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Safety Assessment and Reporting (Part 7 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.bj52kq8e

Coronavirus Method Development Community PATH

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ABSTRACT

This is Part 7 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 Protocol COVID-19 Vaccine - 25AUG2020-version 1.docx

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

GUIDELINES

Site investigators will monitor participants to identify, evaluate, and manage safety events. A Safety Review Team composed of the clinical leads from the participating sites, representatives from **Sponsor** and the Safety Monitoring CRO will be established to periodically discuss safety aspects of the study. The team may be asked to address specific situations related to enrollment, follow up, and safety observations made. Prompt communications across this team will be required to analyze emergent, suspected vaccine-related safety observations of significance.

A subset of study participants will receive a diary card/memory aid to record signs and symptoms of solicited AEs during the week after each study vaccine dose. These participants will return to the clinic on Day 15 (day of 2nd immunization) and on Day **XX** (seven days after subsequent immunizations) with their diary card/memory aid.

All SAEs will be reviewed by the **DSMB or Safety Monitoring Committee**. The CRO Statistical & Data Management Center (SDMC) will provide monthly safety reports of accruing safety data during the active vaccination period. All SAEs will be reported to site ERCs/IRBs and regulatory authority, as required, and according the specific timelines imposed.

7.1. Definitions

7.1.1. Adverse event (AE)

An adverse event is any unfavorable or unintended medical event that occurs in the participant after administration of the study vaccine, including abnormal laboratory findings or disease temporally associated with the use of the study vaccine. An AE does not necessarily have a causal relationship with the study vaccine. This definition includes exacerbations of pre-existing conditions.Stable pre-existing conditions that do not change in nature or severity during the study are not considered AEs; however, these should be reported as part of the medical history.

7.1.2 Solicited AEs are pre-specified AEs that are common or known to be associated with vaccination and actively monitored as potential indicators of vaccine reactogenicity. Investigators will not be required to assess causality of solicited AEs if onset occurs during the solicitation period (the seven days following vaccination). Solicited AEs with onset after the solicitation will be captured as unsolicited AEs.

In this trial solicited AEs will be assessed by study staff 30 minutes following each vaccination, and then by participants daily for seven days (data to be collected for Days 1 through 7). Participants will be provided a diary card/memory aid to record the presence or absence of solicited AEs, their severity, and use of concomitant medication.

This trial will monitor the following specific solicited AEs:

- Local reactogenicity:
  - Pain
  - Tenderness

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- Erythema
- Induration
- Pruritus

- Systemic reactogenicity:
  - Fever
  - Headache
  - Fatigue
  - Chills
  - Myalgia
  - Arthralgia

7.1.3 Unsolicited AEs

Unsolicited AEs are any AEs reported spontaneously by the participant, identified during interview at study visits, observed by the study personnel during study visits, or identified during review of medical records or source documents.

7.1.4 Medically Attended Adverse Events

Medically attended AEs are AEs addressed with no-routine medical care (physical examination or vaccination)—include hospitalization, emergency room visits, or otherwise unscheduled visits to medical personnel (medical doctor) for any reason. Medically attended AEs may include the collection of data relating to specific AESI, including autoimmune or autoinflammatory diseases and exacerbations of chronic disease(s) following a vaccination.

7.1.5 Serious adverse event (SAE)

An SAE is any AE that:
- Results in death.
- Is life-threatening (life-threatening means that the study participant was, in the opinion of the investigator or Sponsor, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital abnormality or birth defect.

Important medical events that may not result in one of the above outcomes but that jeopardize the health of the study participant or (and) require medical or surgical intervention to prevent one of the outcomes listed above are also considered SAEs.

7.1.6 Suspected unexpected serious adverse reaction (SUSAR)

SUSAR is any suspected adverse reaction that is both unexpected and serious.

Reporting period and parameter

Safety events are reported from the time of randomization through completion of the study 12 months after first study vaccination. Specifically, solicited AEs to assess local and systemic reactogenicity will be collected 30 minutes after vaccination and then daily for seven days after each vaccination (through Day 7). If a solicited AE occurs during the seven days post vaccination and continues beyond those seven days, it will continue to be reported as a solicited AE.Unsolicited AEs will be collected for 28 days (day of and for 27 subsequent days) after study vaccination. SAEs will be collected from the day of study vaccination (Day 1) through the end of the study.

Severity of adverse events

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The severity of all AEs will be assessed by the investigator and participant (as applicable). The severity grading criteria (provided in Appendix B) grade AEs from Mild (Grade 1) to Life-Threatening (Grade 4). All AEs that result in death are Grade 5 events. Only AEs Grade ≥2 will be entered into the database, unless the event is associated with a known or suspected case of COVID-19.

Causality of adverse event

The study investigators will assess the causal relationship between the study product and the AE. The causality assessment is made based on the information available at the time of reporting and can be subsequently changed according to follow-up information. Assessment of causality is based on clinical judgment and should take into consideration the following factors:

- Is there a temporal (time-based) relationship between the event and administration of the study vaccine?
- Is there a plausible biological mechanism for the study vaccine to cause the AE?
- Is there a possible alternative etiology for the AE, such as concurrent illness or concomitant medications?
- Are there previous reports of similar AEs associated with the study vaccine or other vaccines in the same class?

For this study, the investigators must classify the causality of the AE according to the categories defined below:

- Related: The AE is known to occur with the vaccine, or there is a reasonable possibility the study vaccine caused the event. “Reasonable possibility” means there is evidence to suggest a causal relationship between the study vaccine and the AE.
- Not Related: There is not a reasonable possibility the study vaccine caused the event, or an alternative etiology has been established.

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity:

- Mild: Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- Moderate: Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

Follow-up of adverse event

All reported AEs should be followed until resolution or stabilization, or until the participant’s participation in the study ends. Participants who have an ongoing study product-related SAE at study completion or at discontinuation from the study will be followed by the PI or designee until the event is resolved or determined to be irreversible, chronic, or stable by the PI.

The outcome of the AE will be assessed at the time of last observation as per the following categories:

- Recovered/resolved (event has fully resolved, with return to baseline).
- Recovered/resolved with sequelae (event has stabilized, without full return to baseline and without anticipation of further improvement).
- Recovering/resolving (event is ongoing and improving).
- Not recovered/not resolved (event is ongoing and not yet improved, but with potential for further change).
- Fatal.
- Unknown.

7.2 General Guidance on Recording Adverse Events

To improve the quality and precision of acquired AE data, the PI should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording AEs on the AE CRF.
- If known, record the diagnosis (i.e. disease or syndrome) rather than component signs, symptoms, and laboratory values (e.g. record congestive heart failure rather than dyspnea, rales, and cyanosis).
- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on the SAE CRF.
- For hospitalizations for surgical or diagnostic procedures, the illness leading to the surgical or diagnostic

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procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.
- Pregnancies that occur in study participants are not considered AEs and will be recorded on a separate Pregnancy CRF. Pregnancy outcomes that include spontaneous abortion, stillbirth, or any congenital anomaly must be reported as SAEs.

7.3 Reporting of SAEs

The details and modalities of safety reporting will be provided in the safety management plan for the study. A brief description follows in the sections below.

7.3.1 Investigator Reporting to *Sponsor*

The **Sponsor** will designate a CRO with authority to coordinate SAE reporting activities. All SAEs that occur during the study, whether considered to be associated with the study vaccine or not, must be reported to the CRO within 24 hours of the site becoming aware of the event by one of the mechanisms provided (e.g., electronic data capture [EDC] system, email, fax, or telephone). Contact details and instructions for submitting SAEs will be provided in a handout located in the Investigator Site File. If the SAE is fatal or life-threatening, the CRO medical monitor should be informed within 24 hours by telephone or by email.

The investigator should not wait for additional information to fully document the event before notifying the CRO. When additional information becomes available, a follow-up submission(s) can be submitted. The initial SAE form should be completed with all information known at the time and should include minimal elements for initial assessment:

- Name and contact information of the investigator submitting the SAE report.
- Participant Identification number.
- Date participant received study vaccine.
- Description of the SAE and date of event onset.
- Investigator's preliminary assessment of severity and causality

When applicable, hospital case records and autopsy reports (including verbal autopsy) should be obtained (without name or personal identifiers).

The investigator will be responsible for notifying the ERC/IRB and the regulatory agency. Reporting procedures for all SAEs will be followed as per prevalent country-specific regulatory guidelines. The safety management plan will contain all the details of regulatory reporting. Copies of each report and documentation of ERC/IRB and regulatory notification and receipt will be kept in the study files.

7.3.2 Notification and Review of SAEs

The CRO medical monitor is be responsible for the initial review of SAE forms submitted by investigators to check for completeness and accuracy. The CRO medical monitor will contact the investigator to obtain additional information and clarification as needed. The CRO is responsible for notifying the **Sponsor** of SAEs within 24 hours. The CRO medical monitor will review all unanticipated events involving risk to participants or others, SAEs, and all participant deaths associated with the protocol and will provide a written report. At a minimum, the CRO medical monitor must comment on the outcomes of the event or problem and, in case of an SAE or death, comment on the relationship to study participation. The CRO medical monitor must also indicate whether he/she concurs with the details of the report provided by the site investigator.

7.3.3 Notification of *LOCAL* Ethical Review Committee (ERC)

All SAEs and deaths considered related or possibly related to the study vaccine should be promptlyreported to the ***LOCAL ERC/IRB*** via telephone or email within 48 hours of the PI becoming aware of the event. Full written reports should be submitted within 10 working days.

7.4. Non-compliance with the regulations or requirements

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The knowledge of any pending compliance inspection/visit by local or other government agencies concerning the study, the issuance of Inspection Reports, warning letters, or actions taken by regulatory agencies—including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements —must be promptly reported to **Sponsor**.

7.5 Safety oversight

While the site PIs and/or designated site staff will be primarily responsible for monitoring the safety of all study participants and for alerting **Sponsor** if unexpected concerns arise, additional layers of safety monitoring need to be established that include a Protocol Safety Review Team (PSRT) and a DSMB. The PSRT is in charge of reviewing cumulative safety data reports from the various sites enrolling participants into the study. It can also be assembled ad hoc for review of specific cases.The PSRT is composed of medical experts from **Sponsor**, the CRO Medical Monitor, and the PIs from each participating site.

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