

Solidarity Trial Vaccines

**An international randomised trial of
candidate vaccines against COVID-19**

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Version 4.1

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R&DBlueprint

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Solidarity Trial Vaccines

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Protocol signature page

Reviewed and approved by the following representatives of the Co-Sponsors :

Signature.....

Representative of the National Ministry of Health

Print name and position _____

Date_____

Signature.....

Representative of the World Health Organization

Print name and position _____

Date_____

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DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled “Solidarity Trial Vaccines an international randomised trial of candidate vaccines against COVID-19 “ and the most recent version of the Investigator’s Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current Protocol, the International Council for Harmonisation (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance, and all applicable government regulations.

I will not make changes to the protocol before consulting with WHO or implement protocol changes without national and regulatory approval except to eliminate an immediate risk to participants.

I agree to administer study vaccine only to participants under my personal supervision or the supervision of a sub-investigator. I will not supply study vaccine to any person not authorized to receive it.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient study staffs and members of the national and regulatory institutions. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent from WHO. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from WHO.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements, and ICH E6(R2) GCP guidelines.

Signature of Principal Investigator (s)

Date

Printed Name of Principal Investigator (s)

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Summary

Background: 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. 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.

Simplicity of procedures: Within each country, the investigator invites selected sites and helps them get ethical and regulatory approval and study vaccines, then volunteers' recruitment can begin. To facilitate collaboration volunteer's enrolment and randomisation (via a cloud-based GCP-compliant platform) and all other trial procedures are greatly simplified, and no paperwork is required. Once consent has been obtained, electronic entry of anonymised details of a few key characteristics of each volunteer takes only a few minutes. At the end of patient entry, a random vaccine allocation is generated.

Eligibility: Adults (age ≥ 16 years), capable of giving personal signed informed consent, healthy participants who are determined by clinical judgment of the investigator to be eligible for inclusion in the study. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests (if randomised and consent given, lifestyle considerations, and other study procedures.

Consent: The study website <https://data.castoredc.com/studies> has printable volunteer information in some UN official languages. Once the information has been explained to volunteers, obtaining consent takes only a few minutes. An electronic image of the signature page is kept (or, if national regulations forbid this, a note to file), and the printed information and original consent stays with the volunteer or legal representative.

Trial entry; randomization: Once electronic data collection has been completed the volunteer automatically enters the trial and a random allocation of their trial vaccine is generated (by an algorithm that ensures eventual balance in the characteristics just recorded between each study vaccines and its placebos) and displayed. The volunteers will be randomly allocated either to placebo or to one of the study vaccines.

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.

Follow-up: Each participant will be contacted weekly for 52 weeks for information as to whether any potentially relevant symptoms have arisen, with laboratory testing triggered if the report suggests COVID-19.

Primary objective: The primary objective is to evaluate the effect of each vaccine on the rate of virologically confirmed COVID-19 disease, regardless of severity.

Secondary and exploratory objectives. Although the study may lack power for formal statistical inference about vaccine efficacy against severe disease and death due to COVID-19,

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this secondary endpoint will be calculated and reported for each vaccine. For vaccines that are shown to be effective, their duration of efficacy also will be formally evaluated as a pre-specified secondary endpoint. Additional exploratory endpoints will include VE between the first and second dose, for two-dose vaccine. In addition, VE against specific SARS-CoV-2 variants of concern (as defined by WHO) will be evaluated as a high priority supportive endpoint. This will also include a VE analysis in terms of variant-specific mutations and/or deletions. Every effort will be made to collect samples for sequencing from cases that occur in the trial. These will be used for various purposes, including assessment of the effects of vaccination on the immune response and on the secondary endpoint of rate of infection with SARS-CoV-2.

For candidate vaccines for which both the independent Vaccine prioritization committee and Trial Steering Committee makes the recommendation on the need for additional safety information before a large number of volunteers is recruited, the following procedures apply. Before proceeding to the recruitment of a larger number of volunteers, the DMC will review the safety data seven days and thirty days post administration of the last dose.

Numbers entered: The trial will rapidly enrol and individually randomize large numbers of adult participants. 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 $< 30\%$.

Adaptive design: A global Data Monitoring Committee will keep the accumulating safety results and major outcome results under regular review. 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. 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.

Add-on studies: Particular countries, or particular groups of sites, may want to collaborate in making further measurements or observations. These could be thought of as Phase 2b trials that are being conducted concurrently with the Phase 3 trial. However, while well-organised additional research studies of 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 could well be valuable, they are not core requirements in every site.

Data security: Patient information will be encrypted and held securely by the WHO. Those analysing it will use only anonymised data, and no identifiable patient details will appear in publications.

Publication: This international collaboration is co-ordinated through the World Health Organisation. Major findings will be disseminated by the WHO and published in the names of the collaborators.

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Goal and Objectives 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.

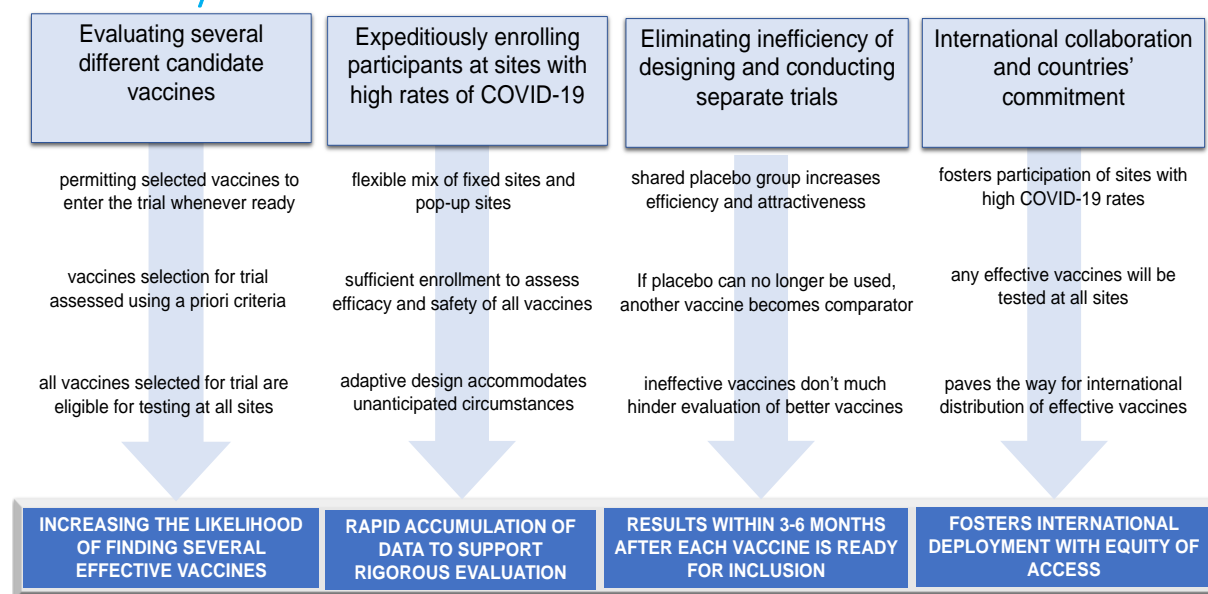
The objectives are to assess their safety and efficacy and to identify those that are likely to be appropriate for deployment to influence the course of the pandemic.

Need for the trial

Although some vaccines are now available in parts of the world, it is clear that supply of existing vaccines that have been rigorously evaluated will be inadequate to meet international needs. The detection of variants that may elude some aspects of vaccine-induced immunity makes clinical testing of new vaccines all the more important, to assure that vaccines that are deployed around the world are truly safe and effective¹.

WHY an international RCT of several candidate vaccines ?

Solidarity trial for vaccines



Adaptive design

While the expectation is that the trial will rapidly enrol 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 enrolment 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). These prioritization criteria are intended to allow vaccines that could

¹ Krause PR et al 2021. Placebo-Controlled Trials of Covid-19 Vaccines - Why We Still Need Them. N Engl J Med 2021 Jan 14;384(2):e2.doi: 10.1056/NEJMp2033538. Epub 2020 Dec 2

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make a large difference (i.e., significant capacity for production and deployment) to enter the trial based on interim phase 2 results or results of a large phase 1 trial, that provide support for safety and immunogenicity, including a Th1-biased immune response (to reduce likelihood of enhanced disease). The link below provides access to the proposed attributes and criteria provide considerations for the evaluation and prioritization of COVID-19 candidate vaccines to be considered for further development by WHO².

- 2) Choice of study population and location of the trial- 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. For enrolment and patient information see SOP – 01: Epidemiological Data Requested for Site selection.
- 3) Monitoring of efficacy – The Data Monitoring Committee (DMC) - will monitor the data for each vaccine 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. (Appendix 1 – DMC Draft Terms of Reference). 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. Choice of control group - The placebo comparator is an integral component of the study design and is particularly important given new uncertainties regarding potential evasion of vaccine-induced immunity by newly discovered variants. 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, simple, international, randomized controlled clinical 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. It allows the most rapid and rigorous conclusions to be reached by:
expeditiously enrolling many participants who are at high risk for COVID-19 at several sites with high rates of COVID-19, enabling successful vaccines to meet a stringent lower statistical confidence bound on efficacy;
 - a. achieving high efficiency (fewer required total participants for evaluation of each vaccine) through use of a shared placebo group;
 - b. increasing the consistency of the evaluation process across vaccines by standardizing the populations enrolled, study screening and follow-up procedures, and endpoint determination; and
 - c. 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. It 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

² <https://www.who.int/publications/m/item/criteria-for-covid-19-vaccine-prioritization>

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- 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. It 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. It 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. Laboratory confirmed COVID-19 disease rates for each vaccine will be compared with COVID-19 rates for the shared concurrently randomized placebo/control group. See SOPs:

- For endpoints definition and classification see SOP- 2: Primary endpoint definitions and role and terms of reference of the adjudication committee
- For COVID 19 laboratory confirmed case (primary endpoint) ascertainment see SOP – 4: Primary endpoint SARS-CoV2 RNA Isolation and RRT-PCR amplification
- For Naso-Oropharyngeal Specimen collection see SOP – 5: Primary endpoint Oro-Nasopharyngeal Specimen Collection
- For Primary endpoint specimen transportation see SOP – 6: Primary endpoint specimen transportation
- For Primary endpoint swab specimen aliquoting see SOP-7: Primary endpoint swab specimen aliquoting
- For primary endpoint samples storage see SOP – 8: Primary endpoint storage recording of oro-nasopharyngeal potential SARS-CoV-2 and specimen aliquots
- For Primary endpoint data collection see SOP – 9: Primary endpoint data entry and management of COVID-19 cases.

The key pre-specified primary analysis of the primary endpoint will include (for each participant) the first COVID-19 disease episode occurring at least 14 days after the last 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 Profile³, and described in the Statistical Analysis Plan (Appendix 2). 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

³ <https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines>

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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 section below).

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 $\geq 60\%$, calculated based on cases diagnosed 14 days or more after the last vaccine dose. 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 be made by the DMC for a vaccine that is favourable with regard to other important criteria, such as safety, ease of deployment and manufacturing capacity for a large quantity of doses.

Hybrid design

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. placebo⁴. 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 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^{5,6}.

Secondary and Supportive Endpoints and their Evaluation

All sites will monitor the incidence of severe COVID-19 (as per WHO definitions⁷ and as defined in SOP-2: Primary endpoint definition and roles and terms of reference of the adjudication committee) and death with recent confirmed COVID-19. Other deaths 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 will be formally evaluated as a prespecified secondary endpoint, by using a standard alpha spending 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 Appendix 2- Statistical Analysis Plan. Efficacy during other time windows may also be evaluated as supportive analyses.

⁴ Singh JA et al 2021. Placebo use and unblinding in COVID-19 vaccine trials: recommendations of a WHO Expert Working Group. *Nature* 16 March 2021. <https://www.nature.com/articles/s41591-021-01299-5>

⁵ Fleming TR et al 2021. COVID-19 vaccine trials: The use of active controls and non-inferiority studies. *Clinical Trials* February 3, 2021. <https://journals.sagepub.com/doi/full/10.1177/1740774520988244>

⁶ Fleming TR, Nason M, Krause PR, Longini IM, Henao-Restrepo AM. COVID-19 vaccine trials: The potential for "hybrid" analyses. *Clin Trials*. 2021 May 27;17407745211018613. doi: 10.1177/17407745211018613. Online ahead of print.

⁷ https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2

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Various subgroup analyses of the primary endpoint will also be undertaken. As COVID-19 mortality increases steeply with age, where feasible, 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 vaccine efficacy (VE), but larger numbers will accumulate with longer follow-up. For enrolment and patient information see SOP – 03: Pre-screening of Participants and Informed Consent. 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 truly differ between subgroups the play of chance may well suggest false results in particular subgroups. Additional secondary endpoints may be included based on the needs of each vaccine developer. However, statistically evaluated endpoints will not be changed after a vaccine has entered the trial.

Additional exploratory endpoints will include VE between the first and second dose, for two-dose vaccine. In addition, VE against specific SARS-CoV-2 variants of concern (as defined by WHO) will be evaluated as a high priority supportive endpoint. This will also include a VE analysis in terms of variant-specific mutations and/or deletions. Every effort will be made to collect samples for sequencing from cases that occur in the trial. Finally, attack rates will be reported for participants in the placebo group who both had and did not have prior SARS-CoV-2 infection.

All sites will obtain samples for sequencing from cases of COVID-19 arising during follow-up. In addition, investigators at some sites that can process blood samples and cryopreservation will collect 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. See the following SOPs:

SOP – 10: Secondary endpoint – Overview

SOP – 11: Secondary endpoint - Blood Collection

SOP – 12: Secondary endpoint - Serum Collection

SOP – 13: Secondary endpoint – Data entry and management

SOP – 14: Secondary endpoint – Labelling

SOP – 15: Secondary endpoint - PBMC and Plasma Collection

SOP – 16: Secondary endpoint - Sample storage

SOP - 17: Secondary endpoint - Handling and Transport of Biological Samples

SOP - 18: Secondary endpoint - SARS-CoV-2 RNA amplification and Next Generation Sequencing

These will 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. 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 and protection for 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.

Study of these endpoints will require coordinated collection of appropriate biological samples. The Trial Steering Committee will review the evidence with progress with development and validation of assays and issue a recommendation on which assays and test to use, which laboratories should conduct the evaluation when collection of samples ends.

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

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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 3: Additional secondary and supportive endpoints. 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 Adverse Events (AEs) and Serious Adverse Events (SAEs) at any time after vaccination, by baseline SARS-CoV-2 serostatus where available. The protocol will follow ICH guidelines. See Following SOPs:

- For Adverse Events (AE) management and reporting see SOP – 19: Clinical observation, management of immediate adverse events post-vaccination and reporting
- For Monitoring and Reporting Serious Adverse Events (SAEs), and Suspected Unexpected Serious Adverse Reactions (SUSARs) see SOP-20: SAE and SUSARs management and reporting
- For Monitoring of pregnancy outcomes see SOP-21: Management and follow-up of pregnancy outcomes for inadvertently vaccinated pregnant women

Individual safety monitoring will be continuous at all sites. AEs of special interest (AESIs), as defined in the Appendix 4 - electronic Case Report Forms (eCRFs) 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. The eCRFs also include unsolicited AEs by body system). Outcomes of pregnancies will be reported.

For candidate vaccines for which both the independent Vaccine prioritization committee and Trial Steering Committee makes the recommendation on the need for additional safety information before a large number of volunteers is recruited, the following procedures apply.

Safety data will be collected in selected sites from up to 200 or more (as recommended by the Trial Steering Committee) participants using the above mentioned safety monitoring procedures. If recommended by the Trial Steering Committee additional safety information will be collected for specific vaccines and the electronic case report form will be adjusted accordingly.

In addition, samples will be collected to evaluate immunogenicity and virus sequencing as described in section Secondary and Supportive Endpoints and their Evaluation above.

Before proceeding to the recruitment of a more than 200 volunteers, the DMC will review the safety data seven days and thirty days post administration of the last dose. The decision of the DMC to recommend expansion of the recruitment will be based solely on the safety information.

Nonetheless, once the immunogenicity and virus sequencing results are available, the DMC will consider them and will provide subsequent recommendations as appropriate.

Safety monitoring will also consider the possibility that some vaccines may increase the incidence or severity of disease (i.e., enhance disease). See eCRFs for documentation of endpoints and disease severity. 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

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to be followed and any necessary advice to recipients put in place. More details of analyses for enhanced disease are provided in the Appendix-2: Statistical Analysis Plan and in the Appendix-1: DMC Draft Terms of Reference.

Participating sites

As per the Trial Steering Committee recommendation (see Appendix-5: Trial Steering Committee Terms of Reference), sites with sufficient current and projected transmission rates at the time of joining the trial can participate (see SOP-01: Epidemiological data requested for sites selection). The criteria is that the expected cumulative incidence of confirmed disease in the placebo arm will exceed 1% during the first 3 months of follow-up.

In addition, participating sites must have experience with clinical trials, training in Good Clinical Practice, and 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.

As per the Trial Steering Committee's recommendation, new study sites may be added as needed to assure a high COVID-19 attack rate. Randomization will preferentially occur at sites with current and predicted high COVID-19 attack rates (which will be monitored before the start and during the trial in individuals not participating in the trial), See SOP-01. Some sites will be fixed sites and some will be mobile, moving to additional areas and allowing the trial to rapidly adapt to changing nature of the COVID-19 infection pandemic.

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).

Participating populations

The trial will recruit volunteers 16 years of age and older who reside in locations with high and forecasted incidence (see SOP-01) based on surveillance data and epidemiologic modelling, or whose circumstances put them at appreciable risk of exposure to SARS-CoV-2 and COVID-19 (e.g., Health Care Workers, Front-Line Workers, essential workers in areas with not yet access to vaccines).

Before the trial starts, a designated community engagement team will identify and engage with stakeholder populations to assess study appropriateness and acceptability. See Good Participatory Practice (GPP) with trial populations for the Global Solidarity Trial of COVID-19 Vaccines and SOPs. See the following SOP and guidance tool:

- For Enrolment and patient information see SOP – 03
- The WHO Tool on Good Participatory Practices during trial⁸SOP- 38: A flipbook for facilitated discussions between study staff and potential research participants
- SOP – 39: Solidarity Trial Vaccines crisis communication planning guide
- SOP- 40: Good Participatory Practice (GPP) with trial populations for the Solidarity Trial Vaccines

⁸ R&D Good Participatory Practice for COVID-19 clinical trials: a toolbox <https://www.who.int/publications/m/item/r-d-good-participatory-practice-for-covid-19-clinical-trials-a-toolbox>

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Inclusion and exclusion criteria

The main inclusion and exclusion criteria are listed below.

Inclusion criteria

- Male or female participants between the ages of 16 and above at randomization
- Living in the area and planning to reside in the area for at least 6 months.
- Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in SOP-03
- Healthy participants who are determined by clinical judgment of the investigator to be eligible for inclusion in the study.
- Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests (if randomised and consent given, lifestyle considerations, and other study procedures.

Exclusion criteria

- Previous laboratory confirmed diagnosis of COVID 19.
- Previous vaccination with any COVID-19 vaccine.
- Receipt of medications intended to prevent COVID 19.
- Participation in other studies involving a study intervention within 28 days prior to study entry and/or during study participation.
- History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (e.g., anaphylaxis) to any component of the study intervention(s).
- Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study.
- Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
- Women who are pregnant or breastfeeding will be informed that there is no data on the safety of these vaccines among these groups and will be given the opportunity to decide if they are willing to participate in the trial.

Recruitment should support generalizability of results, including by important characteristics such as age. Participants must meet inclusion/exclusion criteria of at least one vaccine in the trial. See SOPs below:

- SOP - 03 for Pre-screening of participants, Informed consent, and inclusion and exclusion criteria.
- SOP –22: Biometric Identification System

Randomization

Eligible volunteers will be randomized using a central web-based service. Once electronic data collection has been completed the volunteer automatically enters the trial and a random allocation of their trial vaccine is generated and displayed. The volunteers will be randomly allocated either to placebo or to one of the study vaccines.

As the volunteer is being entered into the trial, neither the volunteer nor the investigator knows which vaccine will be allocated after data entry is complete. Hence, foreknowledge of the vaccine that would be randomly allocated if volunteer entry takes place cannot bias the decision to enter the study and cannot affect the electronic data collection immediately before randomization.

Random allocation takes place automatically as soon as the electronic data entry has been completed. The volunteer is then in the trial (and remains in it whatever vaccine is given, unless the volunteer decides otherwise).

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However, while the study is in progress access to tabular results of study outcomes by allocated vaccine allocation will not be available to the research team, volunteers, or members of the Trial Executive Group (unless the DMC advises otherwise).

Eligibility for a vaccine will be based on local 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.

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 P_B 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.

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.

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(SOP - 23 Blinding). The study will be observer-blinded. As shown in Figure 2, blinding will be enhanced by concurrent enrolment of participants who are randomized to receive the placebo corresponding to each vaccine.

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.

Study product assignments will be accessible to the data management staff at the CRO (Castor edc) and study pharmacists 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.

Blinding of recipients and use of placebo controls will follow well-established ethical principles. (SOP/Handbook: GCP). Participants may be unblinded if unblinding will aid in their clinical care. This may be due to an adverse event for which knowledge of treatment assignment group may be important to clinical care, or in some cases due to availability to that individual participant of alternative treatment.

Such alternative treatment may include the availability of a vaccine that has satisfied the WHO requirements for Emergency Use Listing. Because the Solidarity trial minimizes the number of participants on placebo and is planned to switch to a non-inferiority design when placebo follow-up becomes infeasible, the number of individuals who will need to be unblinded due to availability of an alternative vaccine is not expected to be large.

Study vaccines and study vaccination schedules

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).

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Vaccine characteristics, stability, labelling, preparation, handling, storage and accountability

Study vaccines will be shipped to participating sites from global vaccine repositories. All other supplies will be provided by the participating site with support from the CO-Sponsors. The participating site principal investigator is responsible for study vaccine disposition and accountability. The following SOPs give details:

- SOP – 24: Country reception with cold chain requirements
- SOP – 25: Transport to secondary storage with cold chain requirements
- SOP – 26: Storage, packing, and distribution with cold chain requirements
- SOP – 27: Disposal and waste management
- SOP – 28: Country reception with ultra-cold chain requirements
- SOP – 29: Transport to secondary storage with ultra-cold chain requirements
- SOP – 30: Setup and maintenance of ultra-cold chain infrastructure
- SOP – 31: Ultra Cold Chain (UCC) decommissioning
- SOP– 32: Storage, packing and distribution with ultra-cold chain requirements
- SOP – 33: Pharmacy manual and Vaccination Procedures

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 enrol continuously.

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. See the following SOPs:

- SOP- 19: Clinical observation, management of immediate adverse events post-vaccination and reporting
- SOP-20: Monitoring and Reporting (solicited and unsolicited) Adverse Events, Serious Adverse Events, and Suspected Unexpected Serious Adverse Reactions (SUSARs)
- SOP- 34: Post - vaccination visits

After COVID-19 diagnosis, participants will be referred locally for management, as required. All participants will receive proper management according to the local standard of care, irrespective of location. 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 it is not feasible to follow placebo recipients for this entire time, a crossover design is planned where an active control with known efficacy will be offered to placebo recipients. This will enable continued follow-up of efficacy among vaccine recipients relative to an active control given at a later time⁹. 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.

⁹ Fleming T, Nason M, Krause PR, Longini IM, Henao-Restrepo AM. COVID-19 vaccine trials: The potential for "hybrid" analyses. Clin Trials. 2021 May 27;17407745211018613. doi: 10.1177/17407745211018613. Online ahead of print.

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Schedule of visits

The table below provides an overview of the protocol visits and procedures. The SOPs provide detailed information on each procedure and assessment required for compliance with the protocol. Unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 and Visit XX (12-month follow-up visit).

Overview of the protocol visits and procedures

	MAIN AND SECONDARY ENDPOINTS					EXPLORATORY ENDPOINTS ONLY	
Visit number	1	2	3	4	5	6	7
Visit description	Vaccination Dose 1	Follow-up visit days post -dose 1	Vaccination Dose 2	Follow-up visit 7 days post -dose 2	Safety phone calls	Follow-up visit 180 days post – last dose	Follow-up visit 365 days post -last dose
Visit window (days)	Day 1	Day +7 (6-8) post dose 1	As per vaccine schedule	Day +7 (6-8 days) post dose 2	Day +7 (6-8) Post previous contact/call	Day + 180 (170-190 days) post last dose	Day + 365 (350-380 days) post last dose
Pre-screening and generation of unique ID	X						
Obtain informed consent	X						
Confirm eligibility	X						
Record iris scanning	X	X	X	X			
Use iris scanning to identify participant		X	X	X			
Obtain randomization allocation	X						
Administer vaccine dose	X		X				
Explain participant communication methods, and verify that they receive the first SMS message	X		X				
Assess acute reactions for at least 30 minutes after study intervention administration	X		X				
Record in eCRF AEs (solicited and non solicited), SUSARs and SAEs as appropriate	X	X	X	X	X		
Collect of COVID-19–related clinical and laboratory information (including local diagnosis of COVID)		X	X	X	X		
Explain date of next visit	X	X	X	X	X	X	X
EXPLORATORY ENDPOINTS ONLY Collect blood samples for correlates of protection (only if site eligible and consent given) <i>For immunological assessment samples will be collected from about 200 participants per vaccine in selected sites</i>	X		X	X*		X	X
Record in eCRF AEs and SAEs as appropriate	X		X			X	X
Collect of COVID-19–related clinical and laboratory information (including local diagnosis of COVID)	X		X			X	X
Explain date of next visit	X		X			X	X

*only for about 200 participants per vaccine in selected sites

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Vaccine discontinuation (which does not imply withdrawal from follow-up)

At all times the research team remains solely responsible for decisions about that volunteer's care and safety. Hence, if the research team decide any deviation from the randomly allocated vaccine arm is definitely appropriate then this should be done, although the patient would remain in the trial and should still be reported on. SOP-37: Participants Discontinuation from Study

- Study vaccine administration should be stopped if the investigators suspects any serious unexpected vaccine-related adverse reaction that is life-threatening, and this SUSAR should immediately be reported electronically. The volunteer's outcome will still be reported on in the usual way at the end of their follow-up period.
- Study vaccine administration should be stopped if the investigator considers this is definitely in the volunteer's best interest (including but not limited to life threatening events) or if the volunteer or a legal representative decide it should be stopped. The volunteer should still be reported on in the usual way at the end of their time in the trial, unless it is decided otherwise (see below).

Decision by a volunteer or legal representative to withdraw from follow-up

Volunteers are informed at study entry of their right to withdraw at any time their consent to participate without any adverse consequence and without giving any reason. Withdrawal from the vaccine that was randomly allocated at study entry need not imply withdrawal from information on outcome being reported to the WHO at the end of the follow-up period. But, if the volunteer (or a legal representative) decides the volunteer will withdraw and that no further data will be sent to the WHO study office, then only the date of withdrawal will be reported; no further information will be given, unless an adverse drug reaction report is legally required.

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 interim monitoring boundaries defining

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benefit and lack-of-benefit, based on application of the O'Brien-Fleming method after 100 events, using a boundary for early termination preserving an experimental (one-sided) 0.005 error rate¹⁰. Using these O'Brien-Fleming criteria after 100 events, benefit is established when estimated VE is $\geq 66.7\%$, while lack of benefit (for a single dose vaccine) is established after 100 events when estimated VE is $\leq 23\%$. 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 enrolment 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.

Reporting of Results

Results for a given vaccine will be reported when the study reaches the monitoring boundary for benefit or when there have been 150 endpoints reported in the vaccine and placebo arms. See the following SOPs:

- SOP 36: data management, data security, confidentiality
- Appendix 2 – Statistical Analysis Plan

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 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).

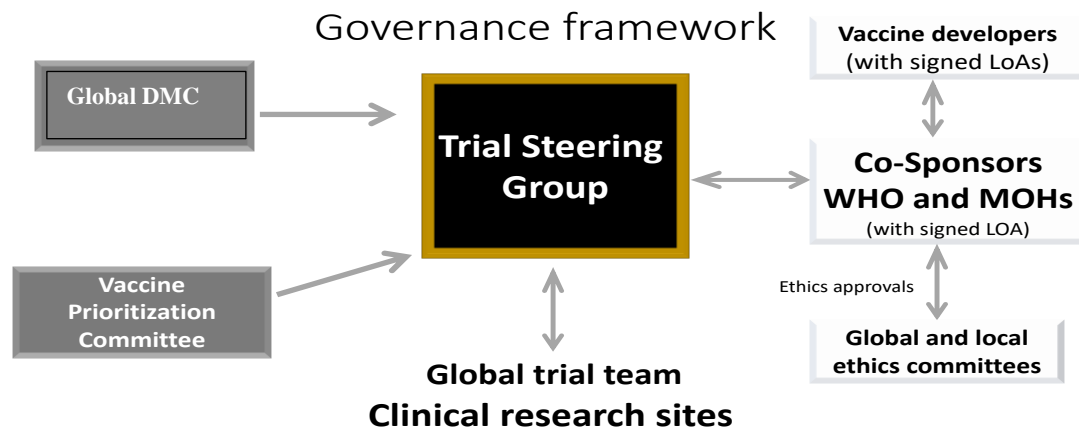
Samples that could be used to study potential immune correlates, the effect of the vaccine on transmission or shedding, or infection (which could be detected serologically) may be unblinded at the time a finding on the primary endpoint is announced. Adverse events that are required to be reported to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

¹⁰ Second Edition of Ellenberg, Fleming and DeMets, Data Monitoring Committees in Clinical Trials, 2019, see Section 8.4.6

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Study governance



Co-Sponsors

The trial will be Co-sponsored by WHO and the Ministry of Health of each participating country. WHO and the Ministry of Health (or the delegated research institution(s)) will organize the trial and its implementation.

The roles and responsibilities of the Co-sponsors and the vaccine developers are defined by generic Letters of Agreement (LoA) between WHO and them. These LoAs follow the generic agreements that WHO has used over the years and that govern its relationships and its role in the context of research projects.

In brief, WHO (via the Global Trial team) will engage and set up the collaborations with the vaccine developers via a signed LoA and interact with them as defined in the LoA. WHO will coordinate the randomization and management in a centralized database run by a CRO (Castor edc), not accessible to WHO staff, to which all trial sites will contribute data. At the end of the trial, after data has been queried, cleaned and locked, WHO will provide trial data and reports to each manufacturer to support regulatory filings when endpoints for each vaccine are reached.

WHO agrees to ensure that its designate (Castor edc) will store and maintain the records for the Trial in accordance with ICH Good Clinical Practice. If at any point, WHO no longer wishes to retain the records from the Trial, then the vaccine developer must be given the option to have the records stored at the vaccine developer's expense, and on terms which are acceptable to WHO and in accordance with ICH Good Clinical Practice. If the records for the Trial are stored at the vaccine developer's expense, the vaccine developer will apply the foregoing *mutatis mutandis* in respect of WHO.

In the event a health authority requests an inspection of the above-mentioned records, WHO will notify the vaccine developer thereof as soon as reasonably possible after becoming aware of such request. Any inspection agreed to by WHO will be without prejudice to WHO's privileges and immunities. WHO will consult with the vaccine developer before any such inspection and provide the vaccine developer with the results thereof when WHO receives them. WHO will consult with the vaccine developer on any response to the health authority. In the event that a health authority inspects the vaccine developer in relation to the Trial, WHO will, at the vaccine developer's request and without prejudice to WHO's privileges and immunities, provide reasonable support to the vaccine developer in

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responding to questions from the health authority concerned, i.e. insofar as such questions relate to WHO activities or WHO records

Vaccine developers

The vaccine developer warrants and represents that the vaccine has been manufactured in accordance with current Good Manufacturing Practices (cGMP), to the extent that each standard of cGMP is or can be applicable; and complies with the label specifications set forth by the Sponsor.

The vaccine developer furthermore warrants and represents that the vaccine developer is lawfully entitled to enter into this trial and provide the candidate vaccine free of charge to WHO for the purpose of the trial; and to the best of the vaccine developer knowledge, as of the date of signature of the agreement with WHO, neither the supply to WHO nor the importation, use and administration of the Vaccine in the countries where the Solidarity Trial Vaccines takes place infringes the valid patent rights of any third party.

As part of the generic LoA terms, the 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.

Vaccine developers will be responsible for interacting with regulators responsible for approving the use for emergency authorization or licensure or . 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.

Trial Steering Committee (TSC)

This is an independent scientific committee established to review scientific elements important for the design, conduct and analysis of the trial. The TSC will provide advice to the study Co-Sponsor(s) and the Global trial team in issues regarding trial design, conduct and analysis. It will provide formal recommendations on the direction of the trial:

- Reviewing the progress of the Solidarity Vaccine trial
- Reviewing initiation of enrolment at new sites
- Reviewing appropriateness of sites for evaluation of specific candidate vaccines
- Considering recommendations provided by the independent DMC
- Ensuring that reports emerging from the trial are scientifically valid
- Making recommendations on trial conduct or adaptive design elements to the WHO Leadership
- In conjunction with WHO Solidarity Trial Vaccine co-Leads, the TSC will liaise with the Sponsor and donor coordination group, vaccine prioritization committee, and WHO Trial Team as appropriate.

The TSC 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. Adaptive aspects of the study, to the extent not predefined in the protocol, will be governed by the TSC, which will not have access to unblinded study data.

Data Monitoring Committee (DMC)

The DMC will have regular access to efficacy and safety data, and information regarding the quality of study conduct. The role of the DMC will be to apply pre- (and TSC-) defined benefit and lack of benefit criteria to the vaccines, and to address potential safety issues as well as data integrity issues. Early data from vaccines that entered the trial based on limited but promising data will receive additional scrutiny. 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

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conduct information as needed, with input provided by the SC during open sessions of DMC meetings. The DMC will be responsible for providing information to the Sponsor and the STV co-Leads, when required to be reported to regulators (normally restricted to serious, unexpected, suspected adverse reactions. This information will also be given 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 to 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 TSC, 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 only if necessary for clarification, discussing them with the study sponsor(s), and making decisions about their implementation.

For candidate vaccines for which both the independent Vaccine prioritization committee and Trial Steering Committee makes the recommendation on the need for additional safety information before a large number of volunteers is recruited, the following procedures apply.

Safety data will be collected in selected sites from 200 participants using the above mentioned safety monitoring procedures. If recommended by the Trial Steering Committee additional safety information will be collected for specific vaccines and the electronic case report form will be adjusted accordingly.

In addition, samples will be collected to evaluate immunogenicity and virus sequencing as described in section Secondary and Supportive Endpoints and their Evaluation above.

Before proceeding to the recruitment of a larger number of volunteers, the DMC will review the safety data seven days and thirty days post administration of the last dose. The decision of the DMC to recommend expansion of the recruitment will be based solely on the safety information.

Nonetheless, once the immunogenicity and virus sequencing results are available, the DMC will consider them and will provide subsequent recommendations as appropriate.

Vaccine prioritization committee

<https://www.who.int/publications/m/item/who-working-group-vaccine-prioritization-for-covid-19-vaccines>

The current global COVID-19 public health emergency underscores the need to accelerate the development of nCoV candidate vaccines. The Working Group for vaccine prioritization aims to provide guidance as well as to prioritize vaccine platform approaches and/or candidates to be considered for further development and potentially consider for late-stage evaluation in the context of the Solidarity Trial Vaccines.

The objectives of this group are:

1. To review the current pipeline of candidate vaccines for COVID-19
2. To review the current pipeline of candidate vaccines for other coronaviruses and discuss their value in protecting against the COVID-19.
3. To make preliminary recommendations on whether the development of COVID-19 candidate vaccines should be prioritized for the Solidarity Trial Vaccines

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Regulatory, ethical, and study oversight considerations

This trial will be conducted in conformity with the principles of ICH E6 (R2). When local ethics committees review this international protocol, it can be approved (after which the study can proceed at that locality) or rejected (in which case it will not proceed) but it cannot be substantially altered or rewritten. Likewise, any substantial amendments made centrally to the core protocol or consent procedure while the trial is in progress can be approved or rejected by local ethics committees but cannot be materially altered or rewritten. Any proposals for amendments of the protocols by the local investigators will be considered and decided upon by the TSC,

Informed Consent Process

When obtaining informed consent (SOP-3), this must be documented by a signed and dated written consent form. As indicated in the eCRF, an electronic image of the signature page is kept (or a note to file if national regulations forbid this) in the trial platform using a secure GCP-compliant application that immediately encrypts and safely stores the data. Printed information and original consent stays with the volunteer or legal representative, isolated from study staff.

Confidentiality and Privacy

Volunteer confidentiality is held in trust by the investigators. No identifiable information will be released to any unauthorized third party. All study data will be encrypted for analysis. Volunteer confidentiality will be maintained during study analysis, when study results are disseminated, and afterwards.

Monitoring protocol compliance

Monitoring to ensure trial volunteers are protected and the trial data are timely and complete will be conducted mainly by central data checks. In addition, every country will identify local monitors to help local site staff resolve any problems, and to provide training focussed on any specific local needs. Monitoring will be implemented in compliance with international regulations.

The Clinical Trial Unit of the University of Bern will conduct the global monitoring. Their SOPs state that the focus of this will be on those factors that are critical to quality (ie, to volunteers' safety and the reliability of the trial findings). Remedial actions would therefore focus on issues with the potential to have a material impact on these issues.

Clinical data monitoring

This will include electronic completeness checks for all records, although the information recorded initially must have appeared complete at the time for the system to have proceeded to patient entry, ie, to generation of a vaccine assignment.

Source records and study record retention

Source data are all electronic. Study-related records, product accountability records, and informed consent records will be maintained for at least 5 years after the investigation ends. If, before or during that period, this study is used in a marketing application for any study drug, then the records will be kept for at least 5 years after that application is approved or rejected. No records will be destroyed without the written consent of the WHO, acting in its role as co-sponsor of the trial. The sponsor and regulatory agencies will have the right to conduct confidential audits of such records (but should be mindful of the workload facing participating hospitals and the infection control requirements during this pandemic).

Protocol deviations and violations

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The study will be conducted in accordance with the principles of International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP) and relevant local, national and international regulations. Any serious breach of GCP will be handled in accordance with regulatory requirements and classified as protocol deviations or violations. (see SOP-35: Protocol Deviations and Violation Reporting).

If this happens, this should be reported within 24 hours on the study website eCRF. The DMC chair will be informed and will then decide whether this constitutes a sufficiently major protocol deviation to be forwarded promptly to the relevant national co-ordinator and ethics committee.

Sponsorship, and management of conflicts of interest

In each country the Co-Sponsors of this study are the National Ministry of Health and the World Health Organization. The study drugs will be available at no cost from the study Sponsors, but the study does not cover any other aspect of patient care. The independence of this study from any actual or perceived financial influence, such as from pharmaceutical companies or their consultants, is critical. Therefore, any conflicts of interest in its design, conduct, analysis, interpretation or publication, will be disclosed and managed by the WHO and the national Co-Sponsor.

Data sharing

After the trial has ended and its results have been reported, anonymized data sharing will occur as per the [Policy Statement on Data Sharing by the World Health Organization](#).

Publications

This international collaboration is co-ordinated through the World Health Organisation, which is also a sponsor of the trial. Any wholly reliable interim findings will be disseminated rapidly by the WHO. There will be group authorship recognizing the contribution of all national and local investigators and guided by the [International Committee of Medical Journal Editors \(ICMJE\) recommendations](#). Although the writing committee will consist of the executive group and the WHO trial secretariat, authorship will include all steering committee members and local collaborators whose hospital, in the view of the national principal investigator, contributed substantially towards the trial.

Insurance

WHO has established a global liability insurance (for individuals suffering serious adverse reactions arising from the use of the investigational therapeutics for COVID-19 as part of the Solidarity trial) that will cover all countries and stakeholders that participate in the trial.

Ethical issues

Including a section on ethical issues will help to ensure these are thoroughly understood and considered, particularly:

1. Processes to mitigate potential risks to study participants.
2. The importance of clear informed consent.
3. Confidentiality and instructions on maintaining confidentiality.

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Appendixes

Appendix 1 – Data Monitoring Committee Draft Terms of Reference

Appendix 2 – Statistical Analysis Plan

Appendix 3 – Additional Secondary and supportive endpoints

Appendix 4 – Electronic Case Report

Appendix 5 – Trial Steering Committee Terms of Reference

Appendix 6 - Recommendations for Vaccine inclusion into the Solidarity Trial Vaccines

Standard Operating procedures (SOPs)

SOP number	Title
01	Epidemiological Data Requested from Site Selection
02	Primary endpoint definitions and role and terms of the adjudication committee
03	Pre-screening of Participants, Informed Consent, Assessing Eligibility, and Vaccination
04	Primary endpoint SARS-CoV2 RNA Isolation and RRT-PCR amplification
05	Primary endpoint Oro-Nasopharyngeal Specimen Collection
06	Primary endpoint specimen transportation
07	Primary endpoint swab specimen aliquoting
08	Primary endpoint storage recording of oro-nasopharyngeal potential SARS-CoV-2 specimen aliquots
09	Primary endpoint data entry and management of COVID 19 cases
10	Secondary endpoint - Overview
11	Secondary endpoint - Blood Sample Collection
12	Secondary endpoint - Serum Collection
13	Secondary endpoint - Data entry and management
14	Secondary endpoint - Labelling
15	Secondary endpoint - PBMC and Plasma Collection
16	Secondary endpoint - Sample storage
17	Handling and Transport of Biological Samples
18	SARS-CoV-2 RNA amplification and Next Generation Sequencing
19	Clinical observation, management of immediate adverse events post-vaccination and reporting
20	Monitoring and Reporting Adverse Events (solicited and non solicited AEs), Serious Adverse Events, and Suspected Unexpected Serious Adverse Reactions (SUSARs)
21	Management and follow-up of inadvertently vaccinated pregnant women
22	Biometric Identification System in Support of The Solidarity Trial Vaccines

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SOP number	Title
23	Blinding
24	Country reception with cold chain requirements
25	Transport to secondary storage with cold chain requirements
26	Storage, packing, and distribution with cold chain requirements
27	Disposal and waste management
28	Country reception with ultra-cold chain requirements
29	Transport to secondary storage with ultra-cold chain requirements
30	Setup and maintenance of ultra-cold chain infrastructure
31	UCC Decommissioning
32	Storage, packing and distribution with ultra-cold chain requirements
33	Pharmacy manual and Vaccination Procedures
34	Post-Vaccination Visits
35	Protocol Deviations and Violations Reporting
36	Data Management data security, confidentiality
37	Participants Discontinuation from Study
38	A flipbook for facilitated discussions between study staff and potential research participants
39	Solidarity Trial Vaccine of COVID-19 Vaccine's crisis communication planning guide
40	Good Participatory Practice (GPP) with trial populations for the Solidarity Trial Vaccine of COVID-19 Vaccines

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Version control

Version	Date	Changes	Rationale
4.0	08.03.2022	Clarification that the endpoint includes events 14 days or more after dose 2	It was not consistently mentioned in various sections of the protocol.