COVID-19 vaccine – FINAL 27Feb21 Placebo-controlled Trials DG -IJME

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**COVID vaccines: Placebo use and rights to post-trial access: Ethics of HIV preventive vaccine trials and public health access as an example**

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***Abstract:***

*The world is currently facing another pandemic, the COVID-19, just 4 decades after the start of AIDS, and the still increasing incidence of HIV infection continue to be one of the greatest global health challenges. The way the latter has being confronted was of fundamental importance for a serious discussion on global health, ethics and human rights, and this experience could and can still be applied to COVID-19.*

*In early 2020, the global spread of SARS-CoV 2 infection began and in March 2020 was characterized as a pandemic by WHO. The COVID-19 pandemic has specific characteristics and these will be discussed, both in relation to vaccine research and to equal access to products that prove to be safe and effective. It will underscore the challenges for the implementation of measures for its eventual control, with an emphasis on research for the development of safe and effective vaccines. It will discuss the ethics of clinical trials, the use (and limits) of placebo and post-trial access.*

*The social, health, political, economic impacts that directly affect human rights will be emphasized. It will also consider the role of social determinants that contribute to its expansion, severity and mortality, the errors and omissions in the global response to the pandemic, and how this can affect the ethics of vaccine research.*

*It defends limits on placebo use in vaccine trials, which include the rights of the placebo arm participants to the vaccine as soon as it is shown to be safe and efficacious; the use of an active control for phase 3 trials after the approval of other safe and efficacious vaccines. It will emphasize that access to COVID-19 vaccines be considered as a human right and also the need to establish appropriate ethical standards to ensure universal, equal and affordable access to vaccines for all.*

*It will list the perspectives to effectively control the COVID-19 pandemic, including but not limited to the protection of human rights to all and the need to address the social determinants of health that have facilitated the spread of this current syndemia.*

**Introduction**

The unequal (dissimilar) access to health care to most vulnerable communities/ populations, not only among countries but also in countries, is having a significant and unacceptable impact in increasing morbidity and mortality of COVID-19. Of note this is not a unique characteristic of the current pandemic as it has occurred and still does with AIDS.

The prevailing inequality includes dissimilar access to diagnosis, to initial care, to ICU beds and to developed vaccines.

To counteract this situation there is an urgent need to boost production of the vaccines that have been authorized to use and most importantly have them deployed in an equalitarian way throughout the globe. As some of the available vaccines have been authorized only for emergency use (six as of February 21), there is also the need to closely follow up the vaccinees, through pharmacovigilance or phase 4 trials.

Both the unequal access and the clinical trials raise several ethical issues, which are not much different from what happened with the AIDS epidemic – these involves the ethics of human trials, the access to affordable products, intellectual property (IP) issues (e.g., compulsory licensing issues, generic production), among others.

This article focusses primarily on issues related to COVID 19 vaccines, especially in the use and limits of placebo use and the right to post-trial access, both to control group participants and more importantly, in public health to all who need them.

Placebo use: currently there are 20 Vaccines in large-scale phase-3 efficacy tests (1) and these trials used placebo or other agents for the control group.

Several ethical dilemmas/difficulties arise regarding placebo use and post-trial access when:

1. a vaccine receives an emergency use authorization and as of this writing there are nine of them in this condition, and this should mean that placebo arm participants are entitled to receive the authorized vaccine.
2. Other vaccines, besides those already authorized for emergency use or to full use, are proposed to still be tested in phase-3 trials using a placebo as a control arm. However, directives for placebo use in three current research ethics guidelines (two international and one regional), state upfront that:

. 2016 CIOMS Guidelines (Guideline 5) (2): “…that research participants in the control group of a trial of a diagnostic, therapeutic, or preventive intervention receive an established effective intervention.”;

. 2013 Declaration of Helsinki (DoH), article 33 (3): “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”;

. 2012 Brazilian National Research Ethics Guidelines (4): “when using placebo, such use shall be fully justified as to its non-maleficence and methodology requirements, where the benefits, risks, difficulties and effectiveness of a new therapeutic method shall be tested, comparing it to the best current prophylactic, diagnostic and therapeutic methods. Placebo or any other treatment may be used when there are no proven methods of prophylaxis, diagnosis or treatment.” However the first two (CIOMS2016 and DoH 2013) allow for departures of this requirement, although adding conditionals for such – in the CIOMS guidelines: “delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of effective mitigation procedures” and in the DoH: when “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.” On the other hand, the Brazilian National Research Ethics Guidelines do not open any exception for allowing placebo use when an active comparator exist.

For a considerable time now, especially after the 2000 Version of the DoH, post-trial access, placebo use and its limits have brought fierce ethical and even scientific discordances involving serious and experienced researchers/bioethicists. There are some that propose the continuation of the trial and the maintenance of placebo, even when the tested vaccine has been authorized for emergency deployment, their rational being that such studies could be ethically acceptable in countries with limited or no access to a known effective vaccine –This is proposed in a publication at the New England Journal of Medicine (24 January 2021) (5), where it is stated:

“What about vaccine candidates that do not become available for phase 3 study until after effective vaccines have already been deployed in some locations? *Countries with limited or no access to a known effective vaccine could thus ethically permit placebo-controlled trials of vaccines of potential relevance to them even if effective vaccines were already being marketed elsewhere.”(emphasis added). Is this not a* clear double-standard situation, as researchers are taking advantage of the unequal distribution of vaccines to perform a trial which would not be approved in countries with access to the emergency use vaccine? This is a déjà vu of arguments used in HIV trials, which were considered a clear case of double-standards and positions against this possibility abound in several publications 6,7,8).

It is also worth quoting the 2010 UNAIDS/WHO guidance point 14, on Care and treatment, in its commentaries, as it can be also applied to COVID-19 vaccine trial participants:

“The obligation on the part of the sponsors and investigators to ensure access to HIV care and treatment, including antiretroviral treatment for participants who become infected derives from some of all of three ethical principles. The principle of *beneficence* requires that the welfare of participants be actively promoted. The principle of *justice as reciprocity* calls for providing something in return to participants who have volunteered their time, been inconvenienced or experienced discomfort by enrolling in the trial. The principle of *justice*, meaning *treating like cases alike*, requires that trial participants in high-income and low- and middle-income countries be treated equally regarding access to treatment and care.”

Post-trial access:

This will be divided in two subitems: Access in a clinical trial environment and access in real world/public health.

1. In clinical trials:

The provision for post-trial access to all participants to safe and effective products of the trial is strictly included in the Brazilian Resolution 466/2012, was also unequivocally stated in the 2000 DoH version but was made a more flexible in the current 2013 version: and it not very clear in the 2016 CIOMS guidelines

1.a. In the Brazilian Research Ethics Commission Resolution 466/2012: III.3.d – *“guarantee to all participants, at the end of the study and for unlimited time, free access to the best prophylactic, diagnostic and therapeutic methods that have proven their efficiency.*” This is probably a unique position and as such has been applied to all clinical trials approved in Brazil since 2012.

1.b. In the 2013 Declaration of Helsinki- **Article 33**: ”*In advance of a clinical trial, sponsors, researchers and host country governments should make provisions (emphasis added) 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*”. When compared to the wording of the 2000 DoH (item 30. *At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study*) (9), the current DoH is laxer in this issue, as “should make provisions” is not equal to post-trial access.

1.c. The 2016 CIOMS guideline 5 is also less clear in this issue as instead of defining the obligations to post-trial access, it just requires that researchers and sponsors make plans (emphasis added) for, among others, “providing continued access to study interventions that have demonstrated significant benefit”. And again, “make plans” is not synonymous to actually ensuring access.

On the other hand, CIOMS 2016 Guideline 1 may be understood as an added protection for post-trial access: “*Scientific and social values cannot legitimate subjecting study participants or host communities to mistreatment, or injustice.”* And also, the UNESCO Universal Declaration on Bioethics and Human Rights (10), especially in articles 2 (*The aims of this declaration are: 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*.) and 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)*.

It must be noted that the COVID-19 pandemic, which must be better considered a Syndemia (11) has characteristics in common with AIDS, such as that they are not caused by “democratic viruses” as many times it mentioned in the lay press – although they may similarly infect exposed individuals, consequences are different and much more severe among the most socially vulnerable. This is confirmed by the much higher morbidity and mortality of non-white individuals, which is more pronounced in LMIC (12) but is also seen in industrialized countries, with the USA as an example (13). And access to technological progress, such as to vaccines, is also very dissimilar and great care should be taken to avoid exploitation and increase their vulnerability.

There is an undisputable need to deploy vaccine or vaccines that have shown to be safe and effective in an egalitarian way to all. To this end, a vaccine or vaccines shown to be safe and efficacious in phase 3 trials must be evaluated and eventually approved by regulatory authorities, locally or using known international agencies. Following this the complexity is increased and these are related to, for example, how to ensure sufficient production, equalitarian local and global distribution, affordability, accountability, long term follow-up, IP issues.

COVID-19 vaccines must be a global public good, aiming at significantly contributing to the equitable protection and promotion of human rights among all people of the world. To reach this objective, the following must be expected. both in research and in public health access:

* The protection and promotion of human rights including health, social, gender and economic security.
* The assurance of equity in vaccine access among people living in all countries, particularly the most socially vulnerable (14).
* The assurance of equity in vaccine access and adequate care within countries for groups experiencing greater burdens from the COVID-19 pandemic, which are usually but not exclusively living in low- and middle-income countries
* The respect for persons and communities, ensuring their privacy. This includes the recognition that all human beings have equal rights and moral status and can not be subject to any kind of discrimination and/or exploitation
* That research must be based in fairness, reciprocity, non-exploitation and without double standards
* That vaccines and other developed products to curb the pandemic must be accessible, affordable, non-patentable (15,16) and available to everyone.
* That decisions on vaccine research, allocation and national decisions on vaccine prioritization must be taken through transparent processes based on shared values, best available scientific evidence, and appropriate stakeholders’ representation and participation
* To make sure that the vaccines already authorized or in the verge of being authorized for emergency use are equitably distributed to all countries. The COVAX Initiative (GAVI, WHO, CEPI) is a good start as it involves around 190 countries, with the participating high-income countries contributing to the access to LMIC but it must be properly financed to really reach its objectives, which is modest, as it assures that at least 20% of the world population are immunized. It is worth quoting the opening remarks of WHO Director-General Tedros Adhanom Ghebreyesus on the ethics of egalitarian access to COVID-19 vaccines at the 148th Session of WHO Executive Board on January 18th, 2021 (17): *“I need to be blunt: the world is on the brink of a catastrophic moral failure – and the price of this failure will be paid with lives and livelihoods in the world’s poorest countries. Even as they speak the language of equitable access, some countries and companies continue to prioritize bilateral deals, going around COVAX* (18)*, driving up prices and attempting to jump to the front of the queue… This is wrong. Forty-four bilateral deals were signed last year, and at least 12 have already been signed this year. The situation is compounded by the fact that most manufacturers have prioritized regulatory approval in rich countries where the profits are highest, rather than submitting full dossiers to WHO*”.

This is confirmed by the fact that as of February 27, only 3.1% of the world population received at least the first dose of one vaccine (19) and 75% of all vaccines were applied in only 10 countries; and one hundred thirty countries have not yet access to any vaccine.

The COVID-19 pandemic will not be controlled without immunizing the majority of the world population and this is clear in WHO motto**:** "No one is safe until everyone is safe", which means that the sooner safe and efficacious vaccines are made available, affordable and widely deployed, the sooner this appalling health and social crises and the unique economic slump could be overcome. The slowest the pace of worldwide vaccination, the highest the risks for the appearance of new viral mutants, which could be not only more infectious but also not effectively be protected by the current vaccines.

**Conclusion**

The position here defended related to COVID 19 vaccines are:

* In clinical trials (placebo and post-trial access):

. Placebo arm participants must have access immediately to the vaccine as soon as phase 3 is completed and the results show safety and efficacy. This is the responsibility of the sponsors/investigators and this right must be clearly stated in the informed consent process/form.

. When vaccine or vaccines are approved for emergency or full use, subsequent phase 3 trials should use one of them for the control arm. Exceptions could be granted when the authorization does not include other specific conditions of the participants, such as other age brackets, pregnancy or new developments (such as new and resistant variants). This considers the ethical guidelines discussed above, including the very stringent Brazilian guidelines regarding placebo, the limits established at the exceptionalities in the CIOMS 2016 and DoH 2013, plus the safety and efficacy data on more than 234.1 million vaccine doses that have been administered worldwide as of 27 February, 2021. This ethical decision is scientifically reinforced by the fact that SARS-CoV-2 infection may be severe and even fatal and there is no pharmacological treatment available to mitigate these risks.

* **Access in public health:** access to safe and efficacious vaccines must be considered a human right and to effectively curb the COVID-19 epidemic, safe and efficacious vaccines must be available and affordable to all the world population.

**Perspectives:** The worldwide confrontation of AIDS can be considered a global health model (20, 21). To effectively combat COVID-19, the lessons previously learned with HIV/AIDS, in both research and in public health, must be used to counteract isolationism, boost international solidarity/cooperation with the participation of all relevant stakeholders, to confront anti-science/anti-vaccine movements, to adequately finance science and quality public health accessible to all, to ensure equalitarian access to technological progress and to avoid exploitation/double standards, both in research and in public health access. This will need strong cooperation among several stakeholders, with WHO leadership, adequate financing, respect for and participation of individuals/communities, government, universities, researchers and health professionals. Only together will it be possible to address the social determinants of health that have facilitated the establishment and spread of the current Syndemia 11 and to prepare for the adequate confrontation of others that will certainly come.

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