# Placebo-controlled trials of Covid-19 vaccines – are they still ethical?

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**Abstract**

A World Health Organization (WHO) Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation recently recommended placebo-controlled trials (PCT) of Covid-19 vaccines. PCTs are ethically acceptable when there is no proven effective and safe treatment for a certain condition. However, there are already some vaccines that have been approved and which have high levels of efficacy and safety. Any new vaccine under development must be tested against the most effective vaccines available. PCTs go against participants best interests, by putting them in a position of disadvantage while taking part in the trial compared with people who are not in the trial, and who could get vaccinated. Particularly in high-income countries, many people are getting vaccinated. This means that, following a recent trend in clinical trials, PCTs would have to be conducted in low- and middle-income countries, where there a number of advantages for drug companies, but where fatality rates of Covid-19 are much higher. For this and other reasons having to do with equal rights, participants in control groups should be protected with the most effective vaccines available.

***Keywords:*** *Covid-19, vaccines, placebo-controlled trials, low- and middle-income countries, exploitation*

On January 14, the World Health Organization (WHO) Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation—a group consisting of vaccine experts of several countries—published a paper in which they advocate for placebo-controlled trials (PCT) of Covid-19 vaccines (1). They argue that even if there are already some effective and safe vaccines available, we are in a crucial point in which we can develop and evaluate the additional vaccines that the world needs. The best way to collect high-quality information about these vaccines, they claim, is through randomized, double blinded, PCTs—what is usually called “the gold standard.” In these trials, there is a double-blinded follow-up of participants who are randomly assigned either a vaccine or a placebo, designed to have no real effect. Participants in these clinical trials are explained that they may receive either one of these, and they are asked to sign an informed consent. Neither the researchers nor the participants know who is getting the real vaccine. The idea behind the placebo is to account for the “placebo effect,” that is, effects from vaccination that do not depend on vaccination itself (such as believing that one is receiving a vaccine or biases or expectations of the vaccine efficacy by researchers when assessing the vaccine). In the absence of a placebo group to compare against, it is usually claimed, there is no way of knowing whether the vaccine itself had any effect or of getting information about the vaccine that would be hard to obtain otherwise, so researchers could get unreliable answers about safety and efficacy. With unreliable results, if unrelated events happen by chance after vaccination, these may be wrongly attributed to the vaccine, and this could generate skepticism and doubts among people who are already hesitant about the vaccine. Anti-vaccination groups may take advantage of this situation as well.

However, even when PCTs are widely accepted whenever there is no proven effective and safe treatment for a certain condition, there is controversy over PCTs when there is already an effective treatment for that condition. In this case, the new treatment must be tested against the best current available treatment. This applies also to PCTs of Covid-19 vaccines. Even when several Covid-19 vaccines have been approved for emergency use, they have already proved to have high levels of efficacy and safety (the Pfizer-BioNTech vaccine has an efficacy rate of 95%, Moderna’s vaccine of 94.5%, AstraZeneca’s of 90%, Novavax’s of 89.3%, and the Russian Sputnik of 91% (2-6)). The clinical research community was expecting efficacy rates of 50 to 70%, and the US Food and Drug Administration (FDA) had said that it would consider granting emergency approval for vaccines that showed at least 50% efficacy (7). According to the WHO, there are 242 vaccine projects around the world, 66 of them in clinical trials on humans, and 19 have already reached phase III (8). Many of these projects may fail, but many others will succeed, as has already happened with the ten approved for emergency or limited use in various countries. Why should new vaccines be tested against placebos rather than some of the highly efficacious vaccines already available? Once there is a current available vaccine, that happens to have a high level of safety and efficacy, new candidate vaccines should be tested against the approved vaccines—and ongoing PCTs of Covid-19 vaccine candidates should be unblinded.

PCTs of new vaccines in conditions for which efficacious vaccines already exist contravene bioethics principle of beneficence. PCTs go against participants best interests, by putting them in a position of disadvantage while taking part in the trial compared with people who are not in the trial. In many countries (especially in high-income countries) all these highly efficacious vaccines are beginning to be available to a considerable number of people. To enroll people in a clinical trial and give them placebos is to harm them, in the sense of making them worse off than they would have been had they not participated. If they had not participated in the trial, they would have probably sought and received one of the Covid-19 vaccines already available. Researchers have a duty not to harm participants in clinical trials, so if they fail to treat participants by giving them placebos this would be ethically objectionable. The harm participants in the control group are exposed to is not minor. The fatality rate of Covid-19 is considerable, and even in young adults it is higher than originally thought (9).

It is not only going to be ethically objectionable, but it is going to be very hard for any pharmaceutical company to get participants in high-income countries, where people are starting to get rapidly vaccinated. It would be easier for them to conduct an active-control trial (ACT) comparing the new vaccines to one of the vaccines already approved. So whoever insists in conducting a PCT for vaccine development should know that these trials would have to be conducted in low- and middle-income countries (LMIC), where the vaccines already used in high-income countries are not likely to be available for some years. According to some estimates, while high-income countries have reserved enough doses to immunize their own populations multiple times over, it could take until 2024 for many LMIC to get enough doses to immunize theirs (10).

As a matter of fact, the number of patients recruited for clinical trials in LMIC, rather than high-income, countries has grown significantly in the last decades; an analysis of FDA approvals showed that 86% of new therapies were supported in part by data of trials conducted outside the US and Canada, mostly in LMIC (11). This is particularly true in the case of Covid-19. Many LMIC are participating in phase III of clinical trials of Covid-19 candidate vaccines: many countries in Latin America, Sub-Saharan Africa, South-East Asia and Eastern Europe. Many of them are participating in the trials with the explicit purpose of securing a certain amount of doses from the pharmaceutical companies once the vaccines have been approved. But there are other reasons for this tendency of recruiting participants in developing countries. It is easier for pharmaceutical companies to recruit participants in countries where treatments and vaccines are not easily available; for many people in these countries this may be their chance to get vaccinated. Otherwise, they may have to wait several years until vaccines become available to the majority of the population. For pharmaceutical companies, the promptness with which they recruit participants for trials is also crucial: more than 80% of clinical trials fail to enroll on time, and this costs them large sums of money (12).

It is more cost-effective to conduct PCTs than ACTs in LMIC because the latter would imply providing vaccines to all the participants and, in some cases, improving the medical facilities of the host country. For instance, many countries in Africa or Latin America do not have the cold-chain infrastructure to handle some of the vaccines already available, such as the Pfizer/BioNTech vaccine, which needs to be transported and stored at ultra cold temperatures (-70oC) prior to use. If an ACT were conducted in some LMIC, this infrastructure would have to be provided. By conducting PCTs there, drug companies not only do not have to provide the infrastructure that an ACT would imply, but they save money because the wages of healthcare personnel, researchers and trial coordinators tend to be lower than in developed countries. Another reason is that ACTs have to be considerably larger than PCTs, thereby costing more and taking longer.

There is another reason for conducting PCTs in LMIC: in many of these countries either there are no regulations regarding PCTs or the existing regulations tend to be lax at approving and supervising the research protocols. Some countries have intentionally weak regulatory frameworks in order to facilitate the direct foreign investment that comes with externally sponsored research. Research ethics committees in these countries tend to be less rigorous, and some of their members lack the required expertise (13). All this makes it easier to conduct trials in LMIC.

Conducting PCTs in LMIC might expose participants in the control groups to excessive risks. Taking into account that Covid-19 is potentially fatal, participants in the control group may be in a significant risk of dying. In fact, participants in control groups of Covid-19 vaccine trials conducted in LMIC have died (14 15). Fatality rates are in average higher in LMIC than in high-income countries. People in the former are hardest hit by Covid-19 because of the non-availability and access to basic health infrastructure, such as ventilators, ICUs, hospital beds per thousand population, among others. The basic infrastructure needed to mitigate the effects of Covid-19 is scarce or absent in numerous LMIC. In general, in these countries there is a greater prevalence of diseases such as hypertension, diabetes and the so-called diseases of poverty (AIDS, malaria and tuberculosis, which account for 18% of all diseases in low-income countries (16)). In a study about the fatality rates differences across countries, Banik et al. state that poverty rate is among the most important factors determining the fatality rate due to Covid-19 (17). This is true about poverty in high-income countries as well as low-income countries, the difference being that poverty is more extensive in the latter.

If people in control groups in PCTs carried out in developing countries contracted Covid-19, access to emergency medical services would have to be provided by the drug company conducting the trial, because in many of these countries access to these services is not as prompt as in developed countries. In fact, participants in these countries should receive equivalent standard of care and the same or similar treatment options as clinical trial participants in the sponsoring country. This position is supported by appealing to the rights to equal access to scientific advancements, to the protection of health, and to non-discrimination (12).

Some clinical research guidelines allow no more than minimal risks, and they exclude any risks of serious or irreversible harm (18 19). The risk of getting Covid-19 is serious and may ultimately be irreversible, since it may result in the death of the participant in the control group. Why will the health and lives of thousands of phase III participants be put at risk by giving them a placebo—basically no treatment at all—when we know that Covid-19 is a life-threatening disease and we already have vaccines to immunize them?

It has been argued that PCTs may be ethically justifiable when the available vaccines are just moderately or inconsistently effective, and a new vaccine is expected to be more effective and safe. However, as already mentioned, some of the available Covid-19 vaccines have high levels of efficacy and safety. And even if they were less effective or safe, new vaccines may be developed comparing them to these already approved vaccines. Participants in a clinical trial should be protected with the most effective vaccines available.

Also, it has been argued that a necessary condition for the ethical justification of PCTs is that participants are among the first people to benefit from the research (20). However, recent experiences in drug developments for HIV/AIDS and other diseases show us that these trials have not benefited participants in LMIC—or if they have, it has been only long after the trial has finished (21). Making sure that participants in clinical trials are going to be among the first beneficiaries of vaccine development may help to avoid the feeling in participants and their communities that they have been used and exploited, particularly when vaccines tested upon a group of people become available long after the trial has been conducted or when vaccines are not affordable by the host government. This situation may foster distrust towards pharmaceutical companies and may make it harder for researchers to conduct future clinical trials in these populations.

There may be situations in which a PCT may be ethically justifiable. In 2014, a WHO expert panel argued that the use of placebos in vaccine trials was ethically justifiable in four situations (22): 1) when an existing vaccine is inaccessible in a country’s public health system and may remain inaccessible in the future, so there is a need to develop locally an affordable vaccine; 2) when there is a need to evaluate the local safety and efficacy of an existing vaccine; 3) when a new vaccine needs to be tested because an existing vaccine is considered inappropriate for local use (for instance, due to epidemiologic or demographic factors); and 4) when the local burden of disease must be determined, i.e., when the vaccine’s effect on the burden of morbidity and mortality due to Covid-19 is unknown or uncertain. None of these seems to be the case in the present situation: even if slowly, approved vaccines are beginning to be available in LMIC; they do not seem to be inappropriate for local use; and the vaccines’ effect on the burden of morbidity and mortality is not unknown.

The WHO Ad Hoc Expert Group seems to be worried that the vaccines already approved will not be enough to meet the world needs. According to them, more vaccines must be developed and tested through PCTs. But the problem does not seem to be that there are not enough vaccines under development and that more need to be tested through PCT as if there were no effective vaccines already approved—as mentioned before, today there are 242 vaccine projects around the world. Many of the successful vaccines that come out of these projects may not reach people in LMIC if the mechanisms of production and distribution of vaccines are not revised and modified. If we want to meet the world needs, and especially those of LMIC, the WHO should better consider the proposal of India and South Africa that have called on the World Trade Organization to temporarily waive intellectual property protections related to Covid-19 vaccines, at least until the world population has developed collective immunity. This temporary waiver of pharmaceutical patents, copyrights and industrial designs would enable LMIC to access active pharmaceutical ingredients and benefit from technology transfer—as was done in the past for HIV treatments. This would also allow them to manufacture vaccine at lower costs. Alternatively, the WHO should consider ways in which pharmaceutical companies could work with local partners to make their vaccines available to LMIC. The Covid-19 Vaccines Global Access (COVAX) should also be revised to ensure global equitable access to Covid-19 vaccines. COVAX is a global initiative, led by the Global Alliance for Vaccines and Immunization (GAVI), WHO, and others, that aims at coordinating international resources to enable equitable access of Covid-19 diagnostics, treatments, and vaccines (23). If the distribution of vaccines continues in the current fashion, many LMIC could have to wait until 2024 to gain access to Covid-19 vaccines—and many people will unnecessarily fall seriously ill or even die in the meantime. We all agree that the world desperately needs more vaccines, so we should look for all the possible ways to develop and produce them, but also to distribute them fairly so that everybody is vaccinated promptly, regardless of where they live. The same is also true about clinical trials: people should be treated fairly, regardless of where they live.

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