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
to prevent epidemics

Table of Contents

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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