Aug 25, 2020

Study Procedures (Part 6 of Phase 3 study of Vaccine Candidate for COVID-19)

In 1 collection

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1 Works for me dx.doi.org/10.17504/protocols.io.bj5ckq2w

Coronavirus Method Development Community

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ABSTRACT

This is part 6 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.

Note: Study procedures are vaccine-specific and will depend upon vaccine administration days (Day 1 and Day 15 versus Day 1 and Day 29) and serology collection days. The below section assumes that vaccine administrations take place on Days 1 and 15 with procedures as indicated.

ATTACHMENTS

Generic Phase 3 Protocol COVID-19 Vaccine - 21AUG2020-version 1.docx

DOI

dx.doi.org/10.17504/protocols.io.bj5ckq2w

PROTOCOL CITATION

Chris Ockenhouse, Chris Gast, Renee Holt, Jorge Flores 2020. Study Procedures (Part 6 of Phase 3 study of Vaccine Candidate for COVID-19). **protocols.io** https://dx.doi.org/10.17504/protocols.io.bj5ckq2w

COLLECTIONS

Collection of Protocols and Guidelines for Phase 3 study of Vaccine Candidate for COVID-19

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Collection of Protocols and Guidelines for Phase 3 study of Vaccine Candidate for COVID-19

GUIDELINES

6.1. Study procedures and evaluation

See the steps tab.

6.2. Laboratory evaluations

6.2.1. Sample collection, distribution, and storage

Blood samples for screening will be obtained and processed at the clinical trial site and transported to the site's designated laboratory for clinical testing. Samples will be stored in monitored, controlled-temperature freezers, with backup power supply to assure proper sample storage. A laboratory manual documents the procedures for obtaining and managing samples.

Samples will be prepared, handled, and stored according to site-specific SOPs. All samples will be labeled with the subject ID number, date/time of collection, study designator, and bar code. No personal identifiers will be included on sample labels. Samples being shipped to **XXX**. A chain of custody will be maintained both at the sending lab and the receiving lab.

Serum samples for immunological endpoints will be obtained and processed at the clinical trial and site and transported to the immunology lab(s).

Nasopharyngeal specimens will be collected from all participants. **<Nasopharyngeal flocked swabs will be collected and placed into viral transport medium (VTM). The VTM with swab stick will be placed in Ziploc bags and carried in a cooler box with ice pack (maintaining 2 to 8˚C) for transportation to XX (Figure 1.) Nasopharyngeal samples will be processed in a dedicated biosafety level (BSL)-2 laboratory for BSL-3 practices, under a certified Class II biological safety cabinet (BSC).>** Once a clinical sample has been treated with lysis buffer for RNA extraction, the samples can be moved to a less restrictive environment to complete the RNA extraction and real time RT-PCR.

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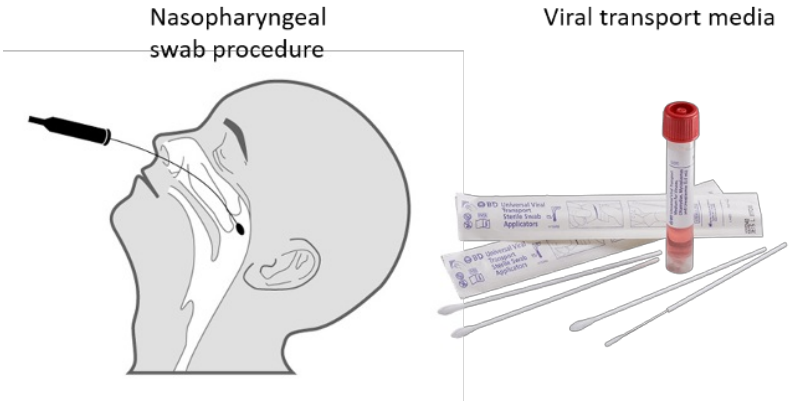

Figure 1

6.2.2. Clinical laboratory tests

COVID-19 case-mandated laboratory tests will be conducted by the site laboratory, which is accredited according to country-specific guidelines. Laboratory results will be reviewed promptly by the PI or designee. Participants will be notified of any clinically significant abnormalities. If clinically significant abnormalities are identified at baseline, participants will be referred to their primary health provider or appropriate medical facility. Any test may be repeated if the investigator suspects test results are spurious.

Sponsor/clinical site to insert a description of the RT-PCR assay for SARS-CoV-2 that identifies the manufacturer and includes specifications such as sensitivity, specificity, validation status, etc.

6.2.3. Immunological laboratory assays

The immunological assays to be performed include:

- Serum anti-SARS-CoV-2 IgG antibodies by ELISA (**note whether the assay has been validated and provide a brief description**).
- Serum neutralizing antibodies may be measured with SARS-CoV-2 or with pseudoviruses carrying the spike protein ofSARS-CoV-2 depending on the availability of BSL-3 facilities and validation of the assay. Alternatively, validated commercial assays currently reaching the market may be considered if fully validated and acceptable by the national regulatory authority (NRA).

6.2.4. Future use of stored samples; correlates analyses

Serum samples may be used for exploratory immunological assays for potential detection of correlates of protection. Samples will be stored for this purpose only if the participant consents to future use of stored samples during the informed consent process. Participants may withdraw permission for future use of specimens at any time, in which case the specimens will be destroyed. The PI will ensure the destruction of all known remaining samples and will report this to both the participant and IRB. Future use of samples will be reviewed and approved by the appropriate ERC/IRB, as applicable.

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Screening visit: **<Day -7>** to Day 0 (Study procedures and evaluation)

1 After the site PI has obtained informed consent from participants, several procedures will be completed during screening to determine study eligibility. Baseline data will be collected during screening between seven days prior to first vaccination and on Day 1, the day of first vaccination; however, it is anticipated it will generally take no more than a few days to determine eligibility, and participants will be randomized and vaccinated as soon as possible after determination of eligibility. All inclusion/exclusion criteria must be assessed from data obtained within that period, unless otherwise specified in the eligibility criteria. Information gathered during screening (medical history, physical examination, and laboratory analysis) will be recorded in the Source Documents and the CRFs. Laboratory reference values specific to each country will be included in a site-specific addendum.

After study information has been provided and the appropriate informed consent has been obtained, the procedures in this "Screening visit" section will be performed before enrollment

2 Confirm written informed consent has been obtained.

3 Assign participant ID once study specific consent form has been signed.

4 Obtain demographic and contact (e.g., address, telephone) information.

5 Obtain medical history, including:
- Details of any previous vaccinations in the past 28 days and reaction to vaccinations.
- Surgery.
- Previous hospitalization.
- Allergy to food/drugs.
- Current medication.
- History of any chronic or recurrent medical conditions.
- An interval medical history collected at subsequent clinic visits to assess for any AEs or concomitant medications.

6 Perform Physical examination, including:

Assessment of head, eyes, ears, nose, oropharynx, neck, chest (auscultation), lymph nodes (neck, supraclavicular, axillary, inguinal), abdomen (auscultation and palpation), musculoskeletal, skin, and neurological assessment.

7 Obtain vaccination history

8 Obtain details of medication use within the past 30 days.

9 Measure height and weight.

- Height should be measured and recorded to the nearest cm.
- Weight should be measured in kg and recorded to the nearest 0.1 kg.

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10 Collect vital signs, including:
- **Temperature**, measured in degrees Celsius (recorded to the nearest 0.1 degree).
- **Respiratory rate**, recorded in breaths per minute.
- **Heart rate**, measured in beats per minute manually or by automated device.
- **Systolic and diastolic blood pressure**, measured in millimeters of mercury (Hg) manually or by automated device.

11 Collect blood (8 mL) for baseline clinical laboratory testing, including:
- Complete blood count (CBC) (WBC, hemoglobin, platelet count)
- Aspartate transaminase (AST or SGOT)
- Alanine transaminase (ALT or SGPT)
- Total bilirubin
- Creatinine

12 Perform urine or blood pregnancy test on women of childbearing potential if within one day of vaccine administration.

13 Screening procedure timelines for any single subject will include a **7-day** window before randomization. Data collection will be by eCRF. The in-person visit days and procedures that include permissible window intervals are described in a Schedule of Events Table (Appendix A).

Randomization

14 Enrollment will take place online using **EDC System**. Randomization will occur on the day participants receive their first study vaccination (Day 1), after confirmation of eligibility and immediately prior to vaccine administration.

15 The participant will be randomized to one of two study groups, determined by block randomization (< 60 year of age; ≥ 60 years of age; male; female). The clinic records will contain a participant's subject number, date of birth, medical history, findings from the physical examination, date of screening visit, enrollment status and location (where applicable), and reasons for exclusion from the study (if applicable).

16 Participants will receive a coded treatment assignment after demographic and eligibility data have been entered into the system and eligibility has been confirmed. The unblinded research pharmacist will receive the treatment assignment codes to prepare the vaccine to be given to each participant. The unblinded research pharmacist will maintain the treatment code list in a secure place.

First vaccination visit (Day 1)

17

Appendix A shows the study day, window periods, blood sampling tests, and volumes for all study procedures.

Day 1 procedures:

18 Check inclusion and exclusion criteria.

19 Verify demographic data.

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20 Measure vital signs prior to immunization.

21 Measure axillary temperature in degrees Celsius (recorded to the nearest 0.1 degree).

22 Record respiratory rate in breaths per minute.

23 Measure heart rate in beats per minute manually or by automated device.

24 Measure systolic and diastolic blood pressure in millimeters of mercury (Hg) manually or by automated device.

25 Verify medical history.

26 Conduct targeted physical examination if indicated.

27 Perform urine pregnancy test for women of reproductive age.

28 Update information on concomitant medications.

29 Collect nasopharyngeal swabs for SARS-CoV-2 virus detection.

30 Obtain blood (serum) for antibody ELISA and neutralizing antibody titers (**X mL**).

31 Clean the prospective deltoid muscle injection site with an alcohol swab and allow it to dry completely.

32 Administer vaccine/placebo in the deltoid region, with clear documentation regarding the arm in which the vaccine is administered.

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33 Observe participants for at least 30 minutes post-vaccination. Address and document any immediate reactions to vaccination.

34 Take vital signs and assess the injection site after at least 30 minutes. Measure and record any redness and/or induration. Document any complaints or reactogenicity signs or symptoms.

The site investigator (PI) (or designee) may determine that a participant requires further on-site observation.

35 Discharge participant from the study clinic once all study related procedures are complete and the site investigator determines that a participant's condition is acceptable.

36 Provide diary card/memory aid to participants selected to assess reactogenicity (reactogenicity cohort, **e.g., 1,000 per country**) to record local and systemic adverse reactions. Review with participants what they should record and how to record it. The following parameters for reactogenicity will be assessed during the seven days after each study injection:

Local Reactogenicity	Systemic Reactogenicity
Pain	Fever
Tenderness	Headache
Erythema (redness)	Vomiting
Induration	Nausea
Pruritus	Fatigue
	Chills
	Myalgia
	Arthralgia

Participants in the reactogenicity cohort will be given a thermometer and measuring tape and will be instructed on entering signs and symptoms daily for seven days. All participants will be given an emergency telephone number to contact a special 24/7 study call center if in need of urgent medical attention. Staff will follow up with phone interviews, email, and SMS text to enter data electronically into the CRF. Participants will be instructed on how to enter and self-assess the severity of these AEs. Participants will also be asked to document unsolicited AEs on the programmed diary card, and whether medication was taken to relieve symptoms for seven days after each immunization.

Second vaccination visit (Day 15 + 7-day window)

37 Check inclusion and exclusion criteria.

38 Collect the diary card/memory aid and have investigator review it with the participant.

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39 Update demographic data.

40 Measure vital signs prior to second vaccination.

41 Update the medical history with any new information.

42 Perform a targeted physical examination (if indicated).

43 Complete a urine pregnancy test for women of reproductive age.

44 Obtain information on concomitant medication use.

45 Obtain blood samples for serological testing (**5 mL**).

46 Clean the prospective deltoid muscle injection site with an alcohol swab and allow to dry completely.

47 Administer the vaccine/placebo in the deltoid region and clearly document in which arm the vaccine was administered.

48 Observe participants at the site for at least 30 minutes following vaccination.

49 Measure and record vital signs after at least 30 minutes. Assess injection site for redness and/or induration. Assess and document any complaints or reactogenicity signs or symptoms.

50 Determine whether a participant requires further on-site observation (responsibility of investigator); additional site or clinical assessments may be completed as needed.

51 Discharge participant from study clinic when all study related procedures are complete and the site investigator determines a participant's condition is acceptable.

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52 Provide participants in the reactogenicity cohort with a diary card/memory aid to record local and systemic adverse reactions over the seven following days. Participants should also be given an axillary thermometer and measuring tape, and be instructed on entering signs and symptoms daily for seven days. All participants will be given an emergency telephone number to contact a special 24/7 study call center if urgent medical attention is needed. Staff will follow up with phone interviews, email, and SMS text to enter data electronically into the CRF. Participants will be instructed on how to enter and self-assess the severity of AEs. Participants will also be instructed to document unsolicited AEs on the diary card, and whether medication was taken to relieve symptoms for seven days after each immunization.

Day 28 (**<+5-day>** window)

53 The investigator reviews the diary card/memory aid with the participant

54 Review unsolicited AEs.

55 Obtain blood samples for serological testing (5 mL).

Day **<XX>** (42-56; two-to-four weeks after final vaccination, depending on vaccine)

56 The investigator reviews the diary card/memory aid with the participant for unsolicited AEs.

57 Update interim medical history.

58 Update concomitant medications.

Day **<XX>** (42-56 to study end)

59 Investigators will contact participants approximately every two weeks (or more frequently without restriction) to remind them of COVID-19 symptoms and the need to seek medical attention and COVID-19 testing as soon as possible.

Day 180

60 Study staff will collect serum from participants to assess seroresponse to both vaccine and non-vaccine antigens in the vaccine that may indicate asymptomatic infection occurring in the interval after vaccine administration.

Day 365/730

61 Study end procedures include end of study serum collection and inquiries about any major medical events (SAEs, AESIs, etc.) in the interim between preceding visits.

Interim contacts and visits

62 Interim contacts and visits (those between regularly scheduled follow-up visits) may be performed at participant request or as deemed necessary by the investigator or designee at any time during the study. All interim contacts and visits will be documented in participants' study records and on applicable case report forms.

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Withdrawal from study

63 Participants can leave the study at any time for any reason without any penalty or loss of benefits to which they are otherwise entitled. Participants can also be withdrawn from the study at the discretion of the investigator. The following reasons may lead to withdrawal of individual participants:

- Withdrawal of informed consent by volunteer.
- Any SAE.
- Any AE that, according to clinical judgment of the investigator, is considered as a definite contraindication to continuing in the study.
- Completely lost to follow-up (after three unsuccessful attempts to establish contact).
- Pregnancy during immunization phase. Women found to be pregnant after the final immunization will not be withdrawn but followed through study end.
- Ineligibility (arising during the study or retrospectively, having been overlooked at screening).
- If the investigator believes that continuation would be detrimental to the subject's well-being.
- Non-compliance with study procedures.
- Any other protocol deviation that results in a significant risk to the subject's safety.

The reason for withdrawal will be recorded in the CRF. If withdrawal is due to an AE or accidental pregnancy after vaccination, appropriate follow-up visits or medical care will be arranged, with the agreement of the participant, until the AE has resolved. If a participant withdraws from the study, data, serum, and RNA collected from nasopharyngeal samples prior to withdrawal may still be used for analysis. Storage of serum/ RNA collected from nasopharyngeal samples will continue unless the participant specifically requests otherwise.

Handling of participant withdrawals or termination

64 Investigators or designees will follow participants who are withdrawn as result of an SAE/AE until resolution of the event. Study staff will make an attempt to contact those participants who do not return for scheduled visits or follow-up. Information relative to the withdrawal will be documented in the CRF. The investigator will document whether the decision to withdraw from the study was made by the subject or the investigator and which of the following possible reasons was responsible for withdrawal:

- SAE.
- Non-serious AE.
- protocol violation (specify).
- Consent withdrawal, not due to an AE.
- Moved from the study area.
- Lost to follow-up.

If a subject withdraws or is terminated from the study after enrollment, including lost to follow-up, they may be replaced. If the reason for withdrawal is pregnancy during the immunization phase of the study, the participant won't receive further immunizations but will be followed for safety until delivery or termination of the pregnancy.

Premature termination or suspensions of study

65 This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause as determined by **Sponsor**. Written notification, documenting the reason for study suspension or termination, will be provided to the investigator, ERC/IRBs, and to regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the ERC/IRB and will provide the reason(s) for the termination or suspension.

The **Sponsor** reserves the right to terminate or curtail this clinical study for any reason, including but not limited to the following:

- Risk to participant safety.
- The scientific question is no longer relevant or the objectives will not be met (e.g., slow accrual).
- Failure to comply with good clinical practice (GCP) or terms of Clinical Trial Agreement.
- Risks that cannot be adequately quantified.
- Ethical concerns raised by the local community or local medical care/health care authorities.
- Failure to remedy deficiencies identified through site monitoring (e.g., data recording is inaccurate and/or

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incomplete on a chronic basis, or failure to meet other identified **Sponsor** performance standards).
- **Sponsor** decides to discontinue development of the study vaccine.
- Unsatisfactory participant enrollment with respect to quality and/or quantity.

If at any time a decision is made to permanently discontinue administration of study product in all participants, the PI will notify the ERC/IRB and the regulatory agency in a timely manner.

In addition, the DSMB may recommend **Sponsor** terminate the study based on a review of the safety data or interim safety analysis. If the study is prematurely discontinued by **Sponsor** for any reason, a summary report will be submitted to regulatory authorities. The summary report will provide a brief description of the study, the number of participants exposed to the vaccine, dose and duration of exposure, details of adverse drug reactions (if any), and the reason for discontinuation of the study or non-pursuit of the new drug application.

Blinding

66 Sufficient measures will be taken to assure that blinding of participants and evaluation staff is maintained. Study product assignments will be accessible to the data coordinating center staff and others who are required to know this information to ensure proper trial conduct. The DSMB members may also be unblinded to treatment assignment as required to review vaccine safety and efficacy. Emergency unblinding decisions are expected to be rare and justified only when that information is needed for the future clinical management of that participant.

If, in the opinion of the investigator, the event the health and safety of the participant will benefit from knowing the treatment code, efforts will be made to contact the medical monitor as long as patient safety is not at imminent risk. If the subject is at imminent risk, the investigator should have the ability to unblind although should notify the Medical Monitor (MM) and **Sponsor** as soon as possible thereafter.

Management of birth control and pregnancy during study

67 Contraception status should be assessed and documented prior to enrollment and study vaccination for female participants of childbearing potential. Adequate methods of contraception include barrier contraception, hormonal birth control, intrauterine device (IUD), surgical sterility, and abstinence from sexual activity that can lead to pregnancy. If a female participant becomes pregnant following randomization, she will be encouraged to complete remaining visits and study procedures (except for any remaining investigational product dosing) unless medically contraindicated. The investigator is required to notify the contract research organization (CR)O within 24 hours of knowledge of a pregnancy. Any participant who becomes pregnant during the period between vaccination and the last study visit will continue to be followed for pregnancy outcome, even if birth occurs after the scheduled end of the study for the subject. The pregnancy and its outcome will be reported on the Pregnancy CRF.

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