1. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to provide guidance in the reporting requirements and responsibilities of the Investigators regarding protocol deviations, including specific definitions which will be used for the COPCOV study.

It is the responsibility of the investigators to ensure that the study is conducted in accordance to the study protocol, study-specific SOPs/instructions, ICH-GCP, local EC and applicable regulatory requirements. Any departure from the above will be considered as either minor or major deviation. Deviations will be recorded and reported to the COPCOV Study Coordinators, monitors, and local EC / regulatory authorities if necessary.

2. PROCEDURE

General definitions of deviations as well as study-specific criteria for COPCOV are listed below.

2.1 Minor deviation: Any departure from the approved protocol, study-specific SOPs/instructions or any other requirements which is not expected to result in harm to the trial participants or to significantly affect the study outcomes.

Examples of minor deviations include, but are not limited to the list below.

- Missed study drug for ≥3 consecutive days at any given time (as long as total drug compliance includes ≥75% of total daily doses, see major PD note below)
- Quality of life assessment was not done due to oversight
- Participant lost the mobile phone during follow-up period and no contact made with site staff for 2 or 3 days
- Dry blood spots not collected repeatedly as per protocol

COPCOV-specific minor protocol deviations:

- Participant lost study drugs, i.e. unused blister is lost or failed to return unused study drugs when discontinued early
- Taking disallowed medication described in section 8.5 of the protocol
- Missing ≥25% eDiary entries in any 30 day follow-up period
- Blood samples for serology not taken per sample schedule whilst enrolled in the study i.e. D0, D90, pre/post vaccination
- COVID/ARI admission questions were not administered during hospitalization
- Participant received COVID-19 vaccines and continued taking study medication after the vaccination date.
- Prior COVID 19 vaccination visit is more than 3 days after first dose
- Post COVID 19 vaccination visit (D28 ±3 days) is off the window
- Blood samples not collected during attendance at Prior and Post COVID-19 vaccination visits
2.2 Major deviation: Any departure from the approved protocol, study-specific SOPs/instructions or other requirements which may affect the safety and rights of trial participants or the study outcomes, including the EC/ regulatory requirements. Note that multiple or repeated minor deviations may be considered a major deviation.

Examples of major deviations may include, but are not limited to, the following:

- Failure to obtain informed consent (i.e. no documentary evidence) from the participant prior to enrolment
- Failure to re-consent as a result of protocol amendment which may affect the participant’s decision to continue in the study
- Enrolment of participants that do not meet the inclusion/exclusion criteria
- Conduct a study without the approval from the EC and implementing the amendment prior to EC approval, or undertaking a study procedure not in the approved protocol
- Failure to report serious adverse events (SAEs) and pregnancy in accordance with the EC and protocol requirements
- Failure to obtain extension of applicable EC/RA approval

COPCOV-specific major protocol deviations:

May include, but are not limited to, the following:

- Missed > 25% of study drug whilst enrolled in the study
- Incorrect loading dose per body weight
- Randomization done not in sequential order
- Nose swab and or throat swab not taken when ARI or COVID-19 is diagnosed
- Unblinding of randomisation without prior authorisation by study team
- Participant continued taking study drugs when diagnosed with COVID-19 and hospitalised

2.3 Recording Protocol Deviations

- All protocol deviations should be recorded in the ‘Protocol Deviation Log’ - see Attachment 1.
- Each deviation should be recorded on one line in the log. However, in an event that the same deviation involves several participants, this can be recorded as one deviation with the Subject numbers of the participants.
  For example, if informed consent was not dated by the participants and this was observed in several participants, this deviation can be recorded as one single deviation and the subject number of each participant involved should be provided.
- Corrective and preventive actions should be provided at minimum for all major deviations.

2.4 Reporting Protocol Deviations

- The Site PI should be informed promptly for major deviations and this should be noted in the Corrective Action section of the form with corrective action. The site PI should review all
protocol deviations no less than monthly, before the log is transmitted to MORU CTSG (see below).

- Protocol deviations should be reported to the local EC and/or other local regulatory authorities by the site PI as required, and to COPCOV Coordinator or monitor when requested. When reported to the local EC / regulatory authorities, a cover letter (or email) should be printed and filed together with the Protocol Deviation Log to identify the version sent.
- The current log and correspondences should be kept in the Investigator Site File.
- The log should be transmitted no less than monthly to the monitors for review. If requested the Coordinator or monitor may request more frequent transmittals or follow-up information.

2.5 Managing Protocol Deviations

- The study monitor and COPCOV Coordinator will review protocol deviations at least monthly and relay findings and requests for further information to the site.
- The site investigator is responsible to identify corrective and preventive actions, and address prevention of protocol deviations including re-training where appropriate.
- Repeated protocol deviations may indicate failure to comply with the study protocol and should be escalated to the site investigator and MORU as soon as possible.

3. RELATED DOCUMENTATION

- Attachment 1 – Protocol Deviation Log

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<th>Protocol Deviations Log</th>
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**STUDY**: Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)
SOP TITLE: Protocol Deviations

SOP VERSION HISTORY

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4. SOP SIGNOFF

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<td>Prayoon Yuentrakul</td>
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<tr>
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STUDY: Chloroquine/hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)