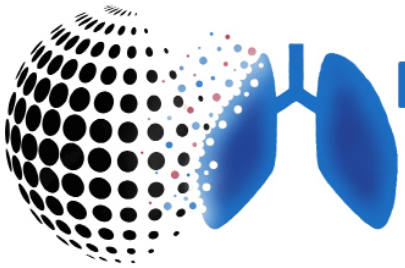

Protocol Amendment to COVID-19 Antiviral Therapy Domain-Specific Appendix

Summary of changes

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

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REMAP-CAP COVID-19 Protocol Amendment Summary Version 1 dated 02 April 2020

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1. CURRENT VERSIONS OF PROTOCOL DOCUMENTS

1.1. The current versions of pandemic specific protocol documents:

- REMAP-CAP Core Protocol Version 3, dated 10 July 2019
- Pandemic Appendix to Core Version 1.1, dated 12 February 2020
- Domain-Specific Appendices
    - COVID-19 Antiviral Therapy Domain-Specific Appendix Version 1, dated 11 March 2020
    - COVID-19 Immune Modulation Domain-Specific Appendix Version 1, dated 11 March 2020

2. AMENDMENT 1

The COVID-19 Antiviral Therapy DSA protocol document underwent an amendment in March 2020.

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2.1. Summary of changes

Section	Original text	New Text	Reason
Front page and whole document header	REMAP-CAP COVID-19 Antiviral Therapy Domain-Specific Appendix Version 1.0 dated 11 March 2020	REMAP-CAP COVID-19 Antiviral Therapy Domain-Specific Appendix Version 2.0 dated 01 April 2020	Administrative change
Summary Page 2	• No antiviral for COVID-19 (no placebo) • Lopinavir/ritonavir	• No antiviral for COVID-19 (no placebo) • Lopinavir/ritonavir • Hydroxychloroquine • Hydroxychloroquine and lopinavir/ritonavir	Addition of new interventions
Summary table Page 3 Nesting	None	There is one nest, comprising all interventions that include an active antiviral agent.	If more than one antiviral agent is effective the application of nesting leads to more rapid identification of the 'no antiviral' intervention as ineffective
Intervention-Specific Exclusions	• 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 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	

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	• Known HIV infection will exclude a patient from receiving lopinavir/ritonavir • 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	• Known HIV infection will exclude a patient from receiving lopinavir/ritonavir • Known or suspected pregnancy will result in exclusion from any intervention 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	Advice from individuals with experience of these agents has indicated that preganancy should be an exclusion for interventions that include lopinavir/ritonvir or hydroxychloroquine Intervention-level exclusion criteria updated for Hydoxychloroquine
SECTION 3 COVID-19 ANTIVIRAL THERAPY DOMAIN-SPECIFIC APPENDIX VERSION	**Original text**	**New Text**	**Reason**
3.1. Version History Page 9	Version 1: Approved by the COVID-19 Domain Specific Working Group (DSWG) on 11 March, 2020	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	Administrative change
SECTION 4 COVID-19 ANTIVIRAL DOMAIN GOVERNANCE	**Original text**	**New Text**	**Reason**

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4.1. Domain members Page 10	Professor Derek Angus Dr Kenneth Baillie Professor Richard Beasley A/Prof Scott Berry Professor Marc Bonten Professor Frank Brunkhorst Professor Allen Cheng Professor Menno de Jong Dr Lennie Derde Dr Rob Fowler Professor Herman Goossens Professor Anthony Gordon Mr Cameron Green Dr Ed Litton Professor John Marshall Dr Colin McArthur Professor Susan Morpeth Dr Srinivas Murthy Dr Mihai Netea Professor Alistair Nichol A/Prof Rachael Parke Ms Jane Parker Professor Kathy Rowan Dr Steve Tong	Professor Derek Angus Dr Kenneth Baillie Professor Richard Beasley A/Prof Scott Berry Professor Marc Bonten Professor Frank Brunkhorst Professor Allen Cheng Professor Menno de Jong Dr Lennie Derde Dr Rob Fowler Professor Herman Goossens Professor Anthony Gordon Dr Thomas Hills Mr Cameron Green Dr Ed Litton Professor John Marshall Dr Colin McArthur Dr Susan Morpeth Dr Srinivas Murthy Dr Mihai Netea Professor Alistair Nichol A/Prof Rachael Parke Ms Jane Parker Professor Kathy Rowan	Addition of an investigator Administrative change to title

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	Dr Tim Uyeki Dr Frank van de Veerdonk Professor Steve Webb	Dr Steve Tong Dr Tim Uyeki Dr Frank van de Veerdonk Professor Steve Webb	
SECTION 5 BACKGROUND AND RATIONALE	**Original text**	**New Text**	**Reason**
5.2.1. Domain-specific background Page 11	On January 30th 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)). 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.	On January 30th 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)). On March 11th 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). 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.	Minor additions to background information

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	Nevertheless, it is recognized that fatal pneumonia is common and that there is potential for widespread disease activity outside China.	Nevertheless, it is recognized that fatal pneumonia is common. COVID-19 is now a pandemic with increasing case numbers across the globe.	
5.2.2.1. Current clinical trials and interventions being evaluated Page 14	The first antiviral agent that will be evaluated in this domain of REMAP-CAP is lopinavir/ritonavir either alone or in combination with interferon-β1a (which is closely related to interferon-β1b). The use of interferon-β1a will be specified in a separate DSA with evaluation of the interaction between these therapies in the statistical model.	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.	Addition to background information regarding new interventions
5.2.4. Lopinavir and ritonavir Page 17	N/A	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	Addition to background information to incorporate recent trial results that are relevant to the interventions included in this domain.

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		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 Page 18	N/A	Hydroxychloroquine is a 4-aminoquinoline medication derived by hydroxylation of chloroquine. Since the mid-20th 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	Addition to background information regarding the hydroxychloroquine

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		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 µM) (Yao et al., 2020, Wang et al., 2020b). These concentrations are predicted to be achievable	

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		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	

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		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.	
SECTION 6 DOMAIN OBJECTIVES	**Original text**	**New Text**	**Reason**
Page 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 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 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 and 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.	Addition of new interventions and associated hypothesis.

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	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.	We hypothesize that the treatment effect of any antiviral agent is different to receiving no antiviral agent. 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.	
SECTION 7 TRIAL DESIGN	**Original text**	**New Text**	**Reason**
7.2.2. Domain exclusion criteria Page 21	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 • In areas where MERS-CoV infection is endemic, the patient has laboratory confirmed MERS-CoV infection	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	Addition to take into account the long elimination half-life of Hydroxychloroquine. If hydroxychloroquine is an intervention in any trials that enroll patients prior to admission to ICU, it is possible that the drug may still be active despite being discontinued.

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	• The treating clinician believes that participation in the domain would not be in the best interests of the patient	• 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 Page 21	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 • 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	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	Advice from individuals with experience of these agents has indicated that pregnancy should be an exclusion for interventions that include lopinavir/ritonvir or hydroxychloroquine, or both.

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		• High clinical risk of sustained ventricular dysrhythmia will exclude a patient from receiving hydroxychloroquine	Intervention-level exclusion criteria included to reflect known potential side-effects of Hydoxychloroquine
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	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	Addition of new interventions
7.3.2.3. Management of potential drug interactions with Lopinavir/ritonavir Page 23	Administration of any drug that is known to interact with Lopinavir/ritonavir is precluded (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.	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.	Rewording, based on advice from clinicians with substantial experience with use of lopinavir/ritonavir to facilitate appropriate clinical practice.

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7.3.3.1. Dosing Page 23	N/A	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.	Updated to include dosing information for new intervention
7.3.3.2. Duration of administration of hydroxychloroquine Page 23	N/A	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	Updated to include dosing information for new intervention

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		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 Page 24	N/A	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.	Updated to include information regarding concomitant care for new intervention
7.3.6. Monitoring of QTc Page 24	N/A	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	Addition of new section containing important safety information relating to a potential interaction between lopinavir/ritonavir and hydroxychloroquine.

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		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 Page 25	Additional agents 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).	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).	Change in nomenclature. *Agents* changed to *drugs* because of possibility that the platform may add monoclonal or other antibodies directed against SARS-CoV-2. If so, these are 'antiviral agents' but would be placed in a separate DSA.
7.5.2. Secondary endpoints Page 25	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) • SAE as defined in Core Protocol and qualified in this DSA	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	Addition because of potential effect on QTc with hydroxychloroquine combined with use of agents, either in concomitant care or in platform, that can potentially interact with

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		• SAE as defined in Core Protocol and qualified in this DSA	hydroxychloroquine and / or Lopinavir/ritonavir to adversely impact on QTc. Need for QTc monitoring has been added to the study operational documents provided to participating sites. All patients admitted to an ICU are routinely monitored with continuous measurement of ECG. Addition of this as a secondary end-point ensures it will be reported and available to DSMB to evaluate safety.
SECTION 9 STATISTICAL CONSIDERATIONS	**Original text**	**New Text**	**Reason**
9.4. Interactions with interventions in other domains Page 27	An a priori interaction with the Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.	An a priori interaction with the influenza Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.	Addition to provide clarity that this applies to a separate domain of REMAP-CAP which

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			comprises antiviral agents active against influenza
9.5. Nesting of interventions Page 28	Nesting is not applicable in this domain.	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.	Adjustment of statistical methods. The creation of a nest that comprises all interventions that include at least one antiviral agent potentially active against COVID-19 results in the comparison of any antiviral agents against no antiviral. This allows removal/declaration of inferiority of the no antiviral intervention as quickly as possible from the platform if more than one antiviral agent is effective. The occurrence of this event will be

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			reported as a platform conclusion. 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
9.8. Informative priors Page 29	This domain will launch with priors that are not informative.	This domain will not include priors that are informative.	Updated to reflect that the domain has been launched. The use of an informative prior was considered following the reports of the LOTUS trial. However, the consensus within the investigator team, including statisticians, was that the strength of evidence regarding

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			lopinavir/ritonavir in the relevant patient population was insufficient to warrant the use of an informative prior.
SECTION 10 ETHICAL CONSIDERATIONS	**Original text**	**New Text**	**Reason**
10.1. Data Safety and Monitoring Board Page 29	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 health authorities, with rapid dissemination of results to the larger community being the goal.	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 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.	Addition to reflect the addition of a secondary end-point related to incidence of VT/VF or unexplained sudden death

10.2.2. Interventions that include lopinavir/ritonavir Page 30	10.2.2 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 • Arrythmia requiring administration of an anti-arrhythmic medication, cardioversion, or any form of cardiac pacing.	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 arrythmia requiring administration of an anti-arrhythmic medication, cardioversion, or any form of cardiac pacing.	Administrative change to heading, to reflect the addition of hydroxychloroquine + lopinavir/ritonavir intervention Clarified to exclude non-life threatening rhythm disturbances that are common in critically ill patients.
10.2.3. Interventions that include hydroxychloroquine Page 30	N/A	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	Updated to include information regarding new intervention

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		• Life-threatening arrhythmia requiring administration of an anti-arrhythmic medication, cardioversion, or any form of cardiac pacing.	

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