# A multi center randomized open label trial on the safety and efficacy of chloroquine for the treatment of hospitalized adults with laboratory confirmed SARS-CoV-2 infection in Vietnam

**Short title: The Vietnam COVID-19 trial (The VICO trial)**

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|---|---|
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## STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____
Print/Type Name

Signed: _____ Date:

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For full details of all trial committees, please see Section 13 Oversight and Trial Committees.

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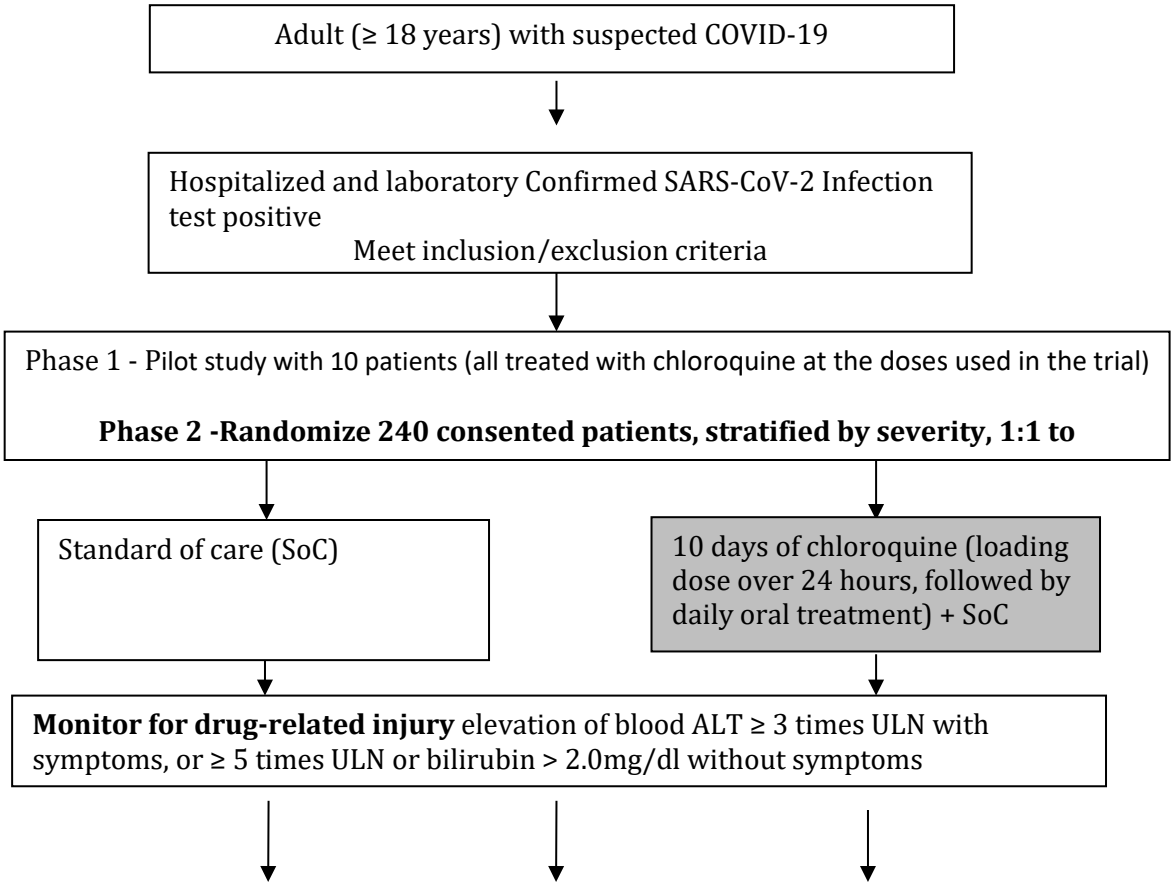
# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| CFR | Code of Federal Regulations |
| CIOMS | Council for International Organizations of Medical Science |
| CLIA | Clinical Laboratory Improvement Amendments |
| CMP | Clinical Monitoring Plan |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| DCC | Data Coordinating Center |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic Case Report Forms |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| ICH E6 | International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: |
| ICMJE | International Committee of Medical Journal Editors |
| IDE | Investigational Device Exemption |
| IND | Investigational New Drug Application |
| IRB | Investigational Review Board |
| ISO | International Organization for Standardization |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MOP | Manual of Procedures |
| MSDS | Material Safety Data Sheet |
| OHRP | Office for Human Research Protections |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SMC | Safety Monitoring Committee |
| SOP | Standard Operating Procedure |
| UP | Unanticipated Problem |

## SUMMARY OF TRIAL

| SUMMARY INFORMATION TYPE | SUMMARY DETAILS |
|---|---|
| **Trial Title** | A multi-center randomized open label trial on the safety and efficacy of chloroquine for the treatment of hospitalized adults with laboratory confirmed SARS-CoV-2 Infection in Vietnam. |
| **ACRONYM** | The VICO trial |
| **Trial Design** | 10 patient pilot observational study (all treated with chloroquine), followed by parallel group, randomized (1:1), multi-centre Phase II trial |
| **Trial Population/Participants** | 10 (pilot) and 240 hospitalized adults with laboratory confirmed SARS-CoV-2 Infection, stratified by disease severity. An interim analysis for futility will be conducted after 120 patients have been enrolled. |
| **Setting** | The Hospital for Tropical Diseases, the Cu Chi Field Hospital, the Can Gio COVID hospital in Ho Chi Minh City, the Cho RayHo Chi Minh City and the National hospital for Tropical Diseases, Ha Noi, Viet Nam |
| **Interventions Compared** | Arm 1: Chloroquine for 10 days and standard of care as per Vietnam Ministry of Health Guidelines<br>Arm 2: Standard of care as per Vietnam Ministry of Health Guidelines |
| **Study Hypothesis** | Chloroquine results in more rapid decline in viral load in throat/nose swabs in patients with COVID-19<br>The **primary objective** is to test this hypothesis.<br>The **secondary objectives** are to:<br>1. Assess the effectiveness of chloroquine in clinical practice. Compare the effect on duration of ICU and hospital stay, the development of acute respiratory distress, and on all-cause mortality<br>2. Define the safety of chloroquine in COVID-19 treatment |
| **Primary Outcome Measures** | ▪ The time to 2 consecutive (daily) negative SARS-CoV-19 RNA throat /nose swabs. |
| **Secondary Outcome Measures** | ▪ We will compare the time to discharge between study groups<br>▪ We will compare the number of ventilator free days over the first 28 days of treatment between groups<br>▪ We will compare the rates of adverse events between treatment groups.<br>▪ We will compare the time to death between treatment groups over the first 7, 14 and 28 days and the estimated hazard of death at day 56 |
| **Participant follow-up** | An individual subject will complete the study in 56 days. |
| **Study Duration** | Recruitment anticipated in 6 to 8 months. Protocol remains active for 2 years. Analysis and write up within 12 months of first patients being enrolled. The result of safety and effectiveness of the first 10 patients can be considerred to be published. |
| **Ancillary Studies** | We will store serial blood samples to assess the immune response to the virus and for later genetic testing, to determine if human genetic variants are associated with disease susceptibiltiy, severity, and outcome. |

## SCHEMATIC OF STUDY DESIGN




**Follow-up:** daily whilst in hospital; then day 14, 28, 42 and 56.

**Primary endpoint:** The primary endpoint is the time to viral clearance from throat/nose swab.

**Secondary endpoints:**

1. The duration of hospital stay from the time or randomization
2. The number of ventilator-free days during the first 28 days following randomization
3. The time to (all-cause) death following over the first 7, 14, 28 and 56 days since randomization
4. The WHO ordinal outcome scale for COVID-19 at days 28. 42 and 56
5. Fever clearance time
6. Development of ARDS defined by the Kigali criteria
7. Oxygenation-free days over the first 28 days
8. Rates of serious adverse events
9. Rates of grade 3 or 4 adverse events

# 1. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

Coronaviruses (CoVs) are positive-sense single stranded enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle Eastern respiratory syndrome coronavirus (MERS-CoV)[1, 2].

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients[3]. This novel coronavirus has been abbreviated as SARS-COV-2 and has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV[4]. This novel coronavirus has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19. Sars-CoV-2 has spread rapidly following its initial identification in Wuhan, Hubei Province, China[5]. On January 5, 2020 there were 59 confirmed cases. As of 21st March 2020, the SARS-CoV-2 pandemic has resulted in more than 275, 000 confirmed infections globally, with disease reported in over 170 countries, and more than 11,000 deaths. The crude global mortality is currently >4%, significantly greater than that reported for seasonal influenza, which affects up to 1 billion people each year and causes between 290 000 and 650 000 deaths[6]. Disease is reported from the majority of countries in the Asia-pacific region, with large numbers affected in south Korea (< 8000), and disease also confirmed in Vietnam, Thailand, Singapore, Malaysia, Philippines and Indonesia. Lack of reporting of cases from Laos PDR and Myanmar likely reflect undeveloped testing facilities rather than lack of cases. Outside the Asia-Pacific region, exponential growth in number of cases is seen in most European countries, notably Italy, Spain, Germany, France, Switzerland and the United Kingdom. Similar patterns of spread are seen in the Americas, with the USA now reporting more than 20, 000 cases[6].

The main route of spread of COVID-19 is believed to be through respiratory droplets; however other routes including direct person to person, faeco-oral and fomites may be important[5]. Currently there is no proven effective prophylaxis, treatment or vaccine. The estimated COVID-19 basic reproductive ratio (R0) 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)[7, 8]. The use of personal protective equipment is paramount for healthcare staff - significant numbers have been infected in both Italy and China[9]. There is a pressing need to identify effective treatments and preventive measures for COVID-19. Testing, isolation and quarantine measures are key in managing the epidemic, but the development of treatments that shorten disease duration, improve outcome, and reduce infectivity is clearly essential, helping both the individual patient and potentially also limiting spread. While novel agents, such as remdesivir, are in development, these will not be available to the vast majority of patients within coming months[10, 11]. However, repurposing older drugs that are currently licensed and manufactured has the potential to have dramatic impact at both individual and population levels, since roll-out of treatment to the wider population is feasible, affordable and safe. The choice of such drugs to trial should be driven by evidence of in vitro efficacy, plausibility and deliverability of the intervention.

## 1.2. SCIENTIFIC RATIONALE

COVID-19 is a respiratory disease caused by a novel coravirus (SARS-CoV-2) and causes substantial morbidity and mortality. There is currently no vaccine to prevent COVID-19 or therapeutic agent to treat COVID-19. This clinical trial is designed to evaluate potential therapeutics for the treatment of hospitalized COVID-19.

We hypothesise that chloroquine slows viral replication in patients with COVID-19, attenuating the infection, and resulting in more rapid declines in viral load in throat/nose swabs. This viral attenuation should be associated with improved patient outcomes. Given the enormous experience of its use in malaria

chemoprophylaxis, excellent safety and tolerability profile, and its very low cost, if proved effective then chloroquine would be a readily deployable and affordable treatment for patients with COVID-19.

**Chloroquine**
Chloroquine is an antimalarial drug discovered in 1934 and widely prescribed for malaria since 1947[12]. It has been safely prescribed to millions of people in all income settings since then. Chloroquine is inexpensive and simple to administer, is a first-line treatment for non-falciparum malaria, and is on the World Health Organization's List of Essential Medicines[13].

**Antiviral Effect**
Chloroquine has recently been reported as a potential broad-spectrum anti-viral drug[14]. It was found to have significant activity in vitro against the SARS coronavirus responsible for the 2003 SARS disease outbreak in China, Vietnam and Canada, where it has been shown to block virus infection by increasing the pH required for viral fusion and by interfering with the glycosylation of cellular receptors of SARS-CoV[15]. More recently it has been shown to also have significant in vitro activity against SARS-CoV-2, where it functioned both at the cell viral entry and post-entry stages during experimental infection of Vero E6 cells[14]. A half-maximal effective concentration (EC50 or the concentration associated with a decrease in replication (in Vero E6 cells) of the virus by 50%) of 1.13 µM was reported, with a corresponding EC90 of 6.9 µM[14]. Several other laboratory studies confirm activities in the low micromolar range for chloroquine[16]. This effect occurred when the drug was given either before or after viral inoculation[14]. In addition to its anti-viral effects, chloroquine also has an immunomodulatory effect in vivo which may synergisitically enhance its effect in vivo[14].

**Human use in COVID-19**
Chloroquine has a wide volume of distribution and achieves high lung concentrations following oral administration. The relationship between plasma concentrations and concentrations in respiratory epithelium is not known precisely, though in rats the concentration in lung is between 124 and 748-fold that in plasma[17]. The effective concentration needed to inhibit 90% of viral replication (EC90) of 6.9uM is higher than the therapeutic exposures needed to treat malaria, but should be clinically achievable, and maintained, with daily doses of chloroquine ≥ 500mg/day[14].

Chloroquine has been used in patients with COVID-19 in China and South Korea with reported good effect[18]. However, rigorous, peer-reviewed outcome data are currently lacking and thus it is not possible to draw firm conclusions about its efficacy and safety. A major problem with the non-controlled use of untested treatments in disease emergence is that improvements in outcome that occur naturally over time due to improved general management of cases as clinical experience is accrued, are falsely interpreted as being due to the novel therapy. Despite the lack of data, as of 20th March 2020, chloroquine, in a dose of 500mg twice daily, is recommended for mild, moderate and severe COVID-19 cases in China, and is currently recommended for all patients >70 years old with evidence of pneumonia due to SARS-CoV-19 in Italy[19].

**Safety**
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 [20]. It is safe in all age groups. In addition to its antimalarial use both chloroquine, and the closely related and slightly more hydrophilic hydroxychloroquine, are used in continuous daily dosing for rheumatoid arthritis, systemic and discoid lupus erythematosus and psoriatic arthritis. Chloroquine at a dose of 2.4mg base/kg (155 mg)/day for years is used for rheumatoid arthritis. Chloroquine given at the correct dose has an excellent safety profile.

## 1.3. Potential risks and benefits

### 1.3.1. Known potential risks

The potential risks of participating in this trial are those associated possible reactions to chloroquine, having additional blood drawn for study investigations, and breach of confidentiality.

Risks related to chloroquine phosphate/sulphate/hydrochloride are very low, unless the drug is taken in overdose. Chloroquine is generally safe and well-tolerated 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 and protracted exposures. The main adverse effect is itching in dark-skinned individuals; Africans are much more commonly affected compared to Asians.

The risks of side effects have to be considered within the overall risks of severe morbidity and death from COVID-19. The 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. QTc prolongation is not considered to be problematic unless there is coadministration of other drugs that are recognized to prolong the QT interval (for example, fluoroquinolones, macrolides, some antiemetics). In the event of the unavoidable prescription of such medications the QTc will be monitored with daily ECGs, monitoring and correction of electrolytes (sodium, potassium, calcium and magnesium), and chloroquine stopped and QTc prolonging drugs omitted where the QTc is >500ms. If ventricular tacchyarrhythmias arise on chloroquine the drug will be stopped, electrolytes corrected and intravenous magnesium administered.

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the subject lie down and elevate his/her legs. Bruising at the blood collection sites may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. Intravenous catheterization may cause insertion site pain, phlebitis, hematoma formation, and infusate extravasation; less frequent but significant complications include bloodstream and local infections. The use of aseptic (sterile) technique will make infection at the site where blood will be drawn or at catheter site less likely.

### 1.3.2. Known potential benefits

Chloroquine may or may not improve clinical outcome of an individual adult subject with COVID-19 who participates in this trial. However, there is potential benefit to society from their participation in this study resulting from insights gained about the therapeutic agent under study as well as the natural history of the disease. There may be benefits of participation if a safe, efficacious therapeutic agent can be identified during this global COVID-19 outbreak.

# 2 OBJECTIVES AND PURPOSE

| **Objectives** | **Outcome measures** | **Timepoint(s) of evaluation of this outcome measure (if applicable)** |
|---|---|---|
| **Primary Objective**<br>To determine if chloroquine results | The time to 2 consecutive (daily) negative SARS-CoV-2 RNA throat/nose swabs | During the first 56 days post |

| | | |
|---|---|---|
| in more rapid clearance of SARS-CoV-2 from throat/nose swabs of patients with COVID-19 | | randomization |
| **Secondary Objectives**<br>To determine if Chloroquine shortens the duration of hospital stay | We will compare the time to discharge between study groups | During the trial period |
| To determine if chloroquine results in more ventilator free days | We will compare the number of ventilator free days over the first 28 days of treatment between groups | During the trial period |
| To determine if Chloroquine use results in better survival compared with standard of care | We will compare the time to death between treatment groups over the first 7, 14 and 28 days and the estimated hazard of death at day 56 | During the trial |
| To define the safety profile of chloroquine in COVID-19 | We will compare the rates of adverse events between treatment groups. | Over the first 28 days (due to the prolonged half-life of Chloroquine) |

# 3 STUDY DESIGN AND ENDPOINTS

## 3.1 Description of study design

The study will start with a 10-patient prospective observational pilot study. All these patients will be subject to the same entry and exclusion criteria for the randomized trial, and undergo the same procedures. They will all receive chloroquine at the doses used in the trial (see sections below); they will not be randomized. The purpose of the pilot is to develop the study procedures for the randomized controlled trial, including the safe monitoring of patients, to refine the CRF, and to acquire some preliminary data on the safety of chloroquine in those with COVID-19.

Once the pilot study has been completed, and the data reviewed by the TSC and DMC, and the MOH ethics committee, we will then proceed to the trial. We will aim for minimum delay between completing the pilot study and starting the randomized trial.

The main study is an open label, randomised, controlled trial that will be conducted in in-patients in Ho Chi Minh City. Viet Nam.

**Study population**
All adult patients (≥18 years old) presenting to the study centres with positive throat/nose swabs (polymerase chain reaction) for SARS-CoV-19, and requiring hospital admission be eligible for study inclusion subject to the inclusion and exclusion criteria. Randomization will be stratified by severity of illness with severe disease being defined by a SpO2 ≤ 94%, tachypnea (respiratory rate ≥ 24 breaths/min), and mild-moderate disease begin defined by SpO2 > 94% and respiratory rate < 24 breaths/min without supplemental oxygen.

**Trial location**

The study will recruit at the Hospital for Tropical Diseases, Ho Chi Minh City, and Cu Chi and Can Gio COVID Hospitals in Ho Chi Minh City, Cho Ray Hospital, Ho Chi Minh and National for Tropical Diseases, Ha Noi.
Informed consent will be obtained from all patients or the responsible next of kin where the patient is incapacitated. Treatment allocation will be determined by randomization in a ratio of 1:1.

**Intervention arm**
Patients randomized to the intervention arm receive chloroquine with a loading dose over the first 24 hours, followed by 300mg base orally once daily for 9 days, in addition to standard of care therapy. For details of the dosing, see later sections.

**Control arm**
Patients randomized to the control arm will receive standard of care therapy.

## 3.2 Study endpoints

### 3.2.1 Primary endpoint

The primary endpoint is the time to viral clearance from throat/nose swab.
Viral presence will be determined using RT-PCR to detect SARS-CoV-19 RNA. Throat/nose swabs for viral RNA will be taken daily while in hospital until there have at least 2 consecutive negative results. Virus will be defined as cleared when the patient has had ≥2 consecutive negative PCR tests. The time to viral clearance will be defined as the time following randomization to the first of the negative throat/nose swabs.

### 3.2.2. Secondary endpoints

The secondary endpoints are:

1. The duration of hospital stay from the time or randomization
2. The number of ventilator-free days during the first 28 days following randomization
3. The time to (all-cause) death following over the first 7, 10, 14, 28 and 56 days since randomization
4. The WHO ordinal outcome scale for COVID-19 at days 28, 42 and 56
5. Fever clearance time
6. Development of ARDS defined by the Kigali criteria
7. Oxygenation-free days over the first 28 days
8. Rates of serious adverse events
9. Rates of grade 3 or 4 adverse events

### 3.2.3. Study size and power calculation

Data monitoring committee (DMC) will conduct an interim analysis after 120 patients, assessing safety, efficacy, and futility. The committee will recommend continuation unchanged to 240 patients, or stopping the trial, after this analysis. 120 patients will give **≥80%** power to detect a reduction in the time to viral clearance by **≥0.63.**

If the trial continues, we will enroll 240 patients. We assume the viral clearance time from throat/nose swabs to have a log-normal distribution. Using data from 14 patients in Ho Chi Minh City and Singapore, we estimated the mean time to clearance (log scale) of 2.17 days and standard deviation 0.74. Therefore a sample

size of 240 patients will give ≥80% power to detect a reduction in the time to viral clearance by a factor of ≥0.72.

# 4 STUDY ENROLLMENT AND WITHDRAWAL

## 4.1 Participant inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

1. Laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen < 48 hours prior to randomization, and requiring hospital admission in the opinion of the attending physician.
2. Provides informed consent prior to initiation of any study procedures (or legally authorized representative).
3. Understands and agrees to comply with planned study procedures.
4. Agrees to the collection of OP swabs and venous blood per protocol.
5. Male or female adult ≥18 years of age at time of enrollment.

## 4.2 Participant exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Intractable seizures of history of uncontrolled epilepsy
2. History of cardiac arrhythmia requiring on-going anti-arrhythmic therapy
3. ALT> 5 times the upper limit of normal.
4. Stage 4 Severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30)
5. Anticipated transfer to another hospital which is not a study site within 72 hours.
6. Allergy to any study medication
7. Chloroquine treatment mandated for any other reason e.g. vivax malaria
8. Taking a concomitant as per the table below which cannot be safely stopped or managed:

| Drug | Advice | Reason |
|---|---|---|
| Macrolide antibiotics | Avoid | May prolong QT interval |
| Fluoroquinolones | Avoid | May prolong QT interval |
| Haloperidol | Avoid | May prolong QT interval |
| Loperamide | Avoid | May prolong QT interval |
| Domperidone | Avoid | May prolong QT interval |
| Amitripylline | Avoid | May prolong QT interval |
| Fluconazole | Avoid | May prolong QT interval |
| Ketoconazole | Avoid | May prolong QT interval |
| Prilocaine | Avoid | Risk of methaemoglobinaemia |
| Penicillamine | Avoid | Haematological toxicity |
| Magnesium-based antacids | Avoid | Reduce chloroquine absoprtion |
| Laronidase | Avoid | Reduces laronidase absoprtion |

| | | |
|---|---|---|
| Dapsone | Avoid | Risk of methaemoglobinaemia |
| Cimetidine | Avoid | Increases chloroquine levels |
| Agalsidase | Avoid | Reduces agalsidase levels |
| Abiraterone | Avoid | May increase serum concentrations of this drug |
| Conivaptan | Avoid | May increase serum concentrations of this drug |
| Dabrafenib | Avoid | May decrease serum concentrations of this drug |
| Dacomitinib | Avoid | May increase serum concentrations of this drug |
| Enzalutamide | Avoid | May decrease serum concentrations of this drug |
| Idelasilib | Avoid | May increase serum concentrations of this drug |
| Mifepristone | Avoid | May increase serum concentrations of this drug |
| Mitotane | Avoid | May decrease serum concentrations of this drug |
| Stiripentol | Avoid | May increase serum concentrations of this drug |

**Note: Pregnant or breast-feeding women are not excluded**

## 4.3 Strategies for recruitment and retention

Potential participants from the study hospitals. Recruitment activities will only occur in an in-patient hospital setting and no activities will be carried out outside of the participating hospitals. The target sample size of 240 participants will be enrolled within an anticipated accrual rate of 6-8 months.

To ensure an optimal retention rate, once discharged from hospital the participants will be contacted by phone to remind them of their follow-up visit. In addition, patients who have missed a visit will be contacted by phone for a maximum of three times after which a maximum of three home visits can be conducted. All contact attempts will be recorded.

## 4.4 Participant withdrawal or participation

### 4.4.1 Reasons for withdrawal or termination

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

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Withdrawal of Consent
- Loss to follow up

### 4.4.2 Handling of participant withdrawal or termination

If a participant chooses to discontinue their trial treatment (chloroquine), they should always be followed up (providing they are willing) and they should be encouraged not to leave the whole trial. If they do not wish to remain on trial follow-up, however, their decision must be respected and the participant will be withdrawn from the trial. The OUCRU CTU should be informed of this on the Withdrawal of Consent CRF. The reason for the participant withdrawing should be ascertained wherever possible. Prior to withdrawing from the trial, the participant will be asked to have assessments performed as appropriate for the final visit although they would be at liberty to refuse any or all individual components of the assessment.

If a participant withdraws from the trial, the medical data collected during their previous consented participation in the trial will be kept and used in analysis. Consent for future use of stored samples already collected can be refused when leaving the trial early (but this should be discouraged and should follow a discussion). If consent for future use of stored samples already collected is refused, then all such samples will be destroyed following the policies of the institution where the samples reside at the time (local or central storage).

Participants may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial. Participants who stop trial follow-up early will not be replaced, as the total sample size includes adjustment for losses to follow-up.

### 4.5 Premature termination or suspension of study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <patient, investigator, funding agency, the sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

## 5 TRIAL PROCEDURES

### 5.1 Informed consent

Informed consent to enter into the trial and be randomized must be obtained from all participants or a person with responsibility (e.g. family member/relative as defined by the Vietnam MoH guidelines ) if the participants lack capacity, in their own language before enrolment by the site PI or an appropriately trained doctor. Individuals trained and responsible for taking consent will be documented on the trial's Delegation Log (with signatures). This should be, if appropriate, after explanation of the aims, methods, benefits and potential hazards of the trial and BEFORE any trial-specific procedures are performed or any blood is taken for the trial, including for the screening assessment.

It must be made completely and unambiguously clear that the participant (or their relative) is free to refuse to participate in or withdraw from all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their subsequent treatment. This will be stated explicitly in the participant information sheet. If consent was provided by a relative, the participant should be consulted and consent recorded if and when they have the capacity to do so.

Signed consent forms must be kept in the investigator site file and a copy given to the participant or family. After consent has been obtained from the participant or their relative, clinical information including medical history and examination, and weight will be recorded on the CRF. Routine tests, will also be recorded on the screening CRF as part of the medical history of the current infection. The screening procedures will take place as soon as possible after a potential participant has been identified by the doctors.

Considerating the nature of the diseases, the study patient may be treated in an isolated area, where no paper document is allowed to be moved out of the infectious area. The study will consider applying electronic ICF capture on tablet or any other appropriate method for obtaining valid ICF.

## 5.2 Randomization

Eligibility will be confirmed via the Screening CRF and participants randomized to two parallel groups in a 1:1 ratio: chloroquine for 10 days in addition to standard of care; or standard of care. Randomization will be 1:1 to either chloroquine or standard of care treatment. Randomization with variable block sizes of 4 and 6, will be used to assign subjects to treatment. Randomization will be stratified by recruiting centre and disease severity. The randomization list will be generated according to OUCRU standard operating procedures. In brief, the Research Biostatistician will set up statistical code to generate the randomization list and transfer it to the central Study Pharmacist. The Study Pharmacist will change the random seed, i.e. the initialization of the random numbers generator, in the statistical code in order to blind the Research Biostatistician and then run the code to prepare the final randomization list for treatment preparation. The randomization list will be password protected and stored on a secure server to which only the Study Pharmacist has access.

## 5.3 Initial evaluation

**Clinical assessment**
All patients will have a full clinical assessment including medical history and examination by the study team. Data collected will include presenting symptoms, duration of illness, past medical history, current medications, and physical examination findings including vital signs (pulse, temperature, blood pressure, oxygen saturations and FiO2), and the results of cardiovascular, respiratory, gastrointestinal and neurological examination in line with standard clinical practice.

**Radiology**
The results of any radiological imaging (chest X-ray, CT scan, lung ultrasound) performed during this illness will be recorded in the clinical reporting form. Patients who have not had a chest X-ray will undergo a chest X-ray on study entry.

**Biological Specimens and Laboratory evaluations**
On study entry all patients will have review of clinical investigations so far. Where an investigation has been performed within the last 24 hours, the results will be recorded, and they will only be repeated if clinically indicated. Study entry laboratory tests will be performed as per the study schedule below.

## 5.4 Clinical monitoring

Patients will have daily assessment as per standard of care while in-patients by the hospital staff. While in-patients the study will collect the following data: peripheral oxygen saturation (pulse oximeter), respiratory rate, and FiO2. The use of ventilator or other assisted breathing device will be recorded each day.
Patients will have clinical assessment recorded as per the study schedule.

The decision to discharge patients will be at the discretion of the attending physician and depend upon the clinical status of the patient. According to current standard of care recovery and hospital discharge is dependent upon the patient having had 2 daily consecutive negative PCR throat/nose swabs. Following discharge patients will be seen on days 14, 28, 42 and 56 post-randomization.

In a subset of patients admitted to HTD we will look for ECG changes, using real-time monitoring.
Patients will have up to 1 hour ECG continuous recordings daily. The ECG recording will be downloaded from standard monitor (GE Careview) and stored electronically. ECG changes (including QT interval) will then be analyzed by machine learning.

# 6 ASSESSMENT AND FOLLOW-UP

## 6.1. Trial assessment schedule

| **Procedures** | Screening | Enrollment/Baseline (Visit 1) | Follow-Up (Visit 2) | Follow-Up (Visit 3) | Follow-Up (Visit 4) | Follow-Up (Visit 5) | Follow-Up (Visit 6) | Follow-Up (Visit 7) | Daily visits to discharge | Day 28 visit | Day 42 visit | Final Study Visit (Day 56) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | |
| Randomization | X | | | | | | | | | | | |
| Physical exam | X | X | X | X | X | X | X | X | X | X | X | X |
| Throat swab for viral PCR | | X | x | x | x | x | x | x | X | | | |
| Vital signs | X | X | x | x | X | x | x | X | x | | | |
| Weight | | X | | | | | | | | | | |
| CBC w/diff, plts | | X | | X | | X | | X | | | | |
| Serum chemistry [a] | X | | | X | | X | | X | | | | |
| Blood store (3-5 mls) | | X | | | | | | x | | | | x |
| ECG (as indicated)[b] * | | X | | | | | | | | | | |
| CXR | X | | | | | | | | X (discharge) | | | X |
| Adverse event evaluation | | | x | x | x | x | x | x | X | x | x | X |
| WHO ordinal outcome scale** | | | | | | | | | X (discharge) | X | X | X |
| EQ5D questionnaire** | | | | | | | | | | X | | X |
| Estimated total blood volumes mL per day | 6-10 | 10-12 | | 10-12 | | 10-12 | | 10-12 | | | | 3-5 |
| Total blood volume over course of study mls (both clinical and research purposes) | | | | | | | | | | | | 49-63 |

a Urea, Creatinine, ALT, bilirubin
b Daily ECGs performed if on other medication which can prolong QTc

Additional investigations performed for clinical care can be recorded in the study CRF in order to help understanding of the clinical course.

* In HTD and if the patient is in ICU, ECG will be measured continuously every one hour daily for 14 days or until discharge if earlier.
** May be administered by telephone call
Note: if it is impossible for the patient to attend day 28, 42, and 56 visits (e.g community in lockdown, or hospital closed to non-COVID patients) then follow-up can occur entirely by phone.

## 6.2. Procedures for assessing safety

The safety profile of chloroquine is well understood and the risks related to chloroquine phosphate/sulphate/hydrochloride are very low, unless the drug is taken in overdose. Most side effects are infrequent. 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 and protracted exposures. The main adverse effect is itching in dark-skinned individuals; Africans are much more commonly affected compared to Asians. Adverse effects will be classified and graded according to the CTCAE system. All serious and grade 3 or 4 adverse events will be compared between arms and reported by frequency per arm. For further information on adverse events please see later section.

An independent data monitoring committee (DMC) will oversee the safety of the trial participants. For details on the DSMB and schedule of assessment see later section.

# 7 STUDY AGENT

## 7.1. Introduction

Bottle of 200 tablets.

Composition
Chloroquine phosphate .....250mg
Excipients s.q. for.....1 tablet
(Cassava starch, Corn starch, Lactose, Talc, Sodium starch glycolate, Magnesium stearate, Colloidal silicon dioxide).

Pharmacology
Chloroquine phosphate is a rapid– acting blood schizontocide against P. vivax, P. malariae and almost all strains of P. falciparum (except gametocytes). The mechanism of action is still not clear, but it seems to affect the hemoglobin digestion by raising the intravesical pH in the malaria parasite or it interferes with the synthesis of nucleoproteins by the parasite.

Pharmacokinetics
Chloroquine phosphate is rapidly and almost completely absorbed from the gastrointestinal tract. It is eliminated very slowly but increased when the urine is acidified. It is excreted in the urine unchanged with about half of a dose administered.

## 7.2. Trial treatment

### 7.2.1 Dosing and administration

Chloroquine has complex pharmacokinetic properties with an enormous apparent volume of distribution (200-300 L/kg) and a terminal elimination half-life of 1-2 months, so concentrations in plasma (and rapidly exchanging tissue compartments) are determined predominantly by *distribution* not elimination. Given that EC50 values against the SARS-COV2 virus in the low micromolar range in-vitro, which suggests moderate activity, it is likely that relatively high concentrations will be required for maximum effects in-vivo. Taking into account the benefit-risk relationship and the operating conditions of the study (and thus need for simplicity) the dosage used for an adult ≥ 53 kg is as follows:

| | | **Total Chloroquine Dose** | |
|---|---|---|---|
| **Time** | **Number of tablets** | **CQ phosphate base** | **CQ Phosphate salt** |
| **Initial dose T=0** | 4 | 600mg | 1000mg |
| **T=6 hours** | 2 | 300mg | 500mg |
| **Thereafter** | 2 once daily<br>for 9 days | 300mg once daily | 500mg once daily |

For an adult **52-45 KG**

| | |
|---|---|
| **Time** | **Number of tablets** |
| **Initial dose T=0** | 3.5 |
| **T=6 hours** | 2 |
| **Thereafter** | 2 once daily<br>for 9 days |

For an adult **<45- 38 KG**

| | |
|---|---|
| **Time** | **Number of tablets** |
| **Initial dose T=0** | 3 |
| **T=6 hours** | 1.5 |
| **Thereafter** | 1.5 once daily<br>for 9 days |

For an adult **<38 KG**

| | |
|---|---|
| **Time** | **Number of tablets** |
| **Initial dose T=0** | 2.5 |
| **T=6 hours** | 1.5 |
| **Thereafter** | 1.5 once daily<br>for 9 days |

### 7.2.2 Route of administration

Chloroquine will be administered orally, as tablets. For unconscious patients chloroquine can be crushed and administered as a suspension via a nasogastric tube.

### 7.2.3 Starting dose and dose escalation schedule

The dose administered will be as in the table in section 7.2.1. A loading dose, administered with food where possible, is given on the first study day. Following the first 24 hours, patients will receive a dose of chloroquine phosphate salt of 500mg once daily until 10 days after randomization (unless they are <53Kg, when the dose will be reduced as above).

### 7.2.4 Dose adjustments/modifications/delays

This is a pragmatic trial designed to identify a readily implementable treatment in a pandemic situation. As such the intervention is designed to be simple. All adults will receive the same dose. The large volume of distribution of chloroquine determines its pharmacokinetics rather than rates of elimination; however, patients with severe renal impairment or transaminitis are excluded from the study (see inclusion and exclusion criteria). If a patient develops cardiac arrhythmia or syncope, chloroquine will be stopped and an ECG performed. Electrolytes (Na, K, Ca, Mg) will be checked and corrected as necessary. Where significant asymptomatic QTc prolongation is identified (>500ms), Chloroquine administration will be interrupted, electrolytes checked and corrected, and the drug reintroduced when the QTc is <480ms. Particular care will be taken in those who take other medications which may prolong Qtc.

### 7.2.5 Duration of therapy

The total duration of treatment with Chloroquine will be 10 days.

## 7.3 Formulation, appearance, packaging, and labeling

Based on the randomization list, the CTU Pharmacist will generate identical sealed treatment packs for each study ID and distribute them to the sites in batches as required. Each pack will contain sufficient chloroquine for the 10 days of treatment. Enrolment logs specific to each ward will be used to assign patients to the next available sequential number and corresponding sealed treatment pack.

## 7.4. Study accountability procedures

Study agent or Investigational Medicinal Product (IMP) will be centrally packed by OUCRU CTU and a supply sent to the hospital pharmacy at each of the participating sites. Each pharmacy will document receipt of supplies and returns.

IMP accountability will be maintained and monitored by site staff and OUCRU CTU respectively according to the trial SOPs. At the end of the trial all non-dispensed IMP will be checked against the inventory before disposal on site according to local pharmacy guidelines and applicable regulations. Documentation of disposal or destruction will be provided to OUCRU CTU.

### 7.4.1 Compliance and adherence

As the intervention will start immediately following randomization, suitable participant information and fully informed consent procedures will ensure that participants understand the trial requirements. Therefore, any non-compliance will likely be a consequence of the intervention itself (e.g. drug intolerance or toxicity) which would also likely occur if it were incorporated within clinical practice, i.e. non-compliance will likely be part of

the pragmatic strategy being evaluated and an intention-to-treat comparison will therefore incorporate the level of non-compliance as would be anticipated in general clinical practice.

The study drug will be given in hospital by clinical staff alongside other regular medication. Few problems with compliance and adherence are therefore envisaged. Compliance and adherence will be assessed by visits to the participant by the study team and through review of the medication charts. Missed doses will be detected, if they do occur, and recorded in the CRF.

### 7.2 TREATMENT DATA COLLECTION

Drug doses, frequency, routes of administration, and duration of IMP will be recorded in the CRF.

## 8. SAFETY REPORTING

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol.

### 8.1. Definitions

The definitions of the principles of ICH GCP apply to this trial protocol. These definitions are given in Table 2: Definitions.

**Table 2: Definitions**

| TABLE | DEFINITION |
|---|---|
| Adverse Event (AE) | Any untoward medical occurrence in a participant or clinical trial subject to whom an investigational medicinal product has been administered including occurrences that are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | Any untoward and unintended response to an investigational medicinal product related to any dose administered. |
| Unexpected Adverse Reaction (UAR) | An adverse reaction, the nature or severity of which is not consistent with the information about the investigational medicinal product in question set out in the Summary of Product Characteristics (SPC) for that product. |
| Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR) | Respectively any adverse event, adverse reaction or unexpected adverse reaction that:<br>▪ Results in death<br>▪ Is life-threatening*<br>▪ Requires hospitalisation or prolongation of existing hospitalisation**<br>▪ Results in persistent or significant disability or incapacity |

| | |
|---|---|
| | ▪ Consists of a congenital anomaly or birth defect<br>▪ Is another important medical condition*** |

*The term life-threatening in the definition of a serious event refers to an event in which the participant is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inparticipant admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Adverse Events include:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

### 8.1.1. Medicinal products

An investigational medicinal product is defined as the tested investigational medicinal product (IMP) and the comparators used in the study. This therefore includes:

- Chloroquine

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP or comparator should be reported appropriately.

### 8.1.2. Exempted adverse events

In the context of this trial Adverse Events do not include:

- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, e.g. elective cosmetic surgery, social admissions
- Overdose of medication without signs or symptoms

Death should always be reported as a serious adverse event, regardless of cause.

## 8.2 Investigator responsibilities

All grade 3 or 4, or serious AEs and ARs, whether expected or not, should be recorded in the CRF. Non-serious grade 1 or 2 AEs need not be recorded unless they are thought to be related to the IMP or they result in a change or interruption in treatment.

A laboratory abnormality must be recorded as a clinical adverse event only if it is associated with an intervention. Intervention includes, but is not limited to, discontinuation of a current treatment, dose

reduction/delay of a current treatment, or initiation of a specific treatment. In addition, any medically important laboratory abnormality may be reported as an adverse event at the discretion of the investigator. This would include a laboratory result for which no intervention is needed, but the abnormal value suggests a disease or organ toxicity. Laboratory events will be graded according to CTCAE definitions.

SAEs and SARs should be notified to the OUCRU CTU immediately but no later than 24 hours of the investigator becoming aware of the event.

### 8.2.1. Investigator assessment

#### *8.2.1.1.Seriousness*

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 2: Definitions. If the event is serious **and not only related to COVID-19, or is fatal**, then an SAE Form must be completed and the OUCRU CTU notified within 24 hours.

#### *8.2.1.2. Severity or Grading of Adverse Events*

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity gradings in Toxicity grading and management (CTCAE).

#### *8.2.1.3.Causality*

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy (chloroquine) using the definitions in Table 3: Assigning Type of SAE Through Causality. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

**Table 3: Assigning Type of SAE Through Causality**

| RELATIONSHIP | DESCRIPTION | SAE TYPE |
|---|---|---|
| Unrelated | There is no evidence of any causal relationship | Unrelated SAE |
| Unlikely | There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the participant's clinical condition, other concomitant treatment). | Unrelated SAE |
| Possible | There is some evidence to suggest a causal relationship (for example, 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 (for example, the participant's clinical condition, other concomitant treatments). | SAR |
| Probable | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. | SAR |
| Definitely | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. | SAR |

If an SAE is considered to be related to trial treatment and drug is stopped or the dose modified, refer to Section Dose Modifications, Interruptions & Discontinuations.

#### *8.2.1.4. Expectedness*

If an adverse event or adverse reaction is not expected with COVID-19 disease or with chloroquine, then it is unexpected. An unexpected adverse reaction is one not previously reported in the current Summary of Product Characteristics (SPC) at the time the event occurred, or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in Table 2 of section 8.1 Definitions. If a SAR is assessed as being unexpected, it becomes a SUSAR.

Investigators should always check the current version of the SPC. Expected toxicities associated with chloroquine are:

**Frequency unknown:** Abdominal pain; agranulocytosis; alopecia; anxiety; atrioventricular block; bone marrow disorders; confusion; corneal deposits; depression; diarrhoea; eye disorders; gastrointestinal disorder; headache; hearing impairment; hypoglycaemia; hypotension; insomnia; interstitial lung disease; movement disorders; myopathy; nausea; neuromyopathy; neutropenia; personality change; photosensitivity reaction; psychotic disorder; QT interval prolongation; seizure; severe cutaneous adverse reactions (SCARs); skin reactions; thrombocytopenia; tinnitus; tongue protrusion; vision disorders; vomiting.

**Rare or very rare:** Cardiomyopathy; hallucination; hepatitis

**Overdose:** Overdose is difficult to treat and can result in life-threatening features including arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable). Hypoglycaemia can also feature. However, treatment in this tudy will be directly observed as an in-patient and therefore is extremely unlikely.

## 8.3. Notification

The OUCRU CTU should be notified of all SAEs immediately but no later than 24 hours after the investigator/study team become aware of the event. Investigators should notify the OUCRU CTU of all SAEs occurring from the time of randomization until the participant finishes their follow-up. SARs and SUSARs must be notified to the OUCRU CTU until trial closure. CTU will perform an initial check of the report, request any additional information. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports. All SAE information must be recorded on an SAE form and sent or emailed, to CTU. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and sent to CTU.

The OUCRU CTU is undertaking the duties of trial sponsor with regard to safety reporting and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities and the research ethics committees, as appropriate.
All SAEs will be reported as soon as possible to the site ethics committee (EC). An initial written report of an SAE resulting in death, or that is life threatening, has to be reported urgently within 7 working days of the study team becoming aware of the SAE. Other SAEs must be reported within 15 working days of the study team becoming aware of the SAE. Additional medical information of the SAE's development must be reported in an additional report until the trial subject recovers or stabilises without further changes expected. The format and content of the initial report should follow the Vietnam MoH EC report template and include all information available at the time of reporting. All foreseeable and predefined SAEs will not be reported immediately but will be included in the annual report to the VN MoH EC.

All SAEs will be reported to OxTREC in the annual review form and to the DMC in accordance to the DMC charter.

## 8.4 Study halting rules

An independent DSMB will oversee the trial. Serious adverse events will be reported to the DSMB within 10 days of occurrence and followed-up until resolution. The DSMB will perform a safety analysis after the first 60 patients have completed the allocated 2-week treatment or died. Stopping for harm of chloroquine will be considered if a safety issue emerges which is sufficiently large, in the judgement of the DSMB, to suggest that continued exposure of patients to the drug is unethical. Early stopping for efficacy is not foreseen as this is a pilot study with a virological rather than survival endpoint. However, if chloroquine truly appears to have an extraordinary beneficial effect then the DSMB will be able to recommend this to the trial steering committee. The DSMB will be able to mandate additional safety analyses at any timepoint they deem fit.

At the interim analyses, the DSMB will receive a report including summaries of mortality, serious adverse events, grade 3&4 adverse events, and estimates of early virological activity during the first 10 days by treatment arm. The report will be prepared by the DSMB statistician and distributed to all DSMB members for

review. Based on these data, the committee will make recommendations on the continuation, cessation or amendment of the study. The study statistician will aid in setting-up the code for generating the interim analysis summaries in a blinded fashion, i.e. without access to the randomization assignment. The randomization list will be sent to the DSMB statistician directly from the study central pharmacist.

As the dissemination of preliminary summary data could influence the further conduct of the trial and introduce bias, access to interim data and results will be confidential and strictly limited to the involved independent statistician and the monitoring board and results (except for the recommendation) will not be communicated to the outside and/or clinical investigators involved in the trial.

Further reviews will be at the discretion of the DSMB. All DSMB reports, replies or decisions will be sent to the responsible Research Ethical Committees.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 Statistical and analytical plans

Study analysis will be according to an a priori defined statistical analysis plan which will be completed before database locking. The **primary endpoint** is virological and robust and will be performed by technicians unaware of the treatment allocation of the patient. In that sense the study therefore is blinded. The time to viral clearance will be defined as the time from randomization to the first of at least 2 consecutive daily negative viral PCR tests on throat/nose swab. Data will be illustrated with time to event curves and analysed using the log rank test and Cox model.

**Secondary endpoints**

***Survival until 56 days after randomization***

Overall survival will be visualized using Kaplan-Meier curves and modeled using the Cox proportional hazards regression model with stratification by disease severity. In addition, survival will be modeled with a multivariable Cox regression model including the following covariates in addition to the treatment group: Age, comorbid conditions (hypertension, cardiac disease, diabetes, ACEA inhibitor or angiotensin receptor blocker use).

***Adverse events.***

The frequency of serious and grade 3&4 adverse reactions as well as the frequency of specific adverse events will be summarized (both in terms of the total number of events as well as the number of patients with at least one event). The proportion of patients with at least one such event (overall and for each specific event separately) will be summarized and (informally) compared between the two treatment groups based on Fisher's exact test**.**

***Analysis of other secondary outcomes***

1. The duration of hospital stay from the time or randomization
2. The number of ventilator-free days during the first 28 days following randomization
3. The time to (all-cause) death following over the first 7, 10, 14, 28 and 56 days since randomization
4. The WHO ordinal outcome scale for COVID-19 at days 28. 42 and 56
5. Fever clearance time
6. Development of ARDS defined by the Kigali criteria

7. Oxygenation-free days over the first 28 days

The analyses of these secondary endpoints will be defined in the statistical analysis plan.

## 9.2 Statistical hypotheses

The primary null hypothesis is that the rate of clearance of virus from throat/nose swabs is not different between chloroquine compared with standard of care therapy.

## 9.3 Analysis datasets

The primary analysis population for all analysis is the full analysis population containing all randomized patients except for those mistakenly randomized without COVID-19. Patients will be analyzed according to their randomized arm (intention-to-treat). In addition the primary endpoint will be analyzed on the per-protocol population which will exclude the following patients: major protocol violations and those receiving less than 1 week of administration of chloroquine for reasons other than death.

# 10. DATA MANAGEMENT

## 10.1 Source data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, radiographs, and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

## 10.2 Direct access to participant records

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this must be obtained. Such information will be treated as strictly confidential and will in no circumstances be made publicly available.

The following data should be verifiable from source documents:

- all signed consent forms
- dates of assessments including dates specimens were taken and processed in the laboratory
- eligibility and baseline values for all participants
- all clinical endpoints
- all serious/severe adverse events
- routine participant clinical and laboratory data
- drug compliance
- dates drug dispensed and (if necessary) drugs returned
- pharmacy/clinic drug logs
- concomitant medication.

## 10.3 Data collection and management responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.
Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into CliRes, a 21 CFR Part 11-compliant data capture system provided by the OUCRU IT department. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

## 10.4 Data recording and record keeping

All trial data will be recorded on to paper CRFs and entered into CliRes. The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

## 10.5 Trial records retention

CRFs, clinical notes and administrative documentation will be kept in a secure location and held for 15 years after the end of the trial. Clinical information will not be released without written permission, except as necessary for monitoring, auditing and inspection purposes. During this period, all data should be accessible to the competent authorities with suitable notice. Electronic data will be kept for at least 20 years at the OUCRU CTU.

## 10.6 Protocol violations

A protocol deviation is any non-compliance with the clinical trial protocol or GCP requirements. If such a deviation results in an impact on patient safety or scientific integrity it becomes a protocol violation. The non-compliance may be either on the part of the participant, the investigator, or the study site staff. Whenever violations occur, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigators to use continuous vigilance to identify and report protocol deviations and violations. All deviations and violations must be documented in source documents and reported to the OUCRU CTU within 2 days of being identified. In addition, protocol violations must be reported to the relevant ethics committees.

## 10.7 Publication and data sharing policy

All publications are to be approved by the TMG and TSC before submission for publication. Any publication arising before all patients have completed follow-up (not by randomized groups) will also be approved by the DMC in order to ensure that the primary objective of the trial (the randomized comparison) is not compromised. In particular, no analyses by randomized group of any outcome (primary, secondary or other) in either the main trial or associated substudies will be conducted or presented before all patients have completed follow-up, other than those for interim review by the DMC. The TMG and TSC will resolve problems of authorship and maintain the quality of publications. The prelimanary results about the safety and effectiveness of the chloroquine regimen for the first ten patients of the pilot phase can be considerred for rapid dessimination and publication after advise from the TMG and TSC.

The TMG will maintain a list of investigators to be presented in an appendix at the end of the paper. This list will include investigators who contributed to the investigation being reported but who are not members of the writing committee. In principle, substudy reports should include all investigators for the main study, although in some instances where a smaller number of investigators have made any form of contribution, it may be appropriate to abbreviate the listing. All headline authors in any publication arising from the main study or sub-studies must have a made a substantive academic or project management contribution to the work that is being presented. “Substantive” must be defined by a written declaration of exactly what the contribution of any individual is believed to have been. In addition to fulfilling the criteria based on contribution, additional features that will be considered in selecting an authorship group will include the recruitment of participants who contributed data to any set of analyses contained in the manuscript and/or the conduct of analyses (laboratory and statistical), leadership and coordination of the project in the absence of a clear academic contribution.

In line with Wellcome Trust policy that the results of publicly-funded research should be freely available, manuscripts arising from the trial will, wherever possible, be submitted to peer-reviewed journals which enable Open Access via UK PubMed Central (PMC) within six months of the official date of final publication. All publications will acknowledge the trial's funding sources.

In line with research transparency and greater access to data from trials OUCRU’s clinical trials are registred at ClinicalTrials.gov and a data sharing policy is in place. This policy is based on a controlled access approach with a restriction on data release that would compromise an ongoing trial or study.
Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

# 11. QUALITY ASSURANCE AND QUALITY CONTROL

## 11.1 Risk assessment

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of ICH GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled.

The safety profile of chloroquine is well-known and acceptable, given the potential benefits. Chloroquine has been given to very large numbers of people worldwide in clinical trial settings and in clinical practice. The trial will be recruiting sick participants, but site investigators have considerable experience with this population. This will minimise the risks to the participants and the trial. A detailed risk assessment will be conducted prior to starting the trial.

COVID-19 is an infectious disease and there is a risk of transmission to health care workers and study personnel who visit clinical areas. Personal Protective Equipment will be used as per Vietnamese guidelines and availability.

## 11.2 Central monitoring at OUCRU CTU

Data from each site collected on the paper CRFs will be double entered and stored on a central database in OUCRU. This database will be checked at OUCRU CTU for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, the site will be contacted and asked to verify or correct the data. OUCRU CTU will also send reminders for any overdue and/or missing data with the regular inconsistency reports of errors.

Other essential trial issues, events and outputs will be detailed in the Data Management, Monitoring and Quality Management Plans that are based on the trial-specific Risk Assessment.

### 11.3 On-site monitoring

A site initiation visit will be conducted for each study site by staff from the OUCRU CTU. All essential site staff including the PI, lead pharmacist and lead research nurse must be in attendance. The initiation training will include training in the administration of IMP, as well as the trial procedures. Monitoring will then be carried out approximately annually at each site by OUCRU CTU staff. On site monitoring will also be regularly conducted by the site monitors. The frequency, type and intensity of routine monitoring and the requirements for triggered monitoring will be detailed in the Monitoring Plan which will also detail the procedures for review and sign-off. The monitoring will adhere to the principles of ICH GCP and the Monitoring Plan.

The monitors will require access to all participant medical records including, but not limited to, laboratory test results and prescriptions. The investigator (or delegated deputy) should work with the monitor to ensure that any problems detected are resolved.

## 12. REGULATORY AND ETHICAL CONSIDERATIONS

All regulatory requirements (including safety reporting, see Section 8 and below) will be met by the co-sponsors or their delegated authorities.

### 12.1 Compliance

The trial end is 56 days after the last participant is randomized (end of follow-up for the last randomized participant).

#### REGULATORY COMPLIANCE

The trial complies with the principles of the Declaration of Helsinki (2008) and will be conducted in compliance with the approved protocol and the principles of Good Clinical Practice (GCP).

#### SITE COMPLIANCE

All sites will comply with the above. An agreement will be in place between the site and the OUCRU CTU, setting out respective roles and responsibilities.

The site will inform the CTU as soon as they are aware of a possible serious breach of compliance. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial

### 12.2 Ethical conduct of the study

## ETHICAL CONSIDERATIONS

All participants will receive the best available treatment of COVID-19, following local and national guidelines. They will benefit from the frequent and careful follow-up of their condition throughout the treatment of their disease and for up to 56 days from randomization.

The risks and benefits of participation will be communicated in two ways. First, all potential participants or their family members will be given a participant information sheet clearly listing the risks and benefits of the trial. Second, all potential participants (or their families) will be able to discuss participation with their consulting doctor who will be able to address questions not covered or arising from the participant information sheet.

The trial protocol will seek ethical approval to include incapacitated, comatose adults in the trial as we consider many of these adults will have the most severe disease and therefore represents the group that might stand most to gain from chloroquine.

Participants' confidentiality will be maintained throughout the trial. Data submitted to OUCRU CTU and samples sent to central testing facilities will be identified only by the trial number and participant initials.

## ETHICAL APPROVALS

The trial will be approved by the Oxford Tropical Research Ethics Committee, the Vietnam Ministry of Health. Regulatory approval will be given by the Drug Administration of Vietnam (DAV).

Any further amendments will be submitted and approved by the relevant ethics committee.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. The reason for doing so, however, should be recorded; the participant will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to which they have been allocated. Similarly, the participant must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his/her further treatment.

## CONFIDENTIALITY

The investigator must assure that participants' anonymity will be maintained and that their identities are protected from unauthorised parties. Participants will be assigned a trial identification number and this will be used on CRFs; participants will not be identified by their name. The investigator will keep securely a participant trial register showing identification numbers, surnames and date of birth. This unique trial number will identify all laboratory specimens, case record forms, and other records and no names will be used, in order to maintain confidentiality.

## EXPENSES

Treatment and hospital costs from enrolment to discharge from hospital for all actively enrolled participants will be coverred by the State Budget.

The study funding will cover the following costs:

- Study specific screening tests, PCR diagnostic and study procedures
- Study-related follow-up visits up to day 56 from enrolment
- Travel expenses for the patient to attend follow-up visits.

The study will not cover the cost of treating pre-existing diseases or those unrelated to study participation or the diagnosis and/or treatment of COVID-19.

# 13. OVERSIGHT AND TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial, detailed below.

## 13.1 Trial management group (TMG)

A Trial Management Group (TMG) will be formed to conduct the day-to-day management of the trial at the OUCRU CTU. This will include the Chief Investigator, Trial Statistician, Clinical Project Manager, Trial Manager and Data Manager. The group will meet at least once per month, although may meet more or less often as required. The group will discuss issues related to the progress of the trial at the site and to ensure that the trial is running well. The full details can be found in the TMG Charter.

## 13.2 Trial steering committee (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus independent members, including the Chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.

## 13.3 Data management committee (DMC)

An independent Data Monitoring Committee (DMC) will oversee the safety of the trial. The DMC will be the only group which sees the confidential, accumulating data for the trial separately by randomized group. A DMC Charter will be drawn up that describes the membership of the DMC, relationships with other committees, terms of reference, decision-making processes, and the approximate timing and frequency of interim analyses (with a description of stopping rules and/or guidelines). In addition, an interim analysis plan will be written which details all statistical tables that will be provided to the DMC.

Interim analyses are planned after 120 participants have been enrolled but the DMC has the authority to modify the frequency of interim analyses. See section 3.2.3. Study size and power calculation. At this interim analyses, the DMC will receive a report including summaries of baseline characteristics, the primary endpoint, and adverse events by treatment arm. The report will be prepared by the DMC statistician and distributed to all DMC members before the DMC meeting (on-line or in-person).

The DMC will advise the TSC and can recommend premature closure or reporting of the trial, or that recruitment be discontinued or modified. Such recommendations would be made if, in the view of the DMC, there is proof beyond reasonable doubt that one of the allocated strategies is better than its comparator in terms of a difference of clinically significant magnitude in the primary outcome. The Haybittle-Peto boundary, requiring $p < 0.001$ at interim analysis to consider stopping for efficacy, should be used as a guidance. However, the DMC recommendation should not be based purely on statistical tables but also requires clinical judgement.

As the dissemination of preliminary summary data could influence the further conduct of the trial and introduce bias, access to interim data and results will be confidential and strictly limited to the DMC and

results (except for the recommendation) will not be communicated to the outside and/or clinical investigators involved in the trial. See the DMC charter for membership.

# 14. FINANCE AND INSURANCE

## 14.1 Funding

The trial is funded by Minsitry of Health, Viet Nam.

## 14.2 Insurance

The conduct of this study is sponsored by the University of Oxford. The University has a specialist insurance policy in place: - Newline Underwriting Management Ltd, at Lloyd's of London – which would operate in the event of any participant suffering harm as a result of their involvement in the research.

# 15. CONFLICT OF INTEREST

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest.

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**Appendix.**

1. WHO ordinal outcome scale for COVID

| **Patient state** | **Descriptor** | **Score** |
|---|---|---|
| **Uninfected** | No clinical or virological evidence of infection | 0 |
| **Ambulatory** | No limitation of activities | 1 |
| | Limitation of activities | 2 |
| **Hospitalized mild disease** | No Oxygen therapy | 3 |
| | Oxygen by mask or nasal prongs | 4 |
| **Hospitalized severe disease** | Non-invasive ventilation or high flow oxygen | 5 |

| | | |
|---|---|---|
| | Intubation and mechanical ventilation | 6 |
| | Vnetilation and additional organ support – pressors, RRT, ECMO | 7 |
| **Dead** | Death | 8 |