in order to ensure the contemplation of human rights are essential to respond to ethical demands. In relation to this ethical imperative, it can be concluded that research should be based on the respect for human dignity even when the autonomy of the individual is reduced by vulnerability, compromising the consent process.

As can be seen, the compromising of autonomy may result from intrinsic (mental disorders) and extrinsic (poverty, illiteracy) factors. The fragility of the former makes them difficult to change, but external factors can be altered. The strategies adopted by public policies should be directed towards reducing these factors, so that this reality can be changed, when possible. This would also minimize the difficulties of understanding when inequalities are internal to individuals. While medicine is concerned with studying and shaping internal aspects, politics should address external problems, both of which are based on principles of human rights. And bioethics acts in this scenario as a mediator. Cooperation between nations, development policies aimed at combating poverty and social inequalities, and the adequate training of professionals to contemplate human rights, are essential to respond to ethical demands. In relation to this ethical imperative, it is concluded that a research project should be based on respect for human dignity even when the autonomy of the individual is reduced by vulnerability, compromising the consent process.

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