

WHO R&D Blueprint

novel Coronavirus

COVID-19 Phase IIb/III Vaccine Trial Synopsis

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R&D Blueprint

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to prevent epidemics



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A randomized multi-center, blinded, control vaccine trial to evaluate the efficacy and safety of investigational vaccines for novel coronavirus disease (COVID-19) and infection.

The trial will be carried out under a Master Protocol to continue across outbreak sites until the scientific questions of interest are addressed.

1. Objectives

Primary objective of the trial

- To evaluate the effect on the primary endpoint (to be specified), for one or more investigational vaccines, through pairwise comparisons of each vaccine with a control arm, and under a sequential design.

Secondary objectives of the trial

- To evaluate the safety of each experimental vaccine; this includes the safety assessment of possible antibody dependent enhancement (ADE).
- To evaluate effects of each of the vaccines on secondary endpoints, including mortality.
- To find an immune correlate of risk and, possibly an immune surrogate of protection (efficacy).

2. Endpoints

Primary endpoint

Lab-confirmed acute clinical illness



Secondary endpoints

- Lab-confirmed severe illness
- Lab-confirmed possible ADE
- Lab-confirmed death
- Immune correlates of risk and surrogates of protection (efficacy)

3. Study arms

The trial will include a single placebo/control arm, as well as selected vaccine arms, within each randomized cluster or population.

4. Study Population and Sites

The trial is intended to include as many sites as possible affected by the epidemic.

Study subjects will include adults and children, as appropriate.

Decisions on inclusion of pregnant and lactating women, immunodeficient people, children, infants and neonates should be informed by a risk and benefit analysis of each considered investigational vaccine.

Informed consent by patient or next of kin or legally authorized representatives should be sought, respecting good research practice, age of consent and assent specific to each country.

5. Study and Participant duration

The trial will continue under a master protocol until the evidence reliably answers the questions the trial was designed to address. Individual vaccines will continue to be investigated until there is reliable evidence that they have a favorable efficacy or until futility is established; according to a priori established



clinical and statistical criteria. The period of followup of trial participants is to be determined.

6. Randomization

Individual randomization will be in a 1:1: :1 ratio to placebo/control, vaccine A, vaccine B, etc. The unit of randomization will likely be in a ring structure of individuals at risk of infection or some other definition of a transmission network. Thus, we will have individual level randomization with transmission clusters. However, if transmission is widespread, then it could be individual randomization within communities.

7. Blinding

If a placebo arm is used, the trial will be carried out double-blinded. Otherwise, masking and blinding will be carried out where possible.

8. Statistical Considerations

Primary analyses methods for Primary and Secondary Endpoints

This section will specify the primary and secondary endpoints as well as the pre-specified methods for the analyses of these endpoints. This section will include insights about stratification of analyses. Vaccine efficacy will be measured as one minus the risk ratio comparing vaccinated to unvaccinated individuals.

Primary Analysis Population

This section will specify that how the primary efficacy analyses will be conducted. All randomized patients should be included in the primary analysis.

Statistical Power and Sample Size Calculations

This section will specify the null and alternative hypotheses to be assessed, and the sample size needed to achieve pre-specified false positive and false negative error rates.



Statistical Monitoring Boundaries

This section will provide the pre-specified monitoring boundaries that will guide recommendations of the Data Monitoring Committee regarding continuation or termination recommendations. Adaptive features of the trial design also will be pre-specified.

Secondary Pre-specified Subgroup analyses

This section will specify the baseline covariates used to define descriptive subgroup analyses to enlighten the generalizability of study results.

Methods to enhance quality of retention

This section will provide pre-specified methods to enhance the capture of outcome data, clearly distinguishing multiple reasons for termination of randomized.

9. Data Monitoring Committee, Steering Committee and Interim Analyses

The Steering Committee (SC) and the Data Monitoring Committee (DMC) will be responsible for safeguarding the interests of clinical trial participants and for enhancing the integrity of the trial. To address this mission, the DMC will have regular access to efficacy and safety data, and information regarding the quality of study conduct. The DMC will review emerging evidence provided by the independent statistical center on a periodic basis (e.g. every two to three months, or as appropriate for outbreak circumstances and enrolment) and at appropriate times, where the interpretation of safety will be performed in the context of this emerging efficacy data. The DMC will also have planned formal interim analysis meetings. 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 Steering Committee (SC) will be in place to collaborate with the study Sponsor(s) in issues regarding trial design, conduct and analysis. The SC will ensure the conduct of the trial in each site is harmonized with respect to the important variables such as data collected, laboratory tests and implementation of



vaccination. There will ideally be a centralized database for all the trial sites to 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 vaccine arms or of the entire trial, either due to persuasive evidence of efficacy or futility, or unacceptable safety issues.

In assessing the acceptability of the safety profile of each regimen, the DMC will consider the totality of information regarding benefits and risks. To contribute to enhancing the integrity of the trial, the DMC may also formulate recommendations relating to the rates of recruitment and eligibility of participants, improving adherence to protocol-specified regimens, retention of participants, 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 a recommendation regarding trial continuation, discontinuation or modification. 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, the study sponsor, and making decisions about their implementation.

A separate DMC Charter further describes the role of the DMC and the SC. The Statistical Analysis Plan will provide the complete specification of the statistical methods for the interim analyses.