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.

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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 emergence of SARS-CoV-2 VoC*(43)* is driving the development of modified vaccines*(44)* and next-generation vaccines.*(45)* These developments underscore the need for updated WHO guidance on the ethical issues implicit in placebo control trials in the context of COVID-19 prototype vaccines, modified vaccines and next-generation vaccines. The considerations contained in this guidance are not intended to be considered a comprehensive review of the technical merits of alternative trial designs. The technical aspects of alternative trial designs have been explored elsewhere in greater detail by a WHO expert group.*(46)* Instead, this document will briefly highlight a sample of ethical issues implicit in some of these trial designs. This analysis should not be considered exhaustive.

4 Placebo-control COVID-19 vaccine trials in the context of an increasing number of approved prototype vaccines

In November 2020, the International Coalition of Medicines Regulatory Authorities (ICMRA), a global collaborative coalition of medicine regulators, including the EMA and FDA, published a statement stating that follow-up for treatment and placebo arms should continue 'for as long as possible after any regulatory approval' and recommended a follow-up period of 'at least one year or more from completion of assigned doses'.*(47)* Since then, multiple COVID-19 prototype vaccines have been authorized on the basis of early interim data from ongoing pivotal placebo control randomized clinical trials. The FDA noted its expectation that, following submission of an emergency use authorisation (EUA) request and issuance of an EUA, a sponsor would continue to collect placebo-controlled data in any ongoing trials for as long as feasible.*(48)* Senior FDA officials argued: "The quality of the data available to inform ongoing assessment of a vaccine's benefits and risks will depend on the ability to continue evaluating the vaccine against a placebo comparator in clinical trials for as long as feasible. Moreover, evaluation of other potentially superior vaccines will depend on the ability to continue to maintain placebo controls in ongoing trials. Thus, issuance of an EUA should not, in and of itself, require unblinding of a COVID-19 vaccine trial and immediate vaccination of placebo recipients, since doing so may jeopardize approval of these products."*(49)* In December 2020, a WHO expert group advised that the placebo control arms of these trials should be progressively unblinded as authorized vaccines become available in the host setting, starting with prioritized groups.*(50, 51)* Many trial sponsors have since offered all participants the choice to learn whether they received the study vaccine or placebo, and for those who received the placebo to have the option to receive the study vaccine while staying in the study.*(52)* Before a COVID-19 vaccine trial commences enrolment, if an 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 vaccine. Participants may join the study if they have no intention of getting the locally available authorized/approved COVID-19 vaccine at the time.

Multiple candidate vaccines are currently being tested in phase 1, phase 2 and phase 3 placebo control trials or are in the development pipeline.*(53)* While regulators have indicated their preference for evidence from pivotal trials in the form of placebo control trials, increasing vaccine supply and vaccination coverage in many settings raises concerns about whether any type of placebo control trial in such settings would be ethically acceptable. Various placebo control designs have emerged.

4.1 Randomized, double-blinded parallel group placebo control trial

The conduct of double-blinded placebo control randomized trials to assess vaccine efficacy against clinically relevant, pre-defined endpoints constitutes the gold-standard approach to generate evidence for vaccine licensure and policy decisions.*(54)* The use of a parallel group placebo control may be unethical if an effective vaccine is authorized in the trial setting, the authorized vaccine is locally available and accessible and trial participants meet local programmatic eligibility criteria. Until immune correlates of protection are established, authorized prototype vaccines may still be tested in placebo control trials in cohorts for whom the vaccines have not yet been authorized (such as children and some adolescents).*(55)*

Placebo control booster-dose trials involving authorized vaccines may also be ethically acceptable (for instance, if a booster dose has not yet been authorized and/or is not yet widely available).

Example: A study to evaluate the safety and efficacy of a booster dose of BNT162b2 (Pfizer/BioNTech vaccine) against COVID-19 in participants ≥16 years of age.*(56)* All trial participants previously received 2 doses of BNT162b2 at least 6 months prior to randomization. Arm 1 received an additional dose of BNT162b2. Arm 2 received a placebo.

4.2 Randomized, double-blinded placebo control crossover trial (57)

In placebo control crossover trials, participants are randomized to the investigational vaccine or the placebo group. If the investigational vaccine demonstrates efficacy, the placebo group is offered vaccination so that all willing volunteers receive the efficacious investigational vaccine. To keep the blind, the original vaccine group receives placebo and vice versa. Crossover can occur whenever a participant becomes eligible for an available authorized vaccine outside the trial. Thus, the trial changes into a blinded randomized crossover trial of immediate (investigational vaccine) versus deferred (placebo) vaccination, so that two distinct remaining interventions can be contrasted.

Example: Novavax SARS-CoV-2 rS with Matrix-M1 adjuvant blinded crossover trial*(58)*

The sponsors describe the trial as follows: "Participants in the study will randomly be assigned to receive SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo. Each participant in the study will receive a total of 2 intramuscular injections of either SARS-CoV-2 rS with Matrix-M1 adjuvant or placebo in the initial vaccination period. Up to 33 000 participants will take part in the study*. Following the recommendation of COVID-19 vaccination for all adults 18 years of age and older, adult participants will be scheduled for the administration of 2 injections of the alternate study material 21 days apart ("blinded crossover").* That is, initial recipients of placebo will receive SARS-CoV-2 rS with Matrix-M1 adjuvant and initial recipients of SARS-CoV-2 rS with Matrix-M1 adjuvant will receive placebo. A blinded crossover will be implemented for adolescents 12 to < 18 years of age approximately 6 months after the initial vaccination."

4.3 Adaptive design trial

Traditional vaccine efficacy trials usually use fixed designs with fairly large sample sizes. Recruiting a large number of subjects requires longer follow up time and costs. To save costs and time, adaptive trials have been proposed as an alternative to a fixed design. An adaptive design is defined as a clinical trial design that allows for prospectively planned modification to one or more aspects of the design based on accumulating data from subjects in the trial.*(59)* Adaptive designs attempt to select the right treatment arm and population and reduce sample size more efficiently.*(60, 61)*

With an adaptive platform trial of multiple vaccines and a common control, sample sizes can change, vaccines with an unfavourable benefit-harm profile can be dropped from the trial and new candidates can be added.*(62)* Host sites and target cohorts can also be changed. If and when it is no longer appropriate to continue randomization to placebo given availability of a different vaccine that demonstrated persuasive evidence of efficacy and safety in a previous randomized placebo control trial, a placebo control adaptive trial can switch to a 'hybrid analysis' trial (merging control groups receiving placebo and an active control).

4.3.1 Adaptive trial involving a hybrid analysis

In a hybrid analysis trial, the trial begins as a placebo control trial and may involve more than one candidate vaccine (in such instances, the trial is recommended to have a shared placebo arm). During the conduct of the trial, due to emerging availability of effective vaccines in regions participating in the trial, a time-sensitive decision can be made to replace the placebo arm with an authorized COVID-19 vaccine. In such trial designs, aggregate evidence to formally test, as well as to estimate, the efficacy of the experimental vaccine is determined by combining placebo control data during the first period of trial conduct, with active-control data during the second period.*(63)*

Example: WHO Solidarity COVID-19 Vaccine Trial.*(64)*

The Solidarity COVID-19 Vaccine Trial is designed to allow different candidate vaccines to enter the trial at different times. For each candidate vaccine, the primary efficacy results are expected within three to six months of the vaccine entering the trial. The trial uses a shared placebo/control group and a common core protocol to evaluate multiple candidates.

The design of the Solidarity COVID-19 Vaccine Trial incorporates adaptive features that respond to changes in standards of prevention and care, varying availabilities of candidate vaccines at different times and uncertainties about the course of the epidemic in different geographic locations and populations. The trial protocol describes the placebo comparator as "an integral component of the study design and is particularly important given new uncertainties regarding potential evasion of vaccine-induced immunity by newly discovered variants." Randomization to placebo will continue until it is no longer considered appropriate. In this situation, a vaccine regimen that has been found to be efficacious may serve as a positive control for the evaluation of other candidate vaccines currently in the trial or later added to the trial and new benefit and lack-of-benefit criteria introduced. Cognizant that at some point in the conduct of the trial – likely due to widespread availability of an effective vaccine in many of the countries where trial sites are located – it may no longer be feasible to randomize sufficient participants to placebo to permit direct evaluation of efficacy of new vaccines or other vaccines already in the trial. Under those circumstances the trial will need to introduce new efficacy/lack of benefit criteria to permit comparison with the available vaccine. Newly randomized participants will be evaluated in a non-inferiority comparison of each vaccine with the available vaccine.

5. Vaccine characteristics

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.

5.1. Prototype vaccines

A prototype COVID-19 vaccine refers to the vaccine based on the original SARS-CoV-2 virus.*(65)* Multiple prototype vaccines have been authorized worldwide, and many more are under various stages of development.

Ethics considerations

It may be ethically justified to test COVID-19 prototype vaccines in placebo control clinical disease endpoint trials under certain circumstances. 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.*(66, 67, 68, 69)*

Before trial enrolment: If an 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 vaccine. Participants may elect to receive the authorized vaccine at any point in the trial.

> 1.1. *Trials in progress:* Placebo control COVID-19 vaccine trials in progress will require modification as vaccine supply increases and trial participants increasingly meet local programmatic eligibility criteria. In any placebo control COVID-19 vaccine trial design, as soon as an authorized vaccine becomes locally available during the trial and a trial participant meets local programmatic eligibility criteria, the trial participant should be offered the opportunity to be unblinded and if they choose so, offered the authorized vaccine (or the investigational 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 they meet local programmatic vaccine eligibility criteria. 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.

In the case of crossover trials, as soon as an authorized vaccine becomes locally available and trial participants meet local programmatic eligibility criteria for that authorized vaccine, the participants in the placebo arm should be switched to the authorized vaccine.

As COVID-19 vaccine coverage increases, investigators and sponsors of prototype vaccines should consider trial designs that are not based on placebo controls.*(70)* Annex 1 highlights examples of such approaches.

5.2. Modified vaccines

A modified/variant COVID-19 vaccine is based on a prototype vaccine that has been modified to enhance its efficacy against COVID-19 caused by a SARS-CoV-2 variant(s). In a modified vaccine, the change is only in the parent/prototype vaccine's virus strain without changes in the manufacturing process, controls and the facilities for vaccine production.*(71)* Research on the development of modified vaccines is prudent given the emergence of SARS-CoV-2 variants that may escape immunity conferred by prototype vaccines.*(72)* Modified vaccines may be intended for primary vaccination or to be administered with the parent vaccine. Modified vaccines should be assessed in comparator efficacy trials or immunobridging studies.

5.2.1   Comparator efficacy trials

Modified vaccines may be assessed in two distinct populations: individuals previously vaccinated against SARS-CoV-2 with the parent vaccine and SARS-CoV-2-naïve individuals (who are unvaccinated and show no evidence of previous infection). WHO has proposed, as an example, an open-label, randomized study comparing the safety and immunogenicity of an approved parent/ prototype vaccine with modified SARS-CoV-2 vaccine in naïve and previously vaccinated individuals. WHO recommends a non-inferiority study that compares the immune response induced by the modified COVID-19 vaccine to that induced by the prototype COVID-19 vaccine.*(73)* The FDA advises that immunogenicity studies should compare immune responses induced by the modified vaccine against the SARS CoV-2 VoC with those induced by the prototype vaccine against the virus on which the prototype vaccine was based, when administered as a primary series to previously unvaccinated and SARS CoV-2 naïve study subjects using the dose and dosing regimen as authorized for the prototype vaccine.*(74)* Similarly, in the absence of an ICP, the EMA recommends conducting immunobridging studies comparing the original and modified vaccines in vaccine naïve individuals.*(75)* In a trial involving unvaccinated individuals, participants could be randomized to receive the full schedule of the authorized parent vaccine or a mixed dose of the parent vaccine and modified vaccine or a full schedule of the modified vaccine alone. In such comparator trials, a placebo control arm would be unnecessary. WHO has advised that the data should, as much as possible, be generated in a naïve population but recognizes that widespread infection and current efforts to vaccinate as many people as possible may mean that data from a non-naïve population can be generated if it is difficult to identify a naïve population. The EMA recommends that trial participants should have participated in previous trials with the parent vaccine so that their post-primary neutralizing antibody titres are available. In a trial involving individuals who had been fully vaccinated with the parent vaccine, the modified vaccine could be tested as a booster dose. In such a trial, participants could be randomized to receive a booster dose of the parent vaccine or a booster dose of the modified vaccine. A placebo control arm in such a trial would be unwarranted.

Access Consortium regulators have noted that if in-vitro assays from sera of individuals vaccinated with the parent vaccine have shown that cross-reactivity with a new variant is not sufficient, a comparative study of the parent and modified vaccines may not be in the best interest of trial participants*(76)* because participants randomized to receive the parent vaccine would receive an inefficacious vaccine. In such instances, a stand-alone immunogenicity and reactogenicity study of the modified vaccine would be appropriate along with a comparison of immune measures in sera from individuals vaccinated with the parent vaccine.*(77, 78)* If it is not possible to enrol participants who have participated in a previous trial with the parent vaccine, the EMA recommend that the

post-primary neutralizing antibody titres used in the primary analysis should be drawn from a population that is matched at least based on age, gender and presence of important underlying comorbidities to the population enrolled into the prospective trial to receive a dose of modified vaccine.*(79)* For the purposes of obtaining the data required to conduct the primary analysis, the EMA notes that it would suffice that all participants enrolled into the trial receive a dose of the modified vaccine.*(80)* In such a scenario, a placebo control arm would be unnecessary.

Annex 2 highlights other potential research approaches regarding modified vaccines that do not involve placebo controls.

Ethics considerations

A modified vaccine should be tested in comparator efficacy trials against the authorized parent/prototype vaccine.

Trial participants should ideally have participated in a previous trial with the parent vaccine so that their post-primary neutralizing antibody titres are available. In a trial involving individuals who had been fully vaccinated with the parent vaccine, the modified vaccine could be tested as a booster dose. In such a trial, participants could be randomized to receive a booster dose of the parent vaccine or a booster dose of the modified vaccine. A placebo control arm in such a trial would be unwarranted.

If it is not possible to enrol participants who have participated in a previous trial with the parent vaccine, all participants enrolled into the trial could receive a dose of the modified vaccine. In such a scenario, a placebo control arm would be unnecessary.

In a trial involving unvaccinated individuals, participants could be randomized to receive the full schedule of the authorized parent vaccine or a mixed dose of the parent vaccine and modified vaccine or a full schedule of the modified vaccine alone. In such comparator trials, a placebo control arm would be unnecessary.

If in-vitro assays from sera of individuals vaccinated with the parent vaccine have shown that cross-reactivity with a new variant is not sufficient, a comparative study of the parent and modified vaccines may not be in the best interest of trial participants because participants randomized to receive the parent vaccine would receive a vaccine that is inefficacious against a new variant. In such instances, a stand-alone immunogenicity and reactogenicity study of the modified vaccine would be appropriate along with a comparison of immune measures in sera from individuals vaccinated with the parent vaccine. A placebo control arm in such a trial would be unwarranted.

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

5.3 Next-generation vaccines

'Next-generation' COVID-19 candidate vaccines include polyvalent vaccines (covering multiple serotypes) and candidates based on novel technology platforms that may be based on different routes of administration (for example, intradermal, intranasal or oral) in contrast to 'first generation' vaccines, which are administered intramuscularly. Data to support the authorization of next-generation vaccines may depend on whether the vaccine will be used for primary series vaccination or for booster vaccination based on primary series vaccination with a different vaccine.*(81)*

Next-generation vaccines will need to be studied on the basis of appropriate study designs that generate robust data to enable regulatory decision-making. The ICMRA has noted that factors to consider in clinical trial designs to determine the effectiveness of next-generation COVID-19 vaccines include the epidemiology and trajectory of the pandemic across countries and regions, including whether there is high or low prevalence of SARS-CoV-2 and vaccine availability and vaccination coverage.*(82)* The ICMRA has noted that next-generation vaccines may be tested in placebo control clinical disease endpoint trials, provided such trials can still be ethically performed. Trials of next-generation candidate vaccines will commence increasingly after one or more authorized (including fully approved) prototype vaccines has been publicly deployed in a proposed trial setting and in the context of increasing vaccine supply and increasing vaccination uptake. Placebo control trials involving next-generation COVID-19 vaccines in progress will require modification as trial participants increasingly meet local programmatic eligibility criteria and vaccine supply increases.

Given increasing COVID-19 vaccination coverage worldwide, 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*(83)* and non-efficacy studies. Annex 3 highlights these research approaches.

Ethics considerations

Under certain circumstances, it may be ethically justified to test next-generation vaccines in placebo control clinical disease endpoint trials. 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.*(84, 85, 86, 87)*

Before trial enrolment: If an 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 vaccine. Participants may elect to receive the authorized vaccine at any point in the trial.

Trials in progress: Placebo control COVID-19 vaccine trials in progress will require modification as vaccine supply increases and trial participants increasingly meet local programmatic eligibility criteria. In any placebo control COVID-19 vaccine trial design, as soon as an authorized vaccine becomes locally available during the trial 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 and offered the authorized vaccine (or the investigational 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. Criteria for unblinding should appear in informed consent documentation, and there should be 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.

6. Conclusion

Developing multiple efficacious COVID-19 vaccines is an urgent research priority. Decision-making should be informed by the highest quality evidence and underpinned by ethical considerations. This guidance document aims to highlight some of the ethical considerations implicit in COVID-19 placebo control trials and alternative research approaches. COVID-19 is a rapidly evolving pandemic, and this document should consequently be considered a living document, subject to revision.

TABLE 1: COVID-19 VACCINE PROFILE AND ETHICAL APPROPRIATENESS OF STUDY METHODOLOGY

	ETHICAL APPROPRIATENESS OF STUDY METHODOLOGY				
	PLACEBO CONTROL EFFICACY TRIAL **(i) Parallel group randomized clinical trial** **(ii) Crossover trial** **(iii) Deferred vaccination** **(iv) Adaptive trial with hybrid analysis plan**	**ACTIVE CONTROL EFFICACY TRIAL** **(i) Active control indicated for another condition** **(ii) Active control is another authorized vaccine for COVID-19** - Superiority trial - Non-inferiority trial	**SYNTHETIC / EXTERNAL CONTROL TRIAL**	**IMMUNE CORRELATES OF PROTECTION**	**IMMUNOBRIDGING TRIAL**
PROTOTYPE VACCINE	Appropriate only in prescribed circumstances. Not appropriate if immune correlates of protection have been established	Appropriate, if no immune correlates of protection have been established.	Appropriate, if no immune correlates of protection have been established. Not yet used in pivotal trial for regulatory decision making	Appropriate, if immune correlates of protection have been established	Appropriate, if immune correlates of protection have been established
MODIFIED VACCINE	Not appropriate	Appropriate, if no immune correlates of protection have been established	Appropriate, in relevant circumstances	Appropriate, if immune correlates of protection have been established	Appropriate, if immune correlates of protection have been established
NEXT GENERATION VACCINE	Appropriate only in prescribed circumstances. Not appropriate if immune correlates of protection have been established	Appropriate, if no immune correlates of protection have been established	Appropriate, if no immune correlates of protection have been established. Not yet used in pivotal trial for regulatory decision making	Appropriate, if immune correlates of protection have been established	Appropriate, if immune correlates of protection have been established

Declarations of interest

All members of the WHO Access to COVID-19 Tools Accelerator Ethics and Governance Working Group declared their interests according to WHO standard procedures. None of the interests declared were found to be significant.

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ANNEX 1

Prototype vaccines

A sample of alternative approaches to placebo control trials

1. Active control trials

An active control trial is designed to compare a new intervention to an active control. The active control might be a different vaccine already licensed for the indication being studied (hereafter 'active comparator') or it might be a licensed vaccine for some other indication that does not affect the acquisition of the study endpoint(s) and thus functions in the same way as a placebo for purposes of assessing efficacy*(88)* (hereafter 'inactive comparator'). In some settings, an active control design may be preferred over a placebo-control design.

1.1. Inactive comparator

In the context of a vaccine trial, a licensed vaccine (unrelated to the disease in question) can be used as an inactive comparator control, in lieu of a placebo. Some COVID-19 vaccine trials tested prototype vaccines against vaccines licensed for another indication, and this did not affect the acquisition of the study endpoint(s).

> Example: In the ChAdOx1 nCoV-19 (AstraZeneca) phase 3 trial, Meningococcal group A, C, W-135, and Y conjugate vaccine (MenACWY) – which protects against 4 different strains of the meningococcal bacteria that cause meningitis and blood poisoning (septicaemia) – served as the control arm. Participants were randomized (1:1 using block randomisation) to receive either the experimental vaccine (ChAdOx1 nCoV-19) or the licensed control vaccine (MenACWY).*(89, 90, 91)*

Ethics considerations

If an authorized vaccine is not available in a study setting and trial participants do not meet local programmatic eligibility criteria for the authorized vaccine, an active control COVID-19 vaccine trial that utilizes an inactive comparator (a vaccine licensed for another condition unrelated to the condition under study) is preferable to a placebo control because it allows participants to gain the potential benefit of protection against the infectious agent(s) that the active control is indicated for, instead of receiving no benefit from a placebo.

1.2. Active Comparator

The control in an active comparator vaccine trial can be another authorized vaccine for the disease or condition in question. The objective in such trials may be to demonstrate:

- the superiority of the new product
- the non-inferiority of the new product or
- the equivalence of the two products.*(92)*

1.2.1. Active comparator superiority trial

COVID-19 vaccine trials may be designed as randomized, observer-blind comparative immunogenicity superiority trials. The primary objective of such trials is to demonstrate the superiority of an investigational candidate vaccine compared to another COVID-19 candidate vaccine. A possible endpoint in such trials would be to demonstrate that the investigational candidate vaccine is superior for geometric mean titre ratio of SARS-CoV-2-specific neutralizing antibodies at a specified time after the vaccination series.

> Example: Valneva's SARS-CoV-2 vaccine candidate, VLA2001, is being tested against the AstraZeneca / Vaxzevria vaccine.*(93)* Approximately 4000 participants will receive two doses of either vaccine. The primary endpoint of the Cov-Compare trial will be to determine the immune response (geometric mean titre [GMT] of SARS-CoV-2-specific neutralizing antibodies) two weeks after completion of a two-dose immunization schedule administered over a four-week interval.

1.2.2 Active comparator non-inferiority trial

In settings where placebo-control trials are deemed no longer ethically appropriate, randomized non-inferiority trials may enable reliable evaluations of experimental vaccines through direct comparison with active comparator vaccines established to have worthwhile efficacy against the same disease.*(94)* The objective of non-inferiority trials is to reliably assess whether the efficacy of an experimental vaccine is not unacceptably lower than that of an active control vaccine previously established as effective, likely in a placebo control trial.*(95)* The FDA has noted that "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."*(96)* WHO has noted that phase IIB/III efficacy trials should be randomized, blinded and conducted with placebo control or active control (when a safe and effective COVID-19 vaccine is available).*(97)*

Non-inferiority studies have been described as an important tool in evaluating the efficacy of a new vaccine when there is a vaccine introduced to a population and when randomization to placebo is not deemed inappropriate on ethics grounds. The goal in a non-inferiority trial is to assess whether the efficacy of an experimental vaccine is not unacceptably lower than that of an active control vaccine that previously had been established to be effective (which is likely in a placebo control trial). This is formally achieved by identifying a minimum threshold for what would constitute an unacceptable loss of efficacy, that is, a noninferiority margin, and then designing the noninferiority trial to rule out that margin.*(98)* Regulators such as the FDA have indicated that for non-inferiority comparison to a COVID-19 vaccine already proven to be effective, the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary relative efficacy point estimate is >-10%.*(99)*

Ethics considerations for active comparator superiority and non-inferiority trials

The use of an authorized active comparator as a control ensures that those who are assigned to the active comparator arm are assured access to a safe and efficacious intervention.

To conduct active comparator trials, the developer of an authorized vaccine may donate/sponsor their vaccine for use as the comparator. This may be challenging in the context of extreme vaccine shortages or supply constraints in relation to the raw ingredients to manufacture the vaccine or where available production capacity is dedicated to ensuring compliance with commercial contractual obligations.

In some instances, contracts between manufacturers and governments for authorized vaccines may restrict their use to improving public health,*(100)* which precludes that vaccine's use as a comparator in a clinical trial. Developers of authorized vaccines should not directly or indirectly bar their candidate vaccine from being used as an active comparator in a clinical trials. Doing so runs counter to the interests of global health.

2. Deferred vaccination

A delayed vaccination comparator offers an alternative to a placebo or active control comparator. In such trials, individuals/clusters are allocated to either immediate or delayed vaccination, with a delay between the two that is shorter than the typical duration of a trial.*(101)* Delayed vaccination involves one-way crossover of participants and is related to the stepped wedge design. All participants obtain access to the experimental vaccine in a phased, staggered manner. In situations where logistical constraints mean that not all eligible persons within the same prioritized population can be vaccinated at the same time and in a timely manner, deferred vaccination through a stepped wedge design (either individually or as a cluster) can be used to obtain information on efficacy and safety. In combination with routinely collected data collection, this may generate randomized real-world evidence.*(102)*

Example: An effectiveness study of the Sinovac's Adsorbed COVID-19 (Inactivated) Vaccine (Projeto S), Serrana, Brazil.*(103, 104)* In this stepped-wedge trial, the town of Serrana was divided into four clusters, which were randomly allocated to one of four subsequent weeks. In each week, all enrolled adults in the cluster were offered the first shot of the vaccine. In the next week, the next cluster was vaccinated. After four weeks, all enrolled adults received the first vaccination and subsequently received the second dose at the scheduled dose interval. In total, more than 27 000 adults were vaccinated against COVID-19 within 4 weeks.

Ethics considerations

If the experimental candidate vaccine has an unfavourable benefit-risk profile, more people may be exposed to the vaccine than would be the case in a trial with placebo/active control. However, if safety signals are recognized before the delay period has elapsed, then the vaccine would not be given to the delayed group, and no more people would be exposed than in a design with a standard placebo/active control comparator.

3. Synthetic or External controls (with or without real-world data)

The FDA defines real-world data (RWD) as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources" and real-world evidence (RWE) as "the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."*(105)* Synthetic or external control arms may leverage RWD from various sources or evaluations of historical clinical data to demonstrate the positive effects of a new intervention, without the need to use a placebo or standard of care as a control.*(106)* Instead of collecting data from patients recruited for a trial who have been assigned to the control or standard-of-care arm, synthetic*(107)* or external control arms model those comparators using data that have previously been collected from sources such as previously conducted clinical trials (including pooled trial data) or RWD (e.g. health data generated during the trial but not for the purpose of research, electronic health records, administrative claims data, health insurance data and disease registries). The FDA and EMA have outlined frameworks to use RWD and for external controls.*(108, 109, 110)*The FDA requires developers who want to utilize RWE to support their applications to highlight: the purpose of using RWE, the study designs that include RWD and all the data sources used to generate RWE.

> Example: RWE has been used to support authorization for COVID-19 candidate vaccines, but, to date, RWE has not yet been used as external control arms in pivotal COVID-19 vaccine trials. This situation may change.

Ethics considerations

The collection, access and sharing of RWD raises privacy and confidentiality concerns.

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4. Non-efficacy trials: authorization based on data of an approved prototype vaccine

The EMA has proposed that a new vaccine can be authorized without an efficacy trial in two circumstances: where there is a well-established immune correlate of protection (ICP) or where immunobridging takes place.*(111)*

4.1. Immune correlate of protection

An ICP is an immunological assay (either humoral or cellular immune response) that reliably predicts protection against disease or infection after vaccination or natural infection.*(112, 113,114)* In the context of vaccine-induced immunity, the EMA defines an immune correlate of protection as "a type and amount of immunological response that correlates with vaccine-induced protection against an infectious disease and that is considered predictive of clinical efficacy".*(115)* It has been argued that correlates of vaccine efficacy could be used to extrapolate efficacy to immunogenicity data for novel vaccines where clinical efficacy results are unlikely to be obtained.*(116)* The data can be used to bridge to new populations and to extrapolate efficacy estimates for new vaccines where efficacy data is unavailable or is unlikely to be obtained.*(117)* Being able to rely on an ICP would simplify and accelerate vaccine development by allowing developers to demonstrate that their candidate vaccines stimulate an accepted immune response in recipients from which efficacy can be inferred.*(118)*

Ethics considerations

When consensus is reached on valid surrogate outcomes (i.e., humoral and/or cellular immune parameters that adequately correlate with reduction in COVID-19 disease severity or mortality), investigational vaccines should not be tested in placebo control trials.

4.2. Immunobridging

Immunobridging refers to a situation where vaccine efficacy can be inferred by demonstrating a non-inferior immune response between an investigational vaccine and an authorized vaccine for which efficacy and/or effectiveness against a specific disease has been estimated.*(119)* WHO has noted that immunogenicity data may be used to provide evidence of efficacy when there is a well-established ICP that can be used to interpret the immune responses to a specific antigenic component; and it is possible to use immune responses to bridge to estimates of vaccine efficacy obtained from prior well-designed clinical trials. Following a June 2021 meeting of the ICMRA, which focused on immunobridging, the design and use of control trials (placebo or other controls) and ICPs,*(120)* ICMRA noted that well-justified and appropriately designed immunobridging studies are an acceptable approach for authorizing COVID-19 vaccines.*(121)* Accordingly, some aligned regulators have taken the position that the weight of evidence from studies with authorized COVID-19 vaccines is sufficient to support using neutralizing antibody titres as a primary endpoint in cross-platform immunobridging trials.*(122)*

Ethics considerations

When consensus is reached on valid surrogate outcomes (i.e., humoral and/or cellular immune parameters that adequately correlate with reduction in disease severity or mortality against COVID-19), and there is broad regulatory consensus on relying on immunobridging for inferring efficacy, investigational COVID-19 vaccines should not be tested in placebo-control trials.

ANNEX 2

1. Modified vaccines

Alternatives to placebo-control trials

1.1. Immunobridging trial

WHO has noted that bridging studies (relying on data of prototype/parent vaccines) for the modified COVID-19 vaccine may be conducted in the 18-55 year-old age group, with extrapolation of results to other age groups for which the prototype vaccine has efficacy data.*(123)*

Some regulators, such as members of the Access Consortium, have noted they will not require prior clinical efficacy studies to support their approval of modified vaccines.*(124)* These regulators have advised developers of modified vaccines to submit bridging data on immunogenicity and safety from a sufficient number of individuals.

1.2. Historical control

WHO has advised that studies comparing the immune response from the modified vaccine with historical data from the prototype vaccine may not be acceptable. However, if the prototype vaccine has been demonstrated to be less effective / ineffective against a variant in a trial setting, its use in the trial as a control will be unethical. In such instances, historical data of the prototype vaccine may be used as a control. In such a situation challenge study data from animal models should also be considered.

ANNEX 3

1. Next-generation vaccines

Alternatives to placebo control trials

1.1 Active comparator efficacy trials

Next-generation vaccines may be assessed in active comparator clinical endpoint efficacy trials. Such trials would involve testing the next-generation vaccine against an authorized vaccine. Such studies could be designed as non-inferiority immunogenicity studies if the comparator authorized vaccine has demonstrated high efficacy in clinical diseases endpoint efficacy trials and/or superiority designs if the comparator vaccine has demonstrated modest efficacy.*(125)*

1.2. Non-efficacy studies

The ICMRA has noted that immunogenicity bridging studies may be needed if an assessment of effectiveness of next-generation COVID-19 vaccines in clinical endpoint efficacy studies are deemed no longer feasible.*(126)* Some regulators, such as members of the Access Consortium, have taken the position that the weight of evidence from studies with authorized COVID-19 vaccines is sufficient to support using neutralizing antibody titres as a primary endpoint in cross-platform immunobridging trials to predict vaccine effectiveness.*(127)* Neutralizing antibody titres should be determined using WHO-certified reference standards.*(128)*