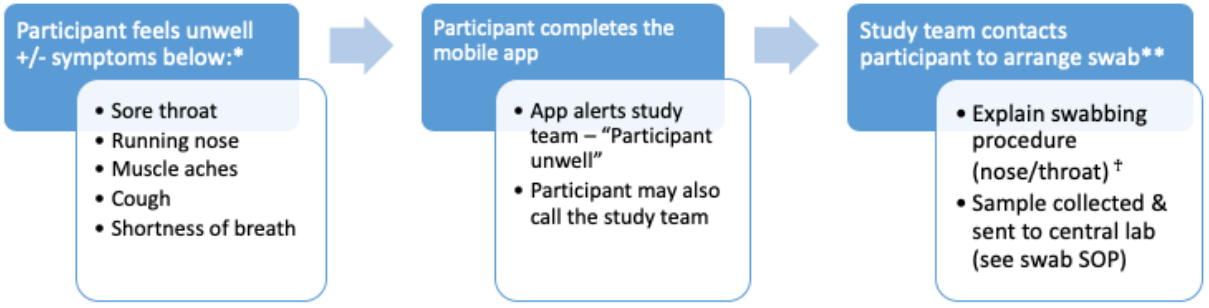
Purpose

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.

Procedures

Participants who become unwell (not admitted to hospital)



*Participants should follow local policies with regards to contacting the health authorities for possible symptomatic COVID-19 and advice on self isolation
** Swab only taken if symptoms suggest COVID-19/ARI (e.g. not for drug side-effects)
† In some instances (productive cough) a sputum sample will be collected

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. If symptoms are suggestive of COVID-19 (new continuous cough and / or fever (≥37.8°C)) the study team will arrange for a combined nose and throat swab to be obtained +/- a sputum sample. The taking of the study drug and the inputting of data into the mobile application should continue unless advised otherwise by the study team.

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, posting in self-taken swabs). Site specific procedures will be developed for this purpose.

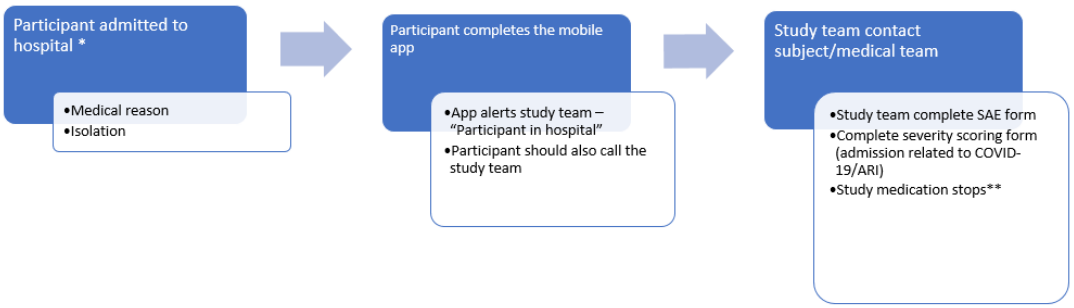
If there is a subsequent significant clinical change in the participant or the participant has further episodes of ARI within the trial period, this process will be repeated.

Diagnosis of possible COVID-19

The participant will follow local or national guidelines about self-isolation, attendance at work, sampling for employment purposes and seek medical help as they would if not taking part in the research.

If at the time of follow-up, a participant is self-isolating, provisions should be made to conduct the follow- up visit (e.g. conducting the interview via phone). It is recommended that study blood samples are only taken when participants are able to attend the study clinic.

Participants who become unwell & are admitted to hospital



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

** Note the terminal $t_{1/2}$ of hydroxychloroquine is long so if medication that may prolong the QT-interval is to be given then an ECG should be done and if necessary unblinding can be undertaken (see unblinding SOP)

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.

An SAE form will be completed for all participants admitted to hospital (consult protocol for details). For those whose admission was clinically required (i.e. not for isolation), the COVID/ARI Admissions Form should also be completed.

The participant will be advised to inform their healthcare professional that he/she is in a prophylaxis study of hydroxychloroquine/placebo. The study medication should be stopped for participants admitted to hospital with a confirmed diagnosis of COVID-19.

Hydroxychloroquine drug-drug interactions should not interfere with the management of pneumonia. If a QT-prolonging drug (e.g. a macrolide) is to be prescribed, an ECG should be done.

Upon being discharged from the hospital, the participant 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.

If at the time of follow-up, a participant still in hospital, provisions should be made to conduct the follow-up visit by telephone. It is recommended that study blood samples are only taken when participants are able to attend the study clinic.

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.

- The study drug should continue to be taken until Day 90 **unless the participant is admitted to hospital** (as hydroxychloroquine may attenuate the illness or prevent a further COVID-19 illness/ARI)
- It should only be stopped if:
    - participant is admitted to hospital
    - advised by a medical professional or the study team
    - to follow national treatment guidelines or to consider a COVID-19 treatment trial (see below)
    - the participant chooses to stop the study drug in consultation with the study team
- The participant 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 that study data are collected (e.g. conducting the interview via phone)
- Follow-up may be extended for a subset of participants dependent upon on the onset of the
    - COVID-19 illness (see below).

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).

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 trials or the prescribing of chloroquine/ hydroxychloroquine or antivirals will interfere with determining the effect of chloroquine/ hydroxychloroquine on disease severity.

At the time of writing chloroquine/ hydroxychloroquine (or other medications) have not been proven to be effective in the prevention or treatment of COVID-19. Studies into use of these drugs are being conducted, and in some countries, despite the lack of evidence, prophylaxis and treatment with these agents are being advocated at local and national levels.

Therefore, we discourage giving prescriptions of chloroquine/ hydroxychloroquine or antivirals outside of a clinical trial (Figure 1).

Participants being considered for enrolment into another clinical trial using chloroquine/ hydroxychloroquine, or other potential antivirals 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 hydroxychloroquine/placebo should be stopped. Nevertheless, participants should continue follow up for COPCOV study investigations.

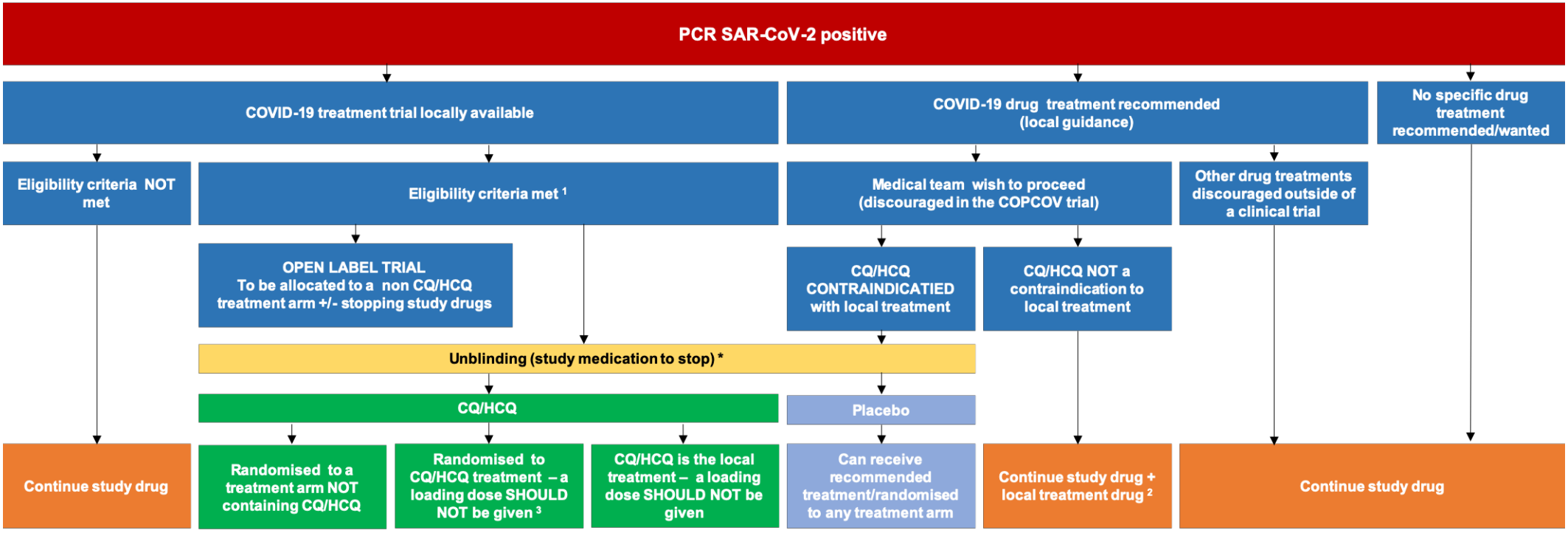
If enrolment of a COPCOV participant into a treatment trial includes a chloroquine/ hydroxychloroquine loading dose, the loading dose should not be given if the COPCOV participant was receiving either of these drugs.

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.

Figure 1: Considerations for COPCOV participants being enrolled into other studies or treatments

We would recommend that if a COPCOV participant is being considered for enrolment into another clinical trial that this is discussed with the COPCOV study team prior to any decision being made.



* Unblinding of COPCOV participants should be discussed with the COPCOV study team prior to treatment/trial decisions being made
[1] Implications to unblinding should be carefully considered (unblinding may reveal that he/she is receiving CQ/HCQ and they may then be randomised to receive a placebo treatment)
[2] CQ/HCQ treatment should not be given whilst taking the study drug
[3] Maintenance dose CQ/HCQ could be given at the discretion of the treatment trials study team