

Emergency Use Designation of COVID-19 candidate vaccines: Ethical considerations for current and future COVID-19 placebo-controlled vaccine trials and trial unblinding

Policy brief

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The grave public health threat posed by COVID-19 has spurred the development of dozens of COVID-19 candidate vaccines, and the conduct of numerous accelerated COVID-19 vaccine trials, many of which are in Phase 2/3 of testing.¹ Given this severe threat, some drug regulatory authorities including the United States Food and Drug Administration (FDA)¹ and the European Union's European Medicines Agency (EMA) have indicated that, if interim data are sufficiently compelling, they are prepared to issue COVID-19 candidate vaccines conditional / emergency / early approval prior to completion of Phase 3 trials. In such instances the regulatory authority signals that the balance of risk and benefit to designated target populations justifies deployment of the vaccine pending the registration / licensure of that product on public health grounds. Similarly, to assist World Health Organization (WHO) Member States and UN procurement agencies in decision-making on the acceptability for use of specific products in the context of a public health emergency, WHO has established an Emergency Use Listing (EUL) procedure to expedite the availability of interventions needed in public health emergency (PHE) situations.² The validity of a WHO EUL in the context of a public health emergency is generally 12 months. All decisions to grant an EUL are reassessed at 12 months (or sooner, if further data become available that could alter the original opinion). EUL is contingent upon the vaccine developer completing the development of the product and its trial, and submitting the candidate vaccine for registration/licensure and WHO prequalification.³ EUL is not equivalent or an alternative to WHO prequalification, and should not be thought of as such.³ For the purposes of this policy brief, all mechanisms that facilitate the public accessibility of investigational vaccines prior to the conclusion of their respective clinical trials or their licensure, shall hereinafter collectively be referred to as 'Emergency Use Designation' or EUD.

As of 1 December 2020, developers of several candidate vaccines that have yielded promising interim results, have applied, or signaled their intention to apply, for EUD for their respective candidates.³⁻⁵ To date, some candidates have attained EUD^{6,7} from Stringent Regulatory Authorities.⁸ The issuance of such designation will result in these candidates being made publicly accessible, prior to their respective trial conclusions and/or the collection of longer-term safety and efficacy data. The burden of making the decision to allow COVID-19 vaccines to be used for public deployment based on an EUD in the absence of these data is especially high because millions of people are likely to receive them. Doing so could also impact current and future COVID-19 vaccine research, as well as a more robust characterization of the benefits and risks of vaccines granted EUD. From the standpoint of public health, it is important for the clinical trials of vaccines granted EUD to continue to their completion. But the provision of the vaccine under an EUD to millions of people raises questions about the continuation of the control arm of these trials and whether trial blinding is still warranted. Given such dilemmas, the *WHO Access to COVID-19 Tools (ACT) Accelerator Ethics and Governance Working Group* has developed a policy brief to guide ethical decision-making on COVID-19 vaccine trial unblinding and the use of active or placebo controls in the context of COVID-19 candidate vaccines attaining EUD and becoming available in settings hosting current or future COVID-19 vaccine trials. These considerations may be summarized as follows:

Considerations for the conduct of COVID-19 vaccine trials in the context of a candidate vaccine being granted emergency use designation

- (1) Given that the emergency use designation of a COVID-19 candidate vaccine is based on an early interim analysis of trial data, such designation should not be regarded as triggering the stopping rules of that candidate vaccine's ongoing trial. Accordingly, emergency use designation should not be deemed to warrant the blanket unblinding of trial participants of the ongoing trial involving the candidate granted such designation. The potential effects of early stopping on the analysis of other important variables because the candidate vaccine attains emergency use designation, should be carefully considered as deviations from the planned study procedure could invalidate trial results and threaten registration / licensure of the candidate vaccine.
- (2) A candidate vaccine's attainment of emergency use designation does not, in itself, render that candidate the "best proven intervention" (Declaration of Helsinki, article 33), an "established effective intervention" (CIOMS, article 5), or a "highly efficacious and safe vaccine" (WHO Expert Panel) for the prevention of COVID-19, and there is not yet sufficient evidence that available vaccines meet these thresholds. Accordingly, the continued use of placebos or active controls in the control arm of the ongoing trial testing that candidate vaccine granted EUD, or in current or future trials testing other candidate vaccines during the period EUD, and where no other authorisation applies, should not be regarded as violating the Declaration of Helsinki, CIOMS, or WHO's previous guidance.
- (3) Candidate vaccines granted EUD will likely be deployed in a phased manner to ensure the prioritisation of those deemed to be at significant risk of COVID-19 infection or mortality, such as healthcare workers at high to very high risk of acquiring and transmitting infection, and individuals above 65 years of age. Should a candidate vaccine attain EUD in a setting hosting a COVID-19 vaccine trial, investigators should explain the scientific benefit of continued trial participation, the clinical factors that support the participant's administration of the EUD vaccine outside the trial, and the implications of unblinding, to trial participants immediately eligible to access the EUD vaccine. Following such counselling, such participants should be offered the opportunity to be unblinded so they may make an informed choice about whether to access the EUD vaccine programmatically as soon as practically possible, should they wish to do so. If such participants request unblinding, investigators and sponsors have an ethical duty to abide their request. This will necessitate the development of an appropriate engagement, communications, and dissemination strategy to explain unblinding eligibility criteria and the implications of unblinding for trial participants. Should a participant opt to withdraw from a trial, their follow-up could continue as part of an observational study, should they agree.
- (4) Trial participants hailing from cohorts not deemed to be at significant risk of COVID-19 infection or mortality, and who do not meet prevailing eligibility criteria for vaccine access, should be encouraged to remain enrolled in their respective trials, although the right of trial participants to withdraw from a trial at any point should always be respected. Should a participant opt to withdraw from a trial, their follow-up could continue as part of an observational study, should they agree.
- (5) Should unblinded trial participants assigned to the intervention arm of a COVID-19 vaccine trial wish to access a different candidate vaccine introduced programmatically through an EUD mechanism, such participants should be counselled that no scientific data currently supports such administration and they should receive all relevant counselling related to this decision. Should they still elect to access the EUD candidate vaccine, their follow-up and ongoing monitoring should be strongly encouraged on clinical grounds. Efficacy trials involving candidates granted emergency use designation should include contingency plans for continued follow up and analysis of safety and effectiveness outcomes in the event that a safe and effective vaccine becomes available and the study is stopped (e.g., as demonstrated in a planned interim analysis or as demonstrated in another clinical trial). In such instances, discussion with regulatory authorities and/or the WHO (in the case of EUL) may be necessary to address ethical arguments to break the blind and offer vaccine to placebo or active-control recipients.
- (6) The issuance of emergency use designation to one candidate vaccine should not impact on the conduct of other current or future placebo-controlled COVID-19 vaccine trials in that setting as the programmatic deployment of the candidate vaccine granted emergency use designation does not necessarily mean that the candidate is superior in efficacy and safety compared to other candidate vaccines still being, or still to be, evaluated in that settings, or even elsewhere.
- (7) Participants of COVID-19 vaccine trials should be advised that the issuance of emergency use designation by regulators to a candidate vaccine is based on early interim findings and is time-limited in nature. Further, that such status can be withdrawn by regulators should interim evidence later suggest that the potential risks of the vaccine

outweigh its potential benefits. Moreover, that promising early interim data may be based on apparent efficacy in homogenous groups that are not representative of all target groups for the candidate vaccine and provide limited insight into vaccine efficacy and safety over time. In such instances, it would have to be determined how efficacy data could be extrapolated to potential target populations (taking into account, for example, age, ethnicities, and co-morbidities) for whom there may be insufficient data to determine the vaccine's efficacy and safety in the potential target groups.

- (8) COVID-19 vaccine trial investigators and sponsors should prospectively engage with relevant stakeholders, including trial participants, community advisory structures, host communities, research ethics committees, and relevant regulatory authorities on the implications for trial participants of a candidate vaccine attaining EUD in the study setting (including the trial involving that candidate). This will necessitate the development of an appropriate engagement, communications, and dissemination strategy to explain the implications of such designation for the trial. Similarly, trial design modifications will necessitate the development of an appropriate engagement, communications, and dissemination strategy to explain the implications of such modification for trial participants.

The position of existing global research ethics guidance documents on placebo use

The issuance of EUD to a COVID-19 candidate vaccine raises questions regarding whether such designation amounts to the candidate vaccine being deemed an efficacious intervention and, if so, whether participants assigned to the active control or placebo arm of a COVID-19 vaccine trial are being deprived of an existing efficacious intervention against COVID-19. The EUD of a candidate vaccine also has implications for other COVID-19 trials as it raises concerns regarding whether the vaccine granted EUD is sufficiently efficacious that participants of those trials should be offered access to the vaccine granted EUD.

Article 33 of the Declaration of Helsinki (2013),⁹ published by the World Medical Association, offers guidance on the ethical permissiveness of placebo use in clinical trials. Guideline 5 of guidance published by the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with WHO¹⁰ (hereinafter 'CIOMS Guidelines') also provides guidance on the choice of control in clinical trials. Neither document was drafted to provide guidance in the context of EUD mechanisms, nor specifically in the context of vaccine trials. They do, however, provide a useful starting point. In 2014, the WHO convened an Expert Panel to specifically consider the use of placebos in vaccine trials. The Expert Panel concluded that placebo use in vaccine trials is clearly acceptable when: (a) no efficacious and safe vaccine exists and (b) the vaccine under consideration is intended to benefit the population in which the vaccine is to be tested.¹¹ In this situation, a placebo-control trial addresses the locally relevant question regarding the extent to which the new vaccine is better than nothing, and participants in the placebo arm of the trial are not deprived of the clinical benefits of an existing efficacious vaccine.

The Expert Panel further concluded that the use of placebo controls in vaccine trials may be justified even when an efficacious vaccine exists, provided the risk-benefit profile of the trial is acceptable. This applies to situations where the existing vaccine is available through the local public health system, as well as to situations where the existing vaccine is not available locally, or it is only available on the private market. Specifically, the risk-benefit profile of a placebo-controlled vaccine trial may be acceptable when (1) the study question cannot be answered with an active-controlled trial design; and (2) the risks of delaying or foregoing an existing efficacious vaccine are adequately minimized or mitigated; and (3) the use of a placebo control is justified by the potential public health or social value of the research; and (4) the research is responsive to local health needs. The Expert Panel concluded that the acceptable risks of withholding or delaying administration of an existing vaccine in the placebo arm of vaccine trials may be greater than minimal when the above conditions are met. Accordingly, the Expert Panel deemed the use of a placebo control to be acceptable when an efficacious vaccine exists, provided the above four conditions are met. As is the case with the Declaration of Helsinki and the CIOMS Guidelines, the Expert Panel recommendations were not crafted with EUD mechanisms in mind.

The ethics of continuing the conduct of blinded, placebo-control COVID-19 vaccine trials in the context of a candidate vaccine being issued with EUD and being publicly accessible

Immunisation programmes have been traditionally based on the theory that the benefits of immunisation far outweigh the risks from delayed adverse events, and accordingly, long term safety studies need not be performed before immunisations commence.¹² Some may argue that this reasoning especially applies in the context of a public health

emergency. Others may argue that the public is best served by getting as complete an understanding of the safety and efficacy of investigational COVID-19 vaccines as soon as possible.

One of the primary goals of a vaccine is to provide durable, long-term protection against disease. The issuance of EUD by regulators is based on promising early interim data, only. Evidence about duration of protection will not necessarily be available at time of EUD. Knowing how long protection lasts is crucial to assessing the overall utility of the vaccine. In some cases, the data at the time of EUD evaluation may come from participants who are not representative of all target groups. This means that not only will the duration of protection be unknown at time of EUD but that the vaccine's efficacy in different groups of people, for example people of different ages or with different co-morbidities, will also be unknown.

The safety of a new vaccine is as important as determining its efficacy. While candidate vaccines are required to achieve pre-specified safety data milestones to attain EUD, such milestones are achieved over an abbreviated time period. While the time periods that have been established for assessing safety in the EUD context have been pegged to the period for which most adverse events associated with vaccines for respiratory infections have been identified in the past, the extended follow-up of participants after first interim analysis occurs could highlight longer-term safety issues in post-hoc analyses.¹³ Safety concerns associated with the vaccine, including rare immunologic, neurologic, and other adverse events,¹⁴ could also emerge post-trial. Accordingly, ongoing safety monitoring will be crucial to informing decision-making in regard to registration / licensure and thus, to determining the appropriate place of a candidate vaccine in the public health response to the pandemic over time. In some instances, safety issues may only become apparent post-registration.

A blinded, placebo-control trial that is allowed to continue to completion provides the best possible evidence to fill these efficacy and safety gaps in the medium term, before longer-term safety and effectiveness evidence emerges in post-marketing surveillance studies. Alternative research designs will generate sub-optimal evidence and, in some cases, will take more time to accumulate relevant data than is feasible in the context of a pandemic. The most reliable, fastest way to get the evidence needed to protect the public's health is to continue to conduct blinded, placebo-controlled studies, even after EUD.

The rights and interests of trial participants are also relevant to judgments about the ethics of continuing with these trials. The moral notion of *reciprocity* dictates that we have a moral obligation to benefit those who benefit us. Seen in the context of clinical trials, it could be argued that in return for participants contributing to the social good through their assumption of risk by participating in a clinical trial, they are owed reciprocity in return, regardless of whether they have suffered a research-related harm.¹⁵ In the case of a randomised placebo-controlled clinical trial, where an intervention is deemed to have comprehensively demonstrated efficacy, such gratitude could equate to unblinding trial participants and offering those assigned to the placebo arm, access to the experimental intervention that demonstrated efficacy once trial follow-up is complete, or sooner, on clinical or public health grounds. Such a gesture also speaks to the ethics notions of *beneficence*, which requires investigators to act in the best interests of trial participants, and *justice*, which requires investigators and sponsors to distribute the benefits (and burdens) of research fairly.

As already noted, existing global research ethics guidance suggests that once a candidate vaccine becomes fully licensed/registered, placebo-controlled trials can be conducted under only particular circumstances. However, EUD does not establish a vaccine as safe and efficacious in the sense intended, for example, by the 2014 WHO Expert Panel. In granting an EUD, regulatory or policymaking bodies have determined that in the context of a public health emergency the vaccine is, on balance, appropriate to offer to certain designated population groups. However, in time-limiting the EUD and requiring additional data for full licensure/registration, these authorities intentionally leave open the possibility that evidence yet to be collected may change that calculus.

While there is a scientific imperative to continue with the conduct of a COVID-19 vaccine trial after a candidate vaccine is granted EUD, it can also be argued that there is an ethical imperative to ensure that trial participants who are at significant risk of COVID-19 infection or mortality – such as healthcare workers at high to very high risk of acquiring and transmitting infection, and individuals above 65 years of age – are in a position to access a EUD vaccine as soon as practically possible, should they wish to do so.

Assuming that regulators issue a COVID-19 candidate vaccine with EUD, several factors will impact on its availability and accessibility: (a) Manufacturing and quality controls, product sampling and testing of the final vaccine will have to be conducted to ensure that every batch of the vaccine meets the expected standards of safety and quality; (b) The candidate vaccine's safe supply and distribution must be assured; (c) The health system must possess capacitated human resources and infrastructure to facilitate programmatic deployment; (d) Supply of the candidate vaccine must sustain demand. This may necessitate the establishment of a locally appropriate prioritisation framework to facilitate phased deployment; and (d) If provision of a vaccine granted EUD is not universal, or covered by health insurance, the vaccine must be affordable to facilitate its uptake.

As these factors are addressed and realised in settings hosting COVID-19 vaccine trials, investigators and sponsors may contemplate trial design modifications. For instance, a cross-over trial design¹⁶ will ensure that all participants are eventually assured allocation of the intervention. In such studies, groups of participants receive two or more interventions (including a placebo) in a specific order. For example, one group receives intervention A during the initial phase of the trial, followed by intervention B during a later phase. The other group receives intervention B during the initial phase, followed by intervention A. Accordingly, participants "cross-over" to the other intervention during the trial. All participants receive intervention A and intervention B at some point during the trial but in a different order, depending on the group to which they are assigned. While such a design will ensure that all participants are eventually assured allocation of the intervention, it could be argued that it is ethically permissible for some trial participants to enjoy expedited access to the candidate vaccine because of their elevated risk of COVID-19 infection or mortality.

Candidate vaccines granted EUD will likely be deployed in a phased manner to ensure the prioritisation of those deemed to be at significant risk of COVID-19 infection or mortality. In settings where candidate vaccines are introduced under EUD, assuming the factors described above apply, investigators should explain the scientific benefit of continued trial participation and the implications of unblinding to trial participants deemed to be at significant risk of infection or mortality. Following such counselling, such participants should 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 significant risk of COVID-19 infection or mortality and who do not meet prevailing eligibility criteria to access a candidate vaccine granted EUD, should be informed of the scientific benefits of continuing with the trial and encouraged to remain enrolled – while fully acknowledging their right to withdraw from a trial at any point, without penalty. The continued enrolment of as many participants as possible, for as long as possible, will have significant scientific and public health value, as doing so will yield invaluable data to enable regulatory decision-making regarding product registration / licensure.

Conclusion

The conduct of COVID-19 vaccine trials in the context of a candidate vaccine being issued with EUD raises challenging ethical questions, especially regarding the use of placebo controls and unblinding COVID-19 trial participants. Such a context requires a sensitive balancing of the interests of COVID-19 vaccine trial participants, with the need to conduct valuable and urgently needed COVID-19 vaccine research.

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WHO continues to monitor the situation closely for any changes that may affect this policy brief. Should any factors change, WHO will issue a further update. Otherwise, this policy brief document will expire 2 years after the date of publication.

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