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Placebo use and unblinding in COVID-19 vaccine trials: recommendations of a WHO Expert Working Group

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To the Editor—The grave public-health threat posed by coronavirus disease 2019 (COVID-19) has spurred an unprecedented accelerated approach to vaccine research and deployment. Currently, hundreds of thousands of participants globally are enrolled in COVID-19 vaccine trial research, with more trials imminent or proposed[1]. As of 1 March 2021, multiple regulatory agencies[2,3,4] and the World Health Organization (WHO)[5,6] had granted emergency use designation (EUD) to qualifying candidate vaccines against COVID-19, on the basis of early evidence of efficacy and safety. Consequently, qualifying candidate vaccines are being deployed before conclusion of their trials and/or the collection of longer-term data on safety and efficacy.

From a scientific standpoint, it is important for the clinical trials of vaccines granted an EUD to continue to their completion. But the provision of a candidate vaccine under an EUD to millions of people raises urgent questions about the continuation of the control-group arm of these and other trials, and whether trial blinding is still warranted. Current research-ethics guidance documents[7,8,9]

were not drafted with emergency-use deployment in mind. Given such dilemmas and guidance gaps, the WHO ACT-Accelerator Ethics & Governance Working Group (ACT: Access to COVID-19 Tools; called 'Working Group' here) has developed a policy brief to guide ethical decision-making in these circumstances: 'Emergency Use Designation of COVID-19 candidate vaccines: Ethical considerations for current and future COVID-19 placebo-controlled vaccine trials and trial unblinding'[10].

The Working Group has concluded that although there is a scientific imperative to continue trials of vaccines against COVID-19 after a candidate vaccine is granted an EUD, there is also an ethical imperative to ensure that trial participants who are at substantial risk of infection with the coronavirus SARS-CoV-2, and severe COVID-19 morbidity or mortality—such as healthcare workers at high to very high risk of acquiring and transmitting the disease, and people above 65 years of age—are in a position to access an EUD vaccine as soon as practically possible, should they wish to do so. Candidate vaccines granted an EUD will probably be deployed in a phased manner to ensure the prioritization of those deemed to be at considerable risk. In settings in which candidate vaccines are introduced under an EUD, investigators should explain the scientific benefit of continued trial participation and the implications of unblinding to trial participants deemed to be at substantial risk of infection, severe morbidity or mortality. Participants should then be offered the opportunity to be unblinded, so that they can make an informed decision about whether to withdraw from the trial and access an EUD vaccine programmatically as soon as practically possible, should they wish to do so. Trial participants who are not deemed to be at substantial risk of SARS-CoV-2 infection and COVID-19 morbidity or mortality and who do not meet prevailing eligibility criteria to access a candidate vaccine granted an EUD should be informed of the scientific benefits of continuing with the trial and should be encouraged to remain enrolled, with full acknowledgment of their right to withdraw from a trial at any point, without penalty. The continued enrollment of as many participants as possible, for as long as possible, will have considerable scientific and public health utility, as doing so will yield invaluable longer-term data on the safety and efficacy of candidate vaccines. Continued enrollment could also highlight the potential risk of emerging variants of SARS-CoV-2 of concern in relation to those previously unexposed to the virus, those previously infected and recent vaccinees. Such information will be crucial for regulatory decision-making about product registration and/or licensure.

The severe threat to public health posed by the COVID-19 pandemic requires sensitive balancing of the interests of participants in trials of vaccines against COVID-19 versus the need to conduct valuable and urgently needed research into vaccines against COVID-19, in the interest of public

health. The policy brief developed by Working Group attempts to strike this delicate balance.

Change history

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Ethics declarations

Competing interests

The authors declare no competing interests.

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