World Health Organization

WHO R&D Blueprint

novel Coronavirus

An international randomised trial of candidat vaccines against COVID-19

WHO reference number

19 April 2020, Geneva

R&DBlueprint

Powering research
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version 19 April 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 powered to provide sufficient evidence of safety and vaccine efficacy against COVID-19 to support decision-making about global vaccine deployment.

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 features of the trial

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 the WHO vaccine prioritization group).

2) Choice of success criteria and number of COVID-19 events required to trigger efficacy analyses of a vaccine - Accrual and the blinded COVID-19 attack rate will be monitored, with defined guidelines and operational boundaries indicating unacceptably slow progress to answer the primary study objective. 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. While the trial will start with criteria required for success that allow rapid identification of vaccines that will be of 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.

3) Other study features - If deemed necessary to increase the likelihood that the study will identify efficacious vaccines, other study features may also be modified by the blinded Steering Committee, such as the number of study sites or the sample size at all or selected study sites or refocusing the accrual to certain sub-populations.

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 and/or the placebo arm. Early monitoring for benefit is critical for obtaining data that could support rapid deployment of efficacious vaccines: once a vaccine arm meets definite success criteria then the result pertaining to the specific candidate vaccine is reported. Monitoring for lack of benefit targets trial resources to the study of vaccines that are more likely to be successful: further randomization will be halted for vaccine arms that meet lack-of-benefit criteria at an interim analysis. The lack-of-benefit criteria comprise demonstrated low efficacy relative to placebo/control and very low chance to reach success criteria if randomization into the vaccine arm were continued, and may include inferior efficacy compared to other vaccines in the trial (as described below). Even if recruitment into an arm stops, follow-up of those already randomized continues until an efficacious vaccine is deployed in the country in which the site is located.

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.

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 COVID-19 disease cases occurring starting more than 14 days after the first dose. 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 trial 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 manufacturing and 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 final vaccine dose. Meeting these criteria would result in stopping randomization to that intervention 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.

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 COVID-19. Deaths without any evidence of COVID-19 will also be recorded but will not be part of this composite endpoint, as in some populations they would outnumber the number of cases with severe COVID-19. Although the study may lack power for formal statistical inference about vaccine efficacy against severe COVID-19, this secondary endpoint will be calculated and reported for each vaccine.

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 well 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 statistical stability, 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 will, however, be interpreted very cautiously, as even if vaccine efficacy does not really differ between subgroups the play of chance may well suggest false negative results in particular subgroups.

Additional secondary and supportive endpoints, for which monitoring is valuable but optional at each study site, are summarized in Figure 1.

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. If feasible, these results will be the subject of formal statistical analyses. In addition, some sites may seek viral isolates from cases of COVID-19 arising during follow-up. There are many possible uses of such 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 patterns of transmission within households or other transmission groups, for participants acquiring COVID-19.
- 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.

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.

While safety monitoring will be continuous at all sites, some sites will perform more detailed safety assessments in each treatment arm (i.e., as would typically be done in a phase II study). The DMC will review a detailed early safety assessment of each vaccine after a fixed number of participants have been vaccinated at these study sites to provide sufficient early safety data to justify continuation in the trial. The DMC will also monitor any specific AEs of special interest (AESIs), as required. Safety endpoints that may not be evaluated at all sites will include solicited and unsolicited adverse events (AEs) up to 7 days following each vaccination, other AEs by body system, MDRA

preferred terms up to 28 days post-vaccination, AESIs and medically-attended events (MAEs).

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 interferes with demonstration of efficacy. In addition, the independent 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 is terminated from the study in a timely fashion.

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). Initially, all sites are expected to include a placebo arm in the trial.

Participating populations

The trial will recruit adults 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. 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.

The study will enroll continuously. After supportive safety data are available for a given vaccine, enrollment in some sites may be extended to include participants who may be excluded from enrollment at the initiation of the trial because of a desire for additional safety data prior to inclusion in the study.

Randomization

Participants will be centrally randomized so as to ensure that they have the same chance of receiving a placebo as they have of receiving each individual vaccine, regardless of the number of vaccines being evaluated in the trial. Randomization to the placebo corresponding to each vaccine will occur in a ratio such that at any given time, each site will randomize participants to placebo (in aggregate) in numbers equal to those randomized to each individual vaccine. This will enable direct comparison of each vaccine's results directly to results from an equal number of controls who received placebo at the same time and place. To ensure this, within each time window defined by start of randomization to a new vaccine and that of the next vaccine included in the trial a K:1 allocation of vaccine to matched-placebo is used to ensure a 1:1 allocation of vaccine to shared-placebo within the time window and hence throughout the trial, where K is the number of vaccines being evaluated during the time window. This randomization scheme is illustrated in Figure 2, where candidate vaccines A, B and C, and their matched placebos, PA, PB and PC, 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.

	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 PA enter the trial in time window #1. In this example, Vaccine A utilizes the combined placebo arms (PA, PB and PC) 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 (PA and PB) and #3 (PA, PB and PC). Vaccine C and its matched placebo PC enter in time window #3. In this example, Vaccine C utilizes only the placebo arms (PA, PB and PC) from time window 3.

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. 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.

Even when definite results emerge, the treatment codes in particular sites will, except in emergencies, not be broken until a vaccination program begins to be deployed in the general population containing that site. 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.

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 throat/nasal swabs to enable 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 for treatment, as required, according to the local standard of care. Blinded study follow-up, for COVID-19 disease and for SAEs, is planned to last for at least one year.

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 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; in turn, 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 implies a 90% chance of the actual results being 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 will be based on an O'Brien-Fleming monitoring boundary. Using O'Brien-Fleming criteria evaluated after 50 or 100 events, benefit is established when estimated VE is $\geqslant$76% or $\geqslant$ 59%, respectively, while lack of benefit 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. For example, for the 150-endpoint design noted above, where a 50:100 vaccine:placebo endpoint split just meets success criteria, if the 3-month COVID-19 attack rate in the placebo arm is 1.0%, and participants are enrolled evenly over 3 months, then a total 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 in the central database within 3 months after the median enrollment date. The trial includes a large number of sites at diverse geographical locales to smooth out uncertainty in projected COVID-19 attack rates in specific locales during specific calendar time periods. This is an important advantage of the design, increasing the ability of the trial to deliver timely answers about vaccine efficacy.

Study governance

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. Once one or more vaccines meet specified success criteria, new efficacy/lack of benefit criteria will be introduced.

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.

A SC will be in place to 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. There will be a centralized database to which all trial sites will contribute data.

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.