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.

Trial participants' rights after authorisation of COVID-19 vaccines

Many countries are deploying COVID-19 vaccines under temporary authorisations (ie, emergency use authorisation in the USA, conditional approval in the EU, and emergency use listing by WHO). A WHO expert group provided ethical reasons supporting their proposal to maintain as long as possible large placebo-controlled randomised trials.[1] Although gathering long-term (≤27 months) safety and efficacy data is scientifically important, it will be impossible to achieve with the original trial designs. Once a vaccine is available, participants who received the placebo must have access to the available vaccine, as do all other citizens.[2]

In their argument, the WHO expert group ignores an overarching ethical principle: the interest of society should never prevail over the interests of research subjects.[3] In the dilemma between a common good (scientific knowledge) and an individual right (the chance of being vaccinated during a pandemic), the latter takes priority, as stated in Good Clinical Practice (GCP) guidelines—a set of ethical and scientific requirements that frame the conduct of clinical trials. All large randomised trials of COVID-19 vaccines sponsored by companies in Europe and the USA started between July and November, 2020. Denying access of deployed vaccines to placebo recipients would mean that they will not be vaccinated until perhaps 2022–23. Thinking, from the WHO expert group,[1] that altruistic participants would understand the need to gather long-term data and would stay for months without being vaccinated, while everyone who wants to be vaccinated has already been able to do so by mid-to-late 2021, is unrealistic.

GCP guidelines—and the US 45CFR46.116.c.5 regulations—state that investigators should inform participants in a timely manner of any new information that might affect the participant's willingness to continue in the trial. Participants must be informed that they have the chance of being vaccinated as soon as the population group to which they belong start to be vaccinated with the deployed vaccine. If investigators are not careful enough to inform trial participants of their right to be vaccinated with the available vaccine, participants will request it.[4]

The WHO expert group believes that since vaccines under temporary authorisation are investigational, it would be feasible and ethical to start new placebo-controlled randomised trials.[1] But once a vaccine is deployed, it becomes the standard of prevention, rendering new placebo-controlled trials unethical. The administrative and regulatory situation of interventions is irrelevant, as happens in trials with non-regulated interventions such as surgery, behavioural therapy, or physiotherapy.

The main argument of the WHO expert group is based on an erroneous and unfounded ethical approach that could misguide many public health officials, investigators, and the public.

Once a COVID-19 vaccine starts to be deployed, participants must be adequately informed, and random assignments must be unblinded for participants wanting to know whether they have received placebo or vaccine candidate.[2] At this moment, two trial design alternatives are available (panel). In any case, post-temporary authorisation real-world surveillance will have a major role in the assessment of all COVID-19 vaccines. Yet the scientific and regulatory communities should reflect and decide on the way forward to ensure the successful development of future COVID-19 candidate vaccines.

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For the **GCP guidelines** see https://ichgcp.net/

Panel: **Trial designs suitable once a COVID-19 vaccine is available through temporary authorisation**

Crossover double-blind design

If investigators wish to continue the placebo-controlled trial blinded, they should obtain informed consent[5] again from participants to ascertain if they are willing to remain unaware of the random assignment. The information provided should explain the risks and benefits of staying in the trial blinded when placebo recipients would otherwise have access to vaccine. In this design, participants who initially received placebo will receive the COVID-19 vaccine and those who received the vaccine will now receive the placebo. Investigators could compare the efficacy in participants who were first vaccinated (acting as controls) with those vaccinated several months later. The double-blind fashion will be preserved, but even if enough participants provide consent again, the interest of the data to be compared would be of uncertain usefulness, because of confounding and low numbers of COVID-19 cases that would be expected to occur (unless controls had a significant waning of the immune response). The crossover design could only be feasible in a placebo-controlled trial assessing the first deployed COVID-19 vaccine in a country or territory.

Open-label design

Participants willing to continue in the trial should provide informed consent[5] again to continue participating in an open-label fashion. The open-label design could be feasible with the second deployed COVID-19 vaccine, provided the time elapsed between deployment of the first two vaccines is very short (few weeks).

Regulatory agencies and institutional review boards and research ethics committees should ease the approval of trial protocol amendments to prevent many participants withdrawing before its implementation. Participants of placebo-controlled trials with other COVID-19 vaccines are entitled to withdraw to be vaccinated with available vaccines.

WO reports being a participant in the Moderna COVID-19 vaccine trial, and scientific advisory board membership for Moderna relevant to the content of this Correspondence. ALC reports non-financial support from Janssen (for consultation on compassionate use), personal fees from WIRB (Western Institutional Review Board) for advisory board membership, personal fees from Pfizer for a webinar, and unpaid consultation for Moderna on vaccine allocation issues. RD-R declares no competing interests.

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1 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* 2020; published online Dec 2. https://doi.org/10.1056/NEJMp2033538.

2 Dal-Ré R, Caplan AL, Gluud C, Porcher R. Ethical and scientific considerations regarding the early approval and deployment of a COVID-19 vaccine. *Ann Intern Med* 2020; published online Nov 20. https://doi.org/10.7326/M20-7357.

3 World Medical Association. WMA Declaration of Helsinki: ethical principles for medical research involving human subjects. July 9, 2018. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (accessed Jan 11, 2021).

4 Beckett F. Is it worth carrying on as a guinea pig, if a vaccine has already been found? Nov 28, 2020. https://www.theguardian.com/world/2020/nov/28/is-it-worth-carrying-on-as-a-guinea-pig-if-a-vaccine-has-already-been-found (accessed Jan 11, 2021).

5 Dal-Ré R, Avendaño C, Gil-Aguado, Gracia D, Caplan AL. When should re-consent of subjects participating in a clinical trial be requested? A case-oriented algorithm to assist in the decision-making process. *Clin Pharmacol Ther* 2008; **83:** 788–93.