Double Standards Redux

It is fair to say that nothing is more pressing in the world today than bringing an end to the Covid-19 pandemic. Or to be more precise, if not an end, then the quickest and most effective reduction of mortality and morbidity from the disease in every country where infections exist. This issue of IJME explores a long-standing ethical concern in research with human beings, focused mainly on a question posed about vaccine research for prevention of Covid-19. Contributors from six continents address the question: in what circumstances –if any--is it ethically acceptable to use a research design in which the control group in a randomized controlled trial (RCT) receives a placebo instead of a vaccine already approved for emergency use by regulatory bodies? That ethical question is not new. A controversy arose more than two decades ago in the context of research seeking a method of preventing maternal-to-child transmission of HIV/AIDS. At the heart of that controversy was a question about “double standards” in global research: Is it ethically permissible to conduct a type of research in developing countries that would be impermissible in wealthier countries? The question now rears its head again in the context of the Covid-19 pandemic.

An article published online in the Perspectives section of the *New England Journal of Medicine* on January 14 of this year [WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation, “Placebo-Controlled Trials of Covid-19 Vaccines —Why We Still Need Them,” n engl j med 384;2 January 14, 2021. Hereinafter: WHO Ad Hoc Group] contends that new vaccine research using placebo controls should be carried out in countries that lack access to Covid-19 vaccines already approved for use in other countries. The article says that “while it is still feasible and ethical,” ongoing vaccine trials should use “directly randomized comparisons against placebo” to collect high-quality information. The purpose is “to obtain pivotal data to improve regulatory and public health decision making,” including reliable information on longer-term safety and duration of protection. [p. e2(1)] According to the article, such ongoing vaccine trials may still be occurring in high-income countries as well as in lower- and middle-income countries (LMICs). However, a long-standing practice in research has called for either stopping ongoing trials when a successful product is available outside such trials, or at least informing trial participants that they may leave the study in order to access the newly available product. At the time of this writing, the following six vaccines are being distributed in different countries throughout the world: Pfizer-BioNTech, Moderna, Oxford/AstraZeneca, Johnson & Johnson, Sputnik V, and Sinovac. [Mike Allen, “Latin America turns to China and Russia for COVID-19 vaccines,” Axiox, <https://www.axios.com/russia-chinese-vaccines-latin-america-us-mexico-86a9daf5-4d39-421b-958a-40a457513e1c.html>, accessed 2 March 2021.]

A crucial aspect of the debate over placebo controls in HIV prevention research in the 1990s was the context in which it arose. A medication highly effective for preventing fetal acquisition of AIDS had become available in resource-rich countries. But because of its cost, the method remained out of reach for virtually all LMICs at the time. Pharmaceutical companies and the U.S. National Institutes of Health had begun to conduct placebo-controlled, mother-to-child HIV transmission studies of a new medication in Thailand, Uganda, and other developing countries. Critics argued that this embodied a “double standard” in the conduct of global research: one ethical rule for rich countries and another for poor countries. It would be unethical to withhold a proven prevention from pregnant women in a new clinical trial in the wealthier countries when a successful method was already available. Defenders of the placebo-controlled design argued that this was the best way to obtain an affordable medication in the shortest possible time for the poor countries. Notably, the defenders did not contend that a trial using a proven medication for the control group would not obtain scientifically valid results. The justification was speed—the number of infant lives saved in the placebo control design.

It would appear that speed is also among the factors motivating the Ad Hoc Group’s preference for placebo controls. They acknowledge that “Randomized, noninferiority trials can provide clinically relevant data in some cases, but at a considerable cost to efficiency” [p. e2(3)]. The article does not specify what are the “some cases” in which noninferiority trials can provide such data and in which cases such trials cannot. Efficiency is an important value but it should not take precedence over ethics. With six vaccines already in the process of being deployed worldwide, the existing difficulties are largely those of implementation and logistics, as well as shortages of the products.

The authors of the recently published NEJM paper are a group of outside experts convened by the World Health Organization (WHO), along with three WHO employees. WHO appointed the group to consult on next steps for Covid-19 vaccine evaluation, including what critical additional data should be sought. No one would quarrel with the need to obtain such data, since much is still unknown about features of the vaccines that have been given emergency approval. The key question is why placebo-controlled trials are needed to obtain such information. It is highly likely that new trials with this design would not be carried out in wealthy countries that already have access to the provisionally approved vaccines, even if the vaccine roll-out is slow. And given the large number of LMIC countries that have begun to receive the vaccines manufactured in China and Russia, it is reasonable to question whether authorities in those countries would approve new placebo-controlled vaccine trials. That leaves most countries in Africa and a few in the Middle East and Central Asia that currently lack access to any of the six aforementioned vaccines.

The bold claim made by the Ad Hoc Group that such studies are “still ethical” is not explicitly defended in the article. Instead, the authors provide a rationale relying on a technical point. The stated rationale is that current vaccines are “still investigational…(under Emergency Use Listing…or similar regulatory mechanisms)”. [ WHO Ad Hoc Group, e2(2)] This refers to the status of the vaccines authorized for use but not yet licensed by drug regulatory authorities in the U.S., the U.K, the European Union, and other countries. Yet millions of doses of these vaccines are being deployed around the world, including in many middle-income countries and some low-income countries (Ghana is one example). Calling the vaccines “investigational” is technically correct since they have not been fully licensed. But it is misleading because ongoing data is not being collected from these millions of vaccinated individuals throughout the world. The article is proposing to do so for participants still in current placebo-controlled phase III trials and those who will enroll in future phase III vaccine trials. But that brings us back to the fundamental questions: Are future placebo-controlled Covid-19 vaccine trials ethically permissible even before such vaccines are fully licensed? As for participants in ongoing phase III placebo-controlled trials, they should be informed that they may be eligible for a vaccine that has been approved under an emergency authorization if they choose to leave the trial in which they are enrolled.

The Ad Hoc Group takes the argument further in calling for “firm commitments to maintaining blinded follow-up of participants in ongoing or future placebo-controlled trials until a licensed vaccine is fully deployed in the population.” [WHO Ad Hoc Group, e2(2)] That effectively means that participants cannot find out whether they were in the group that received the vaccines or in the placebo group even after the study formally ends: “…we believe that trial sponsors are not ethically obligated to unblind treatment assignments for participants who desire to obtain a different investigational vaccine.” [WHO Ad Hoc Group e2(1)] This provision effectively prevents past vaccine trial participants who received placebos from obtaining information that would enable them to protect themselves (and potentially other people) by getting one of the other conditionally approved vaccines.

The Ad Hoc Group authors contend that “a 70% effective single-dose vaccine may be more valuable than a two-dose regimen with 90% efficacy and greater implementation challenges. It is noteworthy that such a vaccine could not be identified without using placebo controls” [e2(2)-e2(3)]. No methodological analysis is provided for why placebo controls are necessary, nor do the authors specify the respects in which the 70% effective vaccine is “more valuable.” They go on to say that “participants in trials of such vaccines should have access to the standard of care in their location and, if the trial is successful, their communities should share in the benefit.” It is not clear what is meant by “standard of care” in this context. It surely cannot mean a proven or effective treatment for serious disease in the experimental group or for those participants in the placebo group who acquire Covid-19, since there are no such treatments at the present time. Perhaps the authors mean “standard of prevention,” a phrase used in an international ethical guidance document for HIV prevention research [UNAIDS, “Ethical Considerations in HIV Prevention Trials,” 2021. Available at: <https://www.unaids.org/sites/default/files/media_asset/ethical-considerations-hiv-prevention-trials_en.pdf>. Accessed 2 March 2021] In that case, the “standard of prevention” could only mean a Covid-19 vaccine already in use in the country or community, whether or not it has already been licensed. This makes clear that the authors defend the use of placebo controls in a broader range of countries than the poorest ones currently lacking access to any Covid-19 vaccines. But we must also assume that people willing to enroll in a trial where they may be randomized to placebo are not yet eligible for the vaccine that exists in their country, that they are fully informed of the research design and what it implies for their participation in the trial.

The Ad Hoc Group says: “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.” [WHO Ad Hoc Group, e2(3)] How is this conclusion justified? Presumably, by the requirement that the community would share in the benefit of a successful trial by gaining access to a successful vaccine. But what if the research fails to yield an effective vaccine? Neither the experimental group nor the control group ends up with a preventive vaccine in such countries. The claim that all participants end up with the “standard of care” in such countries is a piece of sophistry. That phrase cannot meaningfully be used to refer to “no care” (in this case, “no prevention”). When people receive no therapeutic or preventive method, there can be no “standard’ of care or prevention. The rationale for the conclusion is simply that no one in the vaccine trial is made worse off than before they entered the trial. This is a clear restatement of the ethically problematic view that “double-standards” in research are justifiable.

Authoritative sources can provide guidance in controversies such as this. Two such internationally recognized documents are the Declaration of Helsinki (DoH), issued by the World Medical Association, which first appeared in 1964 and has undergone numerous revisions since then. [World Medical Association, “WMA Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects,” October 2013. Available at: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>

Accessed 2 March 2021]. A number of countries cite the DoH as their official guidance for ethical review of proposed research, in addition to whatever domestic regulations they may have in place. The other source is a set of guidelines prepared by the Council for International Organizations of Medical Sciences (CIOMS), a non-governmental organization based in Geneva. [International Ethical Guidelines for Health-related Research Involving Humans, Geneva 2016. Available at: <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>, accessed 2 March 2021]

The CIOMS document cites WHO as a collaborator in drafting its guidelines. The cover and title page say: “Prepared by the Council for International Organizations of Medical sciences (CIOMS) in collaboration with the World Health Organization (WHO).” The Acknowledgements page of the document says: “As a result of this collaboration, the guideline development process is consistent with the standards and policies of WHO” (CIOMS, p. iii). The acknowledgement further notes that the guidelines received “organization-wide review by WHO especially by the Ethics Review Committee….” In addition to these two international documents that have guidelines on the use of placebos, specific countries may also have national guidance, as is the case in India, whose guidelines also restrict the use of placebos when an effective option is available in the country. [Indian Council of Medical Research, “National Ethical Guidelines for Biomedical and Health Research Involving Human Participants,” 2017]

Here are the relevant paragraphs in the current versions of the DoH and CIOMS on the acceptability of placebo controls.

**2013 Declaration of Helsinki**

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.

**2016 CIOMS International Guidelines**

**Guideline 5 Choice of Control in Clinical Trials**

As a general rule, the research ethics committee must ensure that research participants in the control group of a trial of a diagnostic, therapeutic, or preventive intervention receive an established effective intervention.

Placebo may be used as a comparator when there is no established effective intervention for the condition under study, or when placebo is added on to an established effective intervention.

When there is an established effective intervention, placebo may be used as a comparator without providing the established effective intervention to participants only if:

* + - there are compelling scientific reasons for using placebo; and
    - 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.

These two ethics guidance documents clearly reject the acceptability of placebo-controlled trials in circumstances like the current pandemic. Neither the DoH nor the CIOMS guidelines have the status of international law. However, the World Health Organization has an obligation in its publications to adhere to the spirit and letter of these guidelines based on its statement of the governance of its own ethics review committee (ERC): “The ERC is guided in its work by the World Medical Association Declaration of Helsinki (1964) last updated in 2013 as well as the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 2016).” [https://www.who.int/ethics/review-committee/en/]

It is clear from the above-quoted paragraphs that the article published in NEJM, under the authorship of a WHO Ad Hoc Expert Group, violates the organization’s own stated ethical commitment to adhere to the relevant international guidelines for research with human beings.