



Contents lists available at ScienceDirect

## Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)

## Review

# WHO guidance on COVID-19 vaccine trial designs in the context of authorized COVID-19 vaccines and expanding global access: Ethical considerations



Jerome Amir Singh<sup>a,b,c,\*</sup>, Sonali Kochhar<sup>d,e</sup>, Jonathan Wolff<sup>f</sup>, Caesar Atuire<sup>g</sup>, Anant Bhan<sup>h</sup>, Ezekiel Emanuel<sup>i</sup>, Ruth Faden<sup>j</sup>, Prakash Ghimire<sup>k</sup>, Dirceu Greco<sup>l</sup>, Calvin Ho<sup>m</sup>, Suerie Moon<sup>n</sup>, Ehsan Shamsi-Gooshki<sup>o</sup>, Aissatou Touré<sup>p</sup>, Beatriz Thomé<sup>q</sup>, Maxwell J. Smith<sup>r</sup>, Ross E.G. Upshur<sup>s</sup>

<sup>a</sup> Howard College School of Law, University of KwaZulu-Natal, Durban, South Africa

<sup>b</sup> Scientific Advisory Group on Emergencies (SAGE), Academy of Science of South Africa (ASSAf), Pretoria, South Africa

<sup>c</sup> Department of Clinical Public Health, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

<sup>d</sup> Department of Global Health, University of Washington, Seattle, WA, USA

<sup>e</sup> Global Healthcare Consulting, Delhi, India

<sup>f</sup> Blavatnik School of Government, University of Oxford, Oxford, UK

<sup>g</sup> Department of Philosophy and Classics, University of Ghana, Accra, Ghana

<sup>h</sup> Department of Community Medicine and Centre for Ethics, Yenepoya University, Mangalore, India

<sup>i</sup> Global Initiatives and Healthcare Transformation Institute, University of Pennsylvania, Philadelphia, PA, USA

<sup>j</sup> Johns Hopkins Berman Institute of Bioethics, Johns Hopkins University, Baltimore, MD, USA

<sup>k</sup> Tribhuvan University, Kirtipur, Nepal

<sup>l</sup> School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil

<sup>m</sup> Faculty of Law and Centre for Medical Ethics, University of Hong Kong, Hong Kong Special Administrative Region, China

<sup>n</sup> International Relations and Political Science Department & Interdisciplinary Programmes, Global Health Centre, Graduate Institute of International and Development Studies, Geneva, Switzerland

<sup>o</sup> Department of Medical Ethics, Tehran University of Medical Sciences, Tehran, Iran

<sup>p</sup> Institut Pasteur, Dakar, Senegal

<sup>q</sup> Departamento de Medicina Preventiva, Universidade Federal de São Paulo, Rua Botucatu, Sao Paulo, Brazil

<sup>r</sup> Faculty of Health Sciences, Western University, London, Ontario, Canada

<sup>s</sup> Department of Family and Community Medicine and Dalla Lana School of Public Health University of Toronto, Toronto, Ontario, Canada

## ARTICLE INFO

## Article history:

Received 7 February 2022

Accepted 8 February 2022

Available online 28 February 2022

## Keywords:

Placebo-controlled trials

Standard of care

Standard of prevention

Trial designs

Research ethics

## ABSTRACT

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. A WHO Expert Group has developed guidance on the ethical implications of conducting placebo-controlled trials in the context of expanding global COVID-19 vaccine coverage. The guidance also considers alternative trial designs to placebo controlled trials in the context of prototype vaccines, modified vaccines, and next generation vaccines.

© 2022 Published by Elsevier Ltd.

## Contents

1. Introduction .....	2141
2. Background .....	2141
2.1. The use of randomized, placebo control arms in COVID-19 vaccine trials .....	2142
2.2. The position of existing global research ethics guidance documents on placebo use. ....	2142

\* Corresponding author at: Howard College School of Law, University of KwaZulu-Natal, King George V Ave, Durban, South Africa.

E-mail address: [singhj9@ukzn.ac.za](mailto:singhj9@ukzn.ac.za) (J.A. Singh).

- 2.3. 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 . . . . . 2142
  - 2.3.1. What constitutes an “established effective intervention” (CIOMS Guidelines)? . . . . . 2143
  - 2.3.2. What constitutes a “best proven intervention” (DoH)? . . . . . 2143
  - 2.3.3. When is a placebo-control COVID-19 vaccine trial “clearly unacceptable” (2013 WHO Guidance)? . . . . . 2143
- 3. Placebo-control COVID-19 vaccine trials in the context of an increasing number of approved prototype vaccines . . . . . 2143
  - 3.1. Randomized, double-blinded parallel group placebo control trial . . . . . 2144
  - 3.2. *Randomized, double-blinded placebo control crossover trial* [35] . . . . . 2144
  - 3.3. Adaptive design trial . . . . . 2144
- 4. Vaccine characteristics . . . . . 2144
  - 4.1. Prototype vaccines . . . . . 2144
  - 4.2. Ethical permissibility of testing prototype vaccines in placebo-controlled trials . . . . . 2144
    - 4.2.1. Before trial enrolment . . . . . 2144
    - 4.2.2. Trials in progress . . . . . 2144
  - 4.3. Alternatives to placebo-controlled trials: Active controls, inactive controls, delayed vaccination, and synthetic or external controls . . . . . 2145
    - 4.3.1. Active control . . . . . 2145
    - 4.3.2. Inactive control . . . . . 2145
    - 4.3.3. Delayed vaccination . . . . . 2145
    - 4.3.4. Synthetic or external controls . . . . . 2145
  - 4.4. Modified vaccines . . . . . 2145
    - 4.4.1. Comparator efficacy trials . . . . . 2145
    - 4.4.2. Immunobridging and historical controls . . . . . 2146
  - 4.5. Next-generation vaccines . . . . . 2146
    - 4.5.1. Before trial enrolment . . . . . 2147
    - 4.5.2. Trials in progress . . . . . 2147
- 5. Conclusion . . . . . 2147
  - Declaration of Competing Interest . . . . . 2147
  - Acknowledgements . . . . . 2147
  - Funding source . . . . . 2148
  - References . . . . . 2148

## 1. Introduction

Since its emergence in 2019, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has continued to evolve [1]. To date, WHO has designated five variants of SARS-CoV-2 as ‘Variants of Concern’ (VOC) – Alpha, Beta, Gamma, Delta and Omicron [2] – due to the ability of these variants to impact on transmission, disease severity, or immune escape. The emergence of VOCs has raised the question of whether current authorised COVID-19 vaccines offer adequate protection against VOCs. Moreover, concerns about whether homologous boosting with original prototype vaccines will be sufficient to generate broadly neutralizing antibody responses against VOCs, or whether an additional boost after the primary vaccine regimen should be matched to the most epidemiologically relevant VOCs, is fuelling intensified COVID-19 vaccine research. As vaccines need to be based on strains that are genetically and antigenically close to the circulating SARS-CoV-2 variant(s), and because vaccines need to elicit immune responses that are broad, strong, and long-lasting in order to reduce the need for successive booster doses [3], modified [4] and new vaccines [5] are being developed against SARS-CoV-2. 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. The World Health Organization (WHO) Access to COVID-19 Tools Accelerator Ethics & Governance Working Group, whose members include external experts and WHO technical staff, has developed guidance on these issues. The guidance also considers alternative trial designs to placebo controlled trials in the context of prototype vaccines, modified vaccines, and next generation vaccines.

## 2. Background

Pivotal clinical trials provide the evidence necessary to support regulatory authorization/licensure [6]. 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 [7]. The FDA [8], EMA [9] and WHO [10] 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” [8]. 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” [3]. 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” [11]. 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 autho-

rization or full approval regulatory mechanisms. Given increasing COVID-19 vaccination coverage globally, the use of placebos as controls in COVID-19 vaccine trials will become increasingly difficult to justify ethically.

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

Randomization is a well-established research methodology [12] to deal with therapeutic or prophylactic uncertainty, and to ensure the absence of systematic differences between intervention and control groups [13]. 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 [14]. Placebos allow the consequences of attention, expectation, suggestion and natural course to be separated from the effects of the experimental intervention [15]. 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 [16]. 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 [17,18]. 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 been elucidated [19].

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

The Declaration of Helsinki (2013), [20] 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 [14]. 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) [21]. 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.

### 2.3. 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.

### 2.3.1. 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 [9]. 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 [22]. 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, [23,24,25] the safety and efficacy of a candidate vaccine cannot reasonably be considered “established” or the “medical professional standard.”

### 2.3.2. 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) [26]. 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 [27] less efficacious in another [28], notwithstanding its authorization and imminent rollout in the face of reduced efficacy [29,30].

### 2.3.3. 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% [8,9,11]. Various COVID-19 candidate vaccines that meet this threshold requirement have been authorized worldwide but have reported varying efficacy in different settings [28,31]. Further, as noted earlier, authorized vaccines may not be universally “highly efficacious” given the emergence of SARS-CoV-2 VoC [32]. 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 [33]. Vari-

ations of the traditional parallel-group placebo-control randomized clinical trial design have also since emerged [34,35,36]. Moreover, to expedite vaccine availability, some regulators, such as the FDA [8] and EMA [9] and WHO [10] 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 [1] is driving the development of modified vaccines [37] and next-generation vaccines [38]. 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 [33]. Instead, this work will briefly highlight a sample of ethical issues implicit in some of these trial designs. This analysis should not be considered exhaustive.

## 3. 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’ [39]. 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 [40]. 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” [41]. 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 [42,43]. 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 [44]. 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 [42,43]. 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 [5]. 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 set-

**Box 1**

## 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.

tings raises concerns about whether any type of placebo control trial in such settings would be ethically acceptable. Various placebo control designs have emerged.

### 3.1. 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 [45]. 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) [46].

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).

### 3.2. Randomized, double-blinded placebo control crossover trial [35]

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.

### 3.3. 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 [47]. Adaptive designs attempt to select the right treatment arm and population and reduce sample size more efficiently [48,49].

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 [50]. 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 adap-

tive trial can switch to a 'hybrid analysis' trial (merging control groups receiving placebo and an active control) [36].

## 4. 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.

### 4.1. Prototype vaccines

A prototype COVID-19 vaccine refers to the vaccine based on the original SARS-CoV-2 virus [51]. Multiple prototype vaccines have been authorized worldwide, and many more are under various stages of development (Box 1).

### 4.2. Ethical permissibility of testing prototype vaccines in placebo-controlled trials

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 [52,53,54,55].

#### 4.2.1. 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.

#### 4.2.2. 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 pro-

grammatic 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 [33].

#### 4.3. Alternatives to placebo-controlled trials: Active controls, inactive controls, delayed vaccination, and synthetic or external controls

##### 4.3.1. Active control

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 [33] (hereafter ‘inactive comparator’).

In some settings, an active control design may be preferred over a placebo-control design. 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,[19] 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.

##### 4.3.2. Inactive control

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.

##### 4.3.3. Delayed 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 [33]. 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 [58]. 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.

##### 4.3.4. Synthetic or external controls

Synthetic or external controls (with or without real-world data) may also serve as an alternative to placebo-controlled trials. 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”[59]. 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 [60]. Instead of collecting data from patients recruited for a trial who have been assigned to the control or standard-of-care arm, synthetic [61] 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 [59,62,63]. The collection, access and sharing of RWD raises privacy and confidentiality concerns and relevant mitigation measures should be developed to counter the risk of such occurrences.

#### 4.4. Modified vaccines

Vaccine composition may need to be adjusted to optimize the performance of COVID-19 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 [51]. Research on the development of modified vaccines has been driven by the emergence of SARS-CoV-2 variants that may escape immunity conferred by prototype vaccines [1]. Modified vaccines may be intended as a primary vaccine regimen for naïve individuals (who are unvaccinated against SARS-CoV-2) and show no evidence of previous infection), or to be administered as booster doses with the parent vaccine. Trials involving modified vaccines will need to establish whether modifying a prototype vaccine to match a dominant variant affects responses against variants which may be antigenically distant from the prevailing dominant variant but close to the prototype. Additionally, some studies may aim to investigate whether cross-reactive B cell recall immunity elicited by boosting with the original prototype vaccine is sufficient to reduce infection and disease severity, or whether there is comparative advantage of boosting with a heterologous vaccine matched to the dominant circulating variant. In such trials, modified vaccines should be assessed in comparator efficacy trials or immunobridging studies (Box 1).

##### 4.4.1. 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/ proto-

type 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 [51]. 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 [40]. Similarly, in the absence of an ICP, the EMA recommends conducting immunobridging studies comparing the original and modified vaccines in vaccine naïve individuals [22]. 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 [56] 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 [22,56]. 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 [22]. 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 [22]. In such a scenario, a placebo control arm would be unnecessary.

#### 4.4.2. Immunobridging and historical controls

Immunobridging trials and historical controls could serve as potential alternative approaches to placebo controls in modified vaccine trials. 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 [51]. 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 [56]. These regulators have advised developers of modified vaccines to submit bridging data on immunogenicity and safety from a sufficient number of individuals.

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.

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.

#### 4.5. 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 [57].

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 [57]. 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 [57,83] and non-efficacy studies (Box 1).

Active comparator clinical endpoint efficacy 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 [57]. Immunogenicity bridging studies, which as non-efficacy in nature, may also serve as an alternative to placebo controls. 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 [57]. 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 [64]. Neutralizing antibody titres should be determined using WHO-certified reference standards [57].

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 [52,53,54,55].

#### 4.5.1. 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.

#### 4.5.2. 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.

## 5. Conclusion

The COVID-19 pandemic has evolved rapidly since its emergence. While multiple authorised vaccines been deployed globally, breakthrough infections across all prototype vaccines underscores why the development of efficacious COVID-19 vaccines remains 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. Cognisant that COVID-19 has proven to be a rapidly evolving pandemic, the WHO has taken the position that its guidance on placebo controls and alternative trials designs in COVID-19 vaccine trials should be considered a living document, subject to periodic revision.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper: [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.].

## Acknowledgements

This policy brief was developed by the World Health Organization Access to COVID-19 Tools Accelerator Ethics and Governance Working Group. The drafting of the document was led by Jerome Amir Singh (Scientific Advisory Group of Emergencies [SAGE], Academy of Science of South Africa; University of KwaZulu-Natal, South Africa and University of Toronto, Canada), with guidance from the Co-Chairs, Sonali Kochhar (University of Washington, Seattle, United States; Global Healthcare Consulting, India) and Jonathan Wolff (University of Oxford, United Kingdom), and input from the members of the Working Group (ordered alphabetically by surname): Caesar Atuire (University of Ghana, Ghana), Anant Bhan (Yenepoya University, India), Ezekiel Emanuel (University of Pennsylvania, USA), Ruth Faden (Johns Hopkins University, USA), Prakash Ghimire (Tribhuvan University, Nepal), Dirceu Greco, (Federal University of Minas Gerais, Brazil), Calvin Ho (University of Hong Kong, China), Suerie Moon (Graduate Institute, Geneva, Switzerland), Ehsan Shamsi (Tehran University of Medical Sciences, Iran), Aissatou Touré (Institute Pasteur, Senegal, ret.), Beatriz Thomé (University of Sao Paulo, Brazil), Max Smith (Western University, Canada), Ross Upshur (University of Toronto, Canada). Dean Follmann (National Institute of Allergy and Infectious Diseases, USA), Lars Hemkens (University of Basel, Switzerland) and Peter Smith (London School of Hygiene & Tropical Medicine, UK), provided additional input on methodological issues. Katherine Littler and Andreas Reis (WHO Health Ethics & Governance Unit) provided support for the WHO Secretariat. Contributions from Rogério Gaspar, Ryoko Miyazaki Krause, Deus Mubangizi, Sergio Andrade Nishioka, David Wood (WHO Regulation and Prequalification Department), as well as Patrik Hummel (WHO Consultant), Owen Schaefer (National University of Singa-



pore), and the WHO Ethics & COVID-19 Working Group are duly acknowledged. Editorial assistance of Deanntha Kanniah (SAGE), is duly acknowledged.

### Funding source

This work was supported by the United Kingdom Foreign, Commonwealth & Development Office (FCDO) and the Wellcome Trust (Grant 214711/Z/18/Z). JAS receives support from the COVID-19 Africa Rapid Grant Fund (UID 130270), which has been jointly established by the National Research Foundation (NRF) of South Africa, the Canadian International Development Research Centre (IDRC), the Swedish International Development Cooperation Agency (SIDA), the United Kingdom (UK) Department for International Development (DFID), UK Research and Innovation (UKRI) through the Newton Fund, South Africa's Department of Science and Innovation (DSI), and Fonds de Recherche du Québec (FRQ).

### References

- [1] Krause PR, Fleming TR, Longini IM, Peto R, Briand S, Heymann DL, Beral V, Snape MD, Rees H, Roper AM, Balicer RD, Cramer JP, Muñoz-Fontela C, Gruber M, Sa Gaspar R, Singh JA, Subbarao K, Van Kerkhove MD, Swaminathan S, Ryan MJ, Henao-Restrepo A. SARS-CoV-2 variants and vaccines. *New England J Med* 2021. DOI: 10.1056/NEJMSr2105280. <https://www.nejm.org/doi/full/10.1056/NEJMSr2105280>.
- [2] World Health Organisation. Tracking SARS-CoV-2 variants. Published online February 3, 2022. <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>.
- [3] WHO Technical Advisory Group on COVID-19 Vaccine Composition. Interim Statement on COVID-19 vaccines in the context of the circulation of the Omicron SARS-CoV-2 Variant from the WHO Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC). Published online January 11, 2022. <https://www.who.int/news/item/11-01-2022-interim-statement-on-covid-19-vaccines-in-the-context-of-the-circulation-of-the-omicron-sars-cov-2-variant-from-the-who-technical-advisory-group-on-covid-19-vaccine-composition>.
- [4] Pfizer. Pfizer and BioNTech Initiate Study to Evaluate Omicron-Based COVID-19 Vaccine in Adults 18 to 55 Years of Age. Published online January 25, 2022. <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-study-evaluate-omicron-based>.
- [5] WHO. COVID-19 vaccine tracker and landscape. Published online January 25, 2022. <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>.
- [6] World Health Organisation (WHO). Guidelines on clinical evaluation of vaccines: regulatory expectations. Revision of WHO TRS 924, Annex 1. 2016. [https://www.who.int/biologicals/expert\\_committee/Clinical\\_changes\\_IK\\_final.pdf](https://www.who.int/biologicals/expert_committee/Clinical_changes_IK_final.pdf).
- [7] International Coalition of Medicines Regulatory Authorities (ICMRA). ICMRA SARS-CoV-2 Vaccines Workshop #2 – Summary. Published online July 2020. <http://www.icmra.info/drupal/news/22june2020/summary>.
- [8] Food and Drug Administration (FDA). Development and Licensure of Vaccines to Prevent COVID-19. Guidance for Industry. Published June 2020. <https://www.fda.gov/media/139638/download>.
- [9] European Medicines Agency (EMA). EMA considerations on COVID-19 vaccine approval. Published 16 November 2020. [https://www.ema.europa.eu/en/documents/other/ema-considerations-covid-19-vaccine-approval\\_en.pdf](https://www.ema.europa.eu/en/documents/other/ema-considerations-covid-19-vaccine-approval_en.pdf).
- [10] WHO. Considerations for the Assessment of COVID-19 Vaccines for Listing by WHO. Published online November 25, 2020. <https://www.who.int/publications/m/item/considerations-for-the-assessment-of-covid-19-vaccines-for-listing-by-who>.
- [11] WHO. Considerations for evaluation of COVID-19 vaccines. Points to consider for manufacturers of COVID19 vaccines. Published online September 24, 2020. [https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/WHO\\_Evaluation\\_Covid\\_Vaccine.pdf](https://www.who.int/medicines/regulation/prequalification/prequal-vaccines/WHO_Evaluation_Covid_Vaccine.pdf).
- [12] Chalmers I. Comparing like with like: some historical milestones in the evolution of methods to create unbiased comparison groups in therapeutic experiments. *Int J Epidemiol*. 2001;30:1156–64.
- [13] Armitage P. The role of randomization in clinical trials. *Stat Med*. 1982;1:345–52.
- [14] Kaptchuk TJ. Intentional ignorance: a history of blind assessment and placebo controls in medicine. *Bull Hist* 1998;72:389–433.
- [15] Di Blasi Z, Kaptchuk TJ, Weinman J, Kleijnen J. Informing participants of allocation to placebo at trial closure: postal survey. *BMJ* 2002;325(7376):1329. <https://doi.org/10.1136/bmj.325.7376.1329>.
- [16] International Conference on Harmonisation. Choice of Control Group and Related Issues in Clinical Trials (ICH-E10). Published online July 2000. [https://database.ich.org/sites/default/files/E10\\_Guideline.pdf](https://database.ich.org/sites/default/files/E10_Guideline.pdf).
- [17] Rid A, Saxena A, Baquic AH, Bhan A, Binese J, Bouesseau MC, et al. Placebo use in vaccine trials: Recommendations of a WHO expert panel. *Vaccine* 2014 Aug 20;32(37):4708–12. <https://doi.org/10.1016/j.vaccine.2014.04.022>.
- [18] WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation. Placebo-controlled trials of COVID-19 vaccines - why we still need them. *N Engl J Med* 2020;384:e2.
- [19] Saville M. COVID-19: release approved vaccines for trials of new ones. *Nature* 2021;597:178. <https://doi.org/10.1038/d41586-021-02398-6>.
- [20] World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects. Ferney-Voltaire: WMA; 2013. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>.
- [21] Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS; 2016. <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>.
- [22] EMA. Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2. 23 February 2021. EMA/117973/2021. [https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-requirements-vaccines-intended-provide-protection-against-variant\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-requirements-vaccines-intended-provide-protection-against-variant_en.pdf).
- [23] FDA. FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine. Published online June 15, 2020. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and>.
- [24] FDA. FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab. Published online April 16, 2021. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-mono-clonal-antibody-bamlanivimab>.
- [25] Herold R, Camarero J, Melchiorri D, Sebris Z, Enzmann H, Pignati F. Revocation of the conditional marketing authorisation of a cancer medicine: The olaratumab experience. *Eur J Cancer*. 2019 Dec;123:25–7. <https://doi.org/10.1016/j.ejca.2019.09.020>. Epub 2019 Oct 23.
- [26] Joint Committee on Vaccination and Immunisation (JCVI), Public Health England. JCVI issues updated advice on COVID-19 vaccination of children aged 12 to 15. Published online September 3, 2021. <https://www.gov.uk/government/news/jcvi-issues-updated-advice-on-covid-19-vaccination-of-children-aged-12-to-15>.
- [27] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Parvinder KA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised control trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99–111. doi: 10.1016/S0140-6736(20)32661-1. Epub 2020 Dec 8. Erratum in: *Lancet*. 2021 Jan 9;397(10269):98.
- [28] Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *N Engl J Med* 2021;384(1885–1898). <https://doi.org/10.1056/NEJMoa2102214>.
- [29] Department of Health, South Africa. Minister Zweli Mkhize on the outcomes of the Coronavirus COVID-19 vaccine efficacy studies. Published online February 10, 2021. <https://www.gov.za/speeches/minister-zweli-mkhize-outcomes-coronavirus-covid-19-vaccine-efficacy-studies-10-feb-2021>.
- [30] Parliamentary Communication Services on behalf of the Chairperson of the Portfolio Committee on Health, Dr Sibongiseni Dhlomo. Committee on Health hears from Minister Mkhize about suspension of distribution of Astrazeneca vaccine. Published online February 11, 2021. <https://www.parliament.gov.za/press-releases/media-statement-committee-health-hears-minister-mkhize-about-suspension-distribution-astrazeneca-vaccine>.
- [31] Mallapaty S. China COVID vaccine reports mixed results – what does that mean for the pandemic? *Nature* 2021.
- [32] Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. *Nature* 2021. <https://doi.org/10.1038/s41586-021-03398-2>.
- [33] WHO. Design of vaccine efficacy trials to be used during public health emergencies – points of considerations and key principles. 2019. <https://www.who.int/docs/default-source/blue-print/working-group-for-vaccine-evaluation-4th-consultation/ap1-guidelines-online-consultation.pdf>.
- [34] Henao-Restrepo AM, Camacho A, Longini IM, Conall CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-generated vaccine in preventing ebola virus disease: final results from the guinea ring vaccination, open-label, cluster-randomized trial (ebola ça suffit!). *Lancet* 2017;389(10068):505–18.
- [35] Follmann D, Fintzi J, Fay MP, Jones HE, Baden LR, El Sahly HM, et al. Deferred-Vaccination Design to Assess Durability of COVID-19 Vaccine Effect After the Placebo Group Is Vaccinated. *Ann Intern Med*. Doi:10.7326/M20-8149.
- [36] Fleming R, Nason TRM, Krause PR, Longini IM, Henao-Restrepo A. COVID-19 vaccine trials: The potential for “hybrid” analyses. *Clin Trials* 2021;18(4):391–7. <https://doi.org/10.1177/17407745211018613>. Epub 2021 May 27.
- [37] Choi A, Koch M, Wu K, Chu L, Ma L, Hill A, et al. Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. *Nat Med* 2021. <https://doi.org/10.1038/s41591-021-01527-y>.
- [38] Afkhami S, D'Agostino MR, Zhang A, Stacey HD, Marzok A, Kanget A, et al. Single-dose respiratory mucosal delivery of next-generation viral-vectored COVID-19 vaccine provides robust protection against both ancestral and variant strains of SARS-CoV-2. *bioRxiv*. 19 July 2021. doi: <https://doi.org/10.1101/2021.07.16.452721>.

- [39] ICMRA. Statement on continuation of vaccine trials. Published online November 2020. [http://www.icmra.info/drupal/covid-19/statement\\_on\\_continuation\\_of\\_vaccine\\_trials](http://www.icmra.info/drupal/covid-19/statement_on_continuation_of_vaccine_trials).
- [40] FDA. Emergency Use Authorization for Vaccines to Prevent COVID-19. Guidance for Industry. Published online May 25, 2021. <https://www.fda.gov/media/142749/download>.
- [41] Krause PR, Gruber MF. Emergency use authorization of Covid vaccines – Safety and efficacy follow-up considerations. *N Engl J Med*. 2020;383.
- [42] WHO Access to COVID-19 Tools Accelerator Ethics and Governance Working Group. Emergency Use Designation of COVID-19 candidate vaccines: Ethical considerations for current and future COVID-19 placebo-control vaccine trials and trial unblinding. Policy brief. Published online December 18 2020. [https://apps.who.int/iris/bitstream/handle/10665/337940/WHO-2019-nCoV-Policy\\_Brief-EUD\\_placebo-control\\_vaccine\\_trials-2020.1-eng.pdf?sequence=1&isAllowed=y](https://apps.who.int/iris/bitstream/handle/10665/337940/WHO-2019-nCoV-Policy_Brief-EUD_placebo-control_vaccine_trials-2020.1-eng.pdf?sequence=1&isAllowed=y).
- [43] Singh JA, Kochhar S, Wolff J. Placebo use and unblinding in COVID-19 vaccine trials: recommendations of a WHO Expert Working Group and the WHO ACT-Accelerator Ethics & Governance Working Group. *Nat Med* 2021. <https://doi.org/10.1038/s41591-021-01299-5>.
- [44] COVID-19 Vaccine Study. Vaccine Transition Option. [https://www.covidvaccinestudy.com/participants?utm\\_source=vto&utm\\_medium=vurl&utm\\_campaign=vto&mpmt=vurl&fbclid=IwAR015FX7x5XcQUjV368xnO42NscqP3qpJx9lbaJiQnaiSKGsURG9bTr7l#vaccine-transition-option](https://www.covidvaccinestudy.com/participants?utm_source=vto&utm_medium=vurl&utm_campaign=vto&mpmt=vurl&fbclid=IwAR015FX7x5XcQUjV368xnO42NscqP3qpJx9lbaJiQnaiSKGsURG9bTr7l#vaccine-transition-option).
- [45] Vekemans J, Crofts J, Baker CJ, Goldblatt D, Heath PT, Madhi SA, et al. The role of immune correlates of protection on the pathway to licensure, policy decision and use of group B Streptococcus vaccines for maternal immunization: considerations from World Health Organization consultations. *Vaccine* 2019;37:3190–8.
- [46] Frenck Jr RW, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. *N Engl J Med* 2021;385:239–50. <https://doi.org/10.1056/NEJMoa2107456>.
- [47] Liu M, Li Q, Lin J, Lin Y, Hoffman E. Innovative trial designs and analyses for vaccine clinical development. *Contemp Clin Trials*. 2021 Jan;100. <https://doi.org/10.1016/j.cct.2020.106225>. Published online 2020 Nov 21.
- [48] Deepak LB, Mehta C. Adaptive designs for clinical trials. *N Engl J Med* 2016;375:65–74. <https://doi.org/10.1056/NEJMra1510061>.
- [49] FDA. Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics. Published online December 2019. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry>.
- [50] ClinicalTrials.gov Identifier: NCT04889209. Delayed Heterologous SARS-CoV-2 Vaccine Dosing (Boost) After Receipt of EUA Vaccines. <https://clinicaltrials.gov/ct2/show/NCT04889209>.
- [51] WHO. Addendum to considerations for evaluation of COVID-19 vaccines for prequalification or emergency use listing considerations for evaluation of modified COVID-19 vaccines. Points to consider for manufacturers of COVID-19 vaccines. Version 12 March 2021. [https://extranet.who.int/pqweb/sites/default/files/documents/Addendum\\_Evaluation\\_Modified\\_Covid-19%20Vaccine.pdf](https://extranet.who.int/pqweb/sites/default/files/documents/Addendum_Evaluation_Modified_Covid-19%20Vaccine.pdf).
- [52] Bhan A, Singh JA, Upshur REG, Singer PA, Daar AS. Grand Challenges in Global Health: Engaging civil society organizations in biomedical research in developing countries. *PLoS Med* 2007;4(9). <https://doi.org/10.1371/journal.pmed.0040272>.
- [53] Berndtson K, Daid T, Tracey SE, Bhan A, Cohen E, Upshur REG, Singh JA, Daar AS, Lavery JV, Singer PA. Grand Challenges in Global Health: ethical, social, and cultural issues based on key informant perspectives. *PLoS Med* 2007;4(9). <https://doi.org/10.1371/journal.pmed.0040268>.
- [54] WHO. WHO community engagement framework for quality, people-centred and resilient health services. 2017. World Health Organization. <https://apps.who.int/iris/handle/10665/259280>.
- [55] WHO. World Health Organization vaccine safety supporting document. Stakeholder Management. [https://www.euro.who.int/\\_\\_data/assets/pdf\\_file/0004/337495/02\\_WHO\\_VaccineSafety\\_SupportDoc\\_StakeholderManagement\\_Proof8-3.pdf](https://www.euro.who.int/__data/assets/pdf_file/0004/337495/02_WHO_VaccineSafety_SupportDoc_StakeholderManagement_Proof8-3.pdf).
- [56] ACCESS Consortium. Points to consider for strain changes in authorized COVID-19 vaccines in an ongoing SARS-CoV-2 Pandemic. Published online March 5, 2021. <https://www.tga.gov.au/points-consider-strain-changes-authorized-covid-19-vaccines-ongoing-sars-cov-2-pandemic>.
- [57] ICMRA. ICMRA COVID-19 Vaccine development: Future steps Workshop. Published online June 24, 2021. .
- [58] Hemkens LG, Goodman SN. Randomized COVID-19 vaccination rollout can offer direct real-world evidence 00160-8. *J Clin Epidemiol*. 2021;S0895–4356 (21). <https://doi.org/10.1016/j.ijclinepi.2021.05.014>.
- [59] FDA. Framework for FDA's Real-World Evidence Program. Published December 2018. <https://www.fda.gov/media/120060/download>.
- [60] Thorlund K, Dron L, Park JJH, Mills EJ. Synthetic and External Controls in Clinical Trials – A Primer for Researchers. 8 May 2020 Volume 2020;12:457–467. <https://doi.org/10.2147/CLEP.S242097>.
- [61] FDA. FDA approves first treatment for a form of Batten disease. Published online April 27, 2017. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-form-batten-disease>.
- [62] FDA. Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry. Published online 2019. <https://www.fda.gov/media/124795/download>.
- [63] EMA. Guideline on clinical trials in small populations. 2006. [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-trials-small-populations\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf).
- [64] MHRA. Alignment with ICMRA consensus on immunobridging for authorising new COVID-19 vaccines. Published online September 15, 2021. <https://www.gov.uk/government/publications/access-consortium-alignment-with-icmra-consensus-on-immunobridging-for-authorising-new-covid-19-vaccines>.