Study Title: Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from the University of Oxford, the Investigator Team and members of the Oxford Tropical Research Ethics Committee (OxTREC) and local Ethics Committee, unless authorised to do so.

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Study Title	Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)	
Protocol number	VIR20001	
Study Design	Randomised double-blind, placebo-controlled trial	
Study Participants	Healthcare workers, those working frontline (patient contact) in healthcare facilities, and other high-risk groups. Adults (exact age is dependent on countries)	
Planned Sample Size	40,000 total participants	
Planned Study Period	12 months; individual trial duration maximum 5 months	
	Objectives	**Outcome Measures**
Co-Primary	To determine if chloroquine or hydroxychloroquine prophylaxis prevents symptomatic COVID-19 infection in health care workers or other groups at high risk.	The number of symptomatic COVID-19 infections will be compared between the chloroquine and placebo groups.
Co-Primary	To determine if chloroquine or hydroxychloroquine prophylaxis attenuates COVID-19 infections.	The symptoms severity and duration of COVID-19 illness, in those who become infected during the study will be compared between the two groups using a respiratory severity score.
Secondary	a) To determine if chloroquine or hydroxychloroquine prophylaxis prevents asymptomatic COVID-19 infection.	a) The number of asymptomatic cases of COVID-19 will be determined by comparing acute and convalescent serology in the two groups.
	b) To determine if chloroquine or hydroxychloroquine prophylaxis prevents all-cause symptomatic acute respiratory illnesses.	b) The number and severity of symptomatic acute respiratory illnesses will be compared in subjects randomised to chloroquine or placebo.
Tertiary	To characterise genetic and baseline biochemical markers associated with symptomatic COVID-19, respiratory illness and disease severity.	Genetic loci and levels of biochemical components will be correlated with occurrence of and disease severity of COVID-19 or other ARIs.

2. ABBREVIATIONS

ARI	Acute Respiratory Illness
COVID-19	Coronavirus Disease 2019. The disease caused by the virus SARS-CoV-2
CPAP/ BiPAP	Continuous Positive Airway Pressure and Bilevel Positive Airway Pressure
CRF	Case Report Form
CUREC	Central University Research Ethics Committee
DSMB	Data Safety and Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
GCP	Good Clinical Practice
ICF	Informed Consent Form
LOMWRU	Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit
LTFU	Lost to follow-up
MORU	Mahidol Oxford Tropical Medicine Research Unit
OxTREC	Oxford Tropical Research Ethics Committee
PI	Principal Investigator
PIS	Participant Information Sheet
PPE	Personal Protective Environment
RR	Respiratory Rate. Number of breaths per minute
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2. The virus responsible for COVID-19
SLE	Systemic Lupus Erythematosus
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
THN	Tropical Health Network
URTI	Upper Respiratory Tract Infection (coryza, sore throat)

3. BACKGROUND AND RATIONALE

As of writing, the novel betacoronavirus SARS-CoV-2 has infected more than 200,000 individuals, killed over 8,000 people and has spread to more than 170 countries[1]. The epicentre of the COVID-19 epidemic was the city of Wuhan, Hubei province, China, where the largest number of those infected reside. After

[1] World Health Organization's COVID-19 situation report

China, the countries most affected are within the Asia Pacific region, including Japan, Korea, Thailand and Vietnam, with recent major outbreaks in Iran and Italy and elsewhere in Europe, but countries in the Asia Pacific region with weaker health systems have only just started to be able to test (and then only in the largest cities).

It is believed that the main mode of transmission of COVID-19 is respiratory droplet spread but it is assumed that spread by direct contact is also likely; with the finding of SARS-CoV-2 in faeces, an oral faecal route of transmission is also possible (1). There is no proven effective prophylaxis, no proven treatment and no vaccine. The crude mortality is currently 4%. This is some ten times higher than seasonal influenza virus which infects up to 1 billion people a year and kills between 290,000 to 650,000 (2)[2]. The estimated COVID-19 basic reproductive ratio (R_0) of 1.25 to 3.0 is similar to or slightly higher than that of seasonal (1.3) or pandemic influenza (1.4 to 1.8) (3, 4).

We are in a race against time to find effective treatments and preventive measures as the pandemic grows. There is major concern that COVID-19 could devastate countries with limited capacity for testing and case isolation, and overwhelm their fragile healthcare systems. The high risk to healthcare workers, as seen with SARS-CoV previously, and now in Wuhan with COVID-19, could be a major threat to healthcare operations overall (5).

Chloroquine, an antimalarial drug discovered in 1934 and introduced generally in 1947, is probably the drug to which humans have been most exposed. With an adult treatment dose of 1.5g for malaria, an annual global consumption of hundreds of metric tonnes for over 50 years, and an elimination half-life of approximately one month, the average person in many tropical countries once had detectable chloroquine in their blood. Chloroquine has a very large apparent volume of distribution because of extensive tissue binding and slow elimination (6-8). Plasma concentration profiles with daily dosing are determined mainly by distribution rather than elimination. The main metabolite desethyl chloroquine also has significant biological activity. Chloroquine is inexpensive and simple to administer. It remains a first-line treatment for non-falciparum malaria and is on the World Health Organization's List of Essential Medicines[3].

Chloroquine has been used extensively as continuous chemoprophylaxis against malaria for individual periods often exceeding five years and has been the prophylactic drug of choice in pregnancy (9). It is safe in all age groups. In addition to its antimalarial use both chloroquine, and the closely related and slightly more hydrophilic hydroxychloroquine, are used in continuous daily dosing for rheumatoid arthritis, systemic and discoid lupus erythematosus and psoriatic arthritis. Chloroquine at a dose of 2.4mg base/kg (155 mg)/day for years is used for rheumatoid arthritis. Chloroquine given at the correct dose has an excellent safety profile. It has even been added to salt to prevent malaria by mass exposure (10).

Chloroquine has significant antiviral activity against SARS-CoV-2 in cell culture, as it does for the related SARS-CoV (11-14). A half-maximal effective concentration (EC50 or the concentration associated with a decrease in the cytopathic effect of the virus by 50%) of 1.13 µM on Vero E6 cells has been reported with a corresponding EC90 of 6.9 µM. Several other laboratory studies confirm activities in the low micromolar range for chloroquine and hydroxychloroquine (15). This effect occurred when the drug was given either before or after viral inoculation. These are relatively high concentrations by comparison with therapeutic exposures in the treatment of malaria but could be achieved with daily oral dosing. Chloroquine has

[2] World Health Organization's Factsheet on Seasonal Influenza
[3] World Health Organization's list of Essential Medications

complex pharmacokinetic properties, having a very large total apparent volume of distribution and a relatively small central compartment with extensive tissue binding, including in the lung. The relationship between plasma concentrations and concentrations in respiratory epithelium is not known precisely, though in rats the concentration in lung is between 124 and 748-fold that in plasma (16). Chloroquine concentrations in the human lung would be expected to exceed those required for the EC90 after an initial dose. There are preliminary reports emerging from China of clinical benefit in the treatment of COVID-19 infections (17), and increasing consensus that chloroquine should be evaluated urgently in the prevention and in the treatment of COVID19 infections.

Hydroxychloroquine was synthesised first in 1946 and has largely replaced chloroquine for the management of autoimmune diseases as it has a slightly better adverse effect profile (higher thresholds for toxicity in experimental animals, less abdominal discomfort, higher threshold for retinal toxicity). It has very similar pharmacokinetic properties except for a smaller apparent volume of distribition, probably because of its greater hydrophilicity. In-vitro it has approximately twice the activity of chloroquine against the SARS-CoV-2 virus (15).

We hypothesise that chloroquine and hydroxychloroquine might both slow viral replication in exposed subjects, attenuating or preventing the infection. Given the enormous experience of use in chemoprophylaxis, excellent safety and tolerability profile and its very low cost, if it proved effective then it would be a readily deployable and affordable preventive measure for high risk individuals such as health care workers.

Main research questions:

The primary objectives are is to determine if prophylactic chloroquine or hydroxychloroquine: (i) prevents symptomatic COVID-19 illness, and (ii) attenuates the clinical severity of COVID-19 infection.

The secondary objectives include:

- preventing asymptomatic COVID-19
- prevents symptomatic all-cause acute respiratory illnesses (ARI)

Brief description of the intervention:

The study is a double-blind, randomised, placebo-controlled trial that will be conducted in healthcare settings. After obtaining fully informed consent, we will recruit healthcare workers, or other individuals at significant risk, who can be followed up reliably for up to 5 months. In Asia they will be randomised to receive either chloroquine or placebo (1:1 randomisation). In Europe they will be randomised to receive either hydroxychloroquine or placebo (1:1 randomisation).

A loading dose of 10 mg base/kg (four 155mg tablets for a 60kg subject), followed by 155 mg daily (250mg chloroquine phosphate salt or 200mg of or hydroxychloroquine sulphate) will be taken for 3 months. Subsequent episodes of symptomatic respiratory illness, including symptomatic COVID-19, clinical outcomes, and asymptomatic infection with the virus causing COVID-19 will be recorded during the follow-up period. If they are diagnosed with COVID-19 during the period of prophylaxis, they will continue their prophylaxis unless advised to do so by their healthcare professional until they run out of their current supply of chloroquine/placebo at home. They will not collect more. They will be followed up for 28 days (up until a maximum of 60 days if not recovered at 28 days).

Investigation of a suspected case:

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 COVID-19 cases. Chloroquine and hydroxychloroquine have very few drug-drug interactions and should not interfere with the management of pneumonia.

Summary of findings of previous studies:

No studies have used chloroquine or hydroxychloroquine for prophylaxis for COVID-19 in humans. However, chloroquine has been used widely and a wealth of experience and data testify to its safety both for mass drug administration (MDA) for malaria, as routinely prescribed antimalarial prophylaxis, and for rheumatological conditions for which people may be take the drug daily at doses comparable to those in this study for decades with few ill-effects. Hydroxychloroquine has been used widely for over 50 years in the treatment of rheumatoid arthritis, SLE and other similar conditions.

The risks of chloroquine or hydroxychloroquine chemoprophylaxis are minimal compared with the risks of COVID-19 and there are currently no other proven chemoprophylactic agents, treatments or a vaccine. Assumptions of the study include that the *in vitro* effects of chloroquine or hydroxychloroquine against the COVID-19 virus will translate to an *in vivo* effect and a benefit in human participants. As described chloroquine or hydroxychloroquine should reach levels in human tissues, including the lungs which were shown to have a viral suppressive effect *in vitro*. However, the exact distribution of chloroquine or hydroxychloroquine within the respiratory tract, and whether these *in vitro* findings will translate into clinical benefit is unknown.

Summary of known and potential risks and benefits of the study:

Risks:

Risks related to chloroquine phosphate/sulphate/hydrochloride and hydroxychloroquine sulphate are very low, unless the drug is taken in overdose. These are very safe and generally well tolerated medications but adverse reactions relating to the cardiovascular system, the central nervous system, the skin, hypoglycaemia, hypersensitivity, gastrointestinal, and retinal toxicity have all been described though usually after high doses or protracted exposures. The main adverse effect is itching in dark-skinned individuals; Africans are much more commonly affected compared to Asians. These risks will be mitigated by excluding participation if people have had a previous serious adverse reaction to chloroquine, or hydroxychloroquine, 4-aminoquinoline compounds, any components of the tablet or retinal or visual field changes of any aetiology.

Benefits:

- Access to a drug which may potentially prevent or ameliorate COVID-19 infection. No other proven preventive medication or vaccine exists currently exists. The main potential benefit is to the subject in the chloroquine or hydroxychloroquine arm (direct protection) but individuals in the placebo arm may benefit from indirect protection through decreased ability of the infection to spread.

- Awareness that their participation may lead to an intervention which may save many lives around the world or, alternatively, may show chloroquine or hydroxychloroquine prophylaxis is ineffective so trials can move on to evaluate other possible interventions with a minimum of delay.

Description of the population to be studied and the population to whom the results of the study may be generalisable:

The population to be studied comprises adult healthcare workers and other frontline staff working in healthcare facilities, or other well circumscribed groups who are at high risk and could be followed in the trial. These could include nurses, healthcare assistants (HCAs), doctors, pharmacists, cleaners, dieticians and anyone who has direct contact with patients with potential COVID-19 within a healthcare facility. Only workers who will be looking after, or otherwise have close contact with COVID-19 patients, will be enrolled. Study participation will be open to hospitals and lower level health centres.

If shown to be beneficial, this study would be generalisable to all people around the world at risk of COVID-19.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Co-Primary Objective To determine if chloroquine or hydroxychloroquine prophylaxis prevents symptomatic COVID-19 infection in health care workers or other groups at high risk.	The number of symptomatic COVID-19 infections will be compared between the chloroquine or hydroxychloroquine and placebo groups.	During the trial period
Co-Primary Objective a) To determine if chloroquine or hydroxychloroquine prophylaxis attenuates COVID-19 infections.	The symptoms, severity and duration of COVID-19, in those who become infected during the study will be compared between the two groups using a severity score.	During the trial period
Secondary Objectives a) To determine if chloroquine or hydroxychloroquine prophylaxis prevents asymptomatic COVID-19 infection.	a) The number of asymptomatic cases of COVID-19 will be determined by comparing acute and convalescent serology in the two groups.	During the trial period
b) To determine if chloroquine or hydroxychloroquine prophylaxis	b) The number and severity of symptomatic acute respiratory illnesses will be compared between the	During the trial period

prevents all-cause symptomatic acute respiratory illnesses.	chloroquine or hydroxychloroquine and placebo groups.	
Tertiary Objectives: To characterise determine genetic and baseline biochemical markers associated with symptomatic COVID-19, respiratory illness and disease severity	Genetic loci and levels of biochemical components will be correlated with frequency of COVID-19, ARI and disease severity.	During and after the trial period

5. STUDY DESIGN

The study is a double-blind, randomised, placebo-controlled trial that will be conducted in healthcare settings. We will recruit healthcare workers, or other individuals at significant risk, who can be followed reliably for 5 months. 40,000 participants will be recruited and we predict an average of 400-800 participants per site in 50-100 sites.

The participant will give written informed consent. As part of the informed consent process the risks and benefits of the study will be explained to them in their language, including potential side-effects of chloroquine. They will also be informed that biological samples will be stored for a maximum of ten years and may be processed for genetic material and other pathogens. They will also consent to having clinical information shared with the study team, although these data will remain anonymised and stored and processed in accordance with national and international standards and in accordance with regulating bodies. The participant will be instructed how to use the simple reporting app on their mobile phone. While well, the participant will continue their normal duties and activities (i.e. in the healthcare facility). The study procedure of reporting side-effects and adverse reactions will be explained (reporting to the site local PI and if necessary stopping the medication). The subject will also be informed what to do if they develop symptoms of an acute respiratory infection (ARI), which will be to alert the study team and follow institutional and governmental guidelines to get tested for COVID-19 (dependent on site).

The participant will be randomised in Asia to receive either chloroquine or placebo (1:1 randomisation) or in European trials to hydroxychloroquine or placebo (1:1 randomisation). A loading dose of 10mg base/kg (four 155mg tablets for a 60kg subject), followed by 155 mg daily (250mg chloroquine phosphate salt/ 200mg hydroxychloroquine sulphate) which will be taken for 3 months or until they are diagnosed with COVID-19, in which case they will take continue to take it, unless advised to stop by their healthcare professional, until they run out of their current supply of study medication (they do not go back to the study site to collect more. If the participant misses a dose, they can take this dose later, up until the time they would take their next dose. If they do not take their dose within this period of time, they will not take it and this dose will be classed as missed. They should continue to take their medication regularly. The missed dose will be reported to the study team at the next assessment at the study site.

Episodes of symptomatic respiratory illness, including symptomatic COVID-19, and clinical outcomes will be recorded in the CRF during the follow-up period.

At the initial visit participants will provide demographic and basic clinical data and have their weight and height measured. 10mls of blood will be taken, centrifuged and the serum, plasma and cell fraction stored

at -80°C for future analysis. This sample will be used for baseline antibody testing, biochemical tests and host genetics related to susceptibility to respiratory illness, and COVID-19 infection.

Participants will be given a card with a Subject ID number, randomised and given 30 days of study medication and asked to see the local PI 28-30 days later. The drug will be taken once daily in the morning (or evening for night shifts). The card will have contact numbers for the study team members whom they are to inform should they develop adverse reactions/ side-effects or symptoms. The initial weight-based loading dose will be observed by the study nurse. Participants will also be given a thermometer, and requested to record their temperature twice a day, as well as any significant exposures or symptoms.

Participants will be requested to record twice daily temperature readings and symptoms via a mobile-based application or web interface. The data will be transferred securely to the team and merged with other study data for analysis. Participants reporting to be unwell or those who do not record their twice daily temperature readings will be contacted within 24 hours by the study team. Should participants be unable to access the mobile application or website, the study team will phone them and record the data on their behalf.

If symptoms consistent with COVID-19 occur, the participant will be asked to alert the study team by 'phone and will be visited by the site study nurse for nose and throat swab samples to be taken (even if a sample has been taken previously for clinical purposes) according to MORU's SOP and strict adherence to PPE. The subject will continue his/her chloroquine/placebo.

If there is a subsequent significant clinical deterioration in the patient or the patient has further episodes of ARI within the trial period, this process will be repeated. Samples taken by the site study nurse will be stored at -80°C and tested for respiratory viruses at the end of the trial. 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 can stop according to local or national guidance.

If the PCR is positive for SARS-CoV-2 then the isolation practices and contact tracing will follow the local practices and guidelines, and chloroquine/placebo or hydroxychloroquine/placebo will continue unless the participant is advised to stop by their healthcare professional or until they run out of their current supply of chloroquine or hydroxychloroquine /placebo at home. They will not collect more. The participant will continue to give an update of their clinical condition on the app, or will be called by mobile phone until recovered and followed up once more at 28 days by phone. If the participant develops an ARI within the final 60 days of the study which is not diagnosed as COVID-19, they will continue chloroquine or hydroxychloroquine /placebo as normal but will be followed up for 28 days after the onset of infection. For all participants with an ARI, including those confirmed to have COVID-19, if the participant has not recovered by 28 days this period can be extended up to 60 days.

As well as twice daily electronic reporting, participants will be reviewed at least monthly to assess drug tolerability, respiratory and other symptoms and fever, and whether the local authorities have taken a swab for COVID-19 (in case they had not contacted the study team). This will be done in person (if the participant is not symptomatic) and will be combined with:

- collection of a study adverse events questionnaire;
- a dried blood spot (DBS) sample on filter paper for chloroquine levels;
- receipt of further study drugs.

Subjects will be requested to give a further 5ml clotted blood sample at the end of the trial. They will be asked not to take their trial medication on the morning of review -the medication will be taken after the interview.

Outcome measures are:

- symptomatic COVID-19 (ARI and RT-PCR positive for SARS-CoV-2)
- asymptomatic COVID-19 (no reported ARI symptoms and seroconversion against SARS-CoV-2)
- symptomatic ARI of another aetiology

For those who acquire symptomatic COVID-19, a continuous severity score will be used to assess severity, and these will be captured longitudinally over time. In order to discriminate between severity at the lower end of the spectrum we will use a logarithmic scale and a Wilcoxon test can then be used to compare ranks between the two groups.

Participants will remain enrolled until one of the following events occur:

- The trial ends
- They choose to withdraw consent or no-longer wish to participate in the trial
- An adverse event warrants removal from the study

6. PARTICIPANT IDENTIFICATION AND RECRUITMENT

6.1. Study Participants

These are of two types:

A. Adult volunteers (exact age is dependent on countries) working as a healthcare worker or frontline (i.e. patient contact) in a healthcare facility or similar institution

B. Provided that they are willing to participate in the trial and can be followed adequately for up to 5 months, we may also enrol hospitalised patients or relatives exposed or potentially exposed to the SARS-CoV-2 virus or other high-risk groups

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study and agrees with the study and its conduct
- Agrees not to self-medicate with chloroquine, hydroxychloroquine or other potential antivirals
- Adults (exact age is dependent on countries)
- Not previously diagnosed with COVID-19
- Not currently symptomatic with an ARI
- Participant A. works in healthcare facility or other well characterised high-risk environment, OR B. is an inpatient or relative of a patient in a participating hospital and likely exposed to COVID-19 infection or another high-risk group

- Possesses an internet-enabled smartphone (Android or iOS)

6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Hypersensitivity reaction to chloroquine, hydroxychloroquine or 4-aminoquinolines
- Contraindication to taking chloroquine as prophylaxis e.g. known epileptic, known creatinine clearance < 10 ml/min
- Already taking chloroquine, hydroxychloroquine or 4-aminoquinolines
- Taking a concomitant medication described in section 8.5, which cannot be safely stopped
- Known retinal disease
- Inability to be followed up for the trial period
- Known prolonged QT syndrome (however ECG is not required at baseline)

7. STUDY PROCEDURES

7.1. Recruitment

Study sites will be initially pre-selected on the following criteria if ALL of the following are met:

- There is prior agreement from the healthcare board of directors that the study can be conducted in the facility
- Local or national ethical/ IRB approval can be put in place rapidly
- It is a healthcare facility, institution or organisation whose staff members are deemed to be at high-risk of COVID-19
- There are adequately trained personnel able to conduct the study procedures described in the protocol
- Each site would be able to recruit a projected 400 participants during the trial period

Study sites *may* then be selected if ANY of the following criteria are met:

- Confirmed nosocomial spread of COVID-19 in the healthcare facility, or neighbouring facilities
- Confirmed cases of COVID-19 in the healthcare facility, or neighbouring facilities
- Confirmed person-to-person transmission of COVID-19 in the local area

Recruitment of individuals into the study once sites are confirmed and local or national ethical/ IRB approval is in place:

Healthcare facilities will contact their staff to inform them of the study through usual means. In addition, with the institution's consent, the site study PI will advertise the study with posters, social networking and through word of mouth. Recruitment into the study will occur in person either in, or nearby, the facility.

7.2. Screening and Eligibility Assessment

Eligibility assessment will occur at the point of screening. If, based on the inclusion and exclusion criteria, the subject is eligible, they will be randomised to receive trial drug packets containing chloroquine or placebo.

7.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part; their samples being stored indefinitely and being processed for host genetic material and other pathogens; and for any clinical data during the trial, being shared with the study team.

It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by one of the Investigators. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

7.4. Clinical examination

There will be no physical clinical examination. Basic demographic information, and details of past medical history, concomitant medications, allergies, smoking, alcohol and other drug intake will be noted. The height and weight will be recorded.

7.5. Randomisation and blinding

Chloroquine phosphate tablets containing 155mg base equivalent and identical placebo pills will be packed in opaque blister packs containing 10 tablets. Hydroxychloroquine sulphate tablets containing 155mg base equivalent and identical placebo pills will also be packed in opaque blister packs containing 10 tablets. Each participant will receive a study box containing up to 100 tablets. The initial dose to be taken from the starter blister pack is 10mg/kg, which will be between three and six tablets depending on the weight of the participant.

A randomisation list will be prepared by a Statistician using block randomisation in a 1:1 ratio for the chloroquine arm versus the placebo. The randomisation will be computer-generated and programmed in Stata 15. An appropriate computer seed will be used to allow reproducibility of the randomisation list. The list will be provided directly to the pharmaceutical company by the trial statistician to allocate a box containing 10 blister packs with 10 tablets in each blister to participants based on the computer pre-generated randomisation list. The allocation of study boxes will be performed by independent staff at the pharmaceutical company and will follow the computer-generated randomisation list provided by the

statistician. Should the company not have capacity to pack treatment, the allocation of study boxes will be performed by independent staff at MORU. At enrolment the subject's kit number will be written on the study box and on each blister pack (if possible), and the starter blister pack and first 30 tablets dispensed to the participant. The kit number will be linked to the treatment that has been allocated to each participant. All study staff will be blinded to the actual treatment and only the trial statistician and the backup statistician will have access to the randomisation code. The unblinded randomisation list and the randomisation programs will be securely kept by the statistician and backed-up. The study box will be kept securely by the study staff. Subsequent 30 tablets (3 blister packs) will be dispensed at each monthly check with the study manager. Individual unblinding will be done only on consultation with the study PI. Only the study statistician will have the drug allocation list.

A separate procedure will be provided to study teams to describe randomisation procedure.

7.6. Baseline Assessments

At Day 0 (D0), Participants will be given a card with a participant ID number, have an app installed on their mobile phone, and be randomised and given 30 days of study medication and asked to see the local PI 28-30 days later. The drugs will be taken in the morning (or evening for night shifts). The card will have contact numbers for the study team members whom they are to inform should they develop adverse reactions, side-effects or symptoms.

Participants will also be given a thermometer, will be requested to record their temperature twice a day, as well as any significant exposures or symptoms on an app (phone-based) reporting software application. The mobile app will be set up on the participant's phone and they will be instructed in its use in the presence of the PI at D0, as well as instructing them on how to report symptoms and use the thermometer. Those reporting to be unwell or those who do not respond on the app will be contacted by the study team.

At the initial visit participants will provide demographic and basic clinical data and have their weight and height measured. 10mls of blood will be taken, centrifuged and the plasma and cell fraction stored at minus 80°C for future analysis.

The participant will be observed taking the first (weight-based dose) dose of study drug by the study staff.

7.7. Subsequent Visits

At Day 28-30, if the subject is asymptomatic they can present in person to collect a further 30 days of study medication. This process will occur every 28-30 days for a total 3 months. If the participant does not present, they will be contacted and the appointment will be arranged, and provision made for the participant to collect the study product.

At each visit (D30, D60 and D90):

- Participant identification will be confirmed. Use of the mobile telephone number given at the initial assessment will suffice as long as the study manager has no reason to suspect the subject is not the same person
- Adherence (question and pill count). The used blister pack will be returned, checked and stored. The time of the last dose will be noted
- Adverse reactions or side-effects will be assessed

- Symptoms compatible with COVID-19, testing for and results of testing for the infection
- A finger prick for DBS and chloroquine/hydroxychloroquine levels at the visits D30 (+/- 2) and D60 (+/- 2)
- At the final visit (D90), 5ml of venous blood will be taken in a clotted bottle

Additionally, during this period the study participant will be asked to record twice daily via a mobile phone app a) whether they are well or unwell b) their temperature readout on the axillary thermometer provided. They will be reminded to take their tablet. These data will be transferred securely to the team and analysed. Those reporting to be unwell or those who do not respond on the mobile app will be contacted by the study team.

If via the app or by phone, the patient reports to feel unwell with an ARI or potential drug side-effects, they will be contacted by the study PI, and a visit to their residence for testing will be organised within 24 hours. The procedure will be explained on the phone and members of the study team will collect a nose and throat swab according to the MORU SOP. They will ask the participant some more detailed questions. In addition, if a significant clinical deterioration should occur, or further ARIs occur in the study period, the nose and throat swab will be repeated. If the patient is producing sputum, a sample will be collected in a pot, or a sputum pot will be left with the participant, for later collection.

The participant will be advised to inform their healthcare professional they are in the study. If the participant's healthcare professional starts a treatment which is known to prolong the QT interval, while the patient is enrolled in the study, then an ECG should be performed by this professional and checked for QT prolongation.

7.8. Sample Handling

On D0, 10mls of venous blood will be taken [EDTA (4mL) and clotted bottle (6mL)]. Both samples will be centrifuged at 1500g for 10 minutes. Three aliquots of serum from the clotted bottle and three aliquots of plasma from the EDTA tube will then be frozen at -80°C and stored until further notice. Additionally, a single aliquot of the cell fraction from the EDTA tube will also be aliquoted and frozen immediately at minus 80°C. Samples maintained at minus 80°C will be transferred eventually to MORU Tropical Health Network laboratories, maintaining the cold chain, where they will undergo testing in accordance with best practice laboratory measures and safety procedures.

On the last day of the trial, or sooner if the participant develops COVID-19, we will collect 5mls of venous blood in a clotted bottle. The sample handling procedure will be the same as above.

At day 30 and day 60 of the trial, when participants attend for review, they will undergo DBS testing. This will involve a finger prick. 200µl of blood will be spotted onto filter paper and allowed to dry. These samples will then be packed and placed with an absorbent packet, stored securely on site and sent to MORU for processing at the ISO accredited Pharmacology laboratory for chloroquine/hydroxychloroquine levels.

Nose and throat swabs will be taken in accordance with the SOP and frozen immediately at minus 80°C in their collection tube, and later transferred to MORU Tropical Health Network laboratories for processing maintaining the cold chain at all times. Sputum will either be frozen in the container in which it is collected (if amenable to freezing) at minus 80°C or a sample will be placed on a viral swab, and frozen at minus 80°C.

Validated antibody tests for SARS-CoV-2 are currently not available, although they are being developed rapidly. The plasma and serum aliquot samples will be stored until a time that validated assays for these have been developed or we have completed our own in-house serological tests and validations. The criteria for a positive test are thus yet to be determined, but as with other serological tests, a four-fold increase in titre of SARS-CoV-2 antibodies between the initial and final sample will likely be used to determine exposure to the virus. Additionally, we will be able to determine if exposure to SARS-CoV-2 has occurred prior to enrolment in the trial if the initial antibody titre is above a predetermined and validated level. Serological tests for other circulating coronaviruses may also be performed to determine the interaction of these with COVID-19, as well as other pathogens which may be of clinical significance.

Testing of the serum samples for other biological parameters which may impact susceptibility to infection, such as ACE2 and vitamin D levels, may also be considered at a later date.

Nose and throat swabs will have validated multiplex RT-PCR performed for SARS-CoV-2 as well as other respiratory viruses including some or all of the following: influenza A, influenza B, respiratory syncytial virus, rhinovirus, other coronaviruses (OC43, NL63, 229E and HKU1), metapneumovirus, parainfluenza 1-4, adenovirus and bocavirus. The Ct value of positive results will be recorded.

The cell fraction aliquot will be processed to assess for host genetic markers of respiratory disease susceptibility. These tests may be done in Thailand or elsewhere in Asia, the UK or Europe, once material transfer agreements are in place.

The samples will be kept for ten years. Consenting participants may rescind their consent at a later date and refuse the use of their samples (which will be destroyed) or data at any time up until the completion of the study (final follow-up of the final participant).

7.9. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up (LTFU)

The reason for withdrawal will be recorded in the Case Report Form.

7.10. Definition of End of Study

The end of the study will be the date of the last visit of the last participant, the last dose of the study drug or 28 days after the diagnosis of COVID-19 of the last subject enrolled in the study (up to 60 days if the participant has not recovered at D28) or whichever comes last.

8. STUDY MEDICATION (CHLOROQUINE or HYDROXYCHLOROQUINE/PLACEBO)

8.1. Study Medication Description

The trial intervention is the administration of the study product. This will either be chloroquine or placebo in Asia or hydroxychloroquine or placebo in Europe.

Chloroquine and hydroxychloroquine will be in the dose of 155mg chloroquine base (250mg of chloroquine phosphate or 200mg of hydroxychloroquine sulphate). On D0 the participant will be supervised taking 10mg base/kg (usually 4 tablets or 600mg chloroquine base) and they will be given a further 30 tablets of 155mg base to be taken once daily. The placebo will comprise identical tablets and the regimen will be the same with 1 tablet/ 15kg at D0 and a further 30 tablets to be taken once daily. Neither the participant, nor those conducting the study will know if the subject is receiving chloroquine/ hydroxychloroquine or placebo.

8.2. Storage of Study Medication

The medication will be stored under lock and key at room temperature in the institution's pharmacy or other secure location. The medication will only be accessible to the study site PI/manager or his/her designee.

8.3. Compliance with Study Medication

Adherence will be assessed by direct questioning of the subject. Participants will receive reminders to take the medication from the app. The monthly pre-dose capillary blood chloroquine or hydroxychloroquine measurement will be an independent measure of exposure. Given that the study will be conducted on healthcare workers and the current concern relating to COVID-19 is so great, we do not anticipate poor adherence. If the study is conducted in other high-risk groups (i.e. patients), the medication will be administered by healthcare workers while an inpatient. In the event of lost medication or more than 3 consecutive missed doses the participant should contact the study team.

8.4. Accountability of the Study Medication

The medication and placebo will be accounted for by keeping these supervised or under lock and key at all times. Medication counts will occur to ensure that no tablets are missing. Dispensation and return of study drugs will be recorded in the Study Drug Accountability Log.

8.5. Concomitant Medication

Chloroquine or hydroxychloroquine may be avoided if the patient is taking the following medications, on medical consultation:

- Abiraterone acetate: May increase serum concentrations of this drug.
- Agalsidase Alfa or Beta: May diminish the therapeutic benefit.
- Conivaptan: May increase serum concentrations of this drug.
- Dabrafenib: May decrease serum concentrations of this drug.
- Dacomitinib: May increase serum concentrations of this drug.
- Enzalutamide: May decrease serum concentrations of this drug.
- Idelalisib: May increase serum concentrations of this drug.
- Mifepristone: May increase serum concentrations of this drug.
- Mitotane: May decrease serum concentrations of this drug.

- Stiripentol: May increase serum concentrations of this drug.

8.6. Post-trial Treatment

We are currently not planning to provide the chloroquine or hydroxychloroquine post-trial. They are readily available and affordable.

9. SAFETY REPORTING

9.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/ incapacity
- consists of a congenital anomaly or birth defect

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

9.2. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out i.e. the relationship is definitely, probably, possibly or unlikely to be related (see below). All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	This is an adverse event that is both serious and is considered a drug reaction.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SUSAR is a SAR that is: • not listed in the summary of product characteristics (SmPC) for that product or • has not been described in the published literature before
Expectedness	An expected AR or SAR is a drug reaction that is listed in the SmPC and or has been described in the published literature before.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.3. Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Definitely related: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Probably related: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Possibly related: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other

factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Unlikely to be related: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication), or there is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Not related: There is no evidence of any causal relationship.

9.4. Procedures for Recording Adverse Events

All AEs occurring during the trial/ or until 28 days after the trial finishes, that are observed by the Investigator or reported by the participant, will be recorded on the CRF, whether or not attributed to trial medication.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed following the Common Toxicity Criteria v5.0: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = fatal.

AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

9.5. Reporting Procedures for Serious Adverse Events

SAEs relating to acquisition of COVID-19 and morbidity and mortality associated with this, do not need to be reported to the local PI immediately, and will be discussed in the next monthly scheduled Safety Monitoring Committee meeting.

All other SAEs, including SARs and SUSARs, detected by the study investigator should be reported to the following within 24h:

- COPCOV safety team, consisting of:
    - Nicholas Day (nickd@tropmedres.ac)
    - William Schilling (William@tropmedres.ac)
    - Prayoon Yuentrakul (Prayoon@tropmedres.ac)

- The local EC and the local regulatory authority by the study PI, if this is required

The safety team and the local PI will gather any additional relevant information and update the local EC and regulatory authority, as needed, within a reasonable time frame.

The safety team will inform the DSMB within 7 days and keep the DSMB updated as needed.

Treatment codes will be unblinded for specific participants after discussion with the study PI.

9.6. Data Safety and Monitoring Board

An independent Data Safety and Monitoring Board (DSMB) will be set up consisting of qualified volunteers with the necessary knowledge of clinical trials. The DSMB will receive summary reports, prior to each meeting. All data reviewed by the DSMB will be in the strictest confidence. A DSMB charter will outline its responsibilities, number of interim reports and how it will operate. Interim reports will be prepared by the Trial Statistician and the Trial coordinator.

All serious adverse events (SAEs) will be reported by the trial coordinator, as above. The PI will be responsible for submitting the written DSMB summary reports with recommendations to the Ethics Committees

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

All participant data will be included in the Intention-To-Treat (ITT) analysis according to the arm they were randomised to, irrespective of the actual study drug that they took. This ITT analysis will be the main strategy for the primary outcome and will be followed by a per protocol (PP) analysis. In the PP analysis, participants with protocol deviations/violations, no final outcome assessed and losses to follow-up prior to the assessment of the final outcome will be excluded from these PP analyses. A detailed Analysis plan will be written by the trial statistician.

10.2. The Number of Participants

Power calculations are based on an assumption of 3% incidence of symptomatic COVID-19 during the trial period. Expert opinion considers that if chloroquine or hydroxychloroquine is effective, it may decrease symptomatic COVID-19 by 23%, and therefore, the chloroquine arm or hydroxychloroquine would have a 2.31% COVID-19 diagnosis. A 95% confidence interval with 80% power would indicate 8,520 subjects randomised to each arm. We will aim to enrol 10,000 subjects in each arm in the two trials which allows for a 20% LTFU, withdrawal rate, protocol deviation and non-adherence. Thus 20,000 would be randomised in Asia and 20,000 in Europe.

10.3. Analysis of Outcome Measures

A mixed effects Poisson model will be used to model the incidence of symptomatic COVID-19 infection to obtain incidence rate ratios comparing the chloroquine arm with the placebo. In the event of over-dispersion of the data, a Negative Binomial model will be considered. Incidence rate ratios and the corresponding 95% confidence intervals will be obtained and reported. As much as possible graphical methods will be used to show trends in the incidence of symptomatic COVID-19 over time and by arm.

Survival methods will be used to estimate the time to resolution and also as a method of handling missing data in case of dropouts. In this approach, participants without outcomes will be censored at their longest observed time.

A continuous severity score will be used to assess severity of symptomatic COVID-19 of those who will acquire this, and these will be captured longitudinally over time. A logarithmic scale and a Wilcoxon test will be used to compare ranks between the two groups in order to discriminate between severities at the lower end of the spectrum.

Normally distributed continuous baseline characteristics will be summarised using means and standard deviations while skewed continuous baseline characteristics will be summarised medians and interquartile ranges. Categorical data will be summarised using counts and percentages. A Fisher's exact test will be used to compare binary outcome data between groups. Statistical significance will be determined at 5% significance level.

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the University of Oxford and any host institution for monitoring and/or audit of the study to ensure compliance with regulations.

11.2. Data Handling and Record Keeping

Clinical study data will be recorded on CRFs and entered on to a password-protected database by the local study PI, a research nurse or designee. The study database will be built in MACRO EDC, a clinical data management system that is compliant with ICH GCP and FDA 21 CFR Part 11 and will be hosted in a secure, access-restricted server in MORU. A system for recording electronic patient reported outcomes (ePRO) will be built and integrated with the study database. The study database and ePRO system will include internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.

Measures will be taken to ensure non-disclosure of information that is potentially harmful to participants. Paper records (for example, patient identifiable information for the purposes of follow-up, the screening logs and signed ICFs) will be kept in locked cabinets; electronic data will only be accessible to staff with user accounts and passwords. The database contains an audit trail that keeps record of changes to data and user activity within the database. All electronic data will be stored on secure servers that are backed up daily, with weekly off-site storage.

Subject records at site will, taking into account the ability of the sites, be stored in binders in the secured access-limited room or scanned and stored electronically. The records will be retained until the youngest participant in the trial reaches 21 or five years following completion of the study, whichever is longer. The study database will be retained indefinitely.

With participant's consent, clinical data and results from blood analyses stored in the database may be shared according to the terms defined in the MORU data sharing policy with other researchers to use in the future.

Data generated from this study will adhere to the 2016 "Statement on data sharing in public health emergencies"(https://wellcome.ac.uk/press-release/statement-data-sharing-public-health-emergencies).

12. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with relevant regulations and standard operating procedures.

The study will be conducted in compliance with this protocol, International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) and any applicable regulatory requirement(s). Monitoring will be performed by the MORU Clinical Trials Support Group (CTSG) according to a prespecified monitoring plan to ensure compliance to the study protocol and applicable guidelines and regulations. Blood samples will be processed, stored and shipped in accordance with MORU SOPs.

Data validation will be performed to identify errors or discrepancies and thus ensure completeness, validity and accuracy of data.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material (if applicable) will be submitted to OxTREC and local ethics committees for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all amendments to the original approved documents.

13.4. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act 2018, which requires that personal data must not be kept as identifiable data for longer than necessary for the purposes concerned.

13.5. Expenses and Benefits

Participants will not be paid for their participation in the research.

13.6. Reporting

The PI shall submit an Annual Progress Report to all applicable ethics committees on the anniversary of the date of approval of the study. In addition, the PI shall submit an End of Study Report to all applicable ethics committees upon completion of the study.

13.7. Other Ethical Considerations

The decision to include only participants with a smartphone potentially runs the risk of violating the "fair subject principal" (18) i.e. introducing a socio-economic bias into the trial. Given the trial will be conducted in healthcare workers, a group in the areas we have identified who would normally expect to have a smartphone, we do not think there will be many who would not be able to be enrolled on this basis. Additionally, as we have already selected a discrete group on whom to conduct the study we do not think excluding those without a smartphone will add any additional meaningful bias which will affect the study objectives.

Given the urgency of the question which this trial aims to answer and the difficulty of collecting the same information without the use of an app-enabled smartphone we believe that the prompt and definitive answering of the trial question is in society's best interests, and given the current equipoise between chloroquine and placebo in prevention of COVID-19, does not disadvantage those ineligible to enrol.

13.8. Community and public engagement

Given the current lack of evidence that chloroquine or hydroxychloroquine will be effective in the prevention of COVID-19, there is currently scientific equipoise which justifies the use of placebo in this study. Although chloroquine or hydroxychloroquine have both been shown to be very safe, the medication is not without side-effects. In addition, the details of the studies in China which show a benefit of chloroquine in treatment of COVID-19 have not been made publicly available (16), and the results would not be able to demonstrate that a lower dose of chloroquine, as per our study, would prevent COVID-19. We are currently monitoring this situation very closely.

As part of our engagement initiative (also called "patient and public involvement", we will be conducting a series of workshops with (1) potential participants e.g. hospital staff and (2) members of the public via existing advisory groups such the Bangkok Health Research Interest Group and community advisory boards, to embed their voices into the research design, implementation and dissemination of findings). (see Appendix C)

14. FINANCE AND INSURANCE

14.1. Funding

Wellcome Trust

14.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

15. PUBLICATION POLICY

All publications will abide by the International Committee of Medical Journal Editors (ICMJE) recommendations of the role of authors and contributors.

The results of the study will be summarised in lay language, in both English and the language(s) commonly spoken at the study sites, and disseminated to key stakeholders, user communities and caretakers of study participants.

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17. APPENDIX A: SEVERITY OUTCOME MEASURES

Observation	Scale
Outpatient	
Feels normal	
Feels unwell	
URTI Symptoms (coryza and/ or sore throat)	
Muscle aches	
Cough	
Afebrile <37.5^{o}C	
Fever ≥37.5 and ≤38.5^{o}C (axillary)	
High fever >38.6^{o}C	
Shortness of breath on exertion	
Shortness of breath at rest	
Mainly chair/ bed bound	
Requires hospitalisation (based on clinical symptoms)	

Inpatient: Hospitalisation	
Hypoxia / Hypoxaemia 90-95% on air (if measured) or requiring supplemental O_2 (not high-flow)	
Hypoxia < 90% on air (if measured) or on supplemental O_2 (up to 15L on non-rebreather)	
Tachypnoea RR 25-40	
Tachypnoea RR ≥ 40	
ARDS	
Non-invasive ventilation: high-flow or CPAP/ BiPAP	
Mechanical ventilation	
Organ support other than respiratory	
ECMO criteria met	
Death	

The above observations will be collected and form the severity outcome scale for participants in the trial who have symptomatic COVID-19 and also for those with an ARI not caused by SARS-CoV-2. Additionally, data will be collected on the duration of symptoms and analysed to determine if a difference in severity exists between the two arms. As part of our analysis plan we will explore grouping, weighting and aggregation of the above observations.

18. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	**Visits**					
	Enrolment Day 0	**Day 30**	**Day 60**	**Day 90**	**Outcome follow-up if symptomatic up until day 60 post illness (normally D28**	**ARI Symptom onset (can be repeated on multiple occasions if illness worsens or new ARI during trial period)**
	1	**2**	**3**	**4**	**5**	
Screening	X					
Eligibility assessment	X					
Informed consent	X					
Demographics	X					
Medical history	X					
Randomisation	X					
Set up mobile app	X					
Given thermometer	X					
Venous blood test	Y			Z		
Observed 1st dose of study medication	X					
Dispensation of study medication (unless diagnosed as COVID-19 before visit)		X	X			
Compliance assessment		X	X	X		
DBS		X	X			
Adverse event assessments		X	X	X		
Questions about illness, COVID-19 diagnosis and clinical severity data	X	X	X	X	X	X
Nose and throat swab						X

Y 10mls of venous blood Z 5mls of venous blood

19. APPENDIX C: EXAMPLE OF COMMUNITY AND PARTICIPANT ENGAGEMENT

We will conduct a series of "Patient & Public Involvement" workshops, interviews and group discussions (virtual or face-to-face) with two different groups of stakeholders (i) potential participants e.g. hospital staff and (ii) members of the public via e.g. existing advisory groups such the Bangkok Health Research Interest Group and community advisory boards.

These activities will be conducted at various stages with the following objectives:

(1) protocol development stage and prior to study start:

- to inform study design, procedures, participant information materials, develop frequently asked questions (FAQs)
- to seek general attitudes about the study, use of placebo and study procedures
- to develop communication materials for dissemination to the wider public and media about the study, how best to communicate the meaning and rationale of "placebo", "blinding", etc
- to identify what could motivate and/or discourage those to meet eligibility criteria to join the study
- to determine to what extent is chloroquine is available from local pharmacies and/or informal vendors

(2) soon after study start:

- to identify any challenges in recruitment, study procedures, understanding of the study, and potential solutions

(3) after study completion:

- to disseminate the study results
- to inform strategies for dissemination of study results to the wider public so that they can use and find value in the research

In all stages, we will also be seeking the general attitudes about the epidemic e.g. fears, perception of risks, measures taken by individuals to protect themselves, likelihood of chloroquine or other drug self-medication, perception of public health measures (e.g. social distancing), and economic consequences. Understanding these social factors will help us with communication with participants, their families and the general public.

20. APPENDIX D: POTENTIAL SITES

Convening partners. MORU is based in the Faculty of Tropical Medicine, Mahidol University, centred in Bangkok and has extensive experience of conducting multi-centre, multi-country randomised controlled trials in infectious diseases and excellent contacts in hospitals and universities through the East and South Asian region. It played a critical role in the SEA Infectious Disease Clinical Research Network, which focused on avian and severe seasonal influenza.

The MORU Tropical Health Network (THN) includes several sites in Thailand, Laos, Cambodia, Myanmar, Bangladesh, India, Afghanistan and the Democratic Republic of the Congo (DRC) and collaborations in several other countries in Asia. In addition, we have excellent collaborative links with our sister unit OUCRU in Vietnam, as well as links with healthcare facilities in sites in India through our ongoing scrub typhus studies in that country.

Implementing partners. The exact choice of study sites will be decided based on the spread of COVID-19 in the region and the likelihood of local and nosocomial transmission. Listed below are a number of potential study sites, large hospitals where we have longstanding relationships and where we are currently carrying out clinical studies. Given the unpredictable nature of secondary outbreaks, we will be flexible but rapidly responsive in choosing suitable sites and implementing the trial.

The Faculty of Tropical Medicine (FTM), Mahidol University, Bangkok, is affiliated and partnered with the Mahidol Oxford Tropical Medicine Research Unit (MORU), which have successfully collaborated together for more than 40 years in the management of Tropical diseases. FTM is the only faculty specialising in tropical medicine in Thailand and runs the Hospital for Tropical Diseases in Bangkok. Both FTM and MORU are fitted with state-of-the-art molecular diagnostic testing facilities.

Sunpasithiprasong Hospital, Ubon Ratchathani. Situated in the East of Thailand on the Laos border, this long-term 1200 bed hospital and MORU collaborator for 34 years has dedicated on-site study nurses currently conducting clinical trials.

Udon Thani Hospital, Udon Thani, (800 beds) is situated in the Northeast of Thailand adjacent to Lao's capital, Vientiane, and has been a study site for previous trials with successful collaboration.

Chiangrai Clinical Research Unit (CCRU) is a MORU-affiliated unit in the North of Thailand. It has a full-time team of a clinician researcher, study nurses and laboratory staff, with a laboratory based in the Prachanukroh Hospital (760 beds).

Shoklo Malaria Research Unit (SMRU), Mae Sot, based on the Thai-Myanmar border in the West of Thailand is the largest of the MORU-affiliated sites. Originally set up to provide basic healthcare and malaria treatment to Myanmar migrants fleeing civil war in Kayin (Karen) state, this unit now supports and runs several in-patient clinics, has a fully accredited laboratory able to test for COVID-19 and other respiratory pathogens and works closely with the Thai Governmental hospital in the city. The porous

nature of the border and poor provision of care in Myanmar, make this site high risk for introduction and spread of the infection.

Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU), a clinical research unit embedded in the 450 bed Mahosot Hospital in Lao PDR's capital, Vientiane, conducts clinical research on diseases of regional public health importance, and has recently developed capability for testing for SARS-CoV-2, as well as other respiratory viruses and causes of febrile illness. Audrey Dubot-Pérès, the head of Virology at LOMWRU and also works at the Institut de Recherche pour le Développement (IRD) in the Unit of Emerging Viruses (Aix-Marseille Univ-IRD 190-Inserm 1207-IHU Méditerranée Infection), Marseille. Additionally LOMWRU has excellent links, and is currently collaborating in, 5 provincial hospitals, which could be potential study sites: **Xieng Khuang**; **Luang Namtha**; **Salavan**; **Savannakhet**; and **Phonhong**. These provinces provide health care to the provinces which have porous borders with China, Myanmar and several geographically distinct regions of Thailand and Vietnam.

Myanmar-Oxford Clinical Research Unit (MOCRU) is a MORU-affiliated unit in Yangon, Myanmar with strong links to Medical Action Myanmar (MAM) a non-governmental organisation which runs a network of 2,000 health workers and 10 clinics as well as strong collaborative links with the Myanmar Ministry of Health and several public hospitals in Yangon and Mandalay.

Cambodia-Oxford Medical Research Unit (COMRU) a collaboration between MORU and the Angkor Hospital for Children (AHC) in Siem Reap, Cambodia. This collaboration started in 2006 and led by Professor Paul Turner, head of COMRU, and Dr Claudia Turner, CEO of AHC, provides free, quality healthcare to approximately 450 children a day, as well as high-quality research. The laboratory is equipped to do respiratory virus testing, including COVID-19 as well as whole genome sequencing of isolates. Given the volume of children presenting with respiratory illnesses, COVID-19 could quite easily spread to healthcare providers and back out to the community.

Hospital of Tropical Diseases (HTD), Ho Chi Minh City, Vietnam The Oxford University Clinical Research Unit (OUCRU), our sister unit based in the HTD, has a long history of conducting hospital-based clinical trials and was at the forefront of the research response to Avian Influenza in 2004 led by Professor Jeremy Farrar. HTD is a regional referral hospital serving a population of 38 million in the South of the country.

The Christian Medical College (CMC), Vellore, India. An institution currently collaborating with MORU, Bangkok on the biggest scrub typhus trial ever conducted and the only trial on severe scrub typhus. CMC comprises 3,000 hospital beds across 6 campuses providing primary to quaternary care management of patients. CMC consistently ranks as one of the top medical institutions in India.

And sites in the UK, Italy, the Netherlands, Indonesia and Bangladesh.

21. APPENDIX E: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made