Emancipation in the struggle for equality in research involving human volunteers

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Abstract

This manuscript presents as a case study the most controversial aspects of a research conducted in Guatemala (1946-1948), sponsored by the United States Public Health Service in which participants were intentionally infected with *Treponema pallidum*. The analysis of changes in the 2008 Declaration of Helsinki and the still insufficient adherence to UNESCO´s Universal Declaration on Bioethics and Human Rights emphasizes the importance of applying internationally accepted ethical standards for human volunteers to prevent unethical research. It concludes that the involvement of scientists and activists is crucial to achieve internationally accepted ethical standards to be equally applied throughout the world, avoiding the risks of double standards, and also that egalitarian participation in research and fair distribution of its benefits will be an important step towards universal access to good quality healthcare for all people.

Keywords: Ethics, research. Public health. Helsinki Declaration. Protection. Effectiveness.

Resumo

Emancipação na luta pela equidade em pesquisas com seres humanos

Este artigo apresenta como estudo de caso os aspectos mais controversos de pesquisa conduzida na Guatemala (1946-1948), patrocinada pelo Serviço de Saúde Pública dos Estados Unidos e envolvendo participantes infectados intencionalmente pelo *Treponema pallidum*. Analisando as alterações de 2008 na *Declaração de Helsinque* e a ainda pequena adesão a outros instrumentos internacionais, como a *Declaração Universal sobre Bioética e Direitos Humanos*, da Unesco, a discussão enfatiza a importância da implantação de diretrizes éticas internacionalmente aceitas para impedir que voluntários humanos sejam envolvidos em pesquisas não éticas. Conclui considerando que é indispensável o envolvimento de cientistas e ativistas para alcançar padrões éticos universalmente aceitos e aplicáveis, para evitar *duplo standard*. Além disso, que a participação igualitária em pesquisas e distribuição justa de seus benefícios será importante passo para atingir o acesso universal a cuidados de saúde de qualidade para todos.

Palavras-chave: Ética em pesquisa. Saúde pública. Declaração de Helsinque. Proteção. Efetividade.

Resumen

Emancipación en la lucha por la equidad en investigaciones con seres humanos

Este artículo presenta como estudio de caso los aspectos más controvertidos de la investigación realizadas en Guatemala (1946-1948), patrocinada por el Servicio de Salud Pública de los Estados Unidos e involucrando participantes infectados por el *Treponema pallidum* por todo el mundo. Analizando los cambios en la Declaración de Helsinki de 2008 y la pequeña adhesión, en aquel entonces, a directrices internacionales como la Declaración Universal sobre Bioética y Derechos Humanos de UNESCO la discusión enfatiza la importancia de aplicar normas éticas aceptadas internacionalmente para impedir que voluntarios humanos participen de investigaciones no éticas y concluye considerando que es indispensable la participación de científicos y activistas para alcanzar las normas éticas universalmente aceptados y aplicables, para evitar el *doble estándar*. Además, que la participación igualitaria en investigaciones y la distribución justa de sus beneficios será un importante paso para lograr el acceso universal a cuidados de una salud de calidad para todos.

Palabras-clave: Ética en Investigación. Salud pública. Declaración de Helsinki. Protección. Efectividad.

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The discussion about the ethical standards for the biomedical research in developing countries has gain considerable visibility in the past few years [1-4]. This interest was initially nurtured by the need for research related to AIDS epidemic and by the migration of clinic assays from the industrialized countries to developing countries. Although some of the researched diseases occur worldwide, partially explaining the inclusion of the the developing countries, it is concerning that this raise does not include the variety of the diseases that affect especially the poorest countries.

Even with progress of science and technology, the benefits rarely reach these populations. More than one third of the worldwide population still lives in unbearable conditions of poverty, with little or none access to health services and to basic medication. So, for the scientific progress to follow the moral progress, it is necessary that the standards of the health services improve and the investments be directed, rather, to the development of ethical and relevant studies of the local priorities, aiming the improvement of the public health for everyone[5].

The record of several unethical researches involving human beings, not only in World War II[6], but also in peaceful times, such as the atrocities in Tuskegee[7,8] and the research barberries recently revealed in Guatemala (1946-1948)[9,10,11], only demonstrated the importance of this discussion, that will be the focus of this article. When presenting and analyzing this cases, it is intended to illustrate the major aspects that still affect the ethical control of the clinical studies around the world.

Ethics in the international research and global health

The need to develop effective vaccines and powerful medication, both accessible to the treatment and to the control of several diseases, including AIDS, and that make research with human volunteers necessary, is unquestionable. That can be confirmed by the daily 7,500 new cases of the infection caused by the HIV virus [12], more than 90% of them in developing countries. The same occurs with other diseases, such as tuberculosis, viral hepatitis, leishmaniasis, malaria and leprosy.However it is unacceptable that such urgency is used to decrease the ethical standard of the clinical assays[3, 13, 16].

If the researchers, in general, are privileged people, many volunteers are from the most vulnerable populations around the globe, living in poverty, fact that facilitates their exploration, with little or no voice in the decisions made were or how the research should occur. The presented explanation, saying that those communities need urgent answers to the specific questions of the research in general, is not true, once the benefits of the research frequently is not accessible to them.

The real and urgent necessity of those communities is to have access to the researched, developed and many times already used products. It is alleged, that there is inequality everywhere and that the specific question of the research can only be answered in a specific community (often poor). Even in the few situations in which this specificity may be defended, the vulnerability of the potential participants makes it almost impossible to get the real and free will consent that is necessary. Consequently, in situations like the ones mentioned and listed in documents of the World Health Organization (WHO), related to the care and ethics of the research about tuberculosis, presented in Chart 1, at the end, it is even recommended that the research do not be executed[17]. In these cases, it is the necessary to adapt to the local conditions or to search for regions\communities in which the research can be conducted, with the commitment that the results will be available were they are needed.

Another current issue is the access to health services during and after the assays. It is more than fair to say that there can be no double standard; everyone should have access to the proven best health care, even when there are economic constraints. The economic discussion cannot be used to reduce the ethical requirements.

These aspects of participants protection in clinical studies reveal controversies regarding ethical standards for conducting research, such as the Declaration of Helsinki (DH)[18], which over the past four decades has become a benchmark in protection of trial subjects. However, recent changes in DH (2008) decreased the effectiveness of their protection. Assuming that we live in an unequal world, any change should aim to make ethical obligations to the most vulnerable even more stringent, as well as its application in all research involving human subjects, wherever they are held - and not to subsume them.

In the 2000 version of the Declaration of Helsinki, one of the key points of the discussion was in items 19 and 30. In the first item, clinical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out benefit from its results. This item was retained in the 2008 version. However, the item 30, which

guaranteed access to researched products, including medicines, regardless of their place of execution, was modified. It also defined that, as the participation as a volunteer requires balance between costs and benefits, there is no justification to interrupt access, upon completion of the study, to the results that proved beneficial during the research. The 2008 modification facilitates its non-compliance, opening the possibility that the benefits to be shared are not the effective access to interventions, but other "appropriate" care, which is vague.

Another frequent and also sophist controversy is that one cannot expect that funders and researchers to assume the burden, for that would inhibit important research for the direct care of the health needs of these populations. Accepting this argument is misguided protectionism in favor of agencies and/or pharmaceutical industries. In general, the argument employs the high costs for not maintaining treatment of volunteers after the end of the experiment, with no systematic evaluation of these costs, which probably represent a tiny fraction of the usually mostly billionaire budgets of research. The argument that, if implemented, provisions of post-trial access (item 30 without modifications 2008) would commit necessary research is similarly faulty. Brazil is an example that proves the fallacy of the argument, because the National Health Council (CNS) / National Council of Research Ethics (Conep) kept this requirement of access, and proposed clinical trials were not reduced, instead, they keep growing.

Precedent and concomitant – Tuskegee

To understand these controversial points, as well as the dynamics surrounding clinical trials, it is necessary to go back to 1932 and remember what happened in Tuskegee, Alabama. At that time, the Public Health Service of the United States of America (USA) initiated a project to study the natural history of syphilis among poor African Americans, workers of cotton farms. This study, known as the Tuskegee experiment, proved to be staggering. 399 men, infected with *Treponema pallidum*, were recruited. Although in the first decade of the study there was no adequate treatment for syphilis, penicillin became available in the early 40s, becoming the standard treatment around 1947. However, none of the "volunteers" received permission to receive this medicine.

As a result, 28 of the 399 participants died of the disease and 100 related complications, 40 wives had been infected and there were at least 19 cases of congenital syphilis. It is unacceptable that the research has continued, even after the condemnation of other atrocities during World War II by the Nuremberg Tribunal (1947). And that it has continued even after the adoption of the first DH in 1964.

The Tuskegee experiment was published in several prestigious journals, describing the natural history of infection, apparently without raising any ethical questioning of the editors or readers. The exception was Peter Buxton, a social worker of the U.S. Public Health Service (PHS), which noted the experiment and embarked on a lonely crusade to stop it. His stance started an internal ethics review process, which concluded by sanctioning the continuation of the study. Disagreeing with this assessment, Buxton tells the story to the press in 1972. Jean Heller, a reporter for *The Washington Star*, publishes a series of articles with immediate effect on televisions and other newspapers, including the cover story in *The New York Times* - which leads finally to the final cessation of the experience[19]. The U.S. Government has provided little compensation to the survivors or their spouses, and 25 years later (1997), President Clinton meets survivors and relatives of the deceased in the Withe House, apologizing publicly[20]:

The United States government did something that was wrong -- deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all our citizens. (...) But we can end the silence. We can stop turning our heads away. We can look at you in the eye and finally say on behalf of the American people, what the United States government did was shameful, and I am sorry. (...)The legacy of the study at Tuskegee has reached far and deep, in ways that hurt our progress and divide our nation. We cannot be one America when a whole segment of our nation has no trust in America. An apology is the first step, and we take it with a commitment to rebuild that broken trust. We can begin by making sure there is never again another episode like this one. We need to do more to ensure that medical research practices are sound and ethical, and that researchers work more closely with communities.[20]

In 1966, just a few years before the cancellation of Tuskegee, another important report on research ethics (or on the lack thereof) was published by Henry Beecher[21]. In this paper, he reports several unethical researches published between 1952 and 1965, in prestigious journals including the New England Journal of Medicine (NEJM) and the Lancet. He described flagrant abuses, inclusively against the principle of respect for the person, as many

participants did not know they were participating in a study and therefore were exposed to situations where there was risk of death without knowledge.

After Buxton's revelations, the publication of Beecher and the end of the Tuskegee experiment in 1972, several investigations were initiated by the U.S. Congress in order to deal with the ethical misconduct in researches. In 1974, they created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, in order to identify the basic ethical principles that should support the conduct of research involving human subjects and to develop guidelines to ensure that they are conducted in accordance with those principles. In this considerations there were included: the boundaries between biomedical and behavioral research and the accepted and routine practice of medicine; the role of the assessment of risk-benefit criteria to determine the appropriateness of research involving human subjects; appropriate guidelines for the selection of participants in research; and the nature and definition of informed consent in various research environments.

In 1979, the Commission published the "Ethical Principles and Guidelines for the Protection of Human Subjects of Research", known as the Belmont Report[22], which established three ethical principles for research with human subjects: the autonomy of the participants must always be respected; beneficence (doing good) must be the conduct base on all research with human beings; justice must always prevail in research with humans. A fourth principle was added later: the principle of no maleficence (not harming).

The basic rules for the protection of human subjects in research funded or conducted by the Department of Health, Education and Welfare was published in 1974, with the approval of the National Research Act (Act 93-348) that created the commission. The standards for the protection of human subjects, based mainly on the Belmont Report, were expanded in the late '70s. It is worth noting that only in 1991 other 14 federal departments and agencies involved with the theme adopted a uniform set of rules for this protection, identical to the Code of Federal Regulations (CFR) 45, Part 46, Subpart A. This set of rules is the U.S. federal policy for the protection of human subjects, known as the Common Rule. The main requirements include: ensuring of compliance of research institutions; obtaining and documenting the informed consent by researchers; establishment of an Institutional Review Board, which may be compare to the Brazilian committees on research ethics - with specification of members, operation, function, review of research and record keeping; and additional protections for specific vulnerable populations - pregnant women, children and prisoners.

The Experience of Guatemala

In 2010, Susan Reverby, of the Wellesley College[9], revealed that in the '40s the Department of Public Health deliberately inoculated prisoners and sex workers in Guatemala with sexually transmitted diseases, especially *T. pallidum*. One of the purposes of the study was to find out whether the prophylactic use of penicillin could prevent infection and to evaluate its effectiveness. The consent was not obtained and many recruited did not have access to proper treatment.

This discovery provoked reactions among ethicists from around the world and the current U.S. government issued an apology to Guatemala: *Although these events occurred more than 64 years ago, we are outraged that such reprehensible research could have occurred under the guise of public health. (...) The study is a sad reminder that adequate human subject safeguards did not exist a half-century ago*[10]. They added that the current guidelines for human medical research, funded by the U.S., prohibit this type of appalling violation:

In the spirit of this commitment to ethical research, we are launching a thorough investigation into the specifics of this case from 1946. In addition, through the Presidential Commission for the Study of Bioethical Issues, we are also convening a body of international experts to review and report on the most effective methods to ensure that all human medical research conducted around the globe today meets rigorous ethical standards[10].

It was then established, in March 2011, the U.S. International Research Panel, with four members of the Presidential Commission for the Study of Bioethical Issues and 13 international experts. President Obama has *asked the Commission to report on the effectiveness of current U.S. rules and international standards for the protection of human subjects in scientific studies supported by the Federal Government and to assure him that "the current rules for research participants protect people from harm or unethical treatment, domestically as well as internationally"*[23]. The Panel met in person three times, most recently in Washington in July 2011[11].

How the volunteers were infected

In the beginning, prostitutes infected with syphilis were recruited to have sex with prisoners. As the transmission rate was low, the researchers prepared infected samples to inoculate participants through many methods. The live spirochetes in the inoculum, prepared from sores scraping of prisoners or infected military, survived for very short periods outside the body, leading to the use of material with heat-killed spirochetes. This material was transferred to the subjects by abrasion of the skin, injection or inoculation through the urethra.

There are other examples of the unacceptable used procedures: in female prisoners, the inoculum was introduced by scarification of the arms, face or mouth[23]. In men, the inoculation was generally more direct. The chosen men had moderately long foreskins [to maintain the mucous membranes moist] and could sit or stand quietly in one place for several hours. The physician held the participant's penis, pulled the foreskin and scarified the penis with a hypodermic needle, and then introduced a cotton swab (or small gauze) and dripped the syphilis emulsion, which was in contact with lacerated penis skin for at least one hour, and at times up to two hours[23].

Other techniques were tested, such as intravenous injection, ingestion of water suspension or placement of the inoculum in the cervix of prostitutes before intercourse. Different types of chemical prophylactic products were supplied to some of the participants and none to the control group. Before the recruitment, it was made sure that they were not infected and had not received the medicine for syphilis.

Hundreds of men and women were involved, many photographed and their photos found in archives. Some participated in multiple experiments. The total numbers calculated by the Presidential Commission was of 696 people exposed to syphilis, 722 with gonorrhea and 142 to chancroid[23].

Lure

The main researcher of the Guatemala experience also played an important role in Tuskegee. John Cutler, a surgeon who oversaw the project Guatemala, became general surgeon assistant in 1958 and attended Tuskegee in the next decade. In his letters with physicians interested in sexually transmitted infections, he admitted that only a few people (not the participants nor the PHS and the scientific community colleagues) were aware of the whole procedure: *we are explaining to the patients and others concerned with but a few key exceptions that the treatment is a new one utilizing serum followed by penicillin. This double talk keeps me hopping at times*[23]. In a letter he says: *for a few words to the wrong person here, or even at home, might wreck it or parts of it*[23].

Participation of Guatemalan employees

A project of this magnitude could not have happened without the collaboration of many people, including Guatemalan authorities and physicians, subject therefore to various conflicts of interest[24]. Among those concerns was the possibility of career advancement through the association with researchers and renowned U.S. Institutions. The project also brought the implementation of laboratory infrastructure, the possibility of access to testing and greater access of the country to penicillin.

Additionally, Cutler added the provision of antimalarial drugs in exchange for the right to continue to do blood tests. Since the discovery of penicillin the PHS was facing budget constraints in work on venereal diseases, making it difficult to justify the project in Guatemala. After several letters, Cutler promised to be careful: we will *use the penicillin sparingly so as to leave it available for "demonstration programs and to build goodwill"*[23]. He also noted: *With the opportunity offered here to study syphilis from the standpoint of pure science just as Chesney studied it in the rabbit it should be possible to justify the project in the event of the impossibility of resolution of the prophylactic program*[23].

A specific question addressed by the President Obama to the International Panel on whether today, there is the risk of similar experiments, draws our attention. Although they consider that *federal regulations and international standards adequately guard the health and well-being of participants in scientific studies*[23], and it is very unlikely that a project such as that of Guatemala is currently allowed, it is necessary to pay attention to the fact there are other ways, subtle and also unethical for clinical trials, both in the United States and in other countries, due to the inequalities of power (vulnerability) and lack of acceptance (or recognition) of the representative international ethical guidelines, such as the Universal Declaration on Bioethics and Human Rights of UNESCO[25],

which was not even mentioned in the final report of the International Panel[26].

It is therefore not possible to conclude that the health and welfare of participants are in fact protected adequately in all studies funded by the federal government and even less in projects supported and developed by the pharmaceutical industry. One way to deal with this issue, at least to begin, is to ensure that universally recognized ethical standards are adopted, that they known by all and that an ethical framework really works independently in each country where the research is being proposed.

Possible Solutions

Something that should be discussed and decided is how to ensure the role of guidelines, or rather, a universal guideline, as the mentioned UNESCO Declaration, to deal effectively with issues of relevance (or responsiveness), fairness and disparities. And just as important is the appropriation by the country of their needed research, through the community, local researchers, and truly independent research ethics committees and health authorities. These issues are really controversial, and although discussed, they are not addressed with rigor. In many countries there is no consensus, and even internationally, on issues of relevance/ responsiveness, fairness, access to research products, use of placebo, exploration risks regarding the performance of questionable research with volunteers / communities / researchers / vulnerable countries.

However, we must give credit to the U.S. President for his decision to reveal once again, like the aforementioned public apology from President Clinton for Tuskegee, another part of the deplorable history of that country. Moreover, in March 2013 the Presidential Commission for the Study of Bioethical Issues released the first data about 55,000 trials funded by the federal government in the period of 2006-2010[27]. This measure reinforces item 30 of the Declaration of Helsinki[18], which defines the obligation of publication or publicity of the positive or negative results of clinical trials, including source of funding, institutional affiliations and any possible conflicts of interest. Evidently, it is not revealing enough, but can and should be used as an opportunity to broaden the discussion and enhance the ethical design issues of autonomy, relevance, equality and risks of exploitation of the vulnerable.

Risks of similar situations in the ethical research structure in Brazil

How does Brazil protect volunteers of the research projects? The ethical research structure is based on the Brazilian CNS Resolution 196/96, which created the Conep. This resolution clearly states the steps needed to create and register local Research Ethics Committees (REC); it defines the structure of a project, with all the safeguards for the protection of human subjects, including, but not limited to, the process of informed consent[28].

The CNS Resolution 196/96 is being updated (2013) and there are several additional resolutions to specific situations/populations at higher risk of vulnerability. With these standards, research proposals similar to the Tuskegee or to the syphilis study in Guatemala would not be allowed in Brazil. However, the pressure for more flexible rules is undeniable, which can weaken the ethical requirements, using the known sophistical arguments of urgency and that it is unrealistic to be more rigid than the rest of the world, beyond the inherent risk of vulnerability of the Brazilian research volunteers, usually recruited in often overloaded public services. These volunteers, when recruited, have privileged access to health care, which they had not before, hindering the truly free consent.

Changes in the Declaration of Helsinki (2008) exemplify how international regulations related to research ethics may not correspond to the interests of developing countries, due to the influence of funding agencies/donors and the pharmaceutical industry in the core countries. This was the case with the latest version of the DH, which could have negatively influenced the Brazilian research guidelines, but that was quickly countered by the sovereign and unequivocal position of the CNS, with the adoption of Resolution 404/ 08[29], and the Federal Council of Medicine (CFM), with Resolution 1885/2008[30], both maintaining the advantages of the 2000 version of the DH.

These decisions of the CNS and the CFM define that autonomy, truly informed consent and access to care and treatment during and after clinical trials are rights of all volunteers in research trials. All these requirements must be integrated into a broader and necessary perspective, which is the expansion of the right of access to the benefits of research in public health. As seen, the last decades have shown impressive expansion of clinical trials originated in developed countries and generally conducted in developing countries [31].

The increase in the number of trials occurs, among other reasons, because of the need to comply with the rules for conducting randomized trials of large scale. The establishment of phase III clinical trials (efficacy evaluation), with thousands of volunteers, and the globalization of the pharmaceutical industry contributed to the expansion of the assays outside the country of origin of the industry. Perhaps most importantly, the ease of recruiting volunteers in poorer environments, often with less organized ethical framework for research, with a high incidence of the disease and less demanding individuals, who often see the opportunity to participate as the only means of obtaining medical care. In addition, stricter standards in developed countries, where the rights of volunteers are at least protected by law, are part of the same framework that facilitates the migration of clinical trials.

Double standard in clinical trials

The migration of randomized controlled trials to the Third World brings the risk of trying to lower the international ethical requirements. There is no intention here to demonize the pharmaceutical industry, which plays a role in the development process of needed products, labeling it as the only one conducting unethical trials. However, there are several reports of unethical trials, in recent times, for drug development or evaluation of preventive methods, sponsored by the pharmaceutical industry[32]. It becomes necessary to detail the specific and recent catalyst of heated discussions about ethical requirements in clinical trials.

In 1997, Marcia Angell's[33] energetic editorial and the article of Wolfe and Lurie[34], published in the same issue of the NEJM, criticized the ethics of studies funded by the National Institute of Health (NIH) on the prevention of vertical transmission of HIV, performed in countries of Africa, in the Dominican Republic and Thailand in the late 80s. Through the study ACTG 076 it was known that the orally intake of zidovudine during pregnancy, intravenously on childbirth and orally to the newborn substantially reduced the risk of transmission. The tests made in these countries used a shorter scheme of AZT, eliminating the intravenous use. Moreover, instead of being compared to the ACTG 076 protocol, the test used placebo as control. Angell, editor in chief of NEJM, questioned the used methodology underpinning it with that of Tuskegee.

The editorial and article provoked heated discussions which, in turn, translated into strong pressure to change the Declaration of Helsinki (1996 version), the leading and most respected group of ethical guidelines for research with human subjects. The goal was to modify two articles, precisely those that dealt with access to the best proven medical treatment to all volunteers, regardless of economic status or country of origin, and restrictions on the use of placebos when effective treatment exists. The General Assembly of the World Medical Association in Edinburgh (2000) maintained the restrictions on the use of placebos (item 29) and added the requirement for post-study access to the product that proves effective (item 30). The pressures of both the pharmaceutical industry and the U.S. agencies were intense enough that these demands got too less rigid in the 2008 version of the DH, as discussed.

Consequently, there was the possibility that the tests evaded the requirements to treat volunteers with respect and equal guarantees, regardless of their origin and economic power, creating the possibility of double standard in clinical research. Pressures also contaminated other important documents, such as *Ethical Considerations in International HIV Vaccine Trials* (UNAIDS, 2000)[35] and the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, 2002)[36]. In both documents, the items related to access to care and use of placebos are long and of complex understanding, enabling volunteers of developing countries to be treated differently, i.e., with fewer rights than those of the industrialized world.

Additionally, there are, in industrialized countries, other documents focused on research in developing countries. An example is the document of the U.S. National Bioethics Advisory Commission - 2001[37]. A following document is one of the Food and Drug Administration (FDA)[38], adopted in 2008, defining that clinical research projects conducted outside the U.S. and not conducted under an application for investigational new drug (IND), no longer need to be in accordance with the standards of the *Declaration of Helsinki*, but only with the *Good Clinical Practice* of the Intentional Conference on Harmonization (ICH). It should be remembered that the primary objective of the ICH guidelines[39] is unifying the European, American and Japanese procedures, in order to facilitate the mutual acceptance of clinical data by the regulatory agencies of these countries. There is - again - the same risks of double standards[40,41].

Counterattack

In the early years of the 21st century, more precisely in 2005, a victory was conquered with the enactment of the *Universal Declaration on Bioethics and Human Rights*, by acclamation of the United States in the 32nd Session of the General Conference of UNESCO. It is the real and effective milestone in the search for justice and equality for all. In General Provisions, item "f " of Article 2 sets among its goals: *to promote equitable access to medical, scientific and technological developments as well as the greatest possible flow and the rapid sharing of knowledge concerning those developments and the sharing of benefits, with particular attention to the needs of developing countries*[26].

The objectives of the Declaration, which are in complete agreement with the scope of this article, include the universality of principles and also procedures, emphasizing the need to respect human dignity and protect human rights and, more importantly, the requirement of equal access to medical developments, science and technology, sharing of achieved benefits and special attention to the needs of developing countries. The Declaration reinforces the position of Brazil issued by the CNS in relation to effective protection to research volunteers against any possible double standards in studies.

A similar document - *Ethical Considerations in Biomedical HIV Prevention Trials*[42] - was published in 2007 by WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS). Replacing and expanding the scope of the guideline *HIV Preventative Vaccine Research* - UNAIDS 2000, it includes direct and explicit recommendation that HIV-infected *participants who acquire HIV infection during the conduct of a biomedical HIV prevention trial should be provided access to treatment regimens from among those internationally recognized as optimal* (Guidance Point 14). In 2010, WHO issued the *Guidance on ethics of tuberculosis prevention, care and control*[17], previously mentioned, which follows the same line of the WHO/UNAIDS document of 2007, including a table that lists the circumstances under which clinical trials should not be performed (Table 1).

Access to adequate health services for all

All discussion on the rights of clinical trial volunteers to equal access to decent medical care, regardless of their economic origin or the country where the research is being conducted, may be considered outdated today. This is because, over this period (1999-2008), discussions about access extrapolated the controlled environment of clinical trials for an expectation of much broader access to products designed for all who need them. The point is not in the controlled clinical trial mostly financed by billionaire industries, but the most important task, more difficult and less visible, is the application of the results in public health, in resource-limited environments.

There are examples for this, coincidentally related to the AIDS epidemic: the *3 by 5* Initiative of WHO/UNAIDS in 2003, proposing that drugs for HIV treatment are indeed available in all developing countries; and the Political Declaration on HIV/AIDS, approved at the high-level meeting of the UN in New York in 2011, that has the goal, among others, to bring the provision of antiretroviral treatment to 15 million people by 2015 (15 by 15)[43]. Another example is the adoption and implementation in Brazil, of Law 9.313/96, which established universal access by the Unified Health System (SUS) to ARVs for all patients that need them, at no additional cost.

That decision helped to reduce mortality, morbidity, hospitalizations, absenteeism at work and new infections rates, and also proves valid by economic point of view[44]. Between 1996 and 2002, the total investment with drugs exceeded US$ 1.6 billion, with incalculable social impact. There was also a significant economic impact, with estimated savings of another US$ 2 billion due to the reduction in hospitalizations, outpatient care, pension expenses and mortality.

Social determinants and power relations

The term *empowerment* has been repeated *ad nauseam* as a way to "empower "individuals regarding their needs and expectations. Unfortunately, it is usually no more than a rhetorical figure, since the power has never been given and rarely been shared. In most cases, the use of the term corresponds to an Illuminist form to marginally provide a bit for the needy, aiming to soothe their claims. It is common for these individuals/countries with economic difficulties to praise their "donors" for helping them to get something that is indeed their right. This attitude may perpetuate dependency: a new kind of colonialism is born (deliver the rings, save your fingers and perpetuate the disparity and dependence).

The term *empowerment* should be replaced by *emancipation* in the sense of Paulo Freire, who in

his comprehensive work on education for freedom used the word in a broad sense of liberation and autonomy, exactly how it should be used when discussing citizenship, rights or combating disparities[45]. Marx also indicated that human emancipation is only performed when man *has recognized and organized his own powers (forces propres) as social powers so that he no longer separated his social power from himself as political power*[46]. Thus, emancipation will not happen by chance, by concession, but it will be an achievement effected by human praxis, that demands uninterrupted fight: *Liberation is thus a child birth* (...) *The man who emerges is a new man, viable only as the oppressor-oppressed contradiction is superseded by the humanization of all men*[47].

Final Thoughts

Trials with new drugs or vaccines are necessary and must be made in places where ethical requirements and independent reviews are available, where exploration can be avoided, when the research proposal addresses local health problems, and when there is guaranteed access to the best proven diagnostic and therapeutic methods.

A well-defined and appropriate research ethics is fundamental and the involvement of scientists, activists, and the whole society is essential to ensure that internationally agreed ethical requirements are used correctly throughout the world, avoiding the risk of double standard, avoiding that people receive different and usually worse treatment in terms of their origin, ethnicity or economic status.

With regard to the research involving human subjects, there are procedures that can reduce these problems in a partial way, including international guidelines on research ethics, approved and universally applicable; the establishment of local/national research ethics committees that are sovereign and independent; and the public disclosure of proposals and research findings. With all these tools it will be possible to prevent not only recurrences as the Tuskegee, Guatemala and testing AZT to HIV-infected mothers experiments, but also many other equally unethical situations. If, at the end of the research, the product was effective, there must be international pressure to make it available and make it affordable for use in other countries. There is urgency, therefore, not only to search for better preventive methods or more effective drugs and vaccines, but mainly to make them available for everyone.

However, the most difficult task, one in which we all must take part, is the challenge of actually fighting against the disparities that separate the few rich, both in developed and developing countries, from the millions of destitute that still have no voice or rights. Unfortunately, health disparities will not be resolved only through standards and guidelines regulating research and researchers, or even the same treatment to all studies involving human subjects.

It is worth emphasizing an important step consensually adopted by countries at the 67th Session of the General Assembly of the United Nations in 2012, for the transition of the national healthcare toward a universal health coverage[48]. Thucydides[49] said that justice will only be achieved when those who are not unfairly treated feel as indignant as those who are. I dare say that fairness can prevail only when those affected and outraged by unfairness are able to emancipate themselves and fight for their rights.

To ensure that equality and rights are respected in research involving humans anywhere in the world is a significant step towards reversing the current unfairness in the allocation of health resources and may contribute to the emancipation of volunteers, researchers and society, so that they may exercise their rights as citizens and have the ability to fight for them.

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Attachment

Chart 1. Selected circumstances in which the trial should not be performed[18]

- When the capacity to conduct independent and adequate scientific and ethical review does not exist;
- Where voluntary participation and freely decided consent cannot be obtained;
- When conditions affecting potential vulnerability or exploitation may be so severe that the risk outweighs the benefit of conducting the trial in that population;
- When agreements have not been reached among all research stakeholders on access to medical care and treatment;
- When agreements have not been reached on responsibilities and plans to make trial products (drugs, other treatments, or preventive measures) that prove to be safe and effective, available to communities and countries where they have been tested, at an affordable price.

Source: WHO Guidance on ethics of tuberculosis prevention, care and control.