World Health Organization

WHO R&D Blueprint

novel Coronavirus

An international randomised trial of candidat vaccines against COVID-19

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R&DBlueprint
Powering research
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Version 2 - 28 May 2020

Summary

This large, international, randomized controlled clinical trial is designed to enable an expeditious, agile and concurrent evaluation of the benefits and risks of multiple candidate preventive vaccines against COVID-19 at international sites with sufficient COVID-19 attack rates. Different candidate vaccines may be available or suitable to enter the trial at different times; for each candidate vaccine, the primary efficacy results are expected within 3-6 months of the vaccine entering the trial.

The trial will rapidly enroll and individually randomize very large numbers of adult participants in many different populations. Each participant will be contacted weekly for information as to whether any potentially relevant symptoms have arisen, with laboratory testing triggered if the report suggests COVID-19. By using a shared placebo/control group and a common Core protocol to evaluate multiple candidate vaccines in the trial, resources allocated to the evaluation of each candidate vaccine are judiciously saved while a high standard of scientific rigor and efficiency is ensured.

The trial is designed to provide sufficient evidence of safety and vaccine efficacy against COVID-19 to support decision-making about global vaccine deployment, which may include licensure and/or WHO pre-qualification. Final decisions about COVID-19 deployment will be made in each jurisdiction.

Goal of the trial

The goal of the trial is to coordinate prompt, efficient, and reliable evaluation of the many preventive candidate SARS-CoV-2 vaccines under development, to assess their safety and efficacy and to identify those that are likely to be appropriate for deployment to influence the course of the pandemic.

Adaptive design

While the expectation is that the trial will rapidly enroll sufficient numbers of participants to expeditiously evaluate all included vaccines, the design of the 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. High enrollment rates are expected, and various adaptive features will assure that the trial achieves results in a defined and short period of time. These adaptive features are:

1) Choice of vaccines under evaluation - Candidate vaccines may be added to the trial as soon as they become available and meet prioritization criteria (to be defined via Criteria for COVID-19 Vaccine Prioritization).

2) Choice of success criteria and number of COVID-19 events required to trigger efficacy analyses of a vaccine - While the trial will start with criteria required for success that allow rapid identification of vaccines that will be of high value in the current public health setting, success criteria may be revised after initiation of the trial to accommodate unanticipated circumstances, including changes in the time available to conduct the trial, blinded attack rates, and observed participant enrollment rates. Likewise, the number of COVID-19 events required to trigger efficacy analyses of vaccines may be changed, depending on these factors. Accrual and the blinded COVID-19 attack rate will be monitored, with defined guidelines and operational boundaries indicating unacceptably slow progress to assess vaccine efficacy. Reaching an operational boundary alerts the Steering Committee to consider adjusting the trial design and conduct to ensure its ability to meet the study objective in a timely manner.

3) Choice of study population - If deemed necessary to increase the likelihood that the study will identify efficacious vaccines, the blinded Steering Committee may also modify the number of study sites, the sample size at all or selected study sites, or refocusing the accrual to certain sub-populations. Some sites may use a mobile trial structure, allowing flexible redirection to populations with high attack rates.

4) Monitoring of efficacy - Each candidate vaccine will be monitored for early evidence of benefit and for early evidence of lack of benefit using prespecified monitoring guidelines and boundaries that may lead to halting further randomization of participants into a vaccine arm. Early monitoring for benefit is critical for obtaining and reporting data that could support rapid deployment of efficacious vaccines. Monitoring for lack of benefit targets trial resources to the study of vaccines that are more likely to be successful.

5) Choice of control group - The placebo comparator is an integral component of the study design. All participants in study vaccine and placebo groups will receive the current, local standard of prevention of COVID-19. 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 will be introduced.

Features and Advantages

This large international multicenter trial to test vaccines is consistent with the collaborative spirit underlying COVID vaccine development and will foster international deployment with equity of access. As compared with conducting separate trials for each candidate vaccine, the trial design, which evaluates candidate vaccines in parallel with a common placebo group:

1. allows the most rapid and rigorous conclusions to be reached by:
    a. expeditiously enrolling many participants who are at high risk for COVID-19 at sites with high rates of COVID-19, enabling successful vaccines to meet a stringent lower statistical confidence bound on efficacy;
    b. achieving high efficiency (fewer required total participants for evaluation of each vaccine) through use of a shared placebo group;
    c. increasing the consistency of the evaluation process across vaccines by standardizing the populations enrolled, study screening and follow-up procedures, and endpoint determination; and
    d. standardizing success criteria across vaccines, assuring that all vaccines receive a rigorous evaluation of their efficacy that will be sufficient to support broad deployment of an effective vaccine; and
2. has the potential to evaluate a large number of vaccines that have a chance of being effective, increasing the likelihood of finding highly effective vaccines by:
    a. including multiple promising vaccine candidates in the trial; and
    b. promoting efficient allocation of world-wide clinical trial resources, reducing the likelihood that sites with high incidence of COVID-19 will contribute only to the evaluation of an ineffective vaccine; and
3. increases the likelihood that participants receive one of the candidate vaccines (relative to placebo) and provides all trial participants a fair chance at receiving ultimately successful vaccines; and
4. has advantages for developers/funders by:
    a. providing rapid evaluation of the efficacy of their vaccine;
    b. reducing uncertainties in endpoint acquisition rates, increasing the likelihood of enrolling enough trial participants to rapidly assess efficacy of each vaccine;
    c. permitting vaccines to enter the trial when ready;
    d. eliminating the inefficiency of designing and conducting separate trials; and
    e. decreasing overall costs of vaccine evaluation.

Primary Efficacy Endpoint and its Evaluation

The primary objective is to evaluate the effect of each vaccine on the rate of virologically confirmed COVID-19 disease, regardless of severity. The primary endpoint is selected for its clinical relevance and because it makes feasible the accrual of sufficient numbers of primary endpoint events to provide adequate power for the trial. COVID-19 disease rates for each vaccine will be compared with COVID-19 rates for the shared concurrently randomized placebo/control group.

The key pre-specified primary analysis of the primary endpoint will include (for each participant) the first COVID-19 disease episode occurring more than 14 days after the first dose. Developers of multidose vaccines may reach an alternative agreement with regulators regarding the primary analysis, which must be prospectively conveyed to the DMC. Subject to adaptation as the trial proceeds (see above), a successful vaccine will have a sequential-monitoring-adjusted 95% lower bound of the confidence interval on vaccine efficacy that exceeds 30%. The point estimate for vaccine efficacy (VE) should be at least 50%, in agreement with the minimum requirement given in the WHO Target Product Profile. If widespread transmission persists such that a meaningfully higher 'null hypothesis (see below)' could be statistically rejected by accumulating more endpoints in an acceptably short period of time, the study will continue in order to accumulate those endpoints to yield greater certainty about vaccine efficacy. To avoid penalizing vaccine developers for evaluating their individual vaccines in a common core trial, there will not be a formal multiplicity adjustment in the statistical analysis of vaccine efficacy based on the number of vaccine regimens under study. In summary, these success criteria have been set so that a vaccine with estimated efficacy of 50% or higher would have high likelihood of being successful in a trial of feasible size and duration. Early termination for benefit will be based on an O'Brien-Fleming monitoring boundary (see below).

The null hypothesis VE value may be adaptively modified to below 30% during the trial, based on a lower-than-projected COVID-19 attack rate or participant accrual rate, with collaborative decision-making by individuals who only have access to blinded data, e.g. the study Steering Committee and blinded study statisticians. Starting with a 30% null hypothesis VE value rather than a lower value helps assure that vaccine efficacy is estimated with sufficient precision to support decision-making about a vaccine, which may include regulatory approval and acceptance of the vaccine for widespread use.

Lack of Benefit criteria for the primary efficacy endpoint: The Data Monitoring Committee (DMC) may recommend terminating the randomization to particular vaccines due to lack of benefit, relative either to placebo or to other vaccines. Relative to placebo, the group sequential monitoring guideline for lack of benefit will rule out vaccine efficacy $\geqslant$60%, calculated based on cases diagnosed 14 days or more after the first vaccine dose. Considerations will be made to ensure that effective multi-dose vaccines are not penalized by this criterion (see SAP). Meeting

these criteria would result in stopping randomization to that vaccine if that had not already occurred, but would not result in an announcement of trial results for a particular vaccine until 150 events had accrued. A recommendation for termination for lack of benefit would be more readily made by the DMC if there were statistically persuasive evidence that the vaccine has inferior efficacy to several other vaccines, and would less readily made by the DMC for a vaccine that is favorable with regard to other important criteria, such as safety, ease of deployment and manufacturing capacity for a large quantity of doses.

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, based on comparisons vs. placebo. When this occurs, new efficacy/lack of benefit criteria will be introduced by the Steering Committee 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. For vaccines already in the trial, this evaluation might be strengthened by analysis using novel methods (to be developed in consultation with regulators) of data collected previously in the trial, i.e., comparisons with concurrently randomized placebo participants and/or comparisons with recipients of the widely available effective vaccine.

Secondary and Supportive Endpoints and their Evaluation

All sites will monitor the incidence of severe COVID-19 (as per WHO classification) and death with recent confirmed COVID-19. Deaths without any evidence of COVID-19 will also be recorded but will not be part of this composite endpoint. Although the study may lack power for formal statistical inference about vaccine efficacy against severe disease and death due to COVID-19, this secondary endpoint will be calculated and reported for each vaccine.

For vaccines that are shown to be effective, their duration of efficacy also be formally evaluated as a prespecified secondary endpoint, by using a standard alpha respending algorithm. It is likely that the longer-term efficacy assessment would be based on evaluating vaccine efficacy during an interval that starts as long after randomization as is possible and still maintains adequate retention of both vaccine and placebo recipients. More detail is provided in the Statistical Analysis Plan. Efficacy during other time windows may also be evaluated as supportive analyses.

For multiple-dose vaccines, vaccine efficacy against COVID-19 onset more than 14 days after the final scheduled dose will also be analyzed, as this may be greater than vaccine efficacy against the primary endpoint of vaccine efficacy more than 14 days after the first dose. Various subgroup analyses of the primary endpoint will

also be undertaken. As COVID-19 mortality increases steeply with age, it will be particularly important to determine whether vaccine efficacy differs substantially by age. When a vaccine is first found to be efficacious the numbers of cases in particular age groups may be insufficient for accurate assessment of age-specific VE, but larger numbers will accumulate with longer follow-up. Further subgroup analyses of vaccine efficacy will explore the possible relevance to vaccine efficacy of other characteristics recorded at enrolment, and of time since enrolment. The subgroup analyses should, however, be interpreted very cautiously, as even if vaccine efficacy does not truly differ between subgroups the play of chance may well suggest false results in particular subgroups.

Investigators at some sites will optionally seek blood samples at baseline, post last vaccination and at longer times after vaccination, with consent explicitly sought for sample storage and research on the stored material. These can be used for various purposes, including assessment of the effects of vaccination on antibody levels and on the secondary endpoint of rate of infection with SARS-CoV-2. This will require the development of a serological assay that can distinguish responses to infection from those to vaccination. In addition, some sites may seek viral isolates from cases of COVID-19 arising during follow-up. There are many possible uses of blood and virus samples, e.g.:
- To characterize immune responses induced by the vaccine, and to evaluate immunological markers as correlates of risk of COVID-19.
- To determine whether there is any COVID-19 risk in participants seropositive for SARS-CoV-2 at enrolment, and whether this is affected by vaccination.
- To evaluate the effect of the vaccine on SARS-CoV-2 viral shedding and (in additional analyses) patterns of transmission within households or other transmission groups following infection or disease in trial participants
- To genotype SARS-CoV-2 viral isolates from vaccine and placebo-allocated COVID-19 cases.

Figure 1. Supportive endpoints that may not be evaluated at all sites, but for which evaluation is strongly encouraged.

Additional secondary and supportive endpoints, for which monitoring is valuable but optional at each study site include infection with SARS-CoV-2, transmission of SARS-CoV-2, and possible immunological markers as correlates of risk as summarized in Figure 1 and in Appendix 2. Study of these endpoints will require coordinated collection of appropriate biological samples.

Additional information supporting trial endpoints will also be collected, including incidence of suspected but unconfirmed cases of COVID-19 (either because of negative or no tests) and use of antivirals or other treatments that could influence disease progression.

Safety

Evaluation of COVID-19 vaccine safety is one of the primary objectives of this trial. All sites will monitor and report serious adverse events (SAEs) at any time after vaccination, by baseline SARS-CoV-2 serostatus where available.

Safety monitoring will be continuous at all sites. AEs of special interest (AESIs), as required, will be reported by investigators and monitored by the DMC. Safety data collection will be performed electronically, which will permit evaluation for solicited adverse events up to 14 days following each vaccination. Safety endpoints that may not be evaluated at all sites will include other (unsolicited) AEs by body system, MedDRA preferred terms up to 28 days post-vaccination, AESIs and medically-attended events (MAEs). Outcomes of pregnancies will be reported.

Safety monitoring will also consider the possibility that some vaccines may increase the incidence or severity of disease (i.e., enhance disease). The monitoring for lack of benefit permits halting further randomization to vaccines if the incidence of enhanced disease negates demonstration of efficacy. In addition, the DMC will review the severity of COVID-19 cases among vaccine recipients (based on WHO criteria) as compared to those assigned to concurrent placebo/control on a sufficiently frequent basis to ensure that randomization to vaccines that lead to more severe illnesses (i.e., an imbalance unlikely due to chance) is terminated from the study in a timely fashion; participants who have already received this vaccine will continue to be followed and any necessary advice to recipients put in place. More details of analyses for enhanced disease are provided in the Statistical Analysis Plan.

Participating sites

Sites with sufficient transmission rates at the time of joining the trial can participate. Participating sites must be able to determine whether trial participants develop COVID-19, perform safety follow-up, and assure multiple ways to contact participants to maintain follow-up and retention. To enhance broad international participation, sites may not evaluate all vaccines (due to local regulatory constraints, product availability or other limiting factors), and may not evaluate all secondary study objectives (due to resource constraints or other limiting factors) (Figure 1). New study sites may be added as needed to assure a high COVID-19 attack rate. Randomization will preferentially occur at sites with the highest COVID-19 attack rates (which will be monitored in individuals not participating in the trial). Initially, all sites will include a placebo arm in the trial. Some sites will be mobile, moving to additional areas and allowing the trial to rapidly adapt to changing nature of the COVID-19 infection pandemic. More detail is provided in a separate Site Operational Guide.

Participating populations

The trial will recruit adults of any age whose locations or circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19, based on surveillance data and epidemiologic modelling. Recruitment should support generalizability of results, including by important characteristics such as age (including elderly). Participants must meet inclusion/exclusion criteria of at least one vaccine in the trial. Participants will need to provide multiple ways to be contacted to assure follow-up and retention. This may include contact information of another person who can assist in locating them. Individuals who have been previously vaccinated against COVID-19 will not be eligible to participate. The study will enroll continuously.

Reporting of Results

Results for a given vaccine will be reported when the study reaches a monitoring boundary or when there have been 150 endpoints (subject to SC adaptation) reported in the vaccine and placebo arms. After this report, study subjects will continue to be followed for additional endpoints. Efficacy against the secondary endpoint of severe disease will be reported at the time that primary endpoint analyses are reported. Subsequent reports may be made if there is sufficient information to report on a key secondary endpoint (i.e., efficacy starting 14 days after final dose) or an endpoint pre-specified by the sponsor as being relevant to an agreement with regulators. With these exceptions, no other efficacy reports will be made until the secondary endpoint evaluating duration of efficacy has been evaluated. Data supporting reported results will be shared by WHO with manufacturers. With the exception of when use of placebo becomes impossible and one vaccine may become the trial comparator, no formal statistical comparisons will be made between vaccines.

If a vaccine meets an early monitoring boundary for the safety endpoint of enhanced disease, randomization to this vaccine will temporarily cease (and may resume only if additional follow-up of these participants fails to confirm this early potential finding). The result will be reported only if necessary to protect trial subjects or if the finding is confirmed with additional follow-up (see Statistical Analysis Plan).

Samples that could be used to study potential immune correlates, the effect of the vaccine on transmission or shedding, or infection (which could be detected serologically) may be unblinded at the time a finding on the primary endpoint is announced.

Adverse events that are required to be reported to regulators will be reported directly to developers.

Randomization

Eligibility for a vaccine will be based on availability of the vaccine at the time of randomization and any specific inclusion/exclusion criteria associated with that vaccine. Participants will be randomized to one of the vaccines (k in number) for which they are eligible or to one of the placebos that correspond (in appearance, dosing interval, and route of administration) to each of those vaccines. The randomization ratio will ensure that participants have the same chance of receiving a placebo (with probability 1/(k+1) for placebo in aggregate, which is the sum of the probabilities 1/k(k+1) for each individual placebo) as they have of receiving each individual vaccine (with probability 1/(k+1)) for which they are eligible. Efforts will be made to harmonize inclusion/exclusion criteria among vaccines in order to simplify the randomization and increase trial efficiency.

Outcomes in recipients of each vaccine candidate will be compared with outcomes in all placebo recipients who were eligible to be randomized to that vaccine. This approach preserves blinding and enables comparison of each vaccine's results directly to results from an equal number of controls who received placebo at the same time and place.

	Time Window #1	Time window #2	Time window #3
Vaccine arms	A	AA BB	AAA BBB CCC
Placebo arms	P_A	P_A P_B	P_A P_B P_C
Individual vaccine : matched-placebo	1:1	2:1 2:1	3:1 3:1 3:1
Individual vaccine : shared-placebo	1:1	1:1	1:1

Figure 2: Randomization scheme. Candidate vaccine A and its matched placebo P_A enter the trial in time window #1. In this example, Vaccine A utilizes the combined placebo arms (P_A, P_B and P_C) from all three time windows. Vaccine B and its matched placebo PB enter in time window #2. In this example, Vaccine B utilizes the combined placebo arms from time windows #2 (P_A and P_B) and #3 (P_A, P_B and P_C). Vaccine C and its matched placebo P_C enter in time window #3. In this example, Vaccine C utilizes only the placebo arms (P_A, P_B and P_C) from time window 3.

This randomization scheme is illustrated in Figure 2, where candidate vaccines A, B and C, and their matched placebos, P_A, P_B and P_C, enter the trial at 3 different times. This design is efficient in allowing the assessment of each vaccine to use a shared placebo arm with concurrent follow-up. Participants may be able to determine, based on specific characteristics, which vaccine they might be receiving, yet will always be blinded to whether they are receiving the active vaccine candidate or the corresponding placebo.

Blinding

Sufficient measures will be taken to assure that study blinding of participants and evaluation staff is maintained; previous experience in trials of similar design demonstrates that blinding is possible. The study will be observer-blinded. As shown in Figure 2, blinding will be enhanced by concurrent enrollment of participants who are randomized to receive the placebo corresponding to each vaccine.

Study product assignments will be accessible to the data coordinating center staff and others who are required to know this information to ensure proper trial conduct. The Data Monitoring Committee members will also be unblinded to treatment assignment as required to conduct review of vaccine safety and efficacy.

Emergency unblinding decisions are expected to be rare and could be justified only when that information is needed for the future clinical management of that participant. The need to identify placebo recipients could only occur when general vaccination using a vaccine that is found to be effective is deployed in the general population containing the sites of those placebo recipients.

In the event that one or more vaccines satisfies benefit or lack of benefit criteria at an interim analysis, further randomization of participants to those arms may cease but blinded follow-up of participants will continue on all vaccine arms and the shared placebo/control arm to ensure valid assessment of efficacy for all vaccines under study, and to enhance data for evaluating the durability of vaccine efficacy. This is possible even when the result of benefit or lack of benefit for the vaccine(s) satisfying these criteria are publicly reported, at least until any established efficacious vaccine becomes a standard of prevention in the country of a particular trial site. The only exception is if a particular vaccine is found, either from the results of the present study or from other evidence, to have had some unexpected adverse effect such that those who had already been given that vaccine would need to be traced and notified about the problem in order to seek appropriate treatment.

Follow-up

Follow-up for assessing vaccine efficacy will include weekly automated active follow-up of participants, where reporting of COVID-19 relevant symptoms (as per

WHO case definitions) will trigger testing for SARS-CoV-2 infection. These weekly contacts will help reduce loss of trial participants and increase the likelihood of detecting COVID-19. After COVID-19 diagnosis, participants will be referred locally for management, as required. Data to determine whether these participants meet criteria for severe COVID-19 or if they receive antivirals that could modify the likelihood of severe COVID-19 will be collected. Blinded study follow-up, for COVID-19 disease and for SAEs, is planned to last for at least one year (and preferably longer). This will enable further analysis of duration of efficacy and potential for risk of vaccine-induced COVID-19 disease enhancement in the presence of waning immunity. In the event that there is evidence of waning efficacy of a successful vaccine over the period of observation, participants in this trial may be randomized to prospectively designed controlled study of a booster dose.

Study sample size

The trial is endpoint driven, as the main analysis for each vaccine arm versus the concurrent shared placebo/control arm is triggered by occurrence of a total of 150 cases of COVID-19 across these two arms, at which point the results will be reported but blinded follow-up will continue. This fixed number of 150 endpoints is set to provide sufficient power to detect a predefined target level of VE, rejecting the initially specified null hypothesis that VE is < 30%.

For example, with a target level VE of 60%, with 150 total endpoints in a pairwise comparison, there is approximately 90% power to reject VE less than or equal to 30% if true VE is 60%, based on a log-rank test with 1-sided type I error rate of 0.025; with 150 total events across each vaccine arm and the concurrent shared placebo/control arm, the lower 95% confidence bound for vaccine efficacy (VE) would exclude 30% if the estimated VE is at least 50%. These statistical properties are only slightly modified by the monitoring of interim results.

In simpler terms, if the true vaccine efficacy is 60%, then analyzing a total of 150 cases would provide a 90% chance that the actual results are at least as promising as 50 vs 100 cases. Such a result would indicate 50% vaccine efficacy (with a 95% confidence interval of 30% to 65% for vaccine efficacy).

Criteria for demonstrating benefit (reliably establishing VE > 30%) and lack of benefit (which would suspend randomization, but not follow-up) will be based on an OBrien-Fleming monitoring boundary for two interim analyses. Using O'Brien-Fleming criteria evaluated after 50 or 100 events, benefit is established when estimated VE is $\geqslant$74% or $\geqslant$58%, respectively, while lack of benefit (for a single dose vaccine) is established after 50 and 100 events when estimated VE is $\leqslant$-14% and $\leqslant$32%, respectively. In both cases, follow-up would continue even after the initial results are released.

To minimize the time to answers about vaccine efficacy, the study size will be large, such that under conservative assumptions about the COVID-19 attack rate and

study accrual, the required number of primary endpoints for a given vaccine:shared-placebo comparison will occur within 3-6 months of starting the vaccine. All efforts will be made to minimize the possibility of missing data. The existence of missing data and reasons for any missing data, will be reported by randomization group.

For example, for the 150-endpoint design noted above, where a 50:100 vaccine:placebo endpoint split just meets success criteria, if the 6-month COVID-19 attack rate in the placebo arm is 1-2%, and participants are enrolled evenly over 3 months, then a total evaluable sample size of about 20,000 per vaccine arm, with an equal number in the shared-placebo arm is expected to yield the needed endpoints within 2 to 4 months after the median enrollment date. The large number of sites at diverse geographical locales will smooth out uncertainty in projected COVID-19 attack rates in specific locales during specific calendar time periods.

Study governance

The trial will be sponsored by WHO. WHO will organize the trial and be responsible for management of the trial data in a centralized database to which all trial sites will contribute data. WHO will be responsible for randomization and for distribution of vaccine to each site. WHO will provide trial data to each manufacturer to support regulatory filings when endpoints for each vaccine are reached.

Developers will agree to transparency in reporting trial results and will provide sufficient data to support inclusion of their vaccine in the trial and the required number of doses of their vaccine and corresponding placebo to WHO. Developers will be responsible for interacting with regulators responsible for approving the use of vaccine at trial sites. Developers may withdraw their vaccine from further randomization, but not from follow-up. Developers will not be expected to make a financial contribution to the trial. Liability considerations will be addressed in the developers' agreement with WHO. A single developer may contribute more than one vaccine to the trial, if all vaccines meet WHO prioritization criteria.

Trial oversight will be provided by a single Steering Committee (SC) and a single data monitoring committee (DMC). Adaptive aspects of the study, to the extent not predefined in the protocol, will be governed by the SC, which will not have access to unblinded study data. The role of the DMC will be to apply pre- (and SC-) defined benefit and lack of benefit criteria to the vaccines, and to address potential safety issues as well as data integrity issues.

The SC will collaborate with the study Sponsor(s) in issues regarding trial design, conduct and analysis. The SC will ensure that the conduct of the trial in each site is harmonized with respect to important aspects such as data collection, laboratory tests, and implementation of vaccination. Representatives of developers may be SC members.

The DMC will have regular access to efficacy and safety data, and information regarding the quality of study conduct. The DMC will frequently review emerging evidence provided by the independent statistical center, where the interpretation of safety will be performed in the context of the emerging efficacy data. The DMC will also have planned meetings for prespecified interim analyses of efficacy (as given above). In addition, the DMC will hold ad hoc teleconference meetings to discuss safety or trial conduct information as needed, with input provided by the SC during open sessions of DMC meetings. The DMC will be responsible for providing information required to be reported to regulators (normally restricted to serious, unexpected, suspected adverse reactions) to developers so that these data may be shared by developers with regulators and used to update the product-specific Investigators Brochure.

The trial will be designed with pre-specified formal statistical monitoring boundaries to guide the DMC in their recommendations regarding continuation or termination of randomization to vaccine arms or of the entire trial, either due to persuasive evidence of benefit or lack of benefit, or unacceptable safety issues. In assessing the acceptability of the safety profile of each vaccine regimen, the DMC will consider the totality of information regarding benefits and risks.

To enhance trial integrity, the DMC may also formulate recommendations in concert with the SC. These recommendations may relate, for example, to participant recruitment rates and eligibility, improving adherence to protocol-specified regimens, participant retention, and the timeliness of data capture and adjudication of trial endpoints.

Based on its insights from emerging evidence, the DMC will provide recommendations to the SC, including recommendations regarding continuation or discontinuation of randomization to arms in the trial. The DMC will be advisory to the SC, who will be responsible for promptly reviewing the DMC recommendations, discussing them with the DMC if necessary, discussing them with the study sponsor(s), and making decisions about their implementation.

Appendix 1. List of supporting documents

Criteria for COVID-19 vaccine prioritization
Target Product Profiles
Statistical Analysis Plan
Data Monitoring Committee Charter
Steering Committee Charter
Case definition, including severe COVID-19
Site operational guide
Case report form
Sample informed consent form
Developers' agreement with WHO

Appendix 2. Collection and disposition of samples for supportive studies

Blood or viral samples will be collected from some study participants or their contacts to enable additional analyses. Because the primary goal of the study is to evaluate vaccine efficacy and there is a desire to allow the participation of sites with high infection rates but lower sample storage capabilities, these samples will not be required to be collected at all sites. However, it is recognized that these supportive endpoints are important, and to the extent possible, collection of samples to permit their evaluation is encouraged. Samples will be collected and stored at each individual site. This appendix provides guidance on harmonized timing of sample collection, to allow samples from different sites to be studied as a group. Sites collecting samples agree to share relevant samples (including from placebo recipients) with each developer for testing using the developer's validated assays but may retain portions of each sample for their own studies. Consent should be explicitly sought for sample storage and research on the stored material. Samples supporting the primary endpoint of virologically demonstrated COVID-19 disease may be retained for subsequent testing, but this is not required.

A. *COVID-19 infection endpoint*. If a serological assay is available (likely based on responses to a non-spike protein) that can distinguish viral infection from vaccine immune responses, this can be used to evaluate as a secondary endpoint vaccine efficacy against infection. Samples pre-vaccination and from 14 days after the final vaccine dose could be used to demonstrate that vaccination does not cause seroconversion in this assay, and one or more additional post-vaccination samples at intervals, ideally at multiples of 3 months apart (i.e, 3, 6, 9, 12 months after vaccination) for standardization purposes).
B. *Humoral immune response markers*. These samples may support analyses to determine correlates of risk of COVID-19. Recognizing that different vaccines

may yield peak responses at different times, standardized time points will be needed in this multi-vaccine blinded study. Samples used to evaluate vaccine humoral immune responses should be obtained pre-vaccination and ideally at approximately 14 days after each vaccine dose (and particularly 14 days after the final vaccine dose). Samples drawn at longer intervals (every 3 months) after vaccination may also have utility by allowing estimation of antibody titers closer to the time a participant becomes infected.

C. *Cellular immune response markers*. These samples, which may be obtained at sites capable of PBMC processing, may also support analyses to determine correlates of risk of COVID-19. Samples used to evaluate cellular immune responses should be obtained pre-vaccination and ideally at 7 and 14 days after vaccine doses.
D. *Assessing vaccine safety and obtaining preliminary data on vaccine efficacy in participants seropositive for COVID-19 at baseline*. Samples used to evaluate these endpoints should be obtained prior to vaccination.
E. *Evaluating the effect of vaccines on virus shedding, for participants acquiring COVID-19*. To evaluate virus shedding, the time of initial symptoms should be sought from participants with COVID-19. Samples for viral nucleic acid testing should be acquired every other day after diagnosis until 21 days after initial symptoms. These samples would ideally be retained and analyzed in a central laboratory that is capable not only of detecting virus, but also quantifying it.
F. *Evaluating the effect of vaccines on patterns of transmission within household or other groups, for participants acquiring COVID-19*. Upon diagnosis with COVID-19, household members who test negative for COVID-19 may be enrolled in a substudy in which they are virologically tested twice a week for three additional weeks.
G. *Genotyping SARS-CoV-2 viral isolates from vaccine and placebo-allocated COVID-19 cases*. Upon diagnosis with COVID-19, virological samples will be retained for sequencing. This will help evaluate whether viruses giving rise to cases in the study evolve over time and will be particularly important if strong durability of protection is not established.