1. **Purpose**

The purpose of this SOP is to describe what should happen if a participant develops symptoms consistent with a COVID-19 illness or an Acute Respiratory Illness (ARI). This SOP will also describe what should happen for those participants formally diagnosed with a COVID-19 illness during their time in the study.

2. **Procedure**

2.1. **Participants who become unwell (not admitted to hospital)**

- Whether via the app or by phone, the participant reports feeling unwell, including with an ARI (potential COVID-19 symptoms) or potential drug side-effects, he/she will be contacted by the study team for assessment and to arrange for swabbing within 48 hours (if applicable). The taking of the study drug and the inputting of data into the mobile application should continue unless advised otherwise by the study team. Further follow-up of initial unwellness by the study team would be at the discretion of the assessing physician.

- It is recognised that the process for collecting the nose and throat swab (+/- sputum samples) from participants will vary between study sites (e.g., participants visiting isolation pods for sample collection). Site-specific procedures will be developed for this purpose.

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**STUDY**: Chloroquine/hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)
If there is a subsequent significant clinical change in the participant or the participant has further episodes of ARI within the trial period, this process will be repeated.

2.2. Diagnosis of possible COVID-19

- The subject will self-isolate, as per local or national guidelines. If a clinical sample has been taken for local analysis and is negative for COVID-19, then self-isolation could stop but would be determined by local or national guidance.

- If at the time of follow-up, a subject is self-isolating, provisions should be made to conduct the follow-up visit and provide the next 30 days of study medication (e.g. conducting the interview via phone and depositing the study medication at the subject’s residence). It is recommended that study blood samples are only taken when participants are able to attend the study clinic.

2.3. Participants who become unwell & are admitted to hospital

At the time of follow-up: If a subject remains in hospital provisions should be made to conduct the follow-up visit and supply the study medication (site dependent)

- Whether via the app or by phone, the participant informs the study team that they have been admitted to hospital, contact will be made with the participant and/or the medical team looking after him/her.

*Participants should follow local policies with regards to contacting the health authorities for possible symptomatic COVID-19 and advice on self isolation

** If hospitalised for non-COVID-19 reasons, the study medication should be continued. If medicines are to be given that may prolong the QT-interval any ECG should be undertaken

† If required, unblinding can be undertaken (see unblinding SOP)
• An SAE form will be completed for all participants admitted to hospital (see Adverse Events SOP for details and definition of hospitalisation). For those whose admission was COVID/ARI related and clinically required (i.e., not for isolation), the COVID/ARI Admissions Form should also be completed.

• If participants are hospitalised with symptoms consistent with COVID-19, they will continue the study medication until they are formally diagnosed with COVID-19 or unless advised to stop by their healthcare professional. If the participant misses a dose, they can take this dose later, up until the time they would take their next daily dose. The participant will be advised to inform their healthcare professional that he/she is in a prophylaxis study of hydroxychloroquine/chloroquine/placebo.

• Chloroquine and hydroxychloroquine have very few drug-drug interactions and should not interfere with the management of pneumonia. If a QT-prolonging drug will be prescribed, an ECG should be done.

• Upon being discharged from the hospital, the subject should alert the study team. The study team should nevertheless continue to monitor a participant’s condition whilst they remain in the hospital. It is important that the study team ensures that the mobile application remains active or is re-activated so that the participant can continue to input data on returning home. Following discharge the participant should restart the study medication if this had previously been stopped however this should be discussed with the study team to ensure there are no contraindications.

• If at the time of follow-up, a subject is isolating or still in hospital, provisions should be made to conduct the follow-up visit and provide the next 30 days of study medication (e.g. providing the medications to the medical team looking after the subject). It is recommended that study blood samples are only taken when participants are able to attend the study clinic.

2.4. PARTICIPANTS WITH A CONFIRMED COVID-19 DIAGNOSIS (NON-STUDY DIAGNOSIS)

The procedures for identifying a case and the subsequent isolation and management will follow local and national guidelines; this study will not interfere in the usual local investigation and management of suspected COVID-19 cases.

If the participant is diagnosed with COVID-19,

• They will take continue to take the study medication until:
SOP TITLE: COVID-19 ILLNESS/ACUTE RESPIRATORY ILLNESS SOP

- 90 days after enrolment (i.e., completion of kit) as hydroxychloroquine/chloroquine may attenuate the illness or prevent a further COVID-19 illness/ARI
- hospitalised due to COVID-19 disease (i.e., not for quarantine/isolation purposes) in which case they will stop, or
- advised to stop by their healthcare professional for other reasons

- They should continue to input their data into the mobile application.

- Study team members should make provisions to undertake scheduled follow-up visits when the participant is unable to visit the study site (i.e. during self-isolation/ admitted to hospital) to ensure the participant receives a further supply of study medication and that study data are collected (e.g. conducting the interview via phone and depositing the study medication at the subject’s residence/ to the subject’s medical team)

- Follow-up may be extended for a subset of participants dependent upon on the onset of the COVID-19 illness (see below).

2.5. PARTICIPANTS WHO BECOME UNWELL WITH PROVEN COVID-19 OR AN ARI WITHIN THE FINAL 60 DAYS OF THE STUDY

- If a participant becomes unwell in the final 60 days of the study they will be followed up until a maximum of 60 days from illness onset.

- The participant will attend the final follow-up on Day 90 if no-longer symptomatic and advised to do so by the study team;

  - if fully recovered, the study will end at this point
  - if they have not yet fully recovered, a follow-up will be undertaken 28 days after illness onset
  - if not fully recovered after 28 days, a final follow-up visit would be undertaken 60 days after illness onset

- Therefore, a participant who became unwell on Day 90, whom was not better 28 days later (D118), would be have a final follow-up at 60 days (D150).
2.6. Considerations for COPCOV Participants Being Enrolled into Other Studies or Being Prescribed Other Treatments:

- The primary objective of the COPCOV study assesses chloroquine/hydroxychloroquine in the prevention of COVID-19 in healthcare workers in a randomised placebo-controlled double-blind trial. A further secondary objective assesses the impact of these medications on the severity of symptoms.

- Enrolment in other interventional clinical trials or the prescribing of chloroquine/hydroxychloroquine or antivirals will interfere with determining the effect of chloroquine/hydroxychloroquine on disease severity.

- Therefore, we discourage giving prescriptions of chloroquine/hydroxychloroquine or antivirals outside of a clinical trial unless the drug is proven in the treatment of COVID-19 and is clinically needed as part of a participant’s medical management.

- Participants being considered for enrolment into another interventional clinical trial should be discussed with the COPCOV study team to determine:
  
  - if there are any potential harmful interactions with the new study drug,
  - whether unblinding is required (see SOP) and,
  - whether the chloroquine/hydroxychloroquine/placebo should be stopped.

- Nevertheless, participants should continue follow up for COPCOV study investigations.

- Unblinding of the COPCOV participant should be discussed with the COPCOV team and a decision taken either to:
  
  - unblind, discontinue COPCOV study drug and enrol into the new trial, or
  - remain blinded and continue in COPCOV.

3. Related Document

- Randomisation SOP: Preparation, Blister And Box (Drug Kit) Packing And Drug Kit Management Instructions

STUDY: Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)
4. **SOP Version History**

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<thead>
<tr>
<th>Version number/date</th>
<th>Major revisions</th>
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<tr>
<td>1/ 16 Apr 2020</td>
<td>Initial version</td>
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<tr>
<td>2 / 14 Aug 2020</td>
<td>1. The section “diagnosis of possible COVID-19” – “If blood samples are to be taken at this time then appropriate precautions should be taken. In order to reduce the exposure risk to study staff, if feasible, it is recommended that blood samples are only taken 10 days after illness onset.” Changed to “It is recommended that study blood samples are only taken when participants are able to attend the study clinic.” (This same sentence was changed on page 2 also). 2. The section “Participants who…admitted to hospital”, the flow diagram was updated so that study medication is stopped in those hospitalized with confirmed COVID-19. The subsequent text was also updated to reflect this and the following was also added “Following discharge the participant should restart the study medication if this had previously been stopped however this should be discussed with the study team to ensure there are no contraindications.” 3. The section “Considerations…prescribed other treatments”, was shortened and updated as chloroquine/hydroxychloroquine had subsequently been proven not to work in treatment. The subsequent flow chart was removed from the SOP.</td>
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<tr>
<td>3/ 26 Feb 2021</td>
<td>1. The participant reports feeling unwell will be contacted by the study team within &quot;24 hours (if applicable)” was updated to “48 hours (if applicable)” 2. “Further follow-up of initial unwellness by the study team would be at the discretion of the assessing physician.” was added into “the participants who become unwell (not admitted to hospital)” section.</td>
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5. **SOP Signoff**

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<thead>
<tr>
<th>Authored by:</th>
<th>Signature:</th>
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<tbody>
<tr>
<td>James Callery</td>
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<tbody>
<tr>
<td>Will Schilling</td>
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