Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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LETTER TO THE EDITOR

Placebo-controlled trials with COVID-19 vaccines: participants first

In the last few months, several commentators have addressed what they believe should be the correct approach with placebo recipients in randomized controlled trials (RCTs) assessing Coronavirus disease 2019 (COVID-19) vaccine candidates, once one or more COVID-19 vaccines have been deployed under temporary use authorization (TUA) (conditional marketing authorization or similar regulatory approaches). Some believe that double-blind placebo-controlled RCTs are not ethically acceptable, since the clinical equipoise that was present at study initiation is not present any longer [1–3]. Others believe that gathering long-term efficacy and safety data is of utmost importance to fully understand the attributes of the vaccine candidate, so trial participants should stay blinded in the trial until its completion [4,5].

Knottnerus [6] has recently published his reflections on what should be the next steps to develop future COVID-19 vaccine candidates. Although he concluded that placebo-controlled RCTs should no longer be allowed, he also believes that it seems reasonable to complete the follow-up of all participants –placebo recipients included– of ongoing RCTs "until sufficient quantities of authorized vaccines are available" [6]. The meaning of this latter statement is unclear. If it means that participants should stay in the trial until all citizens of a community (including healthy 18–25-year-olds) have access to a TUA vaccine, many placebo recipients (e.g., healthy middle-aged adults) will stay in the trial for several months after they could be vaccinated according to the prioritization scheme that local health authorities have put in place to address the current limited availability of TUA vaccines. This way of thinking was previously supported by other commentators. Thus, Wendler et al [7], consider acceptable to invite trial participants with low risk of severe COVID-19 to remain in the trial for a longer period of time, guaranteeing that all placebo recipients will be offered an efficacious vaccine once they have completed their participation in the trial. Singh and Upshur [8] also think that unblinding of participants of vaccines trials "should preferably occur upon analysis of comprehensive or final trial results". Finally, the WHO Ad Hoc Expert Group [5] believes that altruistic participants will likely understand the value of registering long-term vaccine data and that sponsors of placebo-controlled RCTs are not ethically obliged to unblind treatment assignments to inform participants whether they have received the vaccine or placebo. I believe that the viewpoints described above are mistaken since they require many trial participants not to take advantage of the opportunity to be vaccinated when it is their turn.

The elements to consider in developed countries, where all adults and elderly have access to TUA vaccines, comprise two dimensions: clinical research determinants and the availability of TUA vaccines. Regarding clinical research, there are four critical determinants. First, from the ethical perspective, trial participants' rights and interests must always take preference over medical research objectives [9]. In this case, being vaccinated with a TUA vaccine is the right (and interest) of placebo recipients, whereas gathering long-term safety and efficacy vaccine data is the research objective of the RCT. Second, all placebo-controlled RCTs are registration trials. As such, they are bound to comply with the good clinical practice guidelines [10]. Third, all large placebo-controlled RCTs with COVID-19 vaccine candidates have long (12–27 months) follow-up periods [11]. And fourth, it is the investigator responsibility to inform participants in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial [10]. The availability of a TUA vaccine for the prioritization group to which the participant belongs, is likely the most relevant (positive) information that could be communicated to trial subjects. These latter must know whether they have received a placebo or the vaccine candidate to make an informed decision about whether to withdraw from the RCT to be vaccinated with a TUA vaccine, as well as the risks of remaining unblinded in the trial for many more months.

Regarding the availability of TUA vaccines, four are the critical elements to consider. First, several TUA vaccines are currently available in western countries (AstraZeneca, Janssen, Moderna and Pfizer/BioNTech). Second, local health authorities have established prioritization schemes: it will take many months between the first and the last population groups to have access to a TUA vaccine. Third, currently healthcare providers have access to a single TUA vaccine, so individuals must accept the one offered or wait an indetermined number of weeks for a second opportunity to be vaccinated. This is also applicable to trial participants if they change their minds and would like to withdraw from the RCT, in the case they

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had received placebo. Not accepting to be vaccinated with an authorized vaccine when it is offered is an attitude of increasing risk, especially due to the widespread of more transmissible SARS-CoV-2 variants in many countries that increases the chances of being infected [12]. Furthermore, recent data have shown that the B.1.1.7 SARS-CoV-2 variant, that is rapidly spreading across Europe and the USA [13], is more transmissible [14] than other previously circulating variants, with a high probability of an increased risk of mortality [15]. And fourth, TUA vaccines are the standard of prevention [8,16]. In the USA more than 64, 50 and 9 million Americans have been fully vaccinated with the Pfizer/BioNTech, Moderna and Janssen vaccines, respectively [17]. Similarly, 34 million Europeans have received at least one AstraZeneca vaccine dose [18].

Bearing these eight elements in mind, there seems to be no reason supporting that participant should remain blinded in the trial until its completion. Participants in *any* placebo-controlled RCT assessing *any* COVID-19 vaccine candidate must have the chance to decide whether to be vaccinated with a TUA vaccine as soon as they are eligible for vaccination outside the trial. This is applicable to placebo-controlled RCTs conducted for the assessment of COVID-19 vaccine candidates in any developed country.

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