COVID-19 vaccine trial designs in the context of authorized COVID-19 vaccines and expanding global access: ethical considerations

Policy brief

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Executive Summary

In June 2020, global regulators convened under the auspices of the International Coalition of Medicines Regulatory Authorities (ICMRA) and co-chaired jointly by the European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) reached consensus on the study design requirements for Phase 3 COVID-19 vaccine clinical trials. The ICMRA noted that phase 3 clinical trials should be randomized, double-blinded and controlled with a placebo or active comparators. In September 2020, the World Health Organization (WHO) advised: "Phase IIB/III efficacy trials should be randomized, double-blinded and placebo controlled." Since then, multiple COVID-19 vaccines have been authorized worldwide based on interim results of pivotal placebo-controlled efficacy trials, and billions of COVID-19 vaccine doses have been administered under emergency use/conditional marketing authorization or full approval regulatory mechanisms.

In December 2020, a WHO expert group advised that the placebo control arms of COVID-19 vaccine trials should be progressively unblinded as authorized vaccines become available in the community hosting the trial, starting with prioritized groups.

Before a COVID-19 vaccine trial commences enrolment, if one or more authorized/approved COVID-19 vaccine is locally available and the participant meets programmatic eligibility criteria, the study team should advise the participant that they are eligible to receive the authorized vaccine(s). Participants may elect to receive the authorized vaccine at any point in the trial.

The appropriateness of conducting a placebo control trial may depend on whether the candidate vaccine is a prototype vaccine, modified vaccine or next generation vaccine.

Prototype vaccines

Placebo control trials involving prototype vaccines may be ethical if the trial design is supported by the national regulatory agency, governing research ethics committee(s)and the host community. Any trial should be preceded by appropriate stakeholder and community engagement activities.

Placebo control COVID-19 vaccine trials involving prototype vaccines will require modification as trial participants increasingly meet local programmatic eligibility criteria and vaccine supply increases. In any placebo control COVID-19 vaccine trial design, as soon as an authorized vaccine becomes locally available and a trial participant mee ts local programmatic eligibility criteria for that authorized vaccine, the trial participant should be offered the opportunity to be released from blinding. If they choose so, they should be offered the authorized vaccine (or the investigational vaccine if its efficacy has been established by then). Investigators are advised to inform trial participants of their right to be unblinded when they meet local programmatic vaccine eligibility. Criteria for unblinding should appear in informed consent documentation, and there should be relevant trial documentation, such as standard operating procedures, for unblinding.

Until immune correlates of protection are established, authorized prototype vaccines may still be tested in placebo control trials in cohorts for whom the vaccines were not initially authorized (such as children and some adolescents) and in relevant booster dose trials.

Modified vaccines

Modified COVID-19 vaccines should not be tested in placebo control trials. Instead, the modified vaccine may be tested in comparator efficacy trials against the authorized parent/prototype vaccine.

When consensus is reached on humoral and/or cellular immune parameters that correlate with reduction in disease severity or mortality against COVID-19, modified COVID-19 vaccines should be assessed in immunobridging trials.

Next-generation vaccines

Next generation vaccines may be tested in placebo control clinical disease endpoint trials, provided such trials can still be ethically performed. In such instances, the trial design should be supported by the national regulatory agency, governing research ethics committee(s) and the host community. Any trial should be preceded by appropriate stakeholder and community engagement activities.

Placebo control COVID-19 vaccine trials involving next generation vaccines in progress will require modification as trial participants increasingly meet local programmatic eligibility criteria and vaccine supply increases. In any placebo control COVID-19 vaccine trial design, as soon as an authorized vaccine becomes locally available and a trial participant meets local programmatic eligibility criteria for that authorized vaccine, the trial participant should be offered the opportunity to be unblinded, and if they choose so, offered the authorized vaccine (or the investigational next generation vaccine, if the investigational vaccine's efficacy has been established by then). Investigators are advised to inform trial participants of their right to be unblinded when the participants meet local programmatic vaccine eligibility criteria through informed consent documentation and to devise relevant trial documentation, such as standard operating procedures, for unblinding.

Given increasing COVID-19 vaccination coverage globally, the conduct of placebo control clinical disease endpoint trials for next-generation vaccines will become increasingly unjustifiable from an ethics perspective. Alternative research approaches may include relative clinical disease endpoint efficacy studies, human challenge trials and non-efficacy studies. When consensus is reached on humoral and/or cellular immune parameters that adequately correlate with reduction in disease severity or mortality against COVID-19, next-generation COVID-19 vaccines should be assessed in immunobridging trials.

Key terminology

Prototype COVID-19 vaccine: a vaccine based on the original SARS-CoV-2 virus.

Modified/variant COVID-19 vaccine: A vaccine against a SARS-CoV-2 variant of concern for which the change is only in the prototype vaccine's virus strain without changes in the manufacturing process, controls and the facilities for vaccine production.

Next-generation COVID-19 vaccine: A vaccine against SARS-CoV-2 that includes a polyvalent vaccine (covering multiple serotypes) and a vaccine based on novel technology platforms that may be based on a different route of administration (for example, intradermal, intranasal or oral), compared to first generation vaccines, which are administered intramuscularly.

1 Introduction

While the degree of COVID-19 vaccine accessibility and uptake varies at both national and global levels, increasing vaccination coverage raises questions regarding the standard of prevention that ought to apply to different settings where COVID-19 vaccine trials are hosted. This document aims to highlight ethical issues implicit in conducting placebo control COVID-19 trials in the context of multiple authorized vaccines and expanding global vaccination coverage. It was developed by the WHO ACTA Ethics & Governance Working Group, whose members include external experts and WHO technical staff. The document is based on relevant research ethics and technical guidelines and draws on the extensive ethics literature about the use of placebos during past decades.

2 Background

Pivotal clinical trials provide the evidence necessary to support regulatory authorization/licensure.*(1)* In June 2020, global regulators convened under the auspices of the International Coalition of Medicines Regulatory Authorities (ICMRA),co-chaired jointly by the European Medicines Agency (EMA) and United States Food and Drug Administration (FDA). This group reached consensus on the study design requirements for Phase 3 COVID-19 vaccine clinical trials. The ICMRA noted that phase 3 clinical trials should be randomized, double-blinded and controlled with placebo or active comparator.*(2)* The FDA,*(3)* EMA*(4)* and WHO*(5)* also published recommendations regarding the development, emergency use listing and approval of COVID-19 vaccines. With regard to early phase trials, the FDA noted that "while including a placebo control and blinding are not required for early phase studies, doing so may assist in interpretation of preliminary safety data."*(6)* For later phase trials, including efficacy trials, the FDA noted that such trials "should be randomized, double-blinded, and placebo control" and that "an individually randomized control trial with 1:1 randomization between vaccine and placebo groups is usually the most efficient study design for demonstrating vaccine efficacy." *(7)* The FDA also noted: "If the availability of a COVID-19 vaccine proven to be safe and effective precludes ethical inclusion of a placebo control group, that vaccine could serve as the control treatment in a study designed to evaluate efficacy with noninferiority hypothesis testing." In September 2020, WHO advised: "Phase IIB/III efficacy trials should be randomized, double-blinded, and placebo controlled."*(8)* Since then, multiple COVID-19 vaccines have been authorized worldwide based on interim results of pivotal placebo-control efficacy trials, and billions of COVID-19 vaccine doses have been administered under emergency use/conditional marketing authorization or full approval regulatory mechanisms.

2.1 The use of randomized, placebo control arms in COVID-19 vaccine trials

Randomization is a well-established research methodology*(9)* to deal with therapeutic or prophylactic uncertainty and to ensure the absence of systematic differences between intervention and control groups.*(10)* Placebos—surrogates for a control group receiving no intervention—have been adopted to mimic the experimental treatment in appearance, but not in substance or chemical structure.*(11)* Placebos allow the consequences of attention, expectation, suggestion and natural course to be separated from the effects of the experimental intervention.*(12)* The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) explicitly endorses the use of placebo controls, except in cases where an available intervention is known to prevent serious harm, such as death or irreversible morbidity.*(13)* Without blinding and use of placebos, the awareness of having been vaccinated may change behaviour and outcome risk but also change awareness and the detection of outcomes (detection bias). Given these factors, randomized placebo control trials are widely considered the 'gold standard' for evaluating the safety

and efficacy of experimental interventions.*(14, 15)* This situation will change if an immune correlate of protection (ICP) is agreed for COVID-19 vaccines. It should be noted that different ICPs may apply to different COVID-19 vaccine platforms. WHO is convening regular meetings to assess scientific progress towards a definition of an ICP. The situation will also change if scientifically justifiable active comparators are readily accessible for use in clinical trials. Problems with access to approved COVID-19 vaccines to use as active comparators in clinical trials have recently been elucidated.*(16)*

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

The Declaration of Helsinki (2013),*(17)* published by the World Medical Association, offers guidance on the ethical permissibility of placebo use in clinical trials. Article 33 of the Declaration of Helsinki (hereinafter DoH) states:

> The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
>
> - Where no proven intervention exists, the use of placebo, or no intervention, is acceptable.
> - Where, for compelling and scientifically sound methodological reasons, the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention, and the patients who receive any intervention less effective than the best proven one, placebo or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option".

In 2013, WHO convened an expert panel to consider the use of placebos in vaccine trials. The expert panel concluded that placebo use in vaccine trials is clearly acceptable when no efficacious and safe vaccine exists and the vaccine under consideration is intended to benefit the population in which the vaccine is to be tested.*(18)* 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 concluded that placebo use in vaccine trials is clearly unacceptable when a highly efficacious and safe vaccine exists and is currently accessible in the public health system of the country in which the trial is planned and the risks to participants of delaying or foregoing the available vaccine cannot be adequately minimized or mitigated (for example, by providing counselling and education on behavioural disease prevention strategies or ensuring adequate treatment for the condition under study to prevent serious harm). In this situation, a placebo control trial would not address a question that is relevant in the local context: namely, how the new vaccine compares to the one that is currently in use, and participants would be exposed to unacceptable levels of risk from delaying or foregoing a safe and effective vaccine that is accessible through the public health system.

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 and to situations where the existing vaccine is not available locally or is only available on the private market. Specifically, the risk-benefit profile of a placebo control vaccine trial may be acceptable when:

- the study question cannot be answered with an active control trial design

- the risks of delaying or foregoing an existing efficacious vaccine are adequately minimized or mitigated
- the use of a placebo control is justified by the potential public health or social value of the research
- 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 even when an efficacious vaccine exists, provided the above four conditions are met.

In 2016, the Council for the Organisation of Medical Sciences (CIOMS), in collaboration with WHO, published revised research ethics guidance (hereafter CIOMS Guidelines).*(19)* Regarding the choice of control in clinical trials, Guideline 5 of the CIOMS Guideline states:

> As a general rule, the research ethics committee must ensure that research participants in the control group of a trial of a diagnostic, therapeutic or preventive intervention receive an established effective intervention. Placebo may be used as a comparator when there is no established effective intervention for the condition under study or when placebo is added on to an established effective intervention. When there is an established effective intervention, placebo may be used as a comparator without providing the established effective intervention to participants only if:
> - there are compelling scientific reasons for using placebo; and
> - delaying or withholding the established effective intervention will result in no more than a minor increase above minimal risk to the participant and risks are minimized, including through the use of mitigation procedures.

3 The suitability of applying existing guidance, and the rationale for new guidance on placebo control vaccine trials in the context of the COVID-19 pandemic

While existing research ethics guidance documents provide a useful starting point, they were not devised to provide guidance in the context of a rapidly evolving global pandemic, novel research approaches, emergency use regulatory pathways and inequitable vaccine access. These documents and placebo-control trials thus merit consideration in the current and future contexts of the COVID-19 pandemic.

3.1 What constitutes an "established effective intervention" (CIOMS Guidelines)?

CIOMS notes that "an established effective intervention for the condition under study exists when it is part of the medical professional standard." Worldwide COVID-19 candidate vaccines have been granted conditional/emergency use authorization in many settings. Such status is time-limited and reviewable at the end of the authorization period."*(20)* Once the emergency use authorization is granted, the authorization holder must fulfil specific obligations within defined timelines, including completing ongoing or new studies or collecting additional data to confirm that the intervention's benefit-risk ratio remains positive.*(21)* Until the authorization holder complies with the conditions attached to the authorization, and because the authorization may be revoked before the end of the review period,*(22, 23, 24)* the safety and efficacy of a candidate vaccine cannot reasonably be considered "established" or the "medical professional standard."

3.2 What constitutes a "best proven intervention" (DoH)?

Despite an authorized vaccine having demonstrated high efficacy and safety in some cohorts, the same may not necessarily be true for other cohorts. For example, evidence may emerge that suggests that the "best proven intervention" for one cohort (such as adults) raises potential safety concerns for another cohort (such as adolescents).*(25)* The consequence of reduced neutralizing activity on COVID-19 vaccine effectiveness is also not known. SARS-CoV-2 variants of concern (VoC) may render a candidate vaccine that is a "best proven intervention" in one or more settings*(26)* less efficacious in another,*(27)* notwithstanding its authorization and imminent rollout in the face of reduced efficacy.*(28, 29)*

3.3 When is a placebo-control COVID-19 vaccine trial "clearly unacceptable" (2013 WHO Guidance)?

2013 WHO guidance notes that placebo use in vaccine trials is "clearly unacceptable" when a *highly efficacious* and safe vaccine exists and is currently accessible in the public health system of the country in which the trial is planned and the risks to participants of delaying or foregoing the available vaccine cannot be adequately minimized or mitigated.

The FDA, EMA and WHO conditional marketing authorization/emergency use designation for COVID-19 candidate vaccines depends, among other factors, on a point estimate for a placebo control efficacy trial of at least 50%.*(30, 31, 32)* Various COVID-19 candidate vaccines that meet this threshold requirement have been authorized worldwide but have reported varying efficacy in different settings.*(33, 34)* Further, as noted earlier, authorized vaccines may not be universally "highly efficacious" given the emergence of SARS-CoV-2 VoC.*(35)* Nevertheless, while a placebo control trial would yield the highest quality evidence and inform policymakers whether a candidate vaccine is appropriate for a particular setting, conducting a placebo control trial in some of the above contexts would be "clearly unacceptable" according to the 2013 WHO Guidance due to the accessibility of highly efficacious and safe vaccines.

By contrast, the 2013 WHO guidance stipulates that "the risk-benefit profile of a placebo control vaccine trial may be acceptable when the study question cannot be answered with an active control trial design". Since the publication of the above research ethics guidance documents, a WHO Expert Group has highlighted considerations for the design and analysis of trials and studies to evaluate experimental vaccines during public health emergencies.*(36)* Variations of the traditional parallel-group placebo-control randomized clinical trial design have also since emerged.*(37, 38, 39)* Moreover, to expedite vaccine availability, some regulators, such as the FDA*(40)* and EMA*(41)* and WHO*(42)* have adopted new approval pathways and evaluation frameworks in relation to COVID-19 vaccines. Last, although multiple prototype vaccines having been authorized worldwide, the