Invited lecture

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International Collaborative Research and New Trends of Research Ethics

The Past, Present, and Future of Ethics of International Health Research: Research as a stepping-stone to Universal Public Health Care Access *1

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Abstract

Clinical trials have seen a constant expansion since the second half of the 20th century. This increase has been especially related to the need to perform large-scale phase III efficacy trials, usually originated in developed countries, with the globalization of pharmaceutical industries expanded worldwide. The first objective of this presentation is a review of the past, present and a glimpse at the future possibilities of human research. There has been many unethical issues in the past history of human research even with the existence of many international ethical guideline. And one of our roles as researchers and bioethicists is to understand the implications of this past history, critically evaluate the present and join efforts to construct an international infrastructure to ascertain that future research involving humans is ethical and protect human rights.

The evaluation of the risks of such an expansion especially in developing, more vulnerable countries will be discussed. Many contentious concerns have emerged with this expansion. These include the risks of double standards in clinical trials, especially in developing countries: for example, trials not permissible in industrialized countries may and actually have been performed in the developing world, where local vulnerability may facilitate pressures to water down prior gains, such as the clear statement in the 2000 version of the Declaration of Helsinki related to post trial access and restrictions to placebo use.

As a second objective, it will be considered that these concerns have provided an unique opportunity to discuss the role of health research in the much more important issue of universal public health care access for all.

Universal public health care access for all: it will be defended that the debate whether clinical trial participants anywhere in the world should have access to adequate and equal medical care is dated. The unequivocal rights of trial participants to post-trial access must be substituted with a more urgent objective of providing access to all efficacious products of research in public health.

In conclusion, I argue for the approval of an unique research ethics document, which should sanctioned and ideally embedded in an international covenant and/or resolution, issued by the United Nations – it must include the right to access post-trial to efficacious and effective research products.

I also argue for a joint effort to achieve, not only an universal health coverage but to a really universal public health system for all, asserting that the status quo of inequality must not be an immutable fact. This would make it crystal clear that Health is human right and not an economic commodity.

Key words

vulnerable population, post-trial access, placebo-controlled clinical trial, human right, emancipation

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Currently he is responsible for the discipline Seminars in Bioethics at the Graduate Course in Tropical Medicine and Infectious Diseases (UFMG). Main topics of interest include Infectious and Parasitic Illnesses, bioethics, public health and clinical immunology. He has participated in several working groups that gave rise to national/international guidelines related to ethics, prevention, care and treatment of HIV/AIDS and TB. He has frequently acted as temporary advisor to many national/international institutions, such as the Brazilian AIDS Programme, WHO, UNITAID, UNAIDS, UNICEF, UNESCO, CIOMS, the United States Presidential Commission for the Study of Bioethical Issues and The World Medical Association.

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1. Situation in Brazil

It worth mentioning that Brazil is truly a very large country. Comprising 8.5 million square kilometers, it's 22 times as big as Japan, and it has only double the population. It is also a rich country but unfortunately has one of the highest level of disparity in the world. Specifically, 10% of the population lives on less than $2 a day, so poverty is rampant in the country. This is very different from what is seen in Japan, but unfortunately the number of poor people is also increasing here.

2. Hypothesis for research with human subjects

My hypothesis of work is that research with human subjects is necessary. It must be relevant and have social value. However, there have been many unethical issues in the past history of human research even with

the existence of many international ethical guidelines.

In my opinion, in clinical trials, access to the best proven preventive, diagnostic, and therapeutic must be provided without any risk of double standards. And also, participants have the right to post-trial access to a drug or procedure that shows to be effective. The most important issue is that results of human research must be translated into available and accessible public health policies for all. The research itself is just a small part of this much harder challenge that we all face.

3. History of research ethics

A few examples have been selected, which happened during the 20th century.

The first one is Tuskegee study, started in 1932, which enrolled African American male with syphilis in Alabama, USA. This project financed by the Health and Human Services (USA) followed participants for 40 years, without providing penicillin treatment which became widely available in the early 1940's.

The second one was discovered by chance when Susan Reverby while studying the Tuskegee experiment, came across unpublished papers on a study in Guatemala [1], co-sponsored by the US Public Health Service (PHS), the National Institutes of Health, the Pan American Health Sanitary Bureau and the Guatemalan government. In 1946-48, a PHS physician who would later participate in the Tuskegee study, was involved in this study which involved infecting 696 subjects, men and women with *Treponema pallidum*, in a prison, army barracks, orphans, leprosarium patients and in a mental hospital. Permissions were provided by the authorities but not by individuals and supplies were offered to the institutions in exchange for access. Prostitutes

1) Reverby SM. "Normal exposure" and inoculation syphis: PHS 'Tuskegee' doctors in Guatemala, 1946-1948 and at Sing Sing prison, Ossining, N York, 1953-1954. May 2, 2010.

with syphilis were used to pass it to the prisoners. As the infection yield was considered low, direct inoculations with *T. pallidum* was done onto the penises and/or on forearms and faces and even in some cases through spinal punctures. Of course, this is unacceptable. The disclosure of the details of this experiment reverberated widely. And this study with apologies by the US Secretaries of State and Health and Human Services to the people of Guatemala was the focus of an evaluation by an international panel established at the US President's Bioethical Issues Commission to assess the protections provided to participants, especially in studies financed by the US government and performed abroad. I participated as a member of this panel and the proceedings were published in 2011 [2, 3].

The third was in Japan but was related to the United Sates and happened just after the end of World War II. During a visit to the Peace Memorial in Hiroshima one thing was especially striking. There was a panel which described the Atomic Bomb Casualty Commission (ABCC), which was established under the auspices of the US government. This was also in 1946, just one year after they bombed Hiroshima, killing 146,000 people on the spot. Survivors from the blast in Hiroshima were invited to participate in epidemiological study, and most of these wanted to take part because they were expecting to be treated, but the Americans did not treat them. They wanted just to follow the natural history of radiation exposure. In my opinion this is in many ways similar to what was done in the Tuskegee study. It is worth remembering that at this same time the Nuremberg trial was on, and physicians were punished for unethical experiments which happened during the World War II. This was contradictory situation as the German physicians were duly punished but the natural history of radiation exposure of vulnerable people has not been even discussed.

There were other more recent (1997) controversial, and in the opinion of many, unethical experiments of intervention to reduce perinatal transmission in developing countries. At that time, it was already shown by a clinical trial [4] that vertical transmission of HIV could substantially reduce (by two thirds) if zidovudine (an antiretroviral) is administered orally during pregnancy, intravenously during labor, and subsequently to the newborn infants. In the studies criticized by Peter Lurie and Sidney Wolfe [5], the control group received placebo instead of the efficacious and recommended Zidovudine scheme.

I participated in many of the discussions that ensued after criticisms to these studies were published by Lurie and Wolfe [5], followed by a very strong editorial by Marcia Angell [6], at that time editor-in-chief of *The New England Journal of Medicine*. Angell's editorial stated that the justifications for such a study reminded of what was used in Tuskegee. These discussion resulted in or facilitated the issuing of the 2000 version of the Declaration of Helsinki.

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2) Presidential Commission for the Study of Bioethical Issues. Research Across Borders: Proceedings of the International Research Panel of the Presidential Commission for the Study of Bioethical Issues. 2011 Sept. https://bioethicsarchive.georgetown.edu/pcsbi/sites/default/files/IRP-%20Research%20Across%20Borders.pdf

3) Presidential Commission for the Study of Bioethical Issues. "Ethically impossible" STD Research in Guatemala from 1946 to 1948. Washington, DC 2011 Sept. https://bioethicsarchive.georgetown.edu/pcsbi/sites/default/files/Ethically%20Impossible%20(with%20linked%20historical%20documents)%202.7.13.pdf

4) Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Eng J Med.* 1994; 331: 1173-80.

5) Lurie P, Wolfe SM. Unethical trials of interventions to reguce perinatal transmission of the human immunodeficiency virus in developing countries. *N Engl J Med.* 1997; 337: 853-6.

6) Angell M. The ethics of clinical research in the third world. *N Engl J Med.* 1997; 337: 847-9.

All of this is a reminder that the past history of research ethics is not very good. Fortunately, there have been good ethical counterpoints to the facts mentioned above. Some examples include The Nuremberg Code in 1947 [7]; the United Nations Declaration of Human Rights, 1948 [8]; the Declaration of Helsinki, first issued in 1964, the last version published in 2013 [9]; The Belmont Report in 1979 [10] which was very important for the United States and was a response to what happened in Tuskegee. And also, The CIOMS Ethical Guidelines that started in 1982 with its last revision (International Ethical Guidelines for Health-related Research Involving Humans) published in 2016 [11], UNESCO's Declaration on Bioethics and Human Rights in 2005 [12], which is a more comprehensive ethical document and it is probably the only document which was approved by all the 196 countries that at that time participated in UNESCO. UNAIDS and WHO HIV ethical guidance documents are also international but their scope is limited to specific diseases [13].

4. The present of research ethics

Regarding the present of research ethics, one of many questions that should be asked includes what is owed following a clinical trial (Table 1). In the UNESCO document [12], they have several points on the sharing of benefits. The UNAIDS/WHO guidance document [13] has two guidance points, "benefits" and "care and treatment". The 2010 WHO [14], that is even broader because it is about the ethics of access to tuberculosis prevention and access to treatment. It mentions directly that people must have access to free drugs to treat TB. The 2013 Declaration of Helsinki defines post-trial access in its article 34 as does the 2016 CIOMS Guidelines [11]. Both will be further discussed below.

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7) The Nuremberg Code. Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, October 1946-April 1949. Vol. 2, p. 181-2.
https://www.loc.gov/rr/frd/Military_Law/pdf/NT_war-criminals_Vol-II.pdf

8) United Nations. Universal Declaration of Human Rights. Proclaimed by the United Nations General Assembly in Paris on 10 December 1948. (General Assembly resolution 217 A)
https://www.un.org/en/universal-declaration-human-rights/

9) World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and last amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013.
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

10) The Belmont Report. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979.
https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html

11) Council for International Organizations of Medical Sciences. International Ethical Guidelines for Health-related Research Involving Humans. 2016.
https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

12) United Nations Educational, Scientific and Cultural Organization. Universal Declaration on Bioethics and Human Rights. 19 October 2005.
https://en.unesco.org/themes/ethics-science-and-technology/bioethics-and-human-rights

13) Joint United Nations Programme on HIV/AIDS (UNAIDS) 2007. Ethical considerations in biomedical HIV prevention trials: Guidance Document. 2007.
http://data.unaids.org/pub/manual/2007/jc1349_ethics_2_11_07_en.pdf

14) World Health Organization. Guidance on ethics of tuberculosis prevention, care and control. 2010.
https://apps.who.int/iris/bitstream/handle/10665/44452/9789241500531_eng.pdf;jsessionid=A807FA85616DD9B062232400AD281696?sequence=1

There are several documents coming from different institutions/countries that deal with post-trial access, with different views on the right for this access. These are usually originated from developed countries, especially from the United States and Europe, but of course there are other documents from countries in the South. One of them, issued by the Brazilian National Research Ethics Commission [15] takes a very strong stance on post-trial access and placebo use. It may be provocative to affirm that many of the discussions about post-trial access and on placebo use are dated, but the truth is that there are already we have all the tools to ethically protect the participants rights in the controlled settings of clinical trials.

Our efforts should now be directed to truly transform the benefits shown in clinical trials to real access for all in public health. It must also be emphasized that there are substantial differences between universal health systems (as those in the United Kingdom, Canada and Brazil, among others) and the much more limited universal health coverage (as proposed by the UN General Assembly). The former means real access to

Table 1 What is owed following a clinical trial?

2005 UNESCO Universal Declaration on Bioethics and Human Rights
Article 15: Sharing of benefits
https://en.unesco.org/themes/ethics-science-and-technology/bioethics-and-human-rights

2007 UNAIDS/WHO guidance document Ethical considerations in biomedical HIV prevention trials*
Guidance Points 12-Benefits & 14-Care and Treatment
https://www.unaids.org/sites/default/files/media_asset/jc1399_ethical_considerations_en_0.pdf
*Original version is in 2007 and point 20 was added in 2012.

2010 WHO Guidance on ethics of tuberculosis prevention, care and control
Free access to drugs; guidance for research
https://apps.who.int/iris/bitstream/handle/10665/44452/9789241500531_eng.pdf;jsessionid=A807FA85616DD9B062232400AD281696?sequence=1

2013 DoH Paragraph 34: Post-trial access vs 2008 DoH
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

2016 CIOMS
Guideline 6: Caring for participant's health needs (Formely 2002, Guideline 16- Research in populations and communities with limited resources and Guideline 21: Ethical obligation of external sponsors to provide health-care services)
https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf

2012 A developing country position: Brazilian Research Ethics Commission, Resolution 466/2012: Post-trial access (and placebo use)
https://conselho.saude.gov.br/resolucoes/2012/466_english.pdf

Dated discussion because post-trial access must be expanded to include health care for all in the public health setting:
Universal Health System vs WHO on Universal Health Coverage

15) Brazilian National Health Council (CNS), Brazilian National Research Ethics Committee (CONEP/CNS/MS). Guidance Manual: Frequent pending issues in clinical research protocols. Version 1.0. 2015.
https://abracro.org.br/images/legislacao/guidance_manual_frequent_pending_issues_in_clinical_research_protocols_CONEP_V1_2015.pdf

health care for all individuals while the latter signifies only that there is universal coverage without establishing who will pay for it.

5. 2000 to 2013 versions of the Declaration of Helsinki

5.1 Post-trial access (Table 2)

There were many pressures put into international guidelines and it is not in the scope of this manuscript to go in depth on this. But it is worth mentioning WMA 2000 version of the Declaration of Helsinki – at that time WMA president was a well-known Japanese physician, the late Dr. Eitaka Tsuboi. What happened then was that for the first time post-trial access was included, stating that every patient entering in the study must be assured access to the best prophylactic, diagnostic, and therapeutic methods identified by the study. That was also the position defended by the Brazilian representatives at WMA General Assembly in Edinburgh in 2000.

What happened after the DoH was issued in 2000? WMA soon included two notes of clarification for both placebo in 2002 and post-trial access in 2004, which weakened the 2000 version. The 2008 revision was much less stringent than 2000 as it incorporated the two notes of clarification modifying the item on post-trial access to: "*at the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits*". It means that maybe you can have access these interventions but it may be alright to have them substituted for something else, such as strengthening local infrastructure.

Table 2 "Post-trial access" and "placebo" in the Declaration of Helsinki

"Post-trial access" in the Declaration of Helsinki WMA General Assembly, Seoul, 18 October 2008, Fortaleza 2013		
Brazilian Medical Association and Brazilian Medical Council proposal* (defeated at the GA 2008) Every patient entered into the study must be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. ***same as in DoH 2000*** (except that "should" in DoH was changed to "must".)	**2008 version** **33.** At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.	**2013 version** **Post-Trial Provisions** **34**. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.
"Use of Placebo" in the Declaration of Helsinki WMA General Assembly, Seoul, 18 October 2008, Fortaleza 2013		
Brazilian Medical Association & Brazilian Medical Council proposal (defeated at the GA 2008)* The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current method, except in the following circumstance: - The use of placebo, or no treatment, is acceptable in studies where no proven method exists; ***same as in DoH 2000***	**2008 version** **32.** The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; **or** Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. **Extreme care must be taken to avoid abuse of this option.**	**2013 version** **Use of Placebo** **33.** The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; **or** Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. **Extreme care must be taken to avoid abuse of this option.**

(emphasis added)

The 2013 version, had some changes for the better. It stipulates that "*in advance of a clinical trial, sponsors, researchers, and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants in the informed consent process*". It's very good in a way, but it only establishes that

the stakeholders “should make provisions”, and this may mean “provide” but may also be considered as “plan”. And also it would be much better that it “must” instead that it “should”. But it’s much better than 2008 and maybe pragmatically, that was what it could be accomplished at that time. Maybe in the next version, which seems to be due soon, it could be made more precise and stringent.

5.2 Use of placebo (Table 2)

In relation to placebo, the 2000 DoH put it very clear that its use or no treatment is acceptable in studies where no proven methods exists. That was a subject of a very intense discussion because it was just after the unethical mother-child transmission trial discussed previously where half the vulnerable participants received placebo only.

In the 2008 DoH, the restrictions to placebo use were significantly laxed, because just after the statement that “*Where no proven intervention exists, the use of placebo, or no intervention, is acceptable*” it has been included an “***or*** *Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention, and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm*.” With these exceptions, the bar in relation to the protection of the participant was undoubtedly lowered. But I remember very vividly when this discussion arose. I was there in WMA’s General Assembly (Seoul, 2008), and albeit many country representatives had many arguments for the maintenance of the 2000 version, these were not accepted. But it is worth emphasizing that in the end of this paragraph it was included: “*Extreme care must be taken to avoid abuse of this option*”. It would be naïve to believe that this warning is enough to prevent abuse.

The same problem persists in the 2013 version. It has an “or” and again, “extreme care must be taken to

avoid abuse of this option". If you compare the three stages of the same declaration, the 2000 version is the most protective to the participants. At that time, it is important to remember that when the discussion was very intense (especially between 2004 and 2006), the US Food and Drug Administration (FDA), decided to take out completely the requirement of the Declaration of Helsinki of all studies conducted outside the US without investigational new drug application (IND), as support for an IND or new drug application (NDA) [16].

Table 3 General provisions and benefit sharing clause in the UNESCO Declaration 2005

General provisions

Article 1 Aims:

(f) 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;

Article 14 – Social responsibility and health

1. The promotion of health and social development for their people is a central purpose of governments that all sectors of society share.
2. Taking into account that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition, progress in science and technology should advance:

(a) access to quality health care and essential medicines, especially for the health of women and children, because health is essential to life itself and must be considered to be a social and human good;

Article 15 Sharing of benefits

1.Benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community, in particular with developing countries.

....Benefits may take **any** of the following forms:

(a) special and sustainable assistance to, and acknowledgement of, the persons and groups that have taken part in the research;

(b) access to quality health care;

(c) **provision of new diagnostic and therapeutic modalities or products stemming from research**;

(d) support for health services;

(e) access to scientific and technological knowledge;

(f) capacity-building facilities for research purposes;

(g) other forms of benefit consistent with the principles set out in this Declaration

(emphasis added)

16) Food and Drug Administration. Human subject protection; foreign clinical studies not conducted under an investigational new drug application. *Fed Reg.* 2004; 69; June 10, 2004: 32467-75. http://edocket.access.gpo.gov/2004/04-13063.htm

5.3 *The Lancet* publication in 2005

At that time, first in 2005, Peter Lurie and myself published in *The Lancet* criticizing FDA position [17] and a quote of our article was in the cover of this issue of *The Lancet*. When FDA finally approved this new norm, *Nature* had a very strong editorial against it [18]. The probable reason for FDA's decision then was that they were afraid that the coming revision of the Declaration of Helsinki would get more stringent in relation to placebo use and post-trial access.

6. UNESCO in 2005 (Table 3)

UNESCO's 2005 Universal Declaration on Bioethics and Human Rights [12] has a lot on sharing of benefits, but again, it has so many items to choose from as they state that "benefit may take any of the following forms". One of them that in my opinion should be the only one is "**(c) provision of new diagnostic and therapeutic modalities or products stemming from research**". But the problem is that you can choose "any" of the many included as it is considered acceptable sharing of benefits in the form of "(d) support for health service", "(e) access to scientific and technological knowledge", **or** "(f) capacity building".

The above mentioned possibilities in a way contradicts what is stated in the Objectives as it starts with a strong stance on the rights of participants, which includes the promotion of "**equitable access to medical, scientific, and technological development**". And it goes further that the document is "*taking into account that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition, progress in science and technology should advance*", saying that people should have the best that we can afford to have, which is also very important. But then we get to specifics as shown before, it opens for the relaxation of the participant's rights.

7. CIOMS in 2016 (Table 4)

7.1 2016 Revision process and criticisms

The CIOMS ethical guidelines were reviewed in 2016 [11]. This is another important document, the revised edition is better than the 2002 version, but there were criticisms on this new version. According to Udo Schuklenk, in a paper published in 2017 [19]said: the work group used a method of consensus to reach conclusions on controversial points; "the procedures put in place by CIOMS resulted in an authoring group consisting of a majority of authors and advisors hailing from the global North, while the guidelines squarely aim at influencing policies in the global South" and "It is unclear why it should be the role of a small organisation such as CIOMS to try to guide the research ethics policies in countries of the global South". These criticisms were responded by Ruth Macklin [20] which was one of working group members.

17) Lurie P, Greco DB. US exceptionalism comes to research ethics. *Lancet.* 2005 Mar 26-Apr 1;365(9465):1117-9.
18) Trials on trial. *Nature.* 2008 May 22;453(7194):427-8. doi: 10.1038/453427b.
19) Schuklenk U. Revised CIOMS research ethics guidance: on the importance of process for credibility.*Indian J Med Ethics.* 2017; 2(3): 169-72. Published online on March 7, 2017.
http://ijme.in/articles/revised-cioms-research-ethics-guidance-on-the-importance-of-process-for-credibility/?galley=html

Table 4 CIOMS guideline on caring for participants' health needs and its commentary

CIOMS 2016 - Guideline 6:
CARING FOR PARTICIPANTS' HEALTH NEEDS

(Succeded 2002 Guideline 21 Ethical obligation of external sponsors to provide health-care services)

Addressing participants' health needs requires at least that researchers and sponsors make plans for:

- how care will be adequately provided for the condition under study;
- how care will be provided during the research when researchers discover conditions other than those under study ("ancillary care");
- transitioning participants who continue to need care or preventive measures after the research to appropriate health services;
- **providing continued access to study interventions that have demonstrated significant benefit**; and
- consulting with other relevant stakeholders, if any, to determine everyone's responsibilities and the conditions under which participants will receive continued access to a study intervention, such as an investigational drug, that has demonstrated significant benefit in the study.

Limitations: "When access is provided after the research to investigational interventions that have demonstrated significant benefit, the provision may end as soon as the study intervention is made available through the local public health-care system or after a predetermined period of time that the sponsors, researchers and community members have agreed before the start of a trial.
Information on care for participants' health needs during and after the research must be included in the informed consent process".

Commentary on Guideline 6
General Considerations.

..... In some cases, participants may continue to need the care or prevention provided during the research after (the end of the study).

This may include access to an investigational intervention that has demonstrated significant benefit. In all these situations, researchers and sponsors must show care and concern for the health and welfare of study participants. This is justified by **the principle of beneficence**, which requires researchers and sponsors to safeguard the health of participants when it is in their power to do so.

It is also supported by **the principle of reciprocity**; participants assist researchers in generating valuable data and, in return, researchers should ensure that participants receive needed care or preventive measures to safeguard their health.

Importantly, **the obligation to care** for participants' health needs is not specific to research in countries with limited resources (see Guideline 2 – Research conducted in low-resource settings) but is a universal ethical requirement in research.

"Furthermore, even though the provision of care during and after the trial may be an incentive for people in low-resource settings to enroll, **it should not be considered an undue influence".**

(emphasis added)

20) Macklin R. Schuklenk's critique of the CIOMS guidelines: All procedure, no substance. *Indian J Med Ethics*. 2017; 2(3): 173-5. Online First Published March 29.
http://ijme.in/articles/schuklenks-critique-of-the-cioms-guidelines-all-procedure-no-substance/?galley=html

I also was one of the 12 individuals in the 2016 review: eight from the North, four from the South: myself from Brazil, and one each from India, Burkina Faso, and Senegal. It must be also remembered that all the discussion was in English which may skew the discussions towards a more pragmatic view of the participants rights, and this may be aggravated because even if one speaks good English, it is not his or her mother tongue.

7.2 CIOMS 2016 Guideline 6

In relation to access to care, CIOMS Guideline 6, "Caring for participants' health needs" states: "*When access is provided after the research to investigational interventions that have demonstrated significant benefit, the provision may end as soon as the study intervention is made available through the local public health-care system or after a predetermined period of time that the sponsors, researchers and community members have agreed before the start of a trial*". In my opinion this wording has problems: It starts with a "when" instead of "Access must be provided...". It requires that sponsors make plans for **providing continued access to study interventions that have demonstrated significant benefit**. Again, "make plans" may not exactly mean that access will be actually provided.

7.3 CIOMS 2016 Commentary on Guideline 6

Commentaries are interesting because it details and discusses the guideline itself. One of these gives reasons to justify post-trial access following principialistic based decisions. Access is there justified based on the principles of "beneficence" and of "reciprocity". The obligation to care for participants' health is not specific to research in countries with limited resources, but is a universal ethical requirement in research. This commentary and its rational gives strong reasons for the post-trial access, stronger than in the Guideline itself. Unfortunately, there is always the risk that many just read what is in the guideline, and do not pay that much attention to the commentaries.

The last phrase of "General consideration" in Guideline 6 commentary states that "*even though the provision of care during and after the trial may be an incentive for people in low-resource settings to enroll, it should not be considered as an undue influence*". That is a very strong statement because some have criticized that access in a community where they have nothing could be undue influence to participation in a project. Ethically speaking provision of post-trial access should be considered a right.

8. UNAIDS/WHO guidance in 2007 (Table 5)

The initial provocation that these research ethics controversies are dated is based on arguments such as in a controlled clinical trial it is much easier to ensure that the vulnerable will be respected, that exploitation will be avoided and that post-trial access, which as a right, will not even significantly impact costs. That said, the page should be moved to transitioning the results of efficacious research to actual access in public health for all.

There are already some good examples. One is the 2007 UNAIDS/WHO Ethical Considerations in Biomedical HIV prevention trials [13], which is in the process of revision (Dr. Otmar Kloiber, Secretary General of the World Medical Association and myself just participated in November 2019 in a meeting, convened in

Table 5 2007 UNAIDS/WHO guidance document: Ethical considerations in biomedical HIV prevention trials

Guidance Point 12: **Benefits**

- **The research protocol should provide an accurate statement of the anticipated benefit of the procedures and interventions required for the scientific conduct of the trial....**
- **...Some of the activities related to the conduct of HIV biomedical HIV prevention trials which may benefit those who participate may actually be rights.**

Guidance Point 14 - Care and treatment

- **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.**
- Prior to initiation of a trial, all research stakeholders should come to agreement through participatory processes on mechanisms to provide and sustain such HIV-related care and treatment.

Commentary on Guidance Point 14

- **A consensus on the level of care and treatment... to trial participants has emerged** in recent years with increasing accessibility of antiretroviral treatment in low- and middle-income countries, based on strong commitments from countries, development partners and multilateral organizations; dramatic decreases in drug prices; and evidence that treatment programmes in resource-poor settings are feasible and sustainable
- There is **consensus that sponsors need to ensure access to internationally recognized optimal care and treatment regimens, including antiretroviral therapy,** for participants who become HIV infected during the course of the trial.
- There is also agreement that prevention trials ought to contribute constructively to the development of HIV service provision in countries participating in biomedical HIV prevention research, **for the sustainable provision of care and treatment** after the completion of a trial.

(emphasis added)

Montreux, Switzerland by WHO and UNAIDS to start revising this document). In the 2007 version its Guidance Point 12 (Benefits) states that "***some of the activities related to the conduct of HIV biomedical prevention trials which may benefit those who participate may actually be rights***". What they are trying to say is that what participants are receiving, is not a given, but should be considered as their rights. The guidance point 14, which was a contentious issue in 2007, stated that "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", in other words, it said that drugs to treat HIV must be provided to those who get infected during preventive trial.

And it goes on. The commentary on guidance point 14 affirms that "***a consensus on the level of care and treatment .....to trial participants has emerged***" and that "***sponsors need to ensure access to internationally recognized optimal care and treatment regimens, including antiretroviral therapy***". This was a very important change to what have happened many times before – that is, at the end of a study participants would have their treatment discontinued.

9. WHO Guidance on TB, 2010 (Table 6, 7)

As mentioned previously, in 2010 WHO established a guidance on ethics of tuberculosis prevention, care and control [14], where they used questions and answers on different aspects of TB care. One question was: "*Does obligation to access to care means that TB care should be provided for free?*" The answer was "yes". It also specified that research protocols should provide attention to how findings will be translated into public health policy as applicable. So, this document changes the emphasis on what was researched to what is to be available in public health.

Another question, "*do governments have an ethical obligation to provide universal access to TB care? Yes, provision is grounded in their duty to fulfill the human rights to health*". What the document implies is that research is very important to find effective treatments and that these should be provided not only to the research participants but to everyone who needs it.

The two documents have included a novel decision – in both, UNAIDS 2007 [13] and WHO 2010 (Table 7) [14], there is a list of circumstances in which biomedical trials should not be performed. All are very important but the last two are worth stressing: "*When agreements have not been reached among all research stakeholders on access to medical care and treatment*", and "*When agreements have not been reached on responsibilities and plans to make trial products that prove to be safe and effective, available to communities and countries where they have been tested at an affordable price*".

These documents innovated in putting together research and access to effective products in public health. In my opinion, that's the way it should be, in a continuum. And this just confirms the main reason to do health research, that is to improve people's health.

Table 6 WHO 2010 Guidance on ethics of TB prevention, care and control

WHO 2010
Guidance on ethics of TB prevention, care and control
Access to care for all

Does this obligation mean that tb care should be provided for free?

- **Yes.** "Anti-TB drugs should be available free of charge to all TB patients, both because many patients are poor and may find them difficult to afford, and because treatment has benefits that extend to society as a whole (cure prevents transmission to others)" - *Stop TB Strategy*

Considerations are particularly important in designing an ethical research strategy.

- Research should be designed so that the populations in which it is carried out stand to benefit from the results.
- Research results should lead to **technology transfer**, whenever applicable, for the benefit of the affected population.
- Research protocols should provide attention to how findings will be translated into public health policy, as applicable.

2. The obligation to provide access to TB services

Do governments have an ethical obligation to provide universal access to tb care?
Yes. Provision of universal access to TB care is grounded in their duty to fulfill the human right to health.

As stated in **the WHO Constitution,** "the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition".

Similarly, the **International Covenant on Economic, Social and Cultural Rights** recognizes "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health" and specifically calls on State Parties to take steps necessary for "the prevention, treatment and control of epidemic, endemic, occupational and other diseases".

(emphasis added)

Table 7 Circumstances in which biomedical trials should not be performed (WHO 2010)

As much as research on the various aspects of TB care and control is necessary, there are **circumstances/ conditions in which trials should not be performed**:

- 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.**

(emphasis added)

10. A case study – Brazil's response to International pressures on research ethics (Table 8, 9)

A case study will be presented describing how Brazil responded to pressures to lower ethical requirements in human research. Brazil has a National Research Ethics Commission (CONEP), which issued a national Research Ethics Guideline [15] and an Unified Health System (SUS), which provides access to health care for all. In August 2008, just two months before the 2008 revision of the DoH, Brazil decided, as an independent country, that in biomedical research at the end of the study, the sponsors must ensure to all participants access free of charge for all the needed time to the best prophylactic, diagnostic, and treatment that have demonstrated to be efficacious. It also provided guidance for this access, if needed, even before a full regulatory approval. That was a bold step for an underdeveloped country which took this decision based on the 2000 version of the DoH and was in clear confrontation to the notes of clarification issued by the WMA (2004).

When this decision was taken many people said that drug companies would get out of Brazil and would stop doing research there, but this has not occurred. As a matter of fact, what happened was that every time a research protocol came to the National Research Ethics Commission without this provision, it was imme-

Table 8　Brazilian Research Ethics Commission Resolution 466/2012*

III.2 – Research involving human beings in any area of knowledge must:
ensure to the participants adequate conditions of follow up, treatment, access to new drugs (if shown to be safe and effective)

III.3 – In biomedical research:

d) At the end of the study the sponsors must ensure to all participants, access, free of charge and for all needed time, to the best prophylactic, diagnostic and treatment that have demonstrated to be efficacious

d.1) Access will also be warranted between the end of individual participation and the end of the study. In this specific situation access will be permitted through a study extension, according to a consubstantiated analysis of the participant's attending physician.

**** Succeeded Resolution 404/2008 (1 August 2008), which also included:***
To propose further discussion on access to health and to the products that have showed efficacy to all who need them.

(emphasis added)

Table 9　Resolution 1885/2008 Brazilian Medical Council (CFM)

- **Article 1*** - Doctors are forbidden to have any participation in clinical trials where placebo is used as a control when there are efficacious and effective drugs for the disease on trial.
- Approved 23 October, 2008

****This article was incorporated into the Code of Medical Ethics (2009-2019) and the restrictions to use of placebo are also included in the Brazilian Research Ethics Commission Resolution 466/2012***

Table 10 Protection of human rights

Norberto Bobbio
in *Fundamentals of Humans Rights*, 1964
• "...the gravest problem of our times, in relation to the human rights, is not any more to set its foundations but to protect them."

diately sent back to the pharmaceutical industry. Very rapidly they would return a revised protocol abiding to the Brazilian rules. The supposedly high costs for providing for this post-trial access do not even dent what pharma spends with marketing alone.

A similar move was taken by the Brazilian Medical Council. Just two weeks after WMA's General Assembly in Seoul (October 2008), where the changes related to placebo use were approved, the Brazilian Medical Council decided that all Brazilian physicians are forbidden to have any participation in clinical trials where placebo is used as a control when there are efficacious and effective drugs for the disease on trial. This was approved first as a specific resolution in October 2008 and was embedded in the Brazilian Code of Medical Ethics, 2009.

It is worth quoting the well-known late Italian Philosopher Norberto Bobbio (Table 10). Speaking on human rights, he said that the greatest problem of our times in relation to human rights is not any more to set its foundations but to protect them. In this respect, it should be emphasized that there are so many different research ethics guidelines that many times people may choose what they think will be better for their research. Someone may say that he or she do not agree with WMA's DoH, or with UNESCO's Bioethics and Human Rights Declaration, and prefer to follow an American or European directive. Even the US National Institute of Health has one specific guideline for their supported studies, which seems at least akward because instead of abiding to an international issued guideline, they have one of their own.

11. The future of research ethics

The future of research ethics should be, in my opinion, closely associated to access to developed products in public health, as discussed above. But there are many other challenges, risks, and expectations. Just to mention a few – the ethics of the Internet of Things (IoT), artificial intelligence (AI), CRISPR, CAR-T, eugenics. There are many uncertainties on what these developments will mean to the human race; we do not know how and there are doubts on the reasons they should be controlled. However if we do not discuss now, it's going to be even harder when the coming scientific progress becomes a reality. One worrisome example, the first head transplant is due to be performed in China by an Italian neurosurgeon supposedly in 2020. He says that everything is ready for this operation. How can the Declaration of Helsinki, UNESCO's, WHO's or any other declaration be used in such a situation? There are so many challenges to come which clearly justifies the discussion of all the possible ethical and human rights risks, and of course the possible benefits that must come in an equalitarian way.

12. Universal Public Health System versus Universal Health Coverage

Brazil has an Universal Unified Public Health System (SUS) that emanated from our 1988 federal constitution, specifically from one of its articles that affirms that health is a right of all individuals and a duty of the State (Fig. 1). SUS encompasses all the 210 million Brazilians and 150 million of them are cared exclusively in this system. It has the world's largest network of human milk bank, the largest number of organ transplants, funds 90% of preventive vaccines, and most importantly, everything financed by national taxes. No individual money is put on.

Fig. 1　Brazilian Federal Constitution 1988 and Unified Health System (SUS) in Numbers

On Health:

- **Article 196. Health is a right of all and a duty of the State and shall be guaranteed by means of social and economic policies aimed at reducing the risk of illness and other hazards and at the universal and equal access to actions and services for its promotion, protection and recovery.**
- **Article 198. Health actions and public services** integrate a regionalized and hierarchical network and constitute a single system, organized according to specific directives:

  I – **decentralization**, with a single management in each sphere of government;

  II – Comprehensive care, priority being given to preventive activities, without hampering care services;

  III – **participation of the community**.

  Paragraph 1. The unified health system shall be financed, as set forth in article 195, with funds from the social welfare budget of the Union, the states, the Federal District and the municipalities, as well as from other sources.

https://www2.senado.leg.br/bdsf/bitstream/handle/id/243334/Constitution_2013.pdf?sequence=11&isAllowed=y

(emphasis added)

Unified Health System (SUS) in Numbers

- 30,000 Family health teams, 13,000 Dental health teams
- App 40,000 basic health units
- 8,500 Public Hospitals, 504,000 beds
- 17,000+ Emergency facilities

- 150 million+ Brazilian citizens (3/4 of the population) are cared free of charge exclusively at the SUS

SUS Dimensions and funding

- World largest network of human milk bank
- World largest number of organ transplants
- Funds 90% of preventive vaccines
- Funds 80% of oncology treatments in Brazil
- All Antiretroviral drugs and lab exams are funded by SUS
- All Hepatitis treatment, including Protease inhibitors for HepC
- Over 90% of total hemodialysis

Funded exclusively by municipal, state and federal monies

More details on the Brazilian Public Health System can be accessed in a special edition of *The Lancet* May 2011 (Table 11). One of their conclusions is that it is important to have political will to keep such a system working. It's very interesting because with this all change in the world and as previously mentioned, the United Nations are defending what they have called an "Universal Health Coverage". It must be mentioned a meeting in June 2019 here in Tokyo, where many presenters discussed the meaning of Universal Health Coverage. It is not the same as an Universal Health System, as the former means that health coverage may be established in a country, but this will not mean that all people will have the conditions (e.g., economical) to access to all they need. My rational is that this UN proposed transition to Universal Health Coverage should be upgraded to the real Universal Health Systems, such as those already in place in Canada, Brazil and UK.

13. Brazilian AIDS Programme and the Unified Health System [21)]

As a continuation of the arguments to the need to ensure access to developed products in public health, the Brazilian AIDS Programme and the Unified Health System are good examples. In relation to the confrontation of the AIDS epidemic one of the important accomplishments happened in 1996, when a law was passed stating that all people living with HIV(PLH) have the right to access free-of-charge to antiretrovirals. This

21) Greco DB. Thirty years of confronting the Aids epidemic in Brazil, 1985-2015. Cien Saude Colet. 2016 May;21(5):1553-64. doi: 10.1590/1413-81232015215.04402016.
http://www.scielo.br/pdf/csc/v21n5/en_1413-8123-csc-21-05-1553.pdf

Table 11　Special edition on Brazil, *The Lancet* May 2011

Brazil: towards sustainability and equity in health

Brazilian researcher Cesar Victora et al conclude in the final article of this issue: ***"The challenge is ultimately political, and we conclude with a call for action that requires continuous engagement by Brazilian society as a whole in securing the right to health for all Brazilian people***."

in Kleinert S, Horton R. The Lancet- Health in Brazil 2011; 377(9779): 1721-2.

"Global health is about global democracy. But today nations with the greatest needs have the least power and influence. That must change."
Richard Horton (Editor, *The Lancet*)

However
There is increasing pressure to limit the scope and funding of Brazilian Unified Health System (SUS), aiming at transforming this inclusive, free-of-charge Universal System into a much more limited Universal Health Coverage*.

WHO 67th General Assembly 2012 encourages Member States to plan, pursue transition of National Health Care Systems towards Universal Health Coverage

move completely changed the scenario to the eventual control of the epidemic, and in 2019 there were more than 500,000 PLH on antiretrovirals, more than half of them manufactured in Brazil. A few years before this law National AIDS programme was established, with strict respect for human rights and against all forms of prejudice or discrimination. This decision to provide anti-HIV medication was a bold decision. At the time the World Bank released a statement against this provision as this should not be done in such a complex and big country because of significant risks of non-adherence and emergence of resistant viral strains. The country should stick to prevention, and not provide treatment. Time proved them wrong and Brazil became an example to the world.

This is an example of a successful transition from research (development of drugs to confront HIV) to the real access to all in a public health setting, financed by tax money.

Unfortunately, as of January 2019 a far-right government took office and it is already being deleterious to most of the progress on health, education and human rights that the country has accomplished in the last few decades. This has been preceded by a 2018 law that limited health expenditure for the next 20 years, which of course will negatively impact the needed resources to take care of an aging populations.

14. Concluding remarks

14.1 Concluding messages

Lastly I will give you concluding messages:

1. It is crucial to develop universally acceptable ethical guidelines. These principles should be harmonized and approved by a world representative institution (such as UN/WHO);

UNESCO's Declaration on Bioethics and Human Rights and WMA's experience with the DoH should be used as an example in the development of one research ethics document that could be internationally

backed by all countries.

2. **Universal access to current established and future research products must be internationally sanctioned and, enforced through international covenants and resolutions issued by the United Nations. The *status quo* of inequality must not be an immutable fact and we must fight for universal access to health, which is recognized as a human right and it is not an economic commodity;**
3. **If ethical standards are lowered it will certainly be difficult to eventually raise them back;**
4. **There is an indisputable need for better preventive methods, more efficacious and less expensive drugs and for more efficacious vaccines. Clinical trials with these objectives can be performed where vulnerability is lower;**
5. **All researchers, both from developed and developing countries, should participate in all stages of the study, from protocol development to the application of the results. Inclusion of vulnerable individuals warrant special justification and appropriate protection and should occur only when the project objective is for their benefit;**
6. **The discussion on the rights to access to care & treatment in research is dated and the debates on ensuring participants' rights to post trial access must be substituted with the objective of providing access to all efficacious products of research in public health;**
7. **And last but not least, we must be prepared for upcoming ethical challenges and to provide guidance for the expected difficult decisions related to technological progress (Risks, inequalities, access, costs).**

14.2 Emancipation (Table 12)

I will finish with a quotation and a counter argument. Thucydides writing on the Peloponnesian wars said that "*justice will come only when those who are not subjected to injustice are as indignant as those who are*". He was saying that those not directly affected by injustice, but who are very indignant by prevailing injustice, will make things change. I would counterargue that "*justice will prevail when those affected and indignant by injustice are able to fight for their rights*". Instead of the solutions coming top-down, they should be from down to top. The first quote is what the Americans like to define as empowerment. It is heard a lot. People say "We must empower women". Nobody empowers women. Women and men alike have to emancipate to fight for their rights. Emancipation was intensively defended by the very important Brazilian educator, the late Paulo Freire.

Table 12 From empowerment to emancipation

- **Thucydites wrote* that: Justice will come only when those who are not subjected to injustice are as indignant as those who are.**

"Empowerment"

***Peloponesian wars**

I would argue that:

Justice will prevail when those affected and indignant by injustice are able to fight for their rights.

"Emancipation"

＜Q&A＞

Kurihara　I deeply respect Brazil's position on placebo and post-trial access, strong protection of the human subject and human rights. Also your struggle to achieve universal health system.

I have a question about the vulnerable population issue. How is your opinion about reverse theory in CIOMS to facilitate inclusion of the vulnerable population unless there is justification reason? Because Dr. Kloiber said there would be some time incentives to come into the study. And there would be the traditional idea of therapeutic misconception and sometimes it would be tricky idea facilitating inclusion of the vulnerable population, exposed unfairly to unacceptable risks. I myself is one of the advocates of this idea in CIOMS, but would like to ask for your opinion considering such counterargument.

Greco　That's a very good point and Dr. Otmar Klöiber mentioned that this is a big change because for many years vulnerable population, especially some that are not that much vulnerable, such as lactating women, seniors, children should not participate in any research because of their specificities. Things have changed, in my opinion for the better. There was a time when research with children was not permitted, the same with the elderly. What the physician would do? He or she would adapt the dose recommended in studies with adults, with many risks involved. Thus, this change is very good provided the inclusion of these populations is done with adequate care and now we must justify why not include such vulnerable populations when the research could be specifically useful for them.

Question (Web participation in Japanese)　Could you explain the discussion about the use of placebo?

Hiroshi Watanabe, Chairman (in Japanese)　First, where there is no effective intervention, placebo-controlled clinical trial is ethically acceptable. However, where there is effective intervention, placebo use is controversial. Prof. Greco argues it is not acceptable, and this is the position of the 2000 version of the Declaration of Helsinki. In such case, add-on trial would be acceptable.

In addition, there is a debate on placebo trial where established intervention is available in developed countries but not in developing countries. Considering such issues, Prof. Greco argues that universal healthcare access must be established, and we should make all efforts for that.

Another issue is that some special treatments, such as regenerative medicine, have been performed without placebo-controlled trials. It should be discussed more in depth whether it is truly exceptional situation where placebo is not acceptable under any condition; whether it is possible to evaluate efficacy without parallel controlled group . Use of Real World Evidence (RWE) for such situation must be further discussed for development of clinical evaluation methodology.

Kurihara (in Japanese)　I would like to add one explanatory point. Current version of the Declaration

of Helsinki sets the limitation of placebo use where there is best proven intervention saying “no additional risk of serious or irreversible harm”. On the other hand, CIOMS took this wording in 2002 version but in the 2016 version it was changed to “minor increase above minimal risk”.

Brazil took the policy same as the 2000 version of the Declaration of Helsinki, which does not allow placebo control where there is established intervention. This is higher standard of human subject protection than Helsinki, but according to Prof. Greco, there is no problem to conduct necessary clinical trial in Brazil. Meanwhile, many people argue that 2000 version prohibits necessary clinical trial. This is continuing discussion.

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