



## Domain-Specific Appendix: COVID-19 Antiviral Therapy

# REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

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COVID-19 Antiviral Therapy Domain-Specific Appendix Version 2.0 dated 01 April 2020

## Summary

In this domain of the REMAP-CAP trial, participants meeting the platform-entry criteria for REMAP-CAP admitted to participating intensive care units with suspected or microbiological testing-confirmed COVID-19 infection will be randomized to receive one of two interventions:

- No antiviral for COVID-19 (no placebo)
- Lopinavir/ritonavir
- Hydroxychloroquine
- Hydroxychloroquine and lopinavir/ritonavir

This domain will enroll only patients in the pandemic infection is suspected or proven (PISOP) stratum and be analyzed in the Pandemic Statistical Model as outlined from the Pandemic Appendix to Core (PA<sub>T</sub>C).

At this participating site the following interventions have been selected within this domain:

- No antiviral for COVID-19 (no placebo)
- lopinavir/ritonavir
- hydroxychloroquine
- hydroxychloroquine and lopinavir/ritonavir

<b>REMAP-CAP: COVID-19 Antiviral Therapy Domain Summary</b>	
Interventions	<ul style="list-style-type: none"> <li>• No antiviral for COVID-19 (no placebo)</li> <li>• Lopinavir/ritonavir</li> <li>• Hydroxychloroquine</li> <li>• Hydroxychloroquine and lopinavir/ritonavir</li> </ul>
Unit of Analysis and Strata	The default unit-of-analysis for this domain will be the pandemic infection suspected or confirmed (PISOP) stratum. Analysis and Response Adaptive Randomization are applied by PISOP stratum. Unit of analysis may be modified to allow analysis to be stratified by SARS-CoV-2 infection confirmed or not confirmed with borrowing permitted. If this occurs, Response Adaptive Randomization will be applied to patients in the PISOP stratum using probabilities derived from SARS-CoV-2 confirmed stratum.
Evaluable treatment-by-treatment Interactions	Treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the Corticosteroid Domain and with the COVID-19 Immune Modulation Therapy Domain. No other interactions will be evaluated with any other domain.
Nesting	There is one nest, comprising all interventions that include an active antiviral agent.
Timing of Reveal	Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required.
Inclusions	<p>Patients will be eligible for this domain if:</p> <ul style="list-style-type: none"> <li>• COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing</li> <li>• Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur</li> </ul>
Domain-Specific Exclusions	<p>Patients will be excluded from this domain if they have any of the following:</p> <ul style="list-style-type: none"> <li>• More than 24 hours has elapsed since ICU admission</li> <li>• Patient has already received more than 36 hours of treatment with any non-trial prescribed systemic antiviral medication intended to be active against COVID-19 during this hospital admission</li> <li>• Patient has been randomized in a trial evaluating an antiviral intended to be active against COVID-19, where the protocol of that trial requires ongoing administration of study drug</li> <li>• In areas where MERS-CoV infection is endemic, the patient has laboratory confirmed MERS-CoV infection</li> <li>• The treating clinician believes that participation in the domain would not be in the best interests of the patient</li> </ul>
Intervention-Specific Exclusions	<ul style="list-style-type: none"> <li>• Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent</li> <li>• Receiving an agent that is specified as an intervention in this domain as a usual medication prior to this hospitalization will exclude a patient from receiving that agent</li> <li>• Known HIV infection will exclude a patient from receiving lopinavir/ritonavir</li> <li>• Known or suspected pregnancy will result in exclusion from any intervention that includes lopinavir/ritonavir or hydroxychloroquine</li> <li>• Receiving amiodarone as a usual medication prior to this hospitalization or any administration of amiodarone within the 72 hours prior to assessment of eligibility will exclude a patient from receiving lopinavir/ritonavir</li> <li>• High clinical risk of sustained ventricular dysrhythmia will exclude a patient from receiving hydroxychloroquine</li> </ul>
Outcome measures	<p>Primary REMAP endpoint: as defined in an operational document specified from the Pandemic Appendix to the Core Protocol Section 7.5.1</p> <p>Secondary REMAP endpoints: refer to Core Protocol Section 7.5.2</p>

	<p>Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment):</p> <ul style="list-style-type: none"><li>• Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinically indicated testing)</li><li>• Serious Adverse Events (SAE) as defined in Core Protocol</li></ul>
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SUPERSEDED

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## 1. ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
CCP	Clinical Characterization Protocol
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle East respiratory syndrome coronavirus
MMF	Mycophenolate mofetil
PAcC	Pandemic Appendix to the Core Protocol
PISOP	Pandemic infection is suspected or proven
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
WHO	World Health Organization

## 2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study); a Statistical Analysis Appendix (details of the current statistical analysis plan and models); Simulations Appendix (details of the current simulations of the REMAP); multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain); and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions within each domain is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject to a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analytic model will also change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase



over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol, DSAs, RSAs and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website ([www.remapcap.org](http://www.remapcap.org)).

### **3. COVID-19 ANTIVIRAL THERAPY DOMAIN-SPECIFIC APPENDIX VERSION**

The version of the COVID-19 Antiviral Domain-Specific Appendix is in this document's header and on the cover page.

#### **3.1. Version history**

Version 1: Approved by the COVID-19 Domain Specific Working Group (DSWG) on 11 March, 2020

Version 2: Approved by the COVID-19 DSWG on 1 April, 2020

### **4. COVID-19 ANTIVIRAL DOMAIN GOVERNANCE**

#### **4.1. Domain members**

##### **Chair (Antiviral Domain):**

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##### **Members:**

Professor Derek Angus

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### **4.3. COVID-19 Domain-Specific Working Group Authorization**

The COVID-19 Domain-Specific Working Group have read the appendix and authorize it as the official COVID-19 Antiviral Therapy Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair  
Yaseen Arabi



Date 1 April 2020

## **5. BACKGROUND AND RATIONALE**

### **5.1. Domain definition**

This is a domain within the REMAP-CAP to test the effectiveness of different strategies for antiviral therapy for suspected or microbiological testing-confirmed COVID-19 infection in patients with concomitant severe pneumonia who are admitted to an Intensive Care Unit (ICU).

### **5.2. Domain-specific background**

#### 5.2.1. COVID-19 infection

The first report of infection with COVID-19 occurred in Wuhan, China, in late 2019. Since that time, and as of the time of writing of this DSA, there have been tens of thousands of reported cases across the region with a range of severity, several thousand deaths and documented sustained human-human transmission. On January 30<sup>th</sup> 2020, the World Health Organization (WHO) declared this outbreak a Public Health Emergency of International Concern ([https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-\(2005\)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-\(2019-ncov\)](https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov))). On March 11<sup>th</sup> 2020, the WHO declared COVID-19 a pandemic (situation report 51, downloadable as a pdf at: [https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57\\_10](https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10)). Given past history with novel coronaviruses, such as Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV), public health agencies have responded aggressively to the urgent need to acquire knowledge regarding this emerging infection. An important component of this urgently needed knowledge includes understanding the effectiveness of alternative treatment strategies in patients with suspected or proven infection. It should also be noted that clinical guidance issued by the WHO

indicates that unproven therapies should be administered preferably only within the setting of a clinical trial (<https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf>)

Estimates of the burden of critical illness among patients infected with COVID-19 vary, with estimates of case-fatality and proportion of patients who become critically ill being unstable. Several factors contribute to this uncertainty including differential timing between diagnosis and development of critical illness or death, the true incidence of infection being uncertain because of possible under-reporting of asymptomatic or mild cases, the sensitivity of diagnostic methods, possible limitation on the number of diagnostic tests that can be performed, and changing case-definitions. Nevertheless, it is recognized that fatal pneumonia is common. COVID-19 is now a pandemic with increasing case numbers across the globe.

There have been several reports of clinical disease from Chinese investigators. These reports describe a progressive severe pneumonia, with a significant proportion requiring mechanical ventilation and some reports of multi-organ dysfunction. In a report of three patients who developed clinical and radiographic features of pneumonia, one patient required mechanical ventilation and died subsequently (Zhu et al., 2020) In a study of 41 hospitalized patients with laboratory-confirmed COVID-19 infection, 13 (32%) patients were admitted to an ICU and six (15%) died. Invasive mechanical ventilation was required in four (10%) patients, with two patients (5%) receiving extracorporeal membrane oxygenation as salvage therapy (Huang et al.). In another study of 99 hospitalized patients with COVID-19 pneumonia, 23 (23%) were admitted to ICU, 17 (17%) developed acute respiratory distress syndrome (ARDS), three (3%) acute renal failure and four (4%) septic shock. In a study of 138 patients with COVID-19 infection, 36/138 required ICU care. Patients admitted to ICU were older and were more likely to have underlying comorbidities. In the ICU, four patients (11.1% of those admitted to ICU) received high-flow oxygen and 15 (44.4%) received noninvasive ventilation. Invasive mechanical ventilation was required in 17 patients (47.2%), four of whom received extracorporeal membrane oxygenation as rescue therapy. A total of 13 patients received vasopressors and 2 patients received kidney replacement therapy (Wang et al., 2020a).

As with the other coronaviruses that have circulated in outbreaks in recent decades, SARS and MERS-CoV, no specific anti-infective therapy, or any element of supportive care, has been formally evaluated in randomized controlled trials. Currently, randomized trials are ongoing for infected patients with MERS-CoV in Saudi Arabia, examining the role of lopinavir/ritonavir + interferon- $\beta$ 1b, compared to standard care alone (Arabi et al., 2018). These agents were chosen due to biologic plausibility, given *in vitro* evidence suggesting activity against MERS-CoV. For SARS-CoV, there were

case series of patients who received lopinavir/ritonavir associated with benefit compared to historic controls (Chu et al., 2004), but no data from controlled studies. Any specific information, as of writing, remains lacking with COVID-19, with a number of ongoing trials examining various antiviral options in China and widespread off-label use of these medications in China and other locations where spread has occurred. Other proposed strategies for acute management of these patients include immunomodulatory therapies, the use of non-approved antiviral agents, and specific antibody formulations.

Interim recommendations from the WHO for clinical care of infected patients focus upon supportive care, including organ support as needed, prevention of complications, and with no specific antiviral medications recommended at this time. Furthermore, it is recommended that any specific therapy targeted to COVID-19 infection should be provided only as part of a research protocol (<https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf>).

#### 5.2.2. Clinical trials for COVID-19 infection

##### 5.2.2.1. Current clinical trials and interventions being evaluated

As of 24<sup>th</sup> February 2020, more than 150 clinical studies from China had been entered on trial registration sites. Many of these trials are single center and with sample sizes that are unlikely to be sufficient to detect plausible treatment effects, with some studies being uncontrolled or observational. There is also a rapid decline in incidence of new infection in China and many clinical trials are unlikely to achieve their planned sample size.

A wide range of interventions are being evaluated in trials that have been registered including arbidol, lopinavir/ritonavir, darunavir/cobicistat, remdesivir, favipiravir, baloxavir, chloroquine, intravenous immunoglobulin, inhaled and parenteral interferon- $\alpha$  or interferon- $\beta$ , glucocorticoids (different agents and doses), mesenchymal and other stem cells, microbiota transplantation, and a range of traditional Chinese medicines.

WHO has provided guidance regarding both trial design and prioritization of candidate therapies. With regards to trial design, WHO notes that there are no antivirals with proven efficacy in patients with COVID-19. As such, WHO guidance is that trials should utilize a 'standard of care' comparator, that is, a control group that does not receive an antiviral agent intended to be active against COVID-19 infection (<https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4-eng.pdf?ua=1>). WHO identifies remdesivir as the agent most likely to be beneficial but this is an unlicensed therapy, available only as an Investigational Medical Product. The

agent allocated the second highest priority is lopinavir/ritonavir, an antiviral licensed for use in patients with Human Immunodeficiency Virus infection (HIV). WHO recommends that this agent is evaluated in clinical trials either alone or in combination with interferon- $\beta$ 1b (<https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4-eng.pdf?ua=1>). The first antiviral intervention that will be evaluated in this domain of REMAP-CAP is lopinavir/ritonavir. The second antiviral intervention to be evaluated in this domain of REMAP-CAP is hydroxychloroquine. The third antiviral intervention is the combination of lopinavir/ritonavir and hydroxychloroquine. The effect of all antivirals will include an evaluation of interaction with interventions in other domains including specified immune modulation therapies and corticosteroid strategy. The use of these interventions is specified in separate DSAs, with evaluation of the interaction being specified in the statistical model.

#### *5.2.2.2. Need for evidence in patients who are critically ill*

There is need to evaluate interventions for COVID-19 in patients who are critically ill. The number of current studies that are focused on patients who are critically ill is uncertain and, for those studies that are enrolling hospitalized patients, it is unclear if stratification by severity is a design feature. The need for studies that focus on patients who are critically ill arises because of the possibility of differential treatment effect between patients who are critically ill compared with non-critically ill patients.

There are two reasons for this possibility, one generic to all interventions evaluated in the critically ill and one that is specific to antiviral therapy. Firstly, among trials that evaluate interventions in patients who are critically ill it is common for the results of the trial to be different to that which was predicted based on a prior understanding of mechanism of action combined with known mechanism of disease (Landoni et al., 2015, Webb, 2015). This observation reinforces the importance of not necessarily relying on extrapolation of results (both positive and negative) from patients who are not critically ill. Secondly, it is possible that the pathogenesis from viral pneumonitis to ARDS is driven much more by host immune and inflammatory factors than viral load or replication (Peiris et al., 2003). If this is the case, antiviral therapy may have limited efficacy, exposing the patient only to risks of harm from the agent.

#### *5.2.2.3. Need for evidence that takes into account concomitant therapy*

As far as can be ascertained, all current clinical trials for patients with COVID-19 evaluate a single strategy, such as antiviral therapy or immune modulation. However, it is biologically plausible that there is interaction between antiviral and immune modulatory therapies. For example, an immune

modulation strategy that dampens the host immune or inflammatory response may also result in uncontrolled viral replication. As such, administration of immune modulation strategy may be harmful in the absence of co-administration of antiviral agent, an immune modulation strategy may be effective only in the presence of co-administration of an active antiviral agent, and an antiviral agent may be ineffective alone but effective when co-administered with an agent that modulates the immune response.

In this regard, and within REMAP-CAP, the COVID-19 Antiviral Therapy Domain should be considered in conjunction with the COVID-19 Immune Modulation Domain and the pre-existing Corticosteroid Domain of REMAP-CAP. The pandemic statistical model, as described from the Pandemic Appendix to the Core Protocol (PATC), will allow evaluation of interactions between these domains, as specified in DSAs that are specific for COVID-19 infection.

### 5.2.3. Intervention strategy for this domain

It is intended that this domain of REMAP-CAP will evolve, taking into account evidence derived from other clinical trials, as well as availability of potentially effective antiviral therapies. WHO guidance notes the flexibility associated with REMAP-CAP as a platform for the testing of multiple agents, including serial testing of additional interventions (<https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1>)

At the commencement of this domain, a control group is included (i.e. some patients will not receive any antiviral agent that is intended to be active against COVID-19 infection). This is appropriate for two reasons. Firstly, there is relatively limited trial or clinical experience with the administration of antiviral agents in patients who are critically ill and it is not reasonable to presume that such agents do not cause net harm. Secondly, designs that included only active interventions are not able to ascertain if any option is better or worse than no treatment. If, during the evolution of this domain, there is sufficient evidence of effectiveness of agents or clinical practice changes to include the routine use of such agents or both, the control intervention that specifies that no antiviral agent is administered will be abandoned.

Although this domain will commence with a single antiviral agent, it is intended that additional agents can be added (allowing evaluation of several agents against a common control intervention) as well as allowing introduction of combinations of agents (to evaluate potential synergy). Any changes to the intervention structure of the domain will be specified using one or more amendments to this DSA with implementation occurring only after ethical approval has been

obtained. The initial selection of antiviral agent to be evaluated is a combination of lopinavir and ritonavir.

If at any stage evidence of harm or definitive evidence of absence of effectiveness in critically ill patients emerges for any intervention specified in this domain, the ITSC, as advised by the DSWG, may remove an intervention prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to that intervention will occur, so as to contribute additional weight of evidence available in the public domain.

#### 5.2.4. Lopinavir and ritonavir

Lopinavir and ritonavir are antiretroviral protease inhibitors used in combination for the treatment of HIV infection and have an established and satisfactory adverse effect profile (Huang et al., 2015). The combination of lopinavir and ritonavir (Kaletra<sup>®</sup>, Abbott Laboratories, Chicago, IL, USA, [http://hivdb.stanford.edu/pages/linksPages/LPV\\_RTV\\_PI.pdf](http://hivdb.stanford.edu/pages/linksPages/LPV_RTV_PI.pdf)) has also been administered to patients with SARS and MERS. At the time of writing, there is no data regarding the use of this agent in patients with COVID-19 infection.

In an observational study of 41 patients with SARS, the combination of lopinavir/ritonavir was associated with significantly fewer adverse clinical outcomes (acute respiratory distress syndrome or death) evaluated 21 days after the onset of symptoms, in comparison to ribavirin alone used in 111 historical controls (2.4% versus 28.8%,  $p = 0.001$ ) (Chu et al., 2004).

Based on *in vitro* data, the combination of lopinavir and ritonavir has been considered as a candidate therapy for MERS. In a high-throughput screening for antiviral compounds, lopinavir inhibited replication of MERS-CoV at levels below those that occur in the circulation after a single oral dose of lopinavir/ritonavir (400 mg lopinavir with 100 mg ritonavir), suggesting that drug may be able to achieve therapeutic levels *in vivo* (de Wilde et al., 2013). The effects of lopinavir/ritonavir, IFN- $\beta$ 1b and mycophenolate mofetil (MMF), all of which have shown viral inhibitory effects *in vitro*, have been tested in common marmosets with severe MERS-CoV infections (Chan et al., 2015). The animals treated with lopinavir/ritonavir or IFN- $\beta$ 1b had improved clinical, radiological, pathological outcomes as well as viral-load outcomes compared with untreated animals. By contrast, treatment with MMF resulted in severe or fatal disease, with higher mean viral loads than in untreated animals. Untreated animals and MMF-treated animals had a mortality of 67% by 36 hours compared to 0–33% among animals treated with lopinavir/ritonavir or IFN- $\beta$ 1b (Chan et al., 2015).



During the Korean outbreak of MERS, most patients that developed respiratory illness received triple antiviral therapy composed of pegylated interferon (IFN)- $\alpha$ , ribavirin, and lopinavir/ritonavir; however, data about the efficacy of this approach is lacking (Min et al., 2016).

These findings, together with the availability and safety profiles of lopinavir/ritonavir and IFN- $\beta$ 1b, suggest that the combination of these agents has potential efficacy for the treatment of patients with MERS. At present, the MIRACLE trial (the MERS-CoV Infection treated With A Combination of Lopinavir/Ritonavir and Interferon- $\beta$ 1b) is being conducted in Saudi Arabia to assess the efficacy of administering a combination of lopinavir/ritonavir and recombinant IFN- $\beta$ 1b to hospitalized adults with laboratory-confirmed MERS (Arabi et al., 2018).

It should be noted that the COVID-19 Immune Modulatory Therapy domain of REMAP-CAP is intended to include interferon- $\beta$ 1a which, results in an evaluation of the treatment effect of lopinavir/ritonavir in combination with interferon- $\beta$ 1a.

The usual dose for lopinavir/ritonavir is 400/100 mg administered orally twice daily. The medication is formulated as either a tablet or suspension. Patients who are receiving invasive mechanical ventilation are unable to swallow tablets. The placement of an oral or nasal gastric tube is routine in all patients who receive invasive mechanical ventilation and such tubes are used to deliver enteral medication. The suspension formulation of lopinavir/ritonavir is suitable for administration by a gastric tube. The absorption of crushed 200/50 mg lopinavir/ritonavir tablets to children significantly reduced lopinavir and ritonavir exposure with a decrease in AUC by 45% and 47%, respectively (Best et al., 2011).

In a recent open-label randomized controlled trial (n=199) in hospitalized patients with COVID-19, lopinavir/ritonavir with standard of care compared to standard of care alone did not result in a difference in the primary outcome (the time to clinical improvement), mortality, or viral load. However, the time from onset of symptoms to initiation of treatment was a median of 13 days, which may have obscured a beneficial treatment effect. This was in part related to the requirement of having confirmed diagnosis before enrolment. The stratified analysis based on the time from onset of symptoms to starting treatment suggests possible benefit with early treatment, but it was not statistically significant. Therefore, the study does not exclude possible treatment effect from lopinavir/ritonavir. The design of REMAP-CAP allows enrolment based on suspected case definition, so patients would receive treatment early. The relevance of this study to this domain may also be limited by differences in patient characteristic at time of randomization and by insufficient sample size to exclude a beneficial treatment effect (Cao et al., 2020).

### 5.2.5. Hydroxychloroquine

Hydroxychloroquine is a 4-aminoquinoline medication derived by hydroxylation of chloroquine. Since the mid-20<sup>th</sup> century, it has been used extensively in the prophylaxis and treatment of malaria and in the treatment of rheumatological conditions such as systemic lupus erythematosus. The usual dose of hydroxychloroquine in rheumatological disease is 200-400 mg daily, continued long term (often for many years). Enteral bioavailability of hydroxychloroquine is excellent. A common enteral dosing regimen for community treatment of malaria includes a loading dose of 800 mg, followed eight hours later by a dose of 400 mg, followed by 400 mg daily for an additional two days. A single dose of 800 mg has also been used. The dose for malaria suppression is 400 mg weekly.

There is a plausible rationale for an antiviral effect of hydroxychloroquine against SARS-CoV-2. Hydroxychloroquine inhibits acidification of an endocytic pathway important in coronavirus cell entry (Wang et al., 2008). Further, hydroxychloroquine alters the glycosylation of Angiotensin Converting Enzyme 2 (ACE2), the cellular receptor for SARS-CoV (Li et al., 2003). By genetic sequence homology, ACE2 is also predicted to be the receptor for SARS-CoV-2 (Wan et al., 2020). The immunomodulatory effects of hydroxychloroquine in autoimmune disorders poses a further potential theoretical mode of action for this agent in treatment of respiratory failure due to SARS-CoV-2.

*In vitro* data indicate that chloroquine and hydroxychloroquine inhibit SARS-CoV-2 at low micromolar concentrations (hydroxychloroquine  $EC_{50}=0.72 \mu\text{M}$ ) (Yao et al., 2020, Wang et al., 2020b). These concentrations are predicted to be achievable with enteral hydroxychloroquine therapy at doses comparable to those that have been widely used for malaria treatment. Hydroxychloroquine is available as a 200 mg tablet formulation (e.g. Plaquenil, sanofi-aventis). It has a very large volume of distribution (~44,000 litres) and a long elimination half-life (~40 days) (Tett et al., 1988). Hydroxychloroquine concentrates in the tissues and modelling data indicate that levels in the human lung are likely to quickly exceed 1,000 ng/mL and exceed 10,000 ng/mL (Yao et al., 2020).

There is no *in vivo* data on the effectiveness of chloroquine or hydroxychloroquine in animal models of SARS-CoV-2 infection. However, chloroquine acquired transplacentally or via maternal milk protected neonatal mice from a lethal challenge of the human coronavirus HCoV-OC43 (Keyaerts et al., 2009). There are no human studies of the efficacy of hydroxychloroquine (or chloroquine) in coronavirus infection. Importantly, hydroxychloroquine has demonstrated *in vitro* activity against other viruses, such as influenza virus, but that did not translate into benefit when used as prophylaxis against influenza (Paton et al., 2011). Consequently, and because of the limitations

inherent to studying potential coronavirus therapies in animal models that are not natural hosts for human coronavirus infection, randomized clinical trials are needed to ascertain whether the *in vitro* activity of hydroxychloroquine will translate to clinical benefits in humans.

The proposed mechanism of action for lopinavir/ritonavir and hydroxychloroquine in COVID-19 are different. This provides a rationale for possible synergy that is evaluated by administration of the combination of these drugs.

## 6. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of different antiviral agents, including combination of agents, for patients with severe pneumonia who have suspected or microbiological testing-confirmed COVID-19.

We hypothesize that the probability of occurrence of the primary end-point specified from the PATC will differ based on the allocated antiviral strategy. The following interventions will be available:

- No antiviral for COVID-19 (no placebo)
- Lopinavir/ritonavir
- Hydroxychloroquine
- Hydroxychloroquine + lopinavir/ritonavir

We hypothesize that the treatment effect of different antiviral strategies is different depending on whether SARS-CoV-2 infection is confirmed to be present or absent.

We hypothesize that the treatment effect of any antiviral agent is different to receiving no antiviral agent.

We hypothesize that the treatment effect of different antiviral strategies is different depending on allocation status in the Corticosteroid Domain. This is a treatment-by-treatment interaction between the interventions in the COVID-19 Antiviral Therapy Domain and the Corticosteroid Domain.

We hypothesize that the treatment effect of different antiviral strategies is different depending on allocation status in the COVID-19 Immune Modulation Therapy Domain. This is a treatment-by-treatment interaction between the interventions in the COVID-19 Antiviral Therapy Domain and the COVID-19 Immune Modulation Therapy Domain.

Each participating site has the option to opt-in to two or more interventions to be included in the randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the intervention at that site. As long as the 'no antiviral for COVID-19' intervention is retained in the platform it is strongly preferred that this intervention is always included by participating sites and is mandatory so long as there is only a single active intervention within the domain in use at a participating site.

## **7. TRIAL DESIGN**

This domain will be conducted as part of the REMAP-CAP trial (see Core Protocol Section 7). Treatment allocation will be adaptive, as described in the Core Protocol Section 7.5.2 and from the PATC.

### **7.1. Population**

The REMAP enrolls patients with severe pneumonia admitted to ICU (see Core Protocol Section 7.3).

### **7.2. Eligibility criteria**

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria (see Core Protocol Section 7.4 and PATC). Patients eligible for the REMAP may have conditions that exclude them from the COVID-19 Antiviral Therapy Domain.

#### **7.2.1. Domain inclusion criteria**

Patients are eligible for this domain if:

- COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing (i.e. PISOP stratum)
- Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur

#### **7.2.2. Domain exclusion criteria**

Patients will be excluded from this domain if they have any of the following:

- More than 24 hours has elapsed since ICU admission

- Patient has already received more than 36 hours of treatment with any non-trial prescribed systemic antiviral medication intended to be active against COVID-19 during this hospital admission
- Patient has been randomized in a trial evaluating an antiviral intended to be active against COVID-19, where the protocol of that trial requires ongoing administration of study drug or ongoing activity of study drug is anticipated.
- In areas where MERS-CoV infection is endemic, the patient has laboratory confirmed MERS-CoV infection
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

### 7.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons.

Patients who are eligible for only a single intervention at a site (i.e. all other interventions are contraindicated) are not eligible for this domain. Patients who are not eligible for this domain will be treated according to the current standard of care at the clinician's discretion.

Criteria that exclude a patient from a one or more interventions are:

- Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Receiving an agent that is specified as an intervention in this domain as a usual medication prior to this hospitalization will exclude a patient from receiving that agent
- Known HIV infection will exclude a patient from receiving lopinavir/ritonavir
- Severe liver failure will exclude a patient from receiving lopinavir/ritonavir
- Known or suspected pregnancy will result in exclusion from interventions that include lopinavir/ritonavir or hydroxychloroquine.
- Receiving amiodarone as a usual medication prior to this hospitalization or any administration of amiodarone within the 72 hours prior to assessment of eligibility will exclude a patient from receiving lopinavir/ritonavir
- High clinical risk of sustained ventricular dysrhythmia will exclude a patient from receiving hydroxychloroquine

## 7.3. Interventions

### 7.3.1. Antiviral interventions

Patients will be randomly assigned to receive one of the following open-label strategies. All interventions will be commenced immediately after allocation status is revealed.

- No antiviral for COVID-19 (no placebo)
- lopinavir/ritonavir
- hydroxychloroquine
- hydroxychloroquine and lopinavir/ritonavir

### 7.3.2. Lopinavir/ritonavir

#### 7.3.2.1. Dosing

Dosing will be Lopinavir/ritonavir 400/100 mg, administered by the enteral route every 12 hours. The preferred method of administration is two 200/50 mg tablets swallowed whole. In patients with a gastric tube who are unable to swallow tablets, the preferred method of administration is 5ml of 80/20 mg per ml suspension by the gastric tube (a large bore gastric tube is preferred). For a patient who cannot swallow and when the suspension is not available, four crushed tablets (double dose) will be given by enteral tube, noting that systemic absorption is reduced by approximately 50% using this method (Best et al., 2011).

No dose adjustment is necessary for renal dysfunction or concomitant use of renal replacement therapy. Clinicians should consider a dose adjustment in the presence of liver failure. No dose adjustment is necessary for abnormal liver function tests in the absence of liver failure.

#### 7.3.2.2. Duration of administration of Lopinavir/ritonavir

Lopinavir/ritonavir will be administered for a minimum of 5 days, including if discharged from ICU before the end of study day 5. If the patient is discharged from the ICU between study day 6 and the end of study day 14, lopinavir/ritonavir is ceased at ICU discharge. If the patient remains in ICU, lopinavir/ritonavir should be ceased at the end of study day 14. If the patient is readmitted to ICU prior to the end of study day 14, lopinavir/ritonavir should be recommenced.

### *7.3.2.3. Management of potential drug interactions with Lopinavir/ritonavir*

Concomitant treatment with drugs that are known to interact with Lopinavir/ritonavir should be avoided (see Appendix 1). If possible, an alternative agent should be considered, allowing for continuation of study drug. If no alternative is acceptable, the treating clinician will need to choose either not to administer the interacting medication or lopinavir/ritonavir, based on clinical priority. Appendix 1 lists these agents and provides guidance to treating clinicians.

### *7.3.3. Hydroxychloroquine*

#### *7.3.3.1. Dosing*

Dosing will be hydroxychloroquine administered by the enteral route. A loading dose is important because of the large volume of distribution. The loading dose will be 800 mg, administered 6-hourly, until 2 doses have been administered. Subsequently, starting 12 hours after the first loading dose, the dose will be 400 mg administered 12-hourly for 12 doses. The preferred method of administration is tablets swallowed whole but, if a patient is unable to swallow, crushed tablets dispersed in water can be administered via an enteral tube (a large bore gastric tube is preferred). No dose adjustment is required when hydroxychloroquine is administered via a gastric tube.

No dose adjustment is necessary for renal dysfunction or concomitant use of renal replacement therapy. Clinicians should consider a dose adjustment in the presence of liver failure, however no dose adjustment is necessary for abnormal liver function tests in the absence of liver failure.

#### *7.3.3.2. Duration of administration of hydroxychloroquine*

Hydroxychloroquine will be administered until the course of hydroxychloroquine is complete. If ICU discharge occurs before the end of the treatment course, the remaining doses should be prescribed unless the treating clinician considers this not to be in the patient's best interest. Discontinuation at the time of or after ICU discharge will not be considered a protocol deviation.

#### *7.3.3.3. Management of potential drug interactions with hydroxychloroquine*

Concomitant treatment with drugs that are known to interact with hydroxychloroquine should be avoided (see Appendix 2). If possible, an alternative agent should be considered, allowing for continuation of study drug. If no alternative is acceptable, the treating clinician will need to choose either not to administer the interacting medication or hydroxychloroquine, based on clinical priority. Appendix 2 lists these agents and provides guidance to treating clinicians.

#### 7.3.4. Discontinuation of study drug

An antiviral agent for COVID-19 should be discontinued if there is development of a serious adverse event (SAE) (see section 8.13.2). Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

Patients known to have HIV infection at the time enrollment are excluded from receiving lopinavir/ritonavir. Any patient who is discovered to be HIV positive after enrollment may have lopinavir/ritonavir ceased, if the treating clinician believes that this is clinically appropriate.

#### 7.3.5. COVID-19 antiviral strategy in patients negative for SARS-CoV-2 infection

In patients with suspected COVID-19 who receive an allocation status to receive any of the active interventions but for whom all microbiological tests are negative for SARS-CoV-2 infection may have treatment ceased. Ongoing administration of study drug is encouraged as long as there is clinical suspicion of COVID-19. These decisions should take into account the known or suspected sensitivity of testing for SARS-CoV-2.

#### 7.3.6. Monitoring of QTc

An interaction is reported between Lopinavir/ritonavir and hydroxychloroquine to cause prolongation of the duration of the corrected QT interval. The clinical significance of this interaction is not known but it may place patients at risk of serious ventricular rhythm disturbances including ventricular tachycardia and ventricular fibrillation. It is routine for all patients admitted to all ICUs participating in REMAP-CAP to provide continuous ECG monitoring. This mitigates risk by allowing early identification of QTc prolongation, with appropriate intervention including, if necessary, cessation of study drug, and prompt recognition and treatment of any associated life-threatening rhythm disturbances. The duration of treatment and exposure to the combination of agents during any period of time after ICU discharge, when continuous ECG monitoring may not be provided, has been adjusted to reflect this potential interaction.

### **7.4. Concomitant care**

Additional drugs intended to be active against SARS-CoV-2 infection should not be administered. In patients who have received an allocation status in the Antibiotic Domain, and have microbiological testing confirmed SARS-CoV-2 infection, continuation of empiric anti-bacterial agents will be as per the Antibiotic Domain-Specific Appendix (Section 8.3). All treatment that is not specified by assignment within the platform will be determined by the treating clinician.



## **7.5. Endpoints**

### 7.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in an operational document from within the options specified in the PATC.

### 7.5.2. Secondary endpoints

All secondary endpoints as specified from the PATC 7.5.2.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored 90 days after enrollment) will be:

- Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinically indicated testing)
- Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital
- SAE as defined in Core Protocol and qualified in this DSA

## **8. TRIAL CONDUCT**

### **8.1. Microbiology**

Microbiological testing will be performed as per local practice, including bacterial and viral testing to guide clinical care. Results of these tests will be collected but no additional testing is specified in this protocol.

Sites that are participating in this domain are encouraged to also participate in the Clinical Characterization Protocol (CCP) for patients with COVID-19 that has been established by the International Severe Acute Respiratory and Emerging Infectious Consortium (<https://isaric.tghn.org/CCP/>). This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP will be obtained separately.

## **8.2. Domain-specific data collection**

### 8.2.1. Clinical data collection

Additional domain-specific data will be collected.

- Administration of systemic corticosteroids
- Administration of antiviral agents intended to be active against COVID-19
- Administration of immune modulatory agents intended to influence host response to COVID-19

## **8.3. Criteria for discontinuation**

Refer to Core Protocol Section 8.7 for criteria for discontinuation of participation in the REMAP-CAP trial.

## **8.4. Blinding**

### 8.4.1. Blinding

All medication will be administered on an open-label basis.

### 8.4.2. Unblinding

Not relevant.

## **9. STATISTICAL CONSIDERATIONS**

### **9.1. Domain-specific stopping rules**

If a Platform conclusion of equivalence in the primary endpoint is demonstrated, the DSMB and the ITSC may consider continuation of randomization if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated. In all other respects the stopping rules for this domain are those outlined in the Core Protocol Section and from the PATC.

### **9.2. Unit-of-analysis and strata**

The default unit-of-analysis, for both analysis of treatment effect and the Response Adaptive Randomization, will be the PISOP stratum, as specified from the PATC. As determined by the ITSC, and based on an understanding of the sensitivity and availability of testing for SARS-CoV-2 infection, the unit-of analysis may be modified to allow separate analysis of the SARS-CoV-2 infection confirmed stratum and not confirmed stratum. This will be an operational decision.

At the time of a Platform Conclusion, results will be reported for all randomized patients, patients in whom SARS-CoV-2 infection is confirmed by microbiological testing, microbiological tests do not detect or isolate SARS-CoV-2 infection, and testing was not performed.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

The influenza strata will not contribute to unit-of-analysis for this domain.

### **9.3. Timing of revealing of randomization status**

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required for this domain (see section 7.8.3.6 in Core Protocol)

### **9.4. Interactions with interventions in other domains**

An *a priori* interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the influenza Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.

An *a priori* interaction with the Corticosteroid Domain is considered possible and will be incorporated into the statistical models used to analyze this domain. An interaction may exist between antiviral treatment and interventions in the Corticosteroid Domain. For the purposes of

analysis and reporting such combinations are pre-specified to be an 'intervention' i.e. superiority, or inferiority, of the combination can be reported as a conclusion from the study.

An *a priori* interaction with the COVID-19 Immune Modulation Therapy Domain is considered possible and will be incorporated into the statistical models used to analyze this domain. An interaction may exist between interferon-beta 1a and antiviral treatment. For the purposes of analysis and reporting this combination is pre-specified to be an 'intervention' i.e. superiority, or inferiority, of the combination can be reported as a conclusion from the study.

No interaction is evaluable between the Ventilation Domain and this domain.

### **9.5. Nesting of interventions**

There is one nest within this domain, comprising all active interventions (see Section 7.8.3.8 in Core Protocol). The rationale for this is that if more than one antiviral interventions is effective, the inferiority of the no antiviral intervention will be identified more rapidly, leading to that intervention being removed from the platform and the result being disseminated as a platform conclusion.

With modification of the domain to include more than one active antiviral agent, the domain will be analyzed as an N x N factorial where there are N antiviral agents. At the time of commencement of the hydroxychloroquine intervention the analysis structure consists of a two-by-two table consisting of Yes or No for lopinavir/ritonavir and Yes or No for hydroxychloroquine. Structuring the analysis in this way allows the model to learn more quickly about the effectiveness of each antiviral agent recognizing common drug exposure across intervention assignments. Platform conclusions can be reached for an individual agent or combinations of agents.

### **9.6. Threshold probability for superiority and inferiority**

The threshold odds ratio delta for superiority and inferiority in this domain are those specified as the default thresholds in the PATC.

### **9.7. Threshold odds ratio delta for equivalence**

The threshold odds ratio delta for equivalence in this domain is that specified as the default threshold in the PATC.

### **9.8. Informative priors**

This domain will not include priors that are informative. If new antiviral agents are added to the domain, consideration will be given to the use of informative priors at the time of amendment of the DSA.

### **9.9. Post-trial sub-groups**

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* patient sub-groups of interest are:

- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes community-acquired pneumonia from blood, pleural fluid, or lower respiratory tract specimen
- Shock strata
- Influenza strata
- Receiving invasive mechanical ventilation at baseline
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

## **10. ETHICAL CONSIDERATIONS**

### **10.1. Data Safety and Monitoring Board**

The DSMB should be aware that the superiority, inferiority, or equivalence of different interventions with respect to the primary endpoint is possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints.

The DSMB should take into account the public health, as well as clinical significance, of the analyses of this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.

Safety secondary outcomes will be reported to the DSMB who are empowered to require additional analyses regarding these outcomes as required.

## **10.2. Potential domain-specific adverse events**

### 10.2.1. Reporting of SAEs

All reportable SAEs listed in this section should be screened for and reported in all patients in this domain, irrespective of intervention allocation.

### 10.2.2. Interventions that include lopinavir/ritonavir

A number of SAEs have been reported, albeit rarely, in ambulant patients receiving this medication. The occurrence of any of the following should be reported as an SAE and, where clinically appropriate, study drug should be ceased:

- Acute pancreatitis
- Hepatotoxicity with evidence of failure
- Anaphylaxis or other suspected serious immune-mediated reaction
- Life-threatening arrhythmia requiring administration of an anti-arrhythmic medication, cardioversion, or any form of cardiac pacing.

Other SAEs should be reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core Protocol Section 8.13).

### 10.2.3. Interventions that include hydroxychloroquine

A number of SAEs have been reported, albeit rarely, in ambulant patients receiving this medication. The occurrence of any of the following should be reported as an SAE and, where clinically appropriate, study drug should be ceased:

- Severe hypoglycemia
- Anaphylaxis or other suspected serious immune-mediated reaction
- Life-threatening arrhythmia requiring administration of an anti-arrhythmic medication, cardioversion, or any form of cardiac pacing

## **10.3. Domain-specific consent issues**

For patients who are not competent to consent, either prospective agreement or entry via waiver-of-consent or some form of deferred consent can be applied, as required by an appropriate ethical review body. Where prospective agreement is required, a period of up to 24 hours from the time of

establishing eligibility will be available to obtain agreement and commence the assigned therapy. In such situations allocation status will not be revealed until prospective agreement has been obtained.

As noted in the background, and endorsed by the WHO, in the absence of evidence of effectiveness of at least one antiviral agent for COVID-19, the use of a no treatment control is both appropriate and ethical. Also, as noted in the Background, these agents are being used off-label in patients with COVID-19. Commencement of therapy as early as possible is more likely to be effective and, where available, waiver of consent or some form of deferred consent is preferred.

As the domain evolves, if an Investigational Medical Product was included as an intervention, at sites where such treatment assignment was possible randomization in the domain would require prospective agreement, either from the participant or a participant's authorized representative.

During a pandemic, visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods for confirming agreement to participate in this (and other) domains of the platform.

## **11.GOVERNANCE ISSUES**

### **11.1. *Funding of domain***

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding but such funding, from any source, may be obtained during the life-time of the domain.

### **11.2. *Funding of domain interventions and outcome measures***

Lopinavir/ritonavir will be provided by participating hospitals.

### **11.3. *Domain-specific declarations of interest***

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

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## APPENDIX 1. LOPINAVIR/RITONAVIR INTERACTIONS WITH DRUGS COMMONLY

### USED IN THE INTENSIVE-CARE UNIT

Drug	Possible interaction	Management	Action from enrollment until cessation of study drug
Amiodarone	Increased risk of amiodarone toxicity (hypotension, bradycardia, sinus arrest).  Increased QT-interval prolongation.	Concurrent use is contraindicated	Consider alternatives to amiodarone.  If no alternative to amiodarone is available, consider using a reduced dose.  Monitor for altered liver-function test results and evidence of QT-interval prolongation.
Fentanyl	Concurrent use of fentanyl and CYP3A4 inhibitors may result in an increased risk of fentanyl toxicity, resulting in respiratory depression.	In non-mechanically ventilated patients, concurrent use is contraindicated.  In mechanically ventilated patients, avoid fentanyl or use reduced doses.	Consider alternatives to fentanyl.  Use lower doses and adjust the dose to target analgesia and sedative effects.
Fluconazole	Increased ritonavir exposure and risk of QT-interval prolongation.	Avoid concomitant use if possible.  If fluconazole is required, closely monitor electrocardiogram for QT-interval prolongation.	Use alternatives to fluconazole.  Fluconazole-mediated CYP3A4 inhibition may continue for 4–5 days after discontinuation because of its long half-life.
Midazolam	Increased midazolam plasma concentrations, which can lead to midazolam toxicity.	In non-mechanically ventilated patients, concurrent use is contraindicated.  In mechanically ventilated patients, avoid use of midazolam if possible. If needed, use reduced midazolam doses and monitor effects.	Consider alternatives to midazolam.  Use lower doses and adjust the dose to target sedative effects.
Quetiapine	Increased risk of QT-interval prolongation, Torsades de pointes or other notable ventricular tachyarrhythmias.	Concomitant administration is contraindicated.	Use alternatives to quetiapine.  If concomitant use is required, reduce the quetiapine dose to one-sixth of the standard dose, and when the lopinavir/ritonavir is discontinued, the dose of quetiapine should subsequently be increased to the standard dose.
Rifampin	Decreased lopinavir/ritonavir plasma concentrations; in HIV patients, may lead to a loss of virologic response and	Contraindicated for patients receiving hepatitis B virus treatments containing ritonavir, because ritonavir exposure may decrease.  In other situations, concomitant use of rifampin	If concomitant use is required, rifabutin 150 mg every other day or 150 mg three times a week is recommended for concomitant use with a ritonavir-boosted protease inhibitor. Alternatively, some experts recommend using

Drug	Possible interaction	Management	Action from enrollment until cessation of study drug
	a possible resistance to lopinavir/ritonavir.  Rifampin may enhance the toxic effect of lopinavir, specifically increasing the risk of hepatocellular toxicity.	with a protease-inhibitor-containing formulation is not recommended.	rifabutin 150 mg daily or 300 mg three times a week. Monitoring for rifabutin efficacy is recommended.
Sildenafil	Increased sildenafil plasma levels, thereby increasing the risk for sildenafil adverse effects (hypotension, visual changes and priapism).	Concurrent use of lopinavir/ritonavir and sildenafil is contraindicated.	Do not use sildenafil.
Simvastatin	Increased risk of myopathy or rhabdomyolysis.	Concomitant use of lopinavir/ritonavir with simvastatin is contraindicated.	Do not use simvastatin. If needed, consider Fluvastatin, pitavastatin, or pravastatin as alternatives, because these drugs have the least potential for interaction.
Atorvastatin	Atorvastatin AUC increased by 488%. Increased risk of myopathy or rhabdomyolysis.	Monitor for signs of atorvastatin toxicity (rhabdomyolysis and myopathy).	Consider alternative agents (pravastatin, Fluvastatin or rosuvastatin), because these drugs have the least potential for interaction.
Voriconazole	Decreased plasma concentrations of voriconazole and decreased voriconazole efficacy.	Concomitant administration is contraindicated.	Use alternatives to voriconazole or use with Therapeutic Drug Monitoring. Voriconazole dose may need to be increased. If no alternative is available, discontinue lopinavir/ritonavir and continue the use of interferon $\beta$ -1b.  Consider another antifungal for aspergillosis (such as ambisome or caspofungin).
Phenytoin	Both phenytoin and ritonavir plasma concentrations may be decreased.	Use with caution.	Monitor phenytoin levels during co-administration. Adjustment of the phenytoin or fosphenytoin dose may be warranted.

The information in this table was obtained from Lexicomp (<http://www.wolterskluwercli.com/lexicomp-online/>) and Micromedex (<http://micromedex.com/>). Abbreviations: AUC, area under the (receiver operating characteristic) curve; CYP3A4, cytochrome P450-3A4.

## APPENDIX 2. HYDROXYCHLOROQUINE INTERACTIONS WITH DRUGS COMMONLY

### USED IN THE INTENSIVE-CARE UNIT

Drug	Possible interaction	Management	Action from enrollment until cessation of study drug
Digoxin	Increases digoxin concentration up to 3 to 4-fold through inhibitor of p-glycoprotein	Use with caution	Monitor digoxin concentrations before and during treatment. Effects are prolonged due to the long half-life of HCQ.
Chlorpromazine	Potential increase in chlorpromazine concentration up to 3 to 4-fold.	Use with caution or use alternatives	Heavier sedation seen in patients on both agents. Use a lower dose or alternative agents.
Ciclosporin	Increases ciclosporin concentrations by 3-fold	Use with caution	Monitor ciclosporin concentrations before and during treatment. Effects are prolonged due to the long half-life of HCQ.
Antacids	Decrease hydroxychloroquine absorption and concentration by binding to metals	Use with caution or use alternatives	Separate administration by 4 hours either side of dose if required.
<p>The following drugs are listed as potential interactions in the <a href="#">Liverpool COVID-19 list</a> but there is no data in other interaction references to provide details. Caution is required.</p>			
Risperidone	Potential increased risperidone concentrations		
Verapamil	Potential increased HCQ concentrations		
Tacrolimus	Potential increased tacrolimus concentrations		
Sirolimus	Potential increased sirolimus concentrations		
Amiodarone	Potential increased amiodarone concentrations		
Flecainide	Potential increased flecainide concentrations		
Mexiletine	Potential increased mexiletine concentrations		
DAbigatran	Potential increased dabigatran concentrations		
Rivaroxaban	Potential increased rivaroxaban concentrations		
Rifampicin	Potential decreased HCQ concentrations		