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Study Population (Part 4 of Phase 3 study of Vaccine Candidate for COVID-19)

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Coronavirus Method De...



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We use this protocol and it's working

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Abstract

This is Part 4 of "Phase 3 randomized, double-blinded, placebo-controlled trial to evaluate the safety, immunogenicity, and efficacy of **Vaccine Candidate** against COVID-19 in adults > 18 years of age"

This generic Phase 3 protocol was developed by the PATH team with support of the Bill and Melinda Gates Foundation. The aim of the collection is to share recommended best practices in designing and implementing a Phase 3 study of a COVID-19 vaccine candidate. As Phase 3 trials of different Vaccine Candidates proceed around the world, following the same protocols will ensure consistency and comparability of the Phase 3 trial results.

Please note that this is an evolving document, to be versioned and updated, based on community feedback and new data.

Attachments



Generic Phase 3 Prot...

557KB

Guidelines

4.1. Enrollment and sample size adjustment

See Section 9.2. for details.

4.2. Participant inclusion criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

- Willingness to provide a signed, printed, and dated informed consent form.
- Stated willingness to comply with all study procedures and availability for the duration of the study.
- Be a male or female 18 years of age or older.
- Be at high risk of SARS-CoV-2 infection due to location, profession, or activities.
- For females (unless the sponsor has performed DART and Phase 1/2 safety studies): Be of non-childbearing potential or willing to use appropriate contraceptive measures for 30 days prior to vaccination through two months after completion of the vaccine series. Non-childbearing potential means being surgically sterilized or at least one year post-menopausal. Appropriate measures to prevent pregnancy include abstinence or adequate contraceptive precautions (i.e. intrauterine or implantable contraceptive device; oral contraceptives; diaphragm or condom in combination with contraceptive jelly, cream or foam).
- For healthy participants with pre-existing medical conditions: Be in stable condition that hasn't worsened over the three months before enrollment to require hospitalization or significant changes in therapy.

4.3. Participant exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Planned administration/administration of a vaccine not foreseen by the study protocol from within 30 days before the first dose of study vaccine.
- History of COVID-19 disease.
- History of allergic reactions or anaphylaxis to previous immunizations or allergies to any components of the vaccine.
- Fever (oral >38.0 C) within the past 24 hours.
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the study vaccine.
- History of bleeding disorder (e.g. factor deficiency, coagulopathy, or platelet disorder), or prior history of significant bleeding or bruising following intramuscular (IM) injections or venipuncture.
- Being pregnant (i.e. a positive pregnancy test) or lactating during the immunization phase of the study. If a woman becomes pregnant after all vaccinations are complete, she will not be excluded from the remainder of the study but will be followed through delivery.
- Planning to become pregnant or planning to discontinue contraceptive precautions during the vaccination phase through two months after the second immunization.

- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose (for corticosteroids, this means prednisone or equivalent, ≥ 0.5 mg/kg/day; inhaled and topical steroids are allowed).
- Compromised immune system diseases including cancer (except basal cell carcinoma), congenital or acquired immune deficiencies and uncontrolled autoimmune diseases, as per case history and/or physical examination.
- Indications of drug abuse or excessive use of alcohol as deemed by the investigator to confound safety assessments or render the participant unable or unlikely to adhere to protocol requirements or provide accurate safety reports.
- History of asplenia.
- Unavailable for the entire trial period.
- Any other findings the investigator feels would increase the risk of having an adverse outcome from participation in the trial.

Investigators should use good clinical judgment in considering a participant's overall fitness for inclusion in the trial. Some participants may not be appropriate for the study, even if they meet all the eligibility criteria. In addition, the participants should reside within reasonable proximity to the study site, without plans to leave the area prior to the end of the study.

4.4. Description of Study Population

The study population will include approximately **XXX** adults ≥ 18 years of age. **INSERT HERE COUNTRY-SPECIFIC RECRUITMENT STRATEGY.**

The trial will be conducted in **DESCRIBE SITES WHERE TRIAL WILL BE CONDUCTED I.E. HOSPITALS, COMMUNITY, ETC.**

Final determination of eligibility determination will depend on the results of the medical history, clinical examination, screening laboratory tests, fulfillment of all the inclusion criteria and absence of any of the exclusion criteria, appropriate understanding of the study, and completion of the consent process by all participants.

The trial will recruit adults of any age whose locations or circumstances put them at increased risk of exposure to SARS-CoV-2 and of COVID-19, based on surveillance data and epidemiologic modelling. Recruitment should support generalizability of results, including enrollment of healthy participants as well as participants at risk for severe COVID-19, such as persons ≥ 60 years of age and those individuals with co-morbidities such as hypertension, diabetes, obesity, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and chronic heart disease.

4.5. COVID-19 case capture

COVID-19-confirmed cases will be captured by enhanced passive surveillance. Nasopharyngeal swabs will be collected from all participants at baseline to determine their infection status upon enrollment in the trial. Participants will receive a card containing investigator contact information and locations to receive a SARS-CoV-2 RT-PCR test if they have any of the following signs or symptoms at any time up to study end:

- Cough (persistent, dry cough)
- Shortness of breath, or difficulty breathing
- Fever (measured or subjective)
- Chills or rigors
- Myalgia
- Fatigue
- Nausea or vomiting
- Diarrhea
- Headache
- Sore throat
- Loss of taste or smell
- Congestion or runny nose

A 24/7 healthcare communication service will be established to connect with the enrolled participants. Participants will be instructed to call this service for any illness that develops.

- Participants will be contacted by study staff approximately once every two weeks **<(or more frequently without restriction)>** by phone, SMS text message, or other means of communication to inquire whether the participant has experienced any signs/symptoms consistent with COVID-19 and to remind the participant about the vaccine trial.
- Those with any COVID-19 suspected symptoms **<that last more than one day>** will have a nasopharyngeal swab collected and tested by RT-PCR at a designated laboratory. **<Those with a negative result on their first test will have a second test on the following day if symptoms persist>**.
- Surveillance will be supplemented by the following:
 - Participant communication via SMS text or telephone call, about whether they developed an illness during the **<past week>**.
 - Reporting via the 24/7 study healthcare communication service maintained by the study and staffed by doctors and nurses.
 - Notation in the weekly health report about whether participants experienced any illnesses in the past week.
 - Follow-up calls from the study center to participants who do not submit the weekly health report.

All participants will receive clinical care at the clinical site or pre-specified referral hospital.

Symptomatic participants not requiring hospitalization will be assessed regularly over the phone until the symptoms abate. A detailed case report form (CRF) will be completed describing the clinical course and outcome for all hospitalized and non-hospitalized COVID-19 confirmed participants.

4.6. COVID Event Adjudication Committee

Anonymized electronic CRFs (eCRFs) and other source data for each RT-PCR positive case will be submitted to the COVID Event Adjudication Committee, an expert panel consisting of experts in infectious diseases, internal medicine, or pulmonology, for cases suspected, but not clinically or laboratory confirmed to be COVID-19. It is

possible that there will be suspected cases where the RT-PCR result is equivocal, or the symptomatology is suspect and not recorded correctly.

In addition, the COVID Event Adjudication Committee will review any participant deaths that occur to assess whether they were COVID-19-related. **<Sponsor>** will develop a charter for the COVID Event Adjudication. The committee chair will attend DSMB sessions as an ad hoc member.

4.7. Safety assessment strategy

Safety assessment is a critical component and a co-primary endpoint of this trial. There are two separate safety components that will be monitored:

1. Safety related to vaccine administration will capture local and systemic *solicited* AEs for seven days following each of the two immunizations using the diary card provided to a subset of participants (the “reactogenicity” cohort). *Unsolicited* AEs $\geq$ grade 2 will be captured for 28 days following each immunization. SAEs and medically attended AEs will be captured during the entire study period.
2. Safety related to a theoretical risk of VED will be captured throughout the follow-up period beginning after participants have received at least one vaccine dose AND have a confirmed RT-PCR for SARS-CoV-2 infection. The specific likelihood of enhanced respiratory disease is unknown but is theoretically related to an aberrant and exaggerated immunological type II response observed in animal studies with other coronavirus infections such as SARS-CoV or MERS-CoV, but which has not been observed in human infection. As such, study staff will follow up with all participants who experience severe infection to capture data including but not limited to: type of oxygen support requirement (if any), organ system dysfunction, specific therapies initiated, time to resolution, and outcome (survival or death).

4.8. COVID-19 AEs for assessment of VED

Study staff will compare clinical features observed among both placebo and vaccine recipients who become infected with COVID-19 to explore the occurrence of VED.

Observed differences may lead to the development of tools to specifically address VED. Likewise, if disease enhancement is detected, specimens collected from breakthrough infections may lead to the identification of markers of enhancement.

After a COVID-19 case in a participant is virologically-confirmed, the participant will be followed in a manner that captures the patient outcome according to the WHO Clinical Progression Scale (as shown below). The “score” of the worst outcome will be entered into the CRF.

Panel 2: A proposed core outcome measure set for clinical studies of COVID-19**Viral burden**

Semiquantitative viral RNA of severe acute respiratory syndrome coronavirus 2 as measured by quantitative PCR or cycle threshold; nasopharyngeal swabs are associated with the highest viral load

Survival

All-cause mortality at hospital discharge or at 60 days

Clinical progression

WHO Clinical Progression Scale measured daily over the course of the study

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Figure: WHO clinical progression scale

ECMO=extracorporeal membrane oxygenation. FiO_2 =fraction of inspired oxygen. NIV=non-invasive ventilation. pO_2 =partial pressure of oxygen. SpO_2 =oxygen saturation. * If hospitalised for isolation only, record status as for ambulatory patient.

The WHO Clinical Progression Scale may be used to track the progress of patients with COVID-19 and report the distribution cases at the end of the study. The study will recruit participants with a score of 0 and use any progression across the scale as endpoints for assessment of VED/AESI.

Safety follow-up will include follow-up with COVID-19-presenting participants to examine possible progression of disease, requirement for hospitalization, and/or admission to intensive care units.

The severity of enhanced respiratory disease in both the placebo and vaccine arms will be assessed for each clinical case of COVID-19 and categorized.

Case definitions will be harmonized across all participating sites and case adjudication for each disease endpoint will be determined by a central independent committee blinded to the participant vaccine group.

The medical unit (hospital/clinic) where PCR+ participants are examined by study staff should have dedicated personal protective equipment (PPE) donning and doffing areas. Staff should be properly trained in infection control procedures related to COVID-19 and should have periodic serology and nasopharyngeal swabs collected.

Close clinical monitoring of participants is critical, and staff and clinicians should be available at all times. Units chosen for SARS-CoV-2 vaccine candidate studies should have access to hospital or other facilities that can provide access to oxygen, pulse oximetry, and emergency CPR equipment. Clinical management protocols must be in place for initiating care at the clinical site or the referral hospital.

The referral hospitals should have the clinical staff and capability to evaluate and manage complications of SARS-CoV-2 infection.

Should a treatment shown to prevent or arrest the progression from mild and moderate clinical COVID-19 illness to severe clinical illness become available, treatment will be initiated once a case definition has been achieved.

<Sponsor> and the study teams should make all possible attempts to acquire and provide to study participants novel drugs proven to be efficacious and approved for emergency, in accordance with their licensed and recommended use.

Given the study will not be screening out participants seropositive to SARS-CoV-2 or with a positive RT-PCR at the time of first or second vaccination, it is possible some participants may be unknowingly infected at the time of vaccination. Therefore, the safety review team needs to maintain awareness and ensure appropriate questioning of the participant. A physical exam should be conducted to explore that possibility.

Safety procedures to apply during assessment of suspected cases may, depending on severity, include the following:

- Physical examination including but not limited to nose, throat, pulmonary, cardiovascular, neurological, and skin exam, conducted at least twice during the event (at initial visit and two to three days later). The frequency of physical exams would be increased if the volunteer develops clinical signs and symptoms.
- Vital signs at least every 8-12 hours.
- Pulse oximetry
- Cardiac monitoring
- Chest X-rays and pulmonary ultrasound. Should an abnormality be noted, CT scan of chest (if available).
- EKG
- Safety laboratory studies, including metabolic panel, CBC with differential (to document lymphopenia), CRP, IL6 (if available), and PT/PTT/INR.
- Availability of a full crash cart and prompt access to ventilatory support.

All AEs of any grade associated with a known or suspected case of COVID-19 will be captured and entered into the CRF from time of first participant encounter with health system and continuing until final disposition (release

to home or discharge from health care facility) or end of study. The rationale for this rigorous follow-up is to assess AEs of any grade severity due to the potential for VED or AESI. As there are no specific disease processes or symptoms specific for VED, the investigators will depend upon the participant's history and health care provider to provide an overall assessment of clinical course, organ systems affected, and grade severity.

Participant inclusion criteria

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- 2 Stated willingness to comply with all study procedures and availability for the duration of the study.
- 3 Be a male or female 18 years of age or older.
- 4 Be at high risk of SARS-CoV-2 infection due to location, profession, or activities.
- 5 For females (unless the sponsor has performed DART and Phase 1/2 safety studies): Be of non-childbearing potential or willing to use appropriate contraceptive measures for 30 days prior to vaccination through two months after completion of the vaccine series. Non-childbearing potential means being surgically sterilized or at least one year post-menopausal. Appropriate measures to prevent pregnancy include abstinence or adequate contraceptive precautions (i.e. intrauterine or implantable contraceptive device; oral contraceptives; diaphragm or condom in combination with contraceptive jelly, cream or foam).
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Participant exclusion criteria

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Note

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- 14 Being pregnant (i.e. a positive pregnancy test) or lactating during the immunization phase of the study. If a woman becomes pregnant after all vaccinations are complete, she will not be excluded from the remainder of the study but will be followed through delivery.
- 15 Planning to become pregnant or planning to discontinue contraceptive precautions during the vaccination phase through two months after the second immunization.
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- 19 History of asplenia.
- 20 Unavailable for the entire trial period.



- 21 Any other findings the investigator feels would increase the risk of having an adverse outcome from participation in the trial.