Being fair to participants in placebo-controlled COVID-19 vaccine trials

To the Editor—In late 2020, the World Health Organization (WHO) Access to COVID-19 Tools Accelerator Ethics & Governance Working Group (called the 'WHO Expert Group' here) issued a policy brief on ethical considerations for placebo-controlled trials of candidate vaccines against COVID-19[1]. That report was based on the assumption that authorization of a candidate vaccine against COVID-19 under an emergency use designation (an 'EUD vaccine') (e.g., emergency use authorization in the USA, conditional marketing authorization in the European Union, emergency use listing by the WHO) does not, in itself[1], render that vaccine the 'best proven intervention'[2] or an 'established effective intervention'[3]. As described elsewhere[4], we believe that there are problems with this approach, since EUD vaccines can become the standard of prevention immediately after deployment—irrespective of their particular efficacy and safety characteristics. Although long-term safety and efficacy data are still lacking for all EUD vaccines and none has received formal approval as a licensed product, these vaccines are recommended for widespread use by the major national immunization-recommending bodies in many countries. Thus, after having been administered in many countries to tens of thousands to multiple millions of people[5], these vaccines should be considered not only an 'established effective intervention'[3] but also the 'best proven intervention'[2] for preventing SARS-CoV-2 infection in the settings in which they are being rolled out.

The WHO Expert Group has recently discussed the reasons in support of the ethical imperative of vaccinating participants who received placebo during randomized placebo-controlled trials (RCTs) of candidate vaccines against COVID-19 with an EUD vaccine[6]. Trial participants who are at substantial risk of infection with SARS-CoV-2 or severe morbidity or mortality due to COVID-19 (e.g., healthcare workers at high risk, and the elderly (65 years of age or older)) should be appropriately informed of the consequences of unblinding and eventual withdrawal from the trial to be subsequently vaccinated with an EUD vaccine if they meet the eligibility criteria to access it[1,6]. Recipients of the placebo may be vaccinated with any current or emerging EUD vaccine, if they wish to do so. However, and for the sake of gathering long-term safety and efficacy data, the WHO Expert Group considers that trial participants who are not deemed to be at substantial risk of SARS-CoV-2 infection or COVID-19 morbidity or mortality and who do not meet prevailing eligibility criteria to access an EUD vaccine should be encouraged to continue in the trial[1,6]. This last statement, however, leads to the consequence that no one realistically has the possibility of being vaccinated with an EUD vaccine in countries in which access to these vaccines is very limited and is managed only by the health authorities who would deny vaccines to people considered to be in low-risk groups. And this is, for the time being, the prevailing situation in most countries.

We believe that the WHO Expert Group should make clear that once any participant in a placebo-controlled RCT becomes eligible to receive an EUD vaccine, investigators should inform this person and—at the participant's request—should proceed to 'break the blind' to allow the person to make an informed decision on whether to withdraw from the trial in order to be vaccinated. This approach should be implemented with all trial participants irrespective of the risk of SARS-CoV-2 infection or risk of COVID-19 morbidity or mortality. This is especially and urgently needed in the current situation, in which several new SARS-CoV-2 variants with enhanced transmissibility (and some likely being more virulent or pathogenic) are emerging and are becoming—or will become—predominant in many countries[7].

The WHO Expert Group should consider amending their report to clearly state that participants in all placebo-controlled RCTs should have the chance of being immunized with an EUD vaccine as soon as they have the possibility to do so, according to societal prioritization. Moreover, in ongoing placebo-controlled RCTs of the general population or specific groups (such as pregnant women (e.g., NCT04754594) or children (e.g., NCT04796896, NCT0464915 and NCT04816643)), this should be clearly stated in the participants' information sheet provided to potential participants or legal representatives when informed consent is sought. Although the clinical efficacy of EUD vaccines against new SARS-CoV-2 variants is uncertain, albeit possible[8,9], sponsors and investigators should ensure that participants in all placebo-controlled RCTs have the same opportunity of being vaccinated with an EUD vaccine as anyone else has in the same country. The WHO Expert Group should update its policy brief to adapt it to the current pandemic situation, to be fair to all participants in placebo-controlled RCTs, and to reflect the moral duties researchers owe to trial participants. ❐

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Author contributions

R.D.-R. conceived and wrote the first draft; all authors provided comments and edits throughout the drafting process for important intellectual content, approved the final version of the manuscript, and are accountable for all aspects included in it.

Competing interests

W.O. reports being a participant in the Moderna COVID-19 vaccine trial and a member of the Moderna Scientific Board, outside this work. A.L.C. reports non-financial support from Janssen, personal fees from Western Institutional Review Board and from Pfizer, and unpaid consultation on vaccine allocation issues from Moderna, outside this work.