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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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1. SYNOPSIS

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 and other staff working in a facility where there are cases of either proven, or suspected COVID-19. Adults (exact age is dependent on local country requirements).	
Planned Sample Size	40,000 total participants	
Planned Study Period	12 months; individual trial duration maximum 5 months	
	Objectives	**Outcome Measures**
Primary	To determine if chloroquine or hydroxychloroquine prophylaxis prevents symptomatic COVID-19 infection in healthcare workers and other staff working in a facility involved in COVID-19 case management.	The number of symptomatic COVID-19 infections will be compared between participants randomised to chloroquine or hydroxychloroquine, and placebo groups.
Secondary	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.
	To determine if chloroquine or hydroxychloroquine prophylaxis prevents asymptomatic COVID-19 infection.	The number of asymptomatic cases of COVID-19 will be determined by comparing serology in all participants at time of enrolment and at the end of follow up.
	To determine if chloroquine or hydroxychloroquine prophylaxis prevents all-cause symptomatic acute respiratory illnesses.	The number and severity of symptomatic acute respiratory illnesses will be compared in participants randomised to chloroquine or hydroxychloroquine, and placebo groups.
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 Acute Respiratory Infections (ARIs).
	To assess the impact of chloroquine or hydroxychloroquine prophylaxis on	The days lost to work, and the relationship between the

	work and behaviour during the pandemic.	subjective assessment of well-being and the decision to self-isolate when unwell (i.e. not go to work) will be examined in relation to the infection and treatment arm.
	To perform health economic analyses to assess the impact of chloroquine or hydroxychloroquine prophylaxis on costs and quality of life measures.	The trial will collect data on use of health care resources and health related quality of life (EQ-5D-3L) to determine the effects between treatment groups.

See Appendix F for UK specific information

2. ABBREVIATIONS

ARI	Acute Respiratory Infection
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
DBS	Dried Blood Spot
DSMB	Data Safety and Monitoring Board
ECMO	Extracorporeal Membrane Oxygenation
ePRO	Electronic Patient Reported Outcomes
EQ-5D-3L	EuroQol 5 Dimension 3 levels
GCP	Good Clinical Practice
ICF	Informed Consent Form
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 Equipment
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 7,000,000 individuals, killed more than 400,000 people and has spread to more than 200 countries and territories[1]. The original epicentre of the COVID-19 pandemic was the city of Wuhan, Hubei province, China but the infection spread to Europe and the Americas and the infection is now found across the world with the United States being worst affected.

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 widely available proven treatment and no vaccine. The crude mortality is currently greater than 5%. 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 risks to the healthcare system, as seen with SARS-CoV previously, and then 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 and hydroxychloroquine at dose of 2.4mg base/kg (155 mg)/day for years is used for rheumatoid arthritis and other conditions. Daily doses up to 620mg base have been given for months or years. 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 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

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

[2] World Health Organization's Factsheet on Seasonal Influenza

[3] World Health Organization's list of Essential Medications

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.

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). Hydroxychloroquine may cause less itching than chloroquine in dark-skinned patients. The pharmacology appendix contains more information on the pharmacology of these two 4-aminoquinoline drugs.

We hypothesise that chloroquine and hydroxychloroquine might both slow viral replication in exposed participants, attenuating or preventing the infection even if they are shown not to work in treatment or in post-exposure prophylaxis or in treatment. It is a basic principle of infectious diseases that preventing an infection developing (I.e. preventing pathogen multiplication) requires less drug activity (I.e. lower doses or a less active drug) than treatment. In COVID-19 illness the total viral burden is orders of magnitude greater than at the time of initial infection. Indeed viral burdens are often reducing by the time of hospitalisation in COVID-19 so the window of opportunity for antiviral medicines is at the earliest stages of infection. In addition in-vitro studies show the greatest activity of chloroquine and hydroxychloroquine at the initial time of cellular infection and decreasing *in vitro* antiviral effects if the drug is exposed at later time points. We believe these drugs may have their greatest utility in preventing COVID-19 in pre-exposure prophylaxis (8, 17-19). 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 healthcare workers.

Main research questions:

The primary objectives are is to determine if prophylactic chloroquine or hydroxychloroquine prevents symptomatic COVID-19 illness.

The secondary objectives include:

- Attenuation of the clinical severity of COVID-19 infections.
- The prevention of asymptomatic COVID-19.
- The prevention of symptomatic all-cause acute respiratory infections (ARI).

- Overview of primary endpoint ascertainment:

During the study	RT-PCR for SARS-CoV-2	Initial serology	End serology	Diagnosis
Illness	Positive	Negative	Negative or Positive	**COVID-19**
Illness	Positive	Positive	Negative or Positive	**COVID-19**
Illness	Negative	Negative	Positive	**COVID-19**[2]
Illness	Negative	Positive[1]	Negative or Positive	Indeterminate
Illness	Negative	Negative	Negative	ARI not COVID-19
No Illness	-	Negative	Positive	Asymptomatic case
No Illness	-	Positive[1]	Positive	Indeterminate
No Illness	-	Negative	Negative	Not infected

- Participants[1] will be enrolled only if they have not had a previous confirmed diagnosis of COVID-19. It is anticipated some participants may have had asymptomatic infections and so are found during subsequent analysis to have antibody present at study enrolment.
- Unless[2] the PCR from a nose/ throat swab taken during the febrile illness by the hospital is positive for influenza virus. Other viruses isolated will not change the primary end-point determination. Although later studies will look for other viruses in the study swab – for the primary endpoint this will only be a SARS-CoV-2 PCR.

Brief description of the intervention:

The study is a double-blind, randomised, placebo-controlled trial that will be conducted in facilities involved in COVID-19 case management. After obtaining fully informed consent, we will recruit healthcare workers and other staff working in a facility where there are cases of either proven, or suspected COVID-19, who can be followed up reliably for up to 5 months. **See Appendix F for UK specific information.**

A loading dose of 10 mg base/kg (four 155mg tablets for a 60kg participant), followed by 155 mg daily (250mg chloroquine phosphate salt or 200mg of or hydroxychloroquine sulphate) will be taken by all participants 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 participants are diagnosed with COVID-19 during the period of prophylaxis, they will continue their prophylaxis unless advised to discontinue by their healthcare professional, unless they become hospitalised as a result of COVID-19 (not for quarantine reasons), in which case they will be asked to stop. If they are hospitalised prior to the diagnosis of COVID-19, they will continue prophylaxis until the diagnosis of COVID-19 is confirmed unless advised to discontinue by their healthcare professional.

If participants become unwell during the study period due to COVID-19 or other ARI, they will continue to be followed up until 28 days from the beginning of illness. If complete recovery does not occur within 28 days, follow-up will be extended for up to a maximum of 60 days from the beginning of illness. For

participants who become unwell on day 90, follow-up may therefore continue until day 150. **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. Study diagnoses will be made at the end of the study, where possible participants will be informed if they had or did not have COVID-19 infections as defined above. Chloroquine and hydroxychloroquine have very few drug-drug interactions and should not interfere with the management of pneumonia. **See Appendix F for UK specific information.**

Summary of findings of previous studies:

No studies have published results on chloroquine or hydroxychloroquine for the pre-exposure 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, widely available treatments or a vaccine. Assumptions of the study include that the *in vitro* effects of chloroquine or hydroxychloroquine against SARS-CoV-2 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 particular with chloroquine, 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.

A full description for each product is provided in the relevant summary of product characteristics (SmPC). A physician's guidance document for each study medication is also available for reference.

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 participant 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, and the prophylactic use of these drugs around the world can stop.

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 staff working in a facility where there are cases of either proven or suspected COVID-19. These could include nurses, healthcare assistants (HCAs), doctors, pharmacists, physiotherapists, porters and anyone working within the facility who is at risk of exposure to COVID-19. Study participation will be open to hospitals, lower level health centres and other facilities directly involved in COVID-19 case management. **See Appendix F for UK specific information.**

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)
Primary Objective To determine if chloroquine or hydroxychloroquine prophylaxis prevents symptomatic COVID-19 infection in healthcare workers and other staff working in a facility involved in COVID-19 case management.	**Primary Outcome** The number of symptomatic COVID-19 infections will be compared between participants randomised to chloroquine or hydroxychloroquine, and placebo groups.	During the trial period
Secondary Objectives To determine if chloroquine or hydroxychloroquine prophylaxis attenuates COVID-19 infections.	**Secondary Outcomes** 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 respiratory severity score.	During the trial period
To determine if chloroquine or hydroxychloroquine prophylaxis prevents asymptomatic COVID-19 infection.	The number of asymptomatic cases of COVID-19 will be determined by comparing serology in all participants at time of enrolment and at the end of follow up.	During the trial period
To determine if chloroquine or hydroxychloroquine prophylaxis prevents all-cause symptomatic acute respiratory illnesses.	The number and severity of symptomatic acute respiratory illnesses will be compared between the chloroquine or hydroxychloroquine, and placebo groups.	During the trial period
Tertiary Objectives To characterise genetic and baseline biochemical markers	**Tertiary Outcomes** Genetic loci and levels of biochemical components will be correlated with	During and after the trial period

associated with symptomatic COVID-19, respiratory illness and disease severity.	occurrence of and disease severity of COVID-19 or other ARIs.	
To assess the impact of chloroquine or hydroxychloroquine prophylaxis on work and behaviour during the pandemic.	The days lost to work, and the relationship between the subjective assessment of well-being and the decision to self-isolate when unwell (i.e. not go to work) will be examined in relation to infection and treatment arm.	During and after the trial period (to the limit of follow up)
To perform health economic analyses to assess the impact of chloroquine or hydroxychloroquine prophylaxis on costs and quality of life measures	The trial will collect data on use of health care resources and health related quality of life (EQ-5D-3L) to determine the effects between treatment groups.	During and after the trial period

See Appendix F for UK specific information.

5. STUDY DESIGN

The study is a double-blind, randomised, placebo-controlled trial that will be conducted in healthcare settings and other facilities directly involved in COVID-19 case management. We will recruit healthcare workers and other staff working in a facility where there are cases of either proven, or suspected COVID-19, 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. **See Appendix F for UK specific information.**

Before the trial enrolment starts there will be engagement with the potential participants to inform them about the trial and possibly obtain baseline demographic information from potential participants. Eligible participants 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 and hydroxychloroquine. They will also be informed that biological samples will be stored and may be processed for genetic material, biochemical tests, and other pathogens. They will also consent to having clinical information shared with the study team, although these data will remain pseudonymised and stored and processed in accordance with national and international standards and in accordance with regulating bodies. The participant will be instructed how to contact the study team and how to use the simple reporting application (app) on their mobile phone. 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 participant 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). **See Appendix F for UK specific information.**

The participant will be randomised to receive either chloroquine or placebo (1:1 randomisation), or to hydroxychloroquine or placebo (1:1 randomisation). A loading dose of 10mg base/kg (between three and five tablets *e.g.*, four 155mg tablets for a 60kg subject), followed by 155 mg daily (250mg chloroquine phosphate salt/ 200mg hydroxychloroquine sulphate) will be taken for 3 months.

If the participant is diagnosed with COVID-19, they will take continue to take the study medication until:

- 90 days after enrolment (i.e., completion of kit)
- hospitalised due to COVID-19 disease (i.e., not for quarantine purposes) in which case they will stop, or
- advised to stop by their healthcare professional for other reasons

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. If they do not take their dose within this period of time, they should not take it and this dose will be classified as missed. They should continue to take their medication regularly. The missed dose should be reported to the study team via the mobile app and at the subsequent follow up visit 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, chloroquine/ hydroxychloroquine levels, biochemical tests and host genetics related to susceptibility to respiratory illness and COVID-19 infection and chloroquine/ hydroxychloroquine levels.

Participants will be given a participant ID number (a card in most settings), randomised and given 30 days of study medication and asked to see the local PI or study nurse 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 calculated by and observed by the study nurse. **See Appendix F for UK specific information.**

Participants will be given a thermometer and requested to record their temperature twice a day via a mobile-based application. They will also record whether they feel “well” or “unwell” and if they report feeling unwell will be asked to select symptoms from a menu of choices in the application. If they or a member of their household has been diagnosed with COVID-19 this information is also collected. 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 by telephone 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.

See Appendix F for UK specific information.

If symptoms consistent with COVID-19 occur, the participant will alert the study team and will arrange for nose and throat swab samples (even if a sample has been taken previously for clinical purposes) following strict adherence to personal protection. In some instances a sputum sample may also be taken. The participant should continue his/ her chloroquine/ hydroxychloroquine or placebo, unless otherwise advised by a medical professional or the study team, or they are diagnosed with COVID-19 and hospitalised with infection (not for quarantine purposes). Prescribing medical professional should be mindful that participants may or may not be taking chloroquine/ hydroxychloroquine and in some cases, determined per site specific guidance, this may necessitate unblinding.

If symptoms worsen, or a participant has more than one episode of symptoms consistent with COVID-19 infection during the trial period this process will be repeated. Samples will be stored at -80°C and tested for respiratory viruses at the end of the trial. The participant should self-isolate, as per local or national guidelines.

If a diagnosis of COVID-19 from a clinical sample is confirmed 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 they become hospitalised with infection (not for quarantine purposes). 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 should continue chloroquine or hydroxychloroquine/ placebo as normal (unless advised by a medical professional or the study team) 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 by the study team at least monthly to assess drug tolerability, well-being, 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; if symptomatic or diagnosed with COVID-19 separate provisions will be arranged) and will be combined with:

- Collection of a study adverse events questionnaire
- Health-related quality of life questionnaire
- A dried blood spot (DBS) sample on filter paper for hydroxychloroquine/ chloroquine levels +/- COVID-19 diagnostic tests
- Dispensation of further study drugs See Appendix F for UK specific information.

Participants 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.

For those who develop symptomatic COVID-19 illness or ARI, 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

Participants who discontinue study medication early will be encouraged to complete all other study assessments through Day 90.

6. PARTICIPANT IDENTIFICATION AND RECRUITMENT

6.1. Study Participants

The study population is adult healthcare workers and other staff working in a facility where there are cases of either proven, or suspected COVID-19

6.2. Inclusion Criteria:

1. Participant is willing and able to give informed consent for participation in the study
2. Agrees not to self-medicate with chloroquine, hydroxychloroquine or other potential antivirals
3. Adults (exact age is dependent on countries) less than 70 years old at the time of consent. **See Appendix F for UK specific information**
4. Not previously diagnosed with COVID-19
5. Not currently symptomatic with an ARI

6. Participant works in a facility where there are cases of either proven or suspected COVID-19
7. 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:

1. Hypersensitivity reaction to chloroquine, hydroxychloroquine or 4-aminoquinolines
2. Contraindication to taking chloroquine as prophylaxis e.g. known epileptic, known creatinine clearance < 10 ml/min
3. Already taking chloroquine, hydroxychloroquine or 4-aminoquinolines
4. Taking a concomitant medication described in section 8.5
5. Known retinal disease
6. Inability to be followed up for the trial period
7. Known prolonged QT syndrome (however ECG is not required at baseline)
8. Known pregnancy or women who are actively trying to become pregnant
9. Prior diagnosis of porphyria

The investigator may consult the physician's guidance documents for any further questions regarding eligibility of potential participants.

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 local agreement that the study can be conducted in the facility
- Local or national ethical/ IRB approval can be put in place rapidly
- It is a facility where there are cases of either proven or suspected COVID-19
- There are adequately trained personnel able to conduct the study procedures described in the protocol and appropriate equipment
- Each site would be able to recruit a projected 400 participants during the trial period (200 participants per site may be possible on discussion)

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:

Facilities will contact their staff to inform them of the study through usual means. In addition, with the local ethics committee approval and institution's consent, the site study PI may 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. **See Appendix F for UK specific information.**

7.2. Screening and Eligibility Assessment

Eligibility assessment will occur at the point of screening. If, based on the inclusion and exclusion criteria, the participant is eligible, they will be randomised to receive chloroquine / hydroxychloroquine or placebo. **See Appendix F for UK specific information.**

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 and being processed for host genetic material and other pathogens; and for any clinical and other necessary personal 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. **See Appendix F for UK specific information.**

7.4. Clinical examination

There will be no physical clinical examination. Basic demographic information, and details of past medical history, concomitant medications, allergies, smoking and other drug intake will be noted. The height, weight, and temperature 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 five tablets depending on the weight of the participant and will be calculated by the study nurse and administered during the first visit.

A randomisation list will be prepared by a statistician using block randomisation in a 1:1 ratio for the chloroquine/ hydroxychloroquine arm versus the placebo and stratified by site. 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 drug kit containing 10 blister packs with 10 tablets in each blister to participants based on the computer pre-generated randomisation list. The packaging of study drug kits 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 packaging of study drug kits will be performed by independent staff at MORU.

At enrolment the subject's kit number/ ID will be written on the study drug kit and on each blister pack (only if possible), and the starter blister pack and first 30 tablets dispensed to the participant. The kit number/ ID will be linked to the treatment that has been allocated to each participant. All study team members 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 drug kits will be kept securely by the study team. Subsequent 30 tablets (3 blister packs) will be dispensed at each monthly check with the study team. Individual unblinding will be done only on consultation with the study PI. Only the study statistician will have the drug allocation list. **See Appendix F for UK specific information.**

A separate procedure will be provided to study teams to describe details of randomisation and study medication management.

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. **See Appendix F for UK specific information.**

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 study team 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 via telephone by the study team. **See Appendix F for UK specific information.**

At the initial visit participants will provide demographic and basic clinical data, including co-morbidities and concomitant medications, information on well-being, and have their weight and height measured. 10mls of blood will be taken and two blood spots will be collected on filter paper for baseline chloroquine/ hydroxychloroquine levels. The serum, plasma and cell fraction will be 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 team.

7.7. Subsequent Visits

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

The expected schedule for follow up visits is every 28-30 days based from Day 0, a visit window of 27-31 days is allowed to accommodate participant scheduling.

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 team has no reason to suspect the participant 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
- Well-being, 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 2 blood spots will be performed on a filter paper.
- At the final visit (D90), 5ml of venous blood will be taken in a clotted bottle and 2 blood spots will be collected on a filter paper.

Additionally, during this period the study participant will be asked to record entries twice daily via a mobile phone app. 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 via telephone by the study team.

If via the app or by phone, the participant reports to feel unwell with an ARI (potential COVID-19 symptoms) or potential drug side-effects, they will be contacted via telephone by the study team, and a visit to conduct testing will be organised within 24 hours to obtain a nose and throat swab according to study SOP. They will ask the participant some more detailed questions. In addition, if symptoms worsen or if a participant has more than one episode of symptoms consistent with COVID-19 infection, the nose and throat swab will be repeated. If the participant is producing sputum, a sample will be collected in a pot, or a sputum pot will be left with the participant, for later collection. **See Appendix F for UK specific information.**

The participant will be advised to inform their healthcare professional that they are in the study along with the study medications they may be taking. If they are hospitalised with confirmed COVID-19 as a result of the infection (not for quarantine purposes), the study medication should be stopped. If the participant's healthcare professional starts a treatment which is known to prolong the QT interval, while the participant 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 stored at minus 80°C until further notice. Additionally, a single aliquot of the cell fraction from the EDTA tube will also be aliquoted and stored at minus 80°C. Two spots (50 µL each) of blood will be collected on a filter paper and stored in an individual small plastic bag with a desiccant sachet.

At D30 and D60 of the trial, when participants attend for review, finger prick will be performed to collect 2 blood spots on the filter paper.

On the last day of the trial 5mL of venous blood will be collected in a clotted bottle, which will subsequently be centrifuged and aliquoted to 3 cryovials as described above. Two blood spots will also be collected on a filter paper.

Nose and throat swabs will be taken in accordance with the provided study SOP and frozen immediately at minus 80°C in their collection tube, or handled per local procedure if agreed with MORU team. Sputum will either be frozen in the container in which it is collected (if amenable to freezing) at minus 80°C or the sample will be transferred to a viral swab and stored at minus 80°C.

Samples will be transferred to MORU Tropical Health Network laboratories or designated testing facilities in other regions, where they will undergo testing in accordance with best practice laboratory measures and safety procedures.

Validated antibody tests for SARS-CoV-2 are currently 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, zinc and vitamin D levels, may also be considered at a later date.

Nose and throat swabs will be processed using validated multiplex RT-PCR to detect 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 cycle threshold (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.

DBS samples will be used for measurement for chloroquine/ hydroxychloroquine levels and may be used for diagnostic tests for COVID-19 (antibody, antigen or PCR).

The samples will be retained per Oxford and local site regulations (refer to Section 11.2). Consenting participants may rescind their consent at a later date and refuse the use of their samples (which will be destroyed) at any time up until the completion of the study.

7.9. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time and can refuse the use of their data at any time up until the completion of the study (final follow-up of the final participant). 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.

Participants who withdraw or are removed from the study will not be replaced.

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 up to 60 days after the diagnosis of COVID-19/ ARI of the last participant enrolled in the study, whichever comes last. **See Appendix F for UK specific information.**

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, or hydroxychloroquine or placebo. It is expected that chloroquine will be used in Asian sites and hydroxychloroquine in Europe, specific drug allocation will be determined by country prior to activation based upon factors such as inventory availability and importation requirements.

Characteristics of each product are described in the SmPC.

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 3-5 tablets depending on weight where the dose is split then only the initial part of this dose will be observed) 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 participant is receiving chloroquine/ hydroxychloroquine or placebo.

See Appendix F for UK specific information.

8.2. Storage of Study Medication

The medication will be stored securely per manufacturer instructions in the institution's pharmacy or other secure location. The medication will only be accessible to the designated study team members.

Participants will be advised that the IMP should be stored at room temperature, up to 30°C, away from moisture and light and out of reach of children and pets.

See Appendix F for UK specific information.

8.3. Compliance with Study Medication

Adherence will be assessed by direct questioning of the participant. 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. In the event of lost medication or more than 3 consecutive missed doses the participant should contact the study team, if they have not already been contacted by the study team.

8.4. Accountability of the Study Medication

The medication and placebo supplies will be supervised at all times by study teams. 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. **See Appendix F for UK specific information.**

8.5. Concomitant Medication

Chloroquine or hydroxychloroquine must be avoided if the participant is taking the following medications:

Antiarrhythmic medications: digoxin, amiodarone, sotalol, flecainide

Antiparasitic/malarial agents: mefloquine, halofantrine, praziquantel

Antibiotics: levofloxacin, moxifloxacin, ciprofloxacin, azithromycin, clarithromycin, erythromycin

Antifungal drugs: fluconazole, ketoconazole, itraconazole, terfenadine
Psychoactive drugs: lithium, quetiapine, chlorpromazine, thioridazine, ziprasidone, haloperidol, droperidol, methadone
Migraine treatment: sumatriptan
Antihistamines: astemizole
Antiemetics: prochlorperazine, metoclopramide
Cancer treatments: abiraterone, dabrafenib, dacomitinib, enzalutamide, idelalisib, mitotane
Other specific drugs: ciclosporin, conivaptan, agalsidase alfa or beta, mifepristone, stiripentol
PIs will also be directed to **crediblemeds.org** to check other agents that may prolong QT interval

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

The severity of adverse events will be assessed following the Common Terminology Criteria for Adverse Events (CTCAE) v5.0:

1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = fatal.

AEs occurring from time of consent until their D90 visit, (or up until Day 150 for participants who are symptomatic at D90), that are observed by the Investigator or reported by the participant with severity grade of 2 (moderate) or higher 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.

AEs considered related to the trial medication as judged by a medically qualified investigator 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 adverse event. 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

- General reporting procedures for all SAEs are to be managed by the site PI via local / national ethics committee and regulatory requirements.
- In addition, the COPCOV safety team will monitor events and communicate with the study Data Safety and Monitoring Board (DSMB, see Section 9.7). The safety team can be contacted via: COPCOV-Safety@tropmedres.ac

SAEs relating to acquisition of COVID-19, and morbidity and mortality associated with this, do not need to be reported to the COPCOV safety team immediately, but should be reported no less than monthly in order to be included in scheduled Safety Monitoring Committee meetings.

All other SAEs detected by the site investigator should be reported to the COPCOV safety team within 24 hours of site awareness. The safety team and the local PI will gather any additional relevant information. The COPCOV safety team will inform the DSMB within 10 days of initial notification of the SAE and keep the DSMB updated as needed.

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

See Appendix F for UK specific information.

9.6. Reporting Procedures for Pregnancy

If a female participant becomes pregnant after enrolment she should be instructed to discontinue study drug. The site study team is to notify the COPCOV safety team within 24 hours of site awareness through completion of the pregnancy notification form and submission to: COPCOV-Safety@tropmedres.ac.

Pregnant participants will be asked to return unused IMP at their next visit and will continue remaining follow up visits and procedures per protocol.

9.7. 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. The DSMB will consider a formal interim analysis/analyses if the study exceeds certain time periods. The safety and the statistical considerations in the interim analyses such as the stopping rules for trial efficacy including the type 1 error probability, and futility for no treatment benefit have been clearly detailed in the DSMB charter and the statistical analysis plan.

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.

All DSMB recommendations will be communicated to site PIs. The site PI will be responsible for submitting the written DSMB summary reports with recommendations as applicable to local/ national ethics committees and other applicable groups.

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. A per protocol (PP) analysis will be conducted to adjust for non-compliance to study protocols. Under an assumption of no post-randomisation confounding, this is a form of sensitivity analysis of the intention to treat analysis. In the PP analysis, participants who did not take their pills, or those who took extra chloroquine/ hydroxychloroquine (in both cases as determined by PK analyses), no final outcome assessed and losses to follow-up prior to the assessment of the final outcome, and any major protocol violations will be excluded. A detailed Analysis plan will be written by the trial statistician.

10.2. The Number of Participants

A large and definitive study is needed to characterise the benefit of prophylaxis with chloroquine or hydroxychloroquine in protecting heath care workers from COVID-19 illness. Power calculations are based on an assumption of 3% incidence of symptomatic COVID-19 during the trial period (1% per month). This is a conservative estimate and although some sites may have more or less cases, due to the unpredictability of numbers of cases in a site and a country, this assumption remains valid. 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 participants randomised to each arm. We will aim to enrol 10,000 participants in each arm in the two trials which allows for at least a 10% LTFU,

withdrawal rate, protocol deviation and non-adherence. Thus 20,000 would be randomised to chloroquine/ placebo and 20,000 to hydroxychloroquine/ placebo.

10.3. Analysis of Outcome Measures

A mixed effects Negative Binomial 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. Repeated measures and hospital clustering effect will be taken to account in the mixed effects model. 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. In the event that the Negative Binomial models fail to converge, as is the characteristic of these models when the outcome is rare, a Binomial regression model will be considered to model the risk/ odds of symptomatic COVID-19 infection to obtain risk differences/ odds ratios as appropriate comparing the chloroquine/ hydroxychloroquine arm with placebo. 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 (see Appendix A for example) will be used to assess severity of symptomatic COVID-19 and ARIs of those who acquire these, and these will be captured longitudinally over time. A rank-based mixed model approach will be used to analyse these scores, to compare 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. Health economic analyses overall and at the country level will be performed.

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the University of Oxford, local ethics committees and regulatory authorities, 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 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. 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. **See Appendix F for UK specific information.**

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.

Participant 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 for five years following completion of the study, or according to local site regulation. 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 overseen by the MORU Clinical Trials Support Group (CTSG) according to a prespecified risk-based 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/ national ethics committees, and regulatory agencies 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 team 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 team 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. **See Appendix F for UK specific information**

13.5. Expenses and Benefits

Participants will not be paid for their participation in the research. Reimbursement for costs incurred by participants during study participation will be reimbursed per local allowed guidelines and ethics committee policies. **See Appendix F for UK specific information**

13.6. Reporting

The PI will ensure that an Annual Progress Report is submitted 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.

See Appendix F for UK specific information

13.7. Other Ethical Considerations

The decision to include only participants with a smartphone potentially runs the risk of violating the "fair subject principal" (20) 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 / hydroxychloroquine 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.

As part of our engagement initiative (also called "patient and public involvement", MORU will be conducting a series of workshops within Thailand 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).

Similar or additional activities may be implemented at sites outside Thailand.

14. FINANCE AND INSURANCE

14.1. Funding

This study is funded via the COVID-19 Therapeutics Accelerator (Bill & Melinda Gates Foundation, Mastercard and the 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.

REFERENCES

1. Chen Y, Chen L, Deng Q, Zhang G, Wu K, Ni L, et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J Med Virol. 2020;92(7):833-40.
2. Lambert LC, Fauci AS**.** Influenza vaccines for the future. N Engl J Med. 2010;363(21):2036-44.
3. Zhao S, Lin Q, Ran J, Musa SS, Yang G, Wang W, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. Int J Infect Dis. 2020.
4. Biggerstaff M, Cauchemez S, Reed C, Gambhir M, Finelli L**.** Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature. BMC Infect Dis. 2014;14:480.
5. Wang Z, Chen X, Lu Y, Chen F, Zhang W**.** Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci Trends. 2020.
6. White NJ, Miller KD, Churchill FC, Berry C, Brown J, Williams SB, et al. Chloroquine treatment of severe malaria in children. Pharmacokinetics, toxicity, and new dosage recommendations. N Engl J Med. 1988;319(23):1493-500.
7. White NJ, Watt G, Bergqvist Y, Njelesani EK**.** Parenteral chloroquine for treating falciparum malaria. J Infect Dis. 1987;155(2):192-201.
8. Krishna S, White NJ**.** Pharmacokinetics of quinine, chloroquine and amodiaquine. Clinical implications. Clin Pharmacokinet. 1996;30(4):263-99.
9. Villegas L, McGready R, Htway M, Paw MK, Pimanpanarak M, Arunjerdja R, et al. Chloroquine prophylaxis against vivax malaria in pregnancy: a randomized, double-blind, placebo-controlled trial. Trop Med Int Health. 2007;12(2):209-18.
10. Payne D**.** Did medicated salt hasten the spread of chloroquine resistance in Plasmodium falciparum? Parasitol Today. 1988;4(4):112-5.
11. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020.
12. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2:69.
13. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020.
14. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020.
15. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020.
16. McChesney EW, Banks WF, Jr., Fabian RJ**.** Tissue distribution of chloroquine, hydroxychloroquine, and desethylchloroquine in the rat. Toxicol Appl Pharmacol. 1967;10(3):501-13.
17. Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M**.** In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun. 2004;323(1):264-8.
18. Keyaerts E, Li S, Vijgen L, Rysman E, Verbeeck J, Van Ranst M, et al. Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. Antimicrob Agents Chemother. 2009;53(8):3416-21.
19. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020;26(5):672-5.
20. Emanuel EJ, Wendler D, Killen J, Grady C**.** What makes clinical research in developing countries ethical? The benchmarks of ethical research. J Infect Dis. 2004;189(5):930-7.

16. APPENDIX A: EXAMPLE OF SEVERITY OUTCOME MEASURES

Observation	Scale
Outpatient	
Feels normal	
Feels unwell	
URTI Symptoms (coryza and/ or sore throat)	
Muscle aches	
Cough	
Afebrile <37.5°C	
Fever ≥37.5 and ≤38.5°C	
High fever >38.6°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 form an example of what may 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. 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. A more detailed analysis plan can be found in the statistical analysis plan (SAP) document.

17. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	**Visits**					
	Day 0 Enrolment	**Day 30 (-3 / +1)**	**Day 60 (-3 / +1)**	**Day 90 (-3 / +1)**	**Outcome follow-up if symptomatic (≤Day 150)**	**ARI Symptom onset[1]**
	1	**2**	**3**	**4**	**5**	***As needed during trial period***
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	Z[2]	
Observed 1st dose of study medication	X					
Dispensation of study medication (unless diagnosed as COVID-19 before visit)	X	X	X			
Compliance assessment		X	X	X		
DBS	X*	X	X	X*		
Adverse event assessments		X	X	X		
Questions about well-being, illness, COVID-19 diagnosis and clinical severity data	X	X	X	X	X	X
Nose and throat swab (+/- sputum)						X

[1] Can be repeated on multiple occasions if illness worsens or new ARI during trial period.

[2] If not already collected at Day 90.

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

* This sample is expected to be obtained from the venous blood sample drawn at the same visit. If necessary direct finger prick may be performed.

18. 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.

19. APPENDIX D: POTENTIAL SITES

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.

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.

Other potential sites will be located in, but are not limited to, the following countries:

Africa	Benin, Botswana, Burkina Faso, Cameroon, Côte d'Ivoire, Democratic Republic of Congo, Egypt, Ethiopia, Gambia, Ghana, Guinea, Kenya, Mali, Mozambique, Niger, Nigeria, Senegal, Sierra Leone, South Africa, Sudan, Tanzania, Tunisia, Uganda, Zambia, Zimbabwe
Asia	Bangladesh, India, Indonesia, Malaysia, Maldives, Nepal, Pakistan, Saudi Arabia, Vietnam
Europe	Croatia, France, Italy, Netherlands, Russian Federation, Switzerland, Ukraine, United Kingdom
North / South America	Argentina, Brazil, Canada, Chile, Colombia, Cuba, Dominican Republic, Guatemala, Jamaica, Peru, Puerto Rico

20. APPENDIX E: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Major Changes
002	V2.0	26.05.2020	Greig Dougall (Senior Trial Manager)	Participant inclusion has been broadened to include individuals working in healthcare facilities who are not providing direct patient care. Known pregnancy or actively trying to become pregnant added as an exclusion criterion. Pregnancy reporting process added. Clarification of advertisement process to state the poster will be widely distributed by the trial team and local investigators (including to external healthcare organisations.)
003	V3.0	11.06.2020	Greig Dougall (Senior Trial Manager)	Amendments to inclusion criteria excluding participants over 70 years old and with medical conditions which may increase QT interval. Additional detail to the list of concomitant medications. The global protocol has been aligned with UK changes relating to broadening the study population and the exclusion criteria for participants who are pregnant or actively seeking to become pregnant. This information has been removed from appendix F as now include in body of the protocol. Updated rationale and background Updates to Investigators and participating sites and countries and other minor changes.
004	V4.0	31.07.2020	Jo Milton (Head of Clinical Research)	Clarification that a formal direct helpline will not be provided, but that the CI or delegate will be available during business hours to answer any protocol related questions. Clarification of the process for swab sampling; the primary method being self-swabbing by participants and return by post to the Oxford laboratory, rather than to participating sites, for storage until analysis. Amendment to the IMP dispensing process to allow pharmacies to dispense kits to the study team for them to assign to participants. This is for logistical reasons and will increase the efficiency of the initial

				visit and allow recruitment outside of pharmacy hours if required. Other minor clarifications.

21. APPENDIX F: UK VARIATIONS

Section Page	UK variation to Protocol number VIRT20001 Version 5.0	Rationale
Section 1 page 7	Hydroxychloroquine sulphate will be used in the UK.	Per protocol
Section 1 page 7	Planned Sample Size 40,000 total participants UK sample size will be uncapped but expected to be 8,000 to 10,000 participants.	The UK, will recruit around one half of the total European sample size of 20,000 and recruitment will be competitive between European sites
Section 1 page 7	Planned Study Period 12 months; individual trial duration 5 months. In the UK, the study period will include the linkage to health records and passive follow-up via the collection of additional data for up to 15 years.	To perform cost utility analysis in line with NICE standards.
Section 1 page 8	The protocol states, 'The trial will collect data on use of health care resources and health related quality of life (EQ-5D-3L) to determine the effects between treatment groups.' In the UK, linkage to health records including, for example, NHS Digital, will be undertaken to permit an understanding of the consequences and costs of treatment.	To perform cost utility analysis in line with NICE standards.
Section 3 page 13	The protocol states, 'Study diagnoses will be made at the end of the study, where possible participants will be informed if they had or did not have COVID-19 infections as defined above.' This sentence will not apply to the UK.	It is likely in the UK that the public will be tested widely for seroconversion to COVID-19 as part of public health measures. A problem could arise if trial results conflict with results of NHS clinical testing. We propose to make it clear in the UK PIS that trial results will not be made available to participants.
Section 3 page 14	In the UK the inclusion criteria for age is >18 years and <70 years at the time of consent.	
Section 3 page 14	In the UK this could include hospital porters, dieticians, food service workers, ambulance workers, radiographers, cleaners, laboratory workers, among others.	To broaden inclusion criteria in the UK to include all healthcare workers in a facility dealing with Covid-19 rather than just those with direct care responsibilities.
Section 3 page 14	Protocol states, 'Study participation will be open to hospitals and lower level health centres.' In the UK, it is expected that all participating sites will be secondary care acute NHS hospitals	These sites will have the facilities and staff required to conduct the trial.
Section 4 page 15	Tertiary Objective The protocol states 'The days lost to work, and the relationship between the subjective assessment of well-being and the decision to self-isolate when unwell (i.e. not go to work) will be examined in relation to infection and treatment arm.' In the UK, this assessment is within, rather than after the study period, due to the 15 year data linkage.	UK Clarification

Section 4 page 15	Tertiary Objective The protocol states, 'The trial will collect data on use of health care resources and health related quality of life (EQ-5D-3L) to determine the effects between treatment groups.' In the UK, linkage to health records for up to 15 years, including, for example, NHS Digital, to permit an understanding of the consequences and costs of treatment. In the UK, this assessment is within, rather than after the study period, due to the 15 year data linkage.	To perform cost utility analysis in line with NICE standards.
Section 5 page 15	Protocol states, 'Before the trial enrolment starts there will be engagement with the potential participants to inform them about the trial and possibly obtain the baseline demographic information from potential participants.' In the UK, potential participants will be made aware of the study through staff communications channels including email and social media and staff-facing advertising. These communications will direct potential UK participants to a trial web-based eligibility questionnaire and to obtain contact details. Site will use this information to contact potential participants to book a time to enrol in the trial.	To streamline enrolment in the UK
Section 5 page 15	In the UK, posters advertising the trial will be actively circulated by the trial team via the trial website and throughout the healthcare community, including, but not limited to care homes and ambulance trusts, directing potential participants to the website.	UK advertising clarification
Section 5 page 16	Protocol states, 'If symptoms consistent with COVID 19 occur….'. In the UK, we will use wording on the patient information sheet consistent with advice to NHS staff.	To avoid confusion for staff as symptoms triggering study sampling and NHS sampling should be the same.
Section 5 page 16	Protocol states, 'Participants will be given a participant ID (a card in most settings)'. In the UK, the card can be provided electronically if required.	As a practical back-up if cards not available or lost
Section 5 page 16	Protocol states, 'Subjects will also be given a thermometer'	If supplying thermometers becomes a problem because of shortages, UK sites will ask participants to use their own thermometers
Section 5 page 17	Protocol states 'further drug dispensed' at follow-up visits. In the UK, all IMP will be provided at enrolment (D0).	Dispensation of all the study medication at D0 reduces the administrative burden on site and pharmacy staff.
Section 6.2 page 17	In the UK the inclusion criteria for age is >18 years and <70 years at the time of consent.	
Section 7 page 18	Study Procedures In the UK, the CI or delegate will be available to study site staff via the Diabetes Trials Unit during business hours to answer any protocol related questions.	To provide support to sites and answer protocol related queries in the local time zone.
Section 7.2 page 18	Protocol states, 'Eligibility assessment will occur at the point of screening'.	In accordance with MHRA suggestions

	In the UK, potential participants will complete an eligibility questionnaire using a web-based form. This information and contact details will be securely transferred to their local site to allow them to make contact and book an appointment for enrolment. If there is doubt about eligibility, the site physician will be involved. If the potential participant is eligible, then site PI will countersign, and the patient will be prescribed study medication by the nurse or pharmacist.	
Section 7 page 18	Study Procedures In the UK, the CI or delegate will be available to study site staff via the Diabetes Trials Unit during business hours to answer any protocol related questions.	To provide support to sites and answer protocol related queries in the local time zone.
Section 7.1 page 18	In the UK, site and co-ordinating centre research staff can distribute posters and other approved trial advertisements to local healthcare facilities, including care homes and ambulance trusts, which are out with their own trust.	The trial posters can be distributed widely within healthcare facilities that are not participating sites. Potential participants can then express their interest to participate via the website at the nearest participating site.
Section 7.2 page 18	Protocol states, 'Eligibility assessment will occur at the point of screening'. In the UK, potential participants will complete an eligibility questionnaire using a web-based form. This information and contact details will be securely transferred to their local site to allow them to make contact and book an appointment for enrolment. If there is doubt about eligibility, the site physician will be involved. If the potential participant is eligible, then site PI will countersign, and the patient will be prescribed study medication by the nurse or pharmacist.	In accordance with MHRA suggestions
Section 7.3 page 19	Protocol states, 'A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site' In the UK, two originals will be signed and one of those provided to the participants.	More time efficient and avoids the requirement for a photocopier at site.
Section 7.5 page 19	Randomisation and blinding In the UK, the hydroxychloroquine and placebo outer cartons and blister packs will be pre-labelled prior to shipping to the study site pharmacy. The labels will include the kit (carton) number, which is also the subject ID number; this will not need to be written on the packs. All of the study medication for the duration of the trial will be dispensed to the participant at D0. During the dispensing process the tear off section of the label will be attached to the participant accountability log. Depending upon the time of day/night, unblinding of specific participants will either take place in discussion with the Co-PIs based in Thailand and be performed by the trial statistician or in discussion	Clarification provided on UK processes. Dispensation of all the study medication at D0 reduces the administrative burden on site and pharmacy staff.

	with the UK CI and performed by a UK designated member of the co-ordinating centre.	
Section 7.6 page 19	Protocol states, 'At Day 0 (D0), participants will be given a card with a subject ID number' In the UK, the card can be provided electronically if required.	As a practical back-up if cards not available or lost
Section 7.6 page 20	Protocol states, 'Participants will also be given a thermometer'	If supplying thermometers becomes a problem because of shortages, UK sites will ask participants to use their own thermometers
Section 7.7 page 20-21	Protocol states, 'If via the app or by phone, the participant reports to feel unwell with an ARI (potential COVID-19 symptoms) or potential drug side-effects, they will be contacted via telephone by the study team, and a visit to conduct testing will be organised within 24 hours to obtain a nose and throat swab according to local procedures.' 1. In the UK, the options to obtain the swab are: Participant is sent the materials and performs the swab themselves, returning it to the Oxford laboratory (postage pre-paid) for storage prior to analysis. Sputum samples will not be collected in this case. 2. Participant comes to a specified place at the hospital to have a swab taken / collected in the same was as for staff screening 3. Participant comes to occupational health	Clarification provided on UK processes.
Section 7.10 page 22	End of Study In the UK, the end of the study will be after the completion of the follow-up via medical records and organisations such as NHS digital - this will be 15 years after the last participant is randomised in the UK.	Clarification that UK end of study date includes the 15 year indirect patient follow-up period.
Section 8.1, 8.2 and 8.4 page 22-23	Study Medication In the UK, hydroxychloroquine in the dose of 155mg chloroquine base (in the form of 200 mg hydroxychloroquine sulphate) and matching placebo will be packaged in identical packaging (10 blister packs of 10 tablets in each carton) and both the carton and blisters will be labelled in accordance to regulatory requirements, including with the kit (carton) number, which is also the subject ID number. The ingredients of the placebo in the UK are as follows (mg): lactose (208.2), microcrystalline cellulose 102 (45.0), starch 1500 (45.0), colloidal silicon dioxide (0.3), magnesium stearate (1.5) and opadry white. Participant kits will be packaged into boxes of 50 kits and 8 boxes will be shipped to each site pharmacy in one or two shipments. The study medication will securely stored in and dispensed from pharmacy. Following completion of the prescription pharmacy will allocate and dispense the next sequential kit number to the participant. If required for logistical reasons and to allow recruitment outside of pharmacy hours, pharmacy may dispense a number of IMP kits to the study team	Clarification provided on UK processes. Dispensation of all the study medication at D0 reduces the administrative burden on site and pharmacy staff and is acceptable given no special storage conditions are required for the IMP.

	for them to store securely. In this instance, the study team will dispense the next sequential number to the participant following completion of a prescription. The subject ID number will be recorded on the CRF and the removable section of the label will be attached to the accountability records in pharmacy. Participants in the UK will be provided with all the study medication for the duration of the trial at D0.	
Section 9.5 page 26	Reporting Procedures for Serious Adverse Events In the UK, UK co-ordinating centre staff will receive a copy of emails sent to the global COPCOV safety team, thereby receiving copies of reportable SAEs. The UK co-ordinating centre will obtain any required follow-up information and onwardly report SUSARs to regulatory authorities. Local study site investigators will be responsible for any reporting requirements with their NHS Trusts. Depending upon the time of day/night unblinding of specific participants will either take place in discussion with the Co-PIs based in Thailand and be performed by the trial statistician or in discussion with the UK CI and performed by a UK designated member of the co-ordinating centre.	Clarification provided on UK processes
Section 11.2 page 27-28	Data handling and record keeping In the UK, data will be entered into Axiom Fusion and Axiom ePRO data capture systems. Pseudonymized clinical study data, identified by participant ID only, will be recorded on case report forms and entered on to the password-protected database either by the local study PI or Research Nurse via Axiom Fusion or by the participant in Axiom ePRO. Both Axiom tools have been developed in accordance with the requirements identified in the FDA's 21 CFR Part 11: Computerized Systems Used in Clinical Trials. They comply with ICH GCP guidelines including US Regulations 21 CFR Parts 312 and 812 as well as EU Directive 2005/28/EC and ICH E6. Axiom Data Capture Tools are validated per guidelines set for Software Validation provided by the FDA. The UK data (excluding data described in section 13.4) from the Axiom systems will then be integrated with data from the global study database, which will be built in Infermed MACRO, an electronic data capture (EDC) system that is compliant with ICH GCP and FDA 21 CFR Part 11 and will be hosted in a secure, access-restricted server. 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. The Axiom systems and MACRO will include internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate.	Reasons of time efficiency for site staff, and because participants are already recording some of their own data.
Section 13.4	Participant Confidentiality	Clarification provided on UK processes to allow linkage with health records for up to 15 years to obtain an

	In the UK, additional participant identifying data will be collected, including NHS numbers when known, in order to link to health records, including NHS digital. The information will be entered by potential participants on a web-based form and data will be held in a HIPAA compliant Redcap database (https://projectredcap.org/) that is hosted at the Diabetes Trial Unit, University of Oxford. The database is secured and maintained by Medical Sciences Division IT staff (https://www.medsci.ox.ac.uk/divisional-services/support-services-1/information-technology) together with DTU IT staff. Transfer of data will be via encrypted networks. This will involve sharing the personal data with NHS Digital or other organisations. The data will be destroyed within three months for potential participants who do not consent to participate in the trial. For those that consent to participate, the data will be held to enable linkage for up to 15 years. Explicit consent will be obtained to: 1. Allow study site staff to access medical records should participants be hospitalised to obtain information in relation to (serious) adverse events 2. Allow study site staff to write to the participants GP should they become unwell in order to obtain copies of medical records in relation to adverse events, tests or procedures performed or changes in medications	understanding of the costs and consequences of treatment. Clarification provided on UK processes to access medical records during the trial.
Section 13.5 page 29	Expenses and Benefits Protocol states, 'Reimbursement for costs incurred by participants during study participation will be reimbursed per local allowed guidelines and ethics committee policies.' Expenses will not be provided in the UK.	Participant visits will be combined with their attendance at the hospital for work and not providing expenses significantly reduces the administrative burden on sites.
Section 13.6, page 29	Reporting In the UK annual reports and the end of study report will be submitted to the Research Ethics Committee by the UK co-ordinating centre, in collaboration with the Chief Investigator	Clarification provided on UK processes