Supplementary appendix

Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with coronavirus disease -19

I. Supplementary Methods:

The primary analysis was conducted on the REMAP-CAP Severe State cohort, including all randomized patients who met severe COVID-19 criteria as of November 19, 2020, and not just those randomized within the COVID-19 Antiviral Therapy Domain (Supplementary Appendix, Table S3). This approach allowed maximal incorporation of all information, providing robust estimation of the coefficients of all covariates, as per the principle of the REMAP-CAP design. It is important to note that not all patients were eligible for all domains nor for all interventions (dependent on active domains and interventions at the site, eligibility criteria, and patient/surrogate consent). Therefore, the model included covariate terms reflecting each patient's domain eligibility, such that the estimate of an intervention's effectiveness, relative to any other intervention within that domain, was generated only from those patients eligible to be randomized to those interventions within the domain.

The model assumed proportional effects across the ordinal organ support-free days scale. This assumption was assessed in sensitivity analyses estimating the odds-ratio effect for each cumulative dichotomization of the organ support-free days scale. The model was fit using a Markov Chain Monte Carlo algorithm that drew iteratively (10,000 draws) from the joint posterior distribution.

Additional secondary and sensitivity analyses of the primary outcome were undertaken restricting without adjustment for site and time epoch. Sensitivity analyses were performed including less informative standard normal priors on pre-specified combinations of antivirals, corticosteroids, IL-6 antagonists (tocilizumab and sarilumab). Additional post-hoc analyses explored the effect of restricting to Antiviral Therapy Domain patients with no borrowing between antiviral interventions and of using a weaker prior on the interaction term for combination therapy.

Data management and summaries were created using R version 3.5.2, the primary analysis was computed in R version 4.0.0 using the rstan package version 2.19.3. Additional data management and analysis was performed in R, SQL 2016, SPSS version 26, and Stata version 14.2.

II. Supplementary Results:

Platform exclusions. (Please see also Figure 1)

764 patients	Ineligible for platform [a]	
268 patients	Site not active for COVID-19 Antiviral Domain & not enrolled in another domain	
223 patients	COVID-19 Antiviral Domain active, but not enrolled in the COVID-19 Antiviral Therapy Domain because of an exclusion criterion and not enrolled in another domain	
	2	Samples for COVID-19 not taken or intended
	113	Admitted to ICU >24 hours earlier
	20	Already received >36h of treatment with an antiviral against COVID-19
	8	Enrolled in another trial
	0	Confirmed MERS-CoV infection
	26	Contraindication to agents in domain ^
	14	Not considered in patient's best interests
	110	Prospective consent declined

a Patients could meet more than 1 ineligibility criterion (Table S2, Supplementary Appendix).

^ Contraindications include hypersensitivity, receiving the study drug as usual medication prior to hospitalization, human immune deficiency (HIV) infection (contraindication of lopinavir-ritonavir), severe liver failure (contraindication of lopinavir-ritonavir), receiving amiodarone as a usual medication prior to this hospitalization or any administration of amiodarone within the 72 hours prior to assessment (contraindication of lopinavir-ritonavir) and high clinical risk of sustained ventricular dysrhythmia (contraindication of hydroxychloroquine) (Table S2, Supplementary Appendix).

III. Supplementary Tables:

Table S1: Site participation in the COVID-19 Antiviral Therapy Domain in the Severe State. During the study period from March 9, 2020 to November 19, 2020, 187 sites were open for enrollment in the platform across 11 countries, of which 99 were open for enrollment in the COVID-19 Antiviral Therapy Domain across 8 countries.

Region	Country	All Domains			COVID-19 Antiviral Domain		
		Number of Sites	Number of Patients Randomized	Number of Patients w/ Outcomes	Number of Sites	Number of Patients Randomized	Number of Patients w/ Outcomes
Americas	Canada	21	148	119	6	42	39
	United States of America	2	94	94	1	8	8
Europe	France	3	11	11			
	Germany	2	4	4			
	Ireland	2	34	34	2	6	6
	Netherlands	2	96	94	3	20	20
	Portugal	1	3	3			
	United Kingdom	121	1405	1378	74	502	491
Middle East	Saudi Arabia	1	114	114	1	100	100
Oceana	Australia	22	73	68	10	14	11
	New Zealand	5	9	9	2	2	2

Table S2: Eligibility criteria.

A. Platform inclusion criteria

1. Adult patient admitted to hospital with acute illness due to suspected or proven pandemic (COVID-19) infection

B. Platform exclusion criteria

1. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment.
2. Patient is expected to be discharged from hospital today or tomorrow.
3. More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection.
4. Previous participation in this REMAP within the last 90 days.

C. COVID-19 Antiviral Therapy Domain specific inclusion criteria- Severe State

1. Patient meets Severe State, defined by receiving respiratory or cardiovascular organ failure support in an intensive care unit (ICU).
    a. Respiratory organ support is defined as invasive or non-invasive mechanical ventilation including via high-flow nasal cannula if flow rate >30 L/min and FIO 2 >0.4. If non-invasive ventilation would normally be provided but is being withheld, due to infection control concerns associated with aerosol generating procedures, then the patient still meets the Severe State criteria.
    b. Cardiovascular organ support was defined as the intravenous infusion of any vasopressor or inotrope.
    c. Pandemic surge capacity means that provision of advanced organ support may need to occur in locations that do not usually provide ICU-level care. Therefore, an ICU is defined as an area within the hospital that is repurposed so as to be able to deliver one or more of the qualifying organ failure supports (non-invasive ventilation, invasive ventilation, and vasopressor therapy).
2. Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur.

D. COVID-19 Antiviral Therapy Domain specific exclusion criteria

1. More than 24 hours has elapsed since ICU admission.
2. 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.
3. 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.
4. In areas where MERS-CoV infection is endemic, the patient has laboratory confirmed MERS-CoV infection.
5. The treating clinician believes that participation in the domain would not be in the best interests of the patient.

E. Lopinavir-ritonavir and hydroxychloroquine exclusion criteria

1. Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent.
2. 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.
3. Known HIV infection will exclude a patient from receiving lopinavir-ritonavir.
4. Severe liver failure will exclude a patient from receiving lopinavir-ritonavir.
5. Known or suspected pregnancy will result in exclusion from interventions that include lopinavir-ritonavir or hydroxychloroquine.
6. 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.
7. High clinical risk of sustained ventricular dysrhythmia will exclude a patient from receiving hydroxychloroquine.

Table S3: Study cohorts.

		N	N with data on OSFD endpoint
REMAP-CAP Severe State cohort	All patients with suspected or proven COVID-19 who met Severe State definition randomized within at least one domain	1991	1928
Unblinded cohort	Restricted to patients randomized to an intervention in domains that have been unblinded including the COVID-19 Antiviral Therapy Domain and domains that have ceased recruitment (Corticosteroid and reported arms of the Immune Modulation Therapy Domain)	1293	1271
Unblinded Non-negative cohort	All patients within the Unblinded cohort after removing those with >1 negative test for COVID-19 and no positive tests.	1136	1115
Antiviral-specific cohort	Restricted to patients randomized in the COVID-19 Antiviral Therapy Domain.	694	677
Per protocol cohort	Patients in the Antiviral-specific cohort who have been treated as per protocol	629	619

Table S4: Participant characteristics at baseline for patients randomized concurrently with hydroxychloroquine interventions.

	Lopinavir-ritonavir (N=34)	Hydroxychloroquine (N=50)	Combination therapy (N=27)	Control (N=78)
Age – mean (SD), years	56.0 (11.8)	56.3 (13.0)	60.3 (8.9)	59.8 (10.2)
Male Sex – n/N (%)	25/33 (75.8)	35/50 (70.0)	19/27 (70.4)	50/78 (64.1)
Body mass index - mean (SD), kg/m^2	30.6 (6.2)	31.0 (6.3)	30.0 (6.7) N = 25	31.7 (8.6)
Race/Ethnicity [b] - White – n/N (%)	5/8 (62.5)	18/31 (58.1)	6/8 (75.0)	18/27 (66.7)
Asian – n/N (%)	2/8 (25.0)	5/31 (16.1)	1/8 (12.5)	4/27 (14.8)
Black – n/N (%)	0/8 (0.0)	4/31 (12.9)	1/8 (12.5)	2/27 (7.4)
Mixed – n/N (%)	0/8 (0.0)	0/31 (0.0)	0/8 (0.0)	0/27 (0.0)
Other [b] – n/N (%)	1/8 (12.5)	4/31 (12.9)	0/8 (0.0)	3/27 (11.1)
Confirmed SARS-CoV2 infection [c] – n/N (%)	26/34 (76.5)	43/50 (86.0)	22/27 (81.5)	62/78 (79.5)
Pre-existing conditions – n/N (%)				
Diabetes mellitus	5/33 (15.2)	15/50 (30.0)	10/26 (38.5)	25/78 (32.1)
Respiratory disease¤	11/33 (33.3)	9/47 (19.1)	6/26 (23.1)	19/75 (25.3)
Kidney disease	1/32 (3.1)	3/44 (6.8)	4/24 (16.7)	7/74 (9.5)
Severe cardiovascular disease	1/33 (3.0)	2/48 (4.2)	3/26 (11.5)	5/73 (6.8)
Immunosuppressive disease	1/33 (3.0)	2/50 (4.0)	1/26 (3.8)	1/78 (1.3)
Chronic immunosuppressive therapy	2/33 (6.1)	0/47 (0.0)	1/26 (3.8)	3/73 (4.1)
Time to enrollment – median (IQR)				
From hospital admission – days	1.0 (0.9-2.1)	1.0 (0.6-1.7)	1.1 (0.8-1.5)	1.0 (0.7-2.0)
From ICU admission – hours	15.3 (10.8-20.0)	12.6 (5.0-20.4)	14.1 (4.3-18.6)	14.9 (6.7-20.5)
Acute respiratory support				
None/supplemental oxygen only	0/33 (0.0)	0/50 (0.0)	0/27 (0.0)	1/78 (1.3)
High flow nasal cannula	5/33 (15.2)	8/50 (16.0)	3/27 (11.1)	11/78 (14.1)
Non-invasive ventilation only	11/33 (33.3)	16/50 (32.0)	11/27 (40.7)	23/78 (29.5)
Invasive mechanical ventilation	17/33 (51.5)	26/50 (52.0)	13/27 (48.1)	43/78 (55.1)
ECMO – n/N (%)	0/33 (0.0)	0/50 (0.0)	0/27 (0.0)	0/78 (0.0)
Vasopressor support	10/33 (30.3)	13/50 (26)	5/27 (18.5)	26/78 (33.3)
APACHE II score [d] – median (IQR)	14.0 (8.0-19.0)	12.5 (7.8-20.2) N = 48	14.0 (10.2-20.8) N = 26	17.0 (9.0-22.0) N = 73
Glasgow Coma Scale [e] – mean (SD)	13.3 (4.0) N = 32	13.9 (3.1)	13.0 (4.4) N = 26	13.4 (3.7)

Abbreviations: SD, standard deviation; APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation.

[a] Unless otherwise indicated. Percentages may not sum to 100 because of rounding.

[b] Data collection not approved in Canada and continental Europe. 'Other' includes 'declined' and 'multiple'.

[c] Infection confirmed by respiratory tract PCR test.

[d] Range: 0 - 71, with higher scores indicating greater severity of illness.

[e] Range: 3 - 15, with higher scores indicating greater consciousness, using i'values closest to randomization but prior to use of sedative agents.

[f] Value closest to randomization within prior 8h. For creatinine, lactate, platelets and bilirubin, if pre-randomization value missing, the closest value within 2h post-randomization was used. Laboratory values were only added to the case report form on August 6, 2020.

Table S5: Interventions and co-interventions. The columns represent randomized treatment allocation and the rows show treatments given within this domain and other domains.

	Lopinavir-ritonavir (N=255)	Hydroxychloroquine (N=50)	Combination therapy (N=27)	Control (N=362)
Lopinavir-ritonavir				
Patients – n/N (%)	220/247 (89.1)	0/49 (0.0)	21/24 (87.5)	1/345 (0.3)
Duration – median (IQR) – days	7.0 (5.0-12.0)	-	10.0 (5.0-14.0)	10.0 (10.0-10.0)
Hydroxychloroquine				
Patients – n/N (%)	0/247 (0.0)	46/49 (93.9)	23/24 (95.8)	1/345 (0.3)
Duration – median (IQR) – days	-	7.0 (5.0-7.0)	7.0 (2.5-7.0)	21.0 (21.0-21.0)
Lopinavir-ritonavir and hydroxychloroquine combination therapy				
Patients – n/N (%)	0/247 (0.0)	0/49 (0.0)	20/24 (83.3)	0/345 (0.0)
Duration – median (IQR) – days	-	-	11.5 (5.8-14.0)	-
Corticosteroids – n/N (%)	193/254 (76.0)	21/50 (42.0)	10/26 (38.5)	291/362 (80.4)
Randomized in the Corticosteroid Domain[a]	16/27 (59.3)	20/33 (60.6)	9/10 (90.0)	44/62 (71.0)
Not randomized in the Corticosteroid Domain[b]	177/215 (82.3)	1/17 (5.9)	1/16 (6.2)	247/300 (82.3)
Tocilizumab – n/N (%)	65/247 (26.3)	11/49 (22.4)	4/24 (16.7)	89/345 (25.8)
Sarilumab – n/N (%)	9/247 (3.6)	0/49 (0.0)	0/24 (0.0)	15/345 (4.3)
Remdesivir – n/N	45/247 (18.2)	1/49 (2.0)	0/24 (0.0)	85/345 (24.6)

[a] The Corticosteroid Domain was open for recruitment between March 9 and June 17, 2020.
[b] Majority of the patients who were treated with corticosteroids but not randomized in the Corticosteroid Domain were enrolled after closure of the Corticosteroid Domain once corticosteroids were part of normal standard clinical care.

Table S6: Interventions and co-interventions for patients randomized concurrently with hydroxychloroquine interventions.

	Lopinavir-ritonavir (N=34)	**Hydroxychloroquine (N=50)**	**Combination therapy (N=27)**	**Control (N=78)**
Lopinavir-ritonavir				
Patients – n/N (%)	32/33 (97.0)	0/49 (0.0)	21/24 (87.5)	0/72 (0.0)
Duration – median (IQR) – days	10.0 (5.0-12.0)	-	10.0 (5.0-14.0)	-
Hydroxychloroquine				
Patients – n/N (%)	0/33 (0.0)	46/49 (93.9)	23/24 (95.8)	0/72 (0.0)
Duration – median (IQR) – days	-	7.0 (5.0-7.0)	7.0 (2.5-7.0)	-
Lopinavir-ritonavir and hydroxychloroquine combination				
Patients – n/N (%)	0/33 (0.0)	0/49 (0.0)	20/24 (83.3)	0/72 (0.0)
Duration – median (IQR) – days	-	-	11.5 (5.8-14.0)	-
Corticosteroids – n/N (%)	11/34 (32.4)	21/50 (42.0)	10/26 (38.5)	41/78 (52.6)
Tocilizumab – n/N (%)	3/33 (9.1)	11/49 (22.4)	4/24 (16.7)	8/72 (11.1)
Sarilumab – n/N (%)	0/33 (0.0)	0/49 (0.0)	0/24 (0.0)	0/72 (0.0)
Remdesivir – n/N	0/33 (0.0)	1/49 (2.0)	0/24 (0.0)	1/72 (1.4)

Table S7: Additional secondary and sensitivity analyses of primary outcome (Organ support-free days).

Analysis	Lopinavir-ritonavir (N=255)	Hydroxychloroquine (N=50)	Combination therapy (N=27)	Control (N=362)
Analyses to account for concurrent controls				
Secondary analysis, restricted to Antiviral-specific cohort (including control patients randomized concurrently with lopinavir-ritonavir)				
Adjusted OR -median (95% CrI)	0.80 (0.61, 1.06)	0.67 (0.42, 0.97)	0.53 (0.30, 0.90)	1
Probability of harm compared to control, %	94.3	98.4	99.1	-
Post hoc analysis restricted to patients randomized concurrently with hydroxychloroquine interventions*				
Median (IQR)	8 (0, 13)	0 (–1, 9)	– 1(–1, 7)	1 (–1, 13)
Adjusted OR -median (95% CrI)	0.76 (0.48, 1.31)	0.62 (0.37, 0.98)	0.47 (0.22, 1.02)	1
Probability of harm compared to control, %	84.9	98.1	97.2	-
Other analyses				
Secondary analysis, restricted to Unblinded Non-negative cohort				
Adjusted OR -median (95% CrI)	0.83 (0.61, 1.15)	0.53 (0.30, 0.87)	0.44 (0.23, 0.81)	1
Probability of harm compared to control, %	87.1	99.7	99.6	-
Sensitivity analysis, restricted to Unblinded cohort with removal of site and time from the model				
Adjusted OR -median (95% CrI)	0.80 (0.59, 1.08)	0.51 (0.31, 0.79)	0.40 (0.23, 0.70)	1
Probability of harm compared to control, %	93.5	99.9	>99.9	-
Sensitivity analysis, restricted to per protocol cohort, with no adjustment for intervention assignment in other domains				
Adjusted OR -median (95% CrI)	0.74 (0.56, 0.99)	0.68 (0.43, 0.99)	0.50 (0.28, 0.87)	1
Probability of harm compared to control, %	98.0	97.9	99.3	-
Sensitivity analysis with less informative prior on interaction effects, conducted on the REMAP-CAP Severe State cohort				
Adjusted OR -median (95% CrI)	0.69 (0.51, 0.96)	0.55 (0.32, 0.82)	0.37 (0.20, 0.68)	1
Probability of harm compared to control, %	98.7	99.8	99.9	-
Exploratory post-hoc analysis, restricted to Unblinded cohort, with no borrowing between antiviral interventions				
Adjusted OR -median (95% CrI)	0.81 (0.60, 1.09)	0.51 (0.31, 0.80)	0.41 (0.23, 0.72)	1
Probability of harm compared to control, %	91.6	99.8	99.9	-

* This analysis was restricted to patients randomized concurrently with hydroxychloroquine interventions (Lopinavir-ritonavir n= 34, Hydroxychloroquine n=50, combination therapy n=27 and control n=78).

Additional results are reported in the Statistical Analysis Committee Primary Analysis Report, and the ITSC Secondary Analysis Report.
Models are structured such that a higher OR is favorable.
CrI - credible interval; OR - odds ratio.

Table S8: Additional secondary and sensitivity analyses of hospital survival.

Analysis	Lopinavir-ritonavir (N=255)	Hydroxychloroquine (N=50)	Combination therapy (N=27)	Control (N=362)
Analyses to account for concurrent controls				
Secondary analysis, restricted to Antiviral-specific cohort (including control patients randomized concurrently with lopinavir-ritonavir)				
Adjusted OR -median (95% CrI)	0.70 (0.49, 1.01)	0.60 (0.31, 0.96)	0.41 (0.19, 0.84)	1
Probability of harm compared to control, %	97.1	98.4	99.3	-
Post hoc analysis restricted to patients randomized concurrently with hydroxychloroquine interventions*				
n/N (%)	8/33 (24.2)	17/49 (34.7)	13/27 (50)	21/77 (27.3)
Adjusted OR -median (95% CrI)	0.65 (0.37, 1.22)	0.58 (0.31, 1.02)	0.38 (0.14, 1.02)	1
Probability of harm compared to control, %	91.8	97.1	97.2	-
Other analyses				
Secondary analysis, restricted to Unblinded Non-negative Cohort				
Adjusted OR -median (95% CrI)	0.68 (0.46, 1.01)	0.52 (0.25, 0.87)	0.34 (0.16, 0.74)	1
Probability of harm compared to control, %	97.1	99.5	99.7	-
Sensitivity analysis, restricted to Unblinded cohort with removal of site and time from the model				
Adjusted OR -median (95% CrI)	0.69 (0.49, 0.98)	0.57 (0.32, 0.87)	0.38 (0.19, 0.73)	1
Probability of harm compared to control, %	98.1	99.5	99.8	-
Secondary analysis, restricted to per protocol cohort, with no adjustment for intervention assignment in other domains				
Adjusted OR -median (95% CrI)	0.67 (0.47, 0.97)	0.63 (0.35, 1.02)	0.42 (0.20, 0.87)	1
Probability of harm compared to control, %	98.3	97.1	98.9	-
Post hoc sensitivity analysis with less informative prior on interaction effects, conducted on the Unblinded cohort				
Adjusted OR -median (95% CrI)	0.71 (0.48, 1.04)	0.65 (0.34, 1.08)	0.28 (0.11, 0.71)	1
Probability of harm compared to control, %	95.8	95.5	99.7	-
Exploratory post-hoc analysis, restricted to Unblinded cohort, with no borrowing between antiviral interventions				
Adjusted OR -median (95% CrI)	0.71 (0.48, 1.04)	0.50 (0.26, 0.93)	0.35 (0.17, 0.73)	1
Probability of harm compared to control, %	95.8	98.3	99.8	-

Additional results are reported in the Statistical Analysis Committee Primary Analysis Report, and the ITSC Secondary Analysis Report.
Models are structured such that a higher OR is favorable.
CrI - credible interval; OR - odds ratio.

Table S9: Subgroup analyses of primary outcome (Organ support-free days).

Analysis	Pooled Antiviral Therapy (N=332)	Control (N=362)
Secondary Analysis according to baseline mechanical ventilation status		
Not mechanically ventilated		
n	220	247
Median (IQR), days	9 (–1, 16)	10 (–1, 16)
Adjusted OR -median (95% CrI)	0.81 (0.59, 1.11)	1
Probability of harm compared to control, %	90.2	-
Mechanically ventilated		
n	104	106
Median (IQR), days	0 (–1, 4)	0 (–1, 8)
Adjusted OR -median (95% CrI)	0.58 (0.38, 0.88)	1
Probability of harm compared to control, %	99.4	-
Secondary Analysis according to baseline shock status		
No shock		
n	261	281
Median (IQR), days	5 (–1, 15)	8 (–1, 16)
Adjusted OR -median (95% CrI)	0.83 (0.62, 1.11)	1
Probability of harm compared to control, %	89.6	-
Shock		
n	63	72
Median (IQR), days	–1 (–1, 0)	0 (–1, 11)
Adjusted OR -median (95% CrI)	1.00 (0.14, 6.98)	1
Probability of harm compared to control, %	50.1	-

These analyses were conducted on the Antiviral-specific cohort.
Models are structured such that a higher OR is favorable.
CrI - credible interval; OR - odds ratio.

Table S10: Subgroup Analyses of hospital survival.

Analysis	Pooled Antiviral Therapy (N=255)	Control (N=362)
Secondary Analysis according to baseline mechanical ventilation status		
Not mechanically ventilated		
n/N (%)	68/220 (30.9%)	64/247 (25.9%)
Adjusted OR -median (95% CrI)	0.82 (0.54, 1.27)	1
Probability of harm compared to control, %	81.7	-
Mechanically ventilated		
n/N (%)	50/104 (48.1%)	42/106 (39.6%)
Adjusted OR -median (95% CrI)	0.46 (0.27, 0.80)	1
Probability of harm compared to control, %	99.7	-
Secondary Analysis according to baseline shock status		
No shock		
n/N (%)	84/261 (32.2%)	74/281 (26.3%)
Adjusted OR -median (95% CrI)	0.80 (0.55, 1.18)	1
Probability of harm compared to control, %	86.7	-
Shock		
n/N (%)	34/63 (54%)	32/72 (44.4%)
Adjusted OR -median (95% CrI)	1.00 (0.14, 7.05)	1
Probability of harm compared to control, %	50.1	-

These analyses were conducted on the Antiviral-specific cohort.
Models are structured such that a higher OR is favorable.
CrI - credible interval; OR - odds ratio.

Table S11: Interactions between the effects of different COVID-19 antiviral therapies (lopinavir−ritonavir, hydroxychloroquine and combination therapy) and corticosteroids and between COVID-19 antiviral therapies and IL-6ra receptor antagonists (tocilizumab, sarilumab) on organ support-free days. The adjusted OR (95%CrI) for the interaction are reported for the primary model (see also the Statistical Analysis Committee Primary Analysis Report) and with a weaker prior on the interaction term for combination therapy (see also the ITSC Secondary Analysis Report). There was no meaningful interaction between treatment with lopinavir-ritonavir, hydroxychloroquine or combination therapy and the effects of corticosteroids or IL-6 receptor antagonists on organ support-free days.

	Adjusted OR (95%CrI) for the interaction- Primary model	**Adjusted OR (95%CrI) for the interaction- with a weaker prior on the interaction term for combination therapy**
Lopinavir−ritonavir and corticosteroids	1.01 (0.92, 1.11)	1.01 (0.92, 1.11)
Hydroxychloroquine and corticosteroids	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
Combination therapy and corticosteroids	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
Lopinavir−ritonavir and IL-6 receptor antagonist	1.01 (0.92, 1.11)	1.01 (0.91, 1.11)
Hydroxychloroquine and IL-6 receptor antagonist	1.00 (0.91, 1.11)	1.00 (0.91, 1.10)
Combination therapy and IL-6 receptor antagonist	1.00 (0.91, 1.11)	1.00 (0.91, 1.10)

Table S12: Interactions between the effects of different COVID-19 antiviral therapies (lopinavir−ritonavir, hydroxychloroquine and combination therapy) and corticosteroids and between COVID-19 antiviral therapies and IL-6ra receptor antagonists (tocilizumab, sarilumab) on hospital survival. The adjusted OR (95%CrI) for the interaction are reported for the primary model (see also the Statistical Analysis Committee Primary Analysis Report) and with a weaker prior on the interaction term for combination therapy (see also the ITSC Secondary Analysis Report). There was no meaningful interaction between treatment with lopinavir-ritonavir, hydroxychloroquine or combination therapy and the effects of corticosteroids or IL-6 receptor antagonists on hospital survival.

	Adjusted OR (95%CrI) for the interaction- Primary model	**Adjusted OR (95%CrI) for the interaction- with a weaker prior on the interaction term for combination therapy**
Lopinavir−ritonavir and corticosteroids	1.00 (0.91, 1.10)	1.00 (0.90, 1.10)
Hydroxychloroquine and corticosteroids	1.00 (0.91, 1.10)	1.00 (0.91, 1.10)
Combination therapy and corticosteroids	1.00 (0.90, 1.10)	1.00 (0.91, 1.10)
Lopinavir−ritonavir and IL-6 receptor antagonist	1.00 (0.91, 1.10)	1.00 (0.91, 1.11)
Hydroxychloroquine and IL-6 receptor antagonist	1.00 (0.91, 1.10)	1.00 (0.91, 1.11)
Combination therapy and IL-6 receptor antagonist	1.00 (0.91, 1.10)	1.00 (0.91, 1.11)

IV. Supplementary Figures:

Figure S1: Empirical distribution of organ support free days (OSFD) restricted to patients randomized concurrently with hydroxychloroquine interventions in the Antiviral ITT population. Organ support-free days are displayed as horizontally stacked proportions by study group. Red represents worse values and blue represents better values.

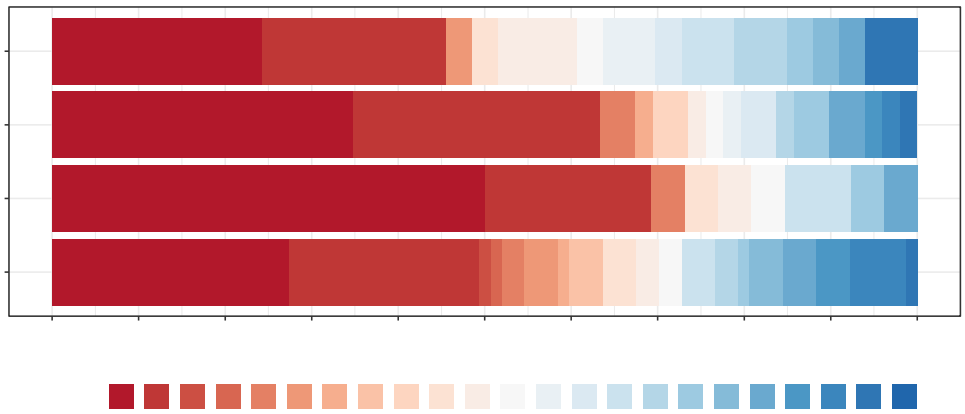
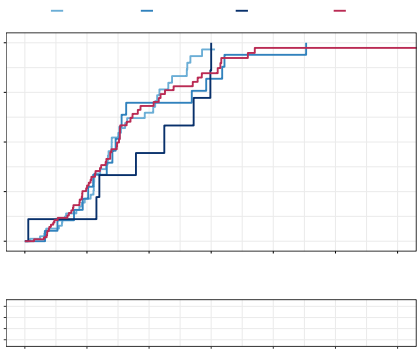
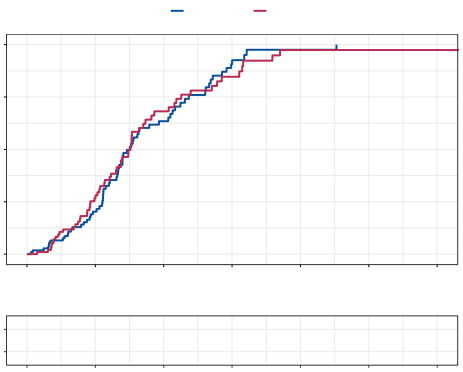


Figure S2: Empirical distribution of SARS-CoV-2 RNA time-to-clearance.

A: Empirical distribution of SARS-CoV-2 RNA time-to-clearance for lopinavir−ritonavir, hydroxychloroquine, combination therapy and control. This plot is restricted to the Antiviral-specific cohort. Full model was not performed for this outcome because of limited follow-up RT-PCR data.

B. Empirical distribution of SARS-CoV-2 RNA time-to-clearance for pooled antiviral therapy groups and control. This plot is restricted to the Antiviral-specific cohort.

A.	**B.**
	

V. Additional Information Regarding Lopinavir-ritonavir and Hydroxychloroquine for Patients with Coronavirus Disease -19, Moderate State

Table S13: Eligibility criteria – Moderate State.

A. Platform inclusion criteria

1. Adult patient admitted to hospital with acute illness due to suspected or proven pandemic (COVID-19) infection

B. Platform exclusion criteria

1. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
2. Patient is expected to be discharged from hospital today or tomorrow
3. More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection
4. Previous participation in this REMAP within the last 90 days

C. COVID-19 Antiviral Therapy Domain specific inclusion criteria- Moderate State

1. Patient meets Moderate State, defined by
2. Not being admitted to an ICU, or
3. Admitted to an ICU but not receiving organ failure support, including any of the following:
   a. Provision of invasive mechanical ventilation
   b. Provision of non-invasive mechanical ventilation (including high flow nasal cannula with a flow rate of at least 30 litres per minutes and a fractional inspired oxygen concentration of 40% or higher)
   c. Receiving infusion of vasopressor or inotropes or both
   4. Microbiological testing for SARS-CoV-2 of upper or lower respiratory tract secretions or both has occurred or is intended to occur

D. COVID-19 Antiviral Therapy Domain specific exclusion criteria

1. More than 24 hours has elapsed since ICU admission
2. 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
3. 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.
4. In areas where MERS-CoV infection is endemic, the patient has laboratory confirmed MERS-CoV infection
5. The treating clinician believes that participation in the domain would not be in the best interests of the patient

E. Lopinavir-ritonavir and hydroxychloroquine exclusion criteria

1. Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
2. 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
3. Known HIV infection will exclude a patient from receiving lopinavir-ritonavir
4. Severe liver failure will exclude a patient from receiving lopinavir-ritonavir
5. Known or suspected pregnancy will result in exclusion from interventions that include lopinavir-ritonavir or hydroxychloroquine.
6. 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
7. High clinical risk of sustained ventricular dysrhythmia will exclude a patient from receiving hydroxychloroquine

Table S14: Patients in the Moderate State.

Outcome/Analysis	Lopinavir-ritonavir (N=6)	Hydroxychloroquine (N=12)	Combination therapy (N=0)	Control (N=14)
Primary Outcome, Organ support-free days (OSFDs)				
OSFDs, median (IQR)	16 (13- 20)	22 (6-22)	-	22 (22 -22)
Subcomponents of OSFDs				
In-hospital deaths, n (%)	1 (17%)	2 (17%)	-	2 (14%)
OSFDs in survivors, median (IQR)	18 (14-20)	22 (22 -22)	-	22 (22 -22)

OSFDs for patients who received no organ support in the ICU were coded as 22 days
OSFD - organ support-free day; IQR - interquartile range.

REMAP-CAP (REMAP-COVID)

Analysis of COVID-19 Antiviral Domain

February 11, 2021

Contents

1 Introduction

1.1 Overview of the Adaptive Design

This trial is a Randomized, Embedded, Multifactorial Adaptive Platform (REMAP) trial that was originally designed to investigate treatments for Community-Acquired Pneumonia (CAP). The platform trial has the ability to investigate multiple interventions within multiple domains, across different patient strata. The number of interventions, domains, and strata may increase or decrease as the trial progresses. The platform trial includes a pandemic stratum that was activated when COVID-19 emerged. The pandemic stratum-specific protocol details are provided in a Pandemic Appendix to the Core (PAtC) protocol. The PAtC investigates therapies for patients with pandemic infection that are classified as suspected or proven (PISOP). This report focuses on the COVID-19 PISOP stratum.

For the PISOP stratum, patients may be randomized to interventions while they are in a Severe disease state or a Moderate disease state. State definitions are in the PAtC. Patients initially randomized in a Moderate state may progress in their disease severity, and subsequently meet the criteria for Severe state, and have additional randomization and reveal of interventions for Severe state domains.

1.2 Purpose of this Report

This report contains the final analysis of the COVID-19 Antiviral domain in Severe state.

The international trial steering committee (ITSC) halted randomization to the hydroxychloroquine arms (including hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir) in the COVID-19 Antiviral domain in the PISOP stratum (both Moderate and Severe) on May 23, 2020 based on concerns regarding the safety and efficacy of hydroxychloroquine which was later substantiated by the press release of the results of the RECOVERY trial. Randomization continued to the remaining interventions within the domain until November 19, 2020 following the disclosure from the Data and Safety Monitoring Board (DSMB) that the lopinavir/ritonavir intervention had met the pre-specified threshold for futility in Severe state. The ITSC prepared a statistical analysis plan (SAP) for the COVID-19 Antiviral domain and provided this plan to the Statistical Analysis Committee (SAC).

Although the ITSC will be unblinded to the interventions within the COVID-19 Antiviral domain, they will not be unblinded to the other domains to which patients have been randomized (except the corticosteroid domain and the two IL-6ra interventions within the COVID-19 Immune Modulation domain, which were previously unblinded). The fully unblinded SAC performed the set of analyses that use the full statistical model including data from all domains in the Severe PISOP stratum. This report summarizes the data and the results for the antiviral interventions resulting from the analyses using the full statistical model. This report is restricted to summaries and results pertaining to the unblinded interventions. Summaries and results for other ongoing domains are contained in a separate unblinded report only viewed by the SAC and DSMB.

The model results presented in this report pertain to patients randomized in Severe state. Descriptive summaries are provided for patients randomized to the COVID-19 Antiviral domain in Moderate state (see Section 7), but these data are not included in the model.

1.3 Endpoints

1.3.1 Primary Endpoint: Organ-Support Free-Days (OSFD)

The primary endpoint is organ support-free days (OSFD) (days alive and free of ICU-based respiratory or cardiovascular support) within 21 days, where patients who die before discharge from the index hospitalization, and before day 90, were assigned a -1 day, even if the death occurred after day 21. The cumulative hours of organ support are computed and then rounded to the nearest day. Patients who receive no organ support in an ICU will be coded as 22 days. An outcome of 22 days is not possible for patients in Severe

state. An outcome of 21 organ-support free-days is only possible in the Severe state if the patient had less than 12 hours of organ support.

1.3.2 Secondary Endpoint: In-Hospital Mortality

The secondary endpoint is a dichotomous endpoint of in-hospital mortality, i.e. those patients with a -1 for the OSFD endpoint.

1.4 Vocabulary

- **Domain:** a specific set of competing alternative interventions within a common clinical mode
- **Intervention:** is a treatment option that is subject to variation in clinical practice (comparative effectiveness intervention) or has been proposed for introduction into clinical practice (experimental intervention) and also is being subjected to experimental manipulation within the design of a REMAP.
- **Regimen:** Each patient is assigned a single intervention from each domain. The regimen is the combination of assigned interventions across the domains.
- **Immediate Reveal Domain:** is one for which all participants are eligible, the allocation status is made known, and the intervention is initiated at the time of randomization.
- **Delayed Reveal Domain:** is one for which all participants received a randomization assignment, but the allocation status is only made known and the intervention initiated if and when eligibility occurs. This occurs for example, when a domain is appropriate only for patients in a certain disease state and the patient transitions to that disease state.
- **Deferred Reveal Domain:** is one for which patients receive a randomization assignment and the allocation status is made known based on eligibility criterion known at the time of randomization, but additional information to assess that eligibility becomes known after some time. This occurs for example, when a test results confirming an eligibiltiy criterion are returned after some time.
- **Nest:** A grouping of interventions within a domain that are modeled hierarchically in order to allow for borrowing among the interventions effect estimates.
- **State:** Defined by the disease characteristics of the patient and may change over time as the disease progresses. States are used to define eligibility for certain domains.

1.5 Current Trial Status

Figure 1.1 gives an overview of the interventions, domains, and strata currently being investigated in the COVID-19 pandemic portion of the trial. Each intervention is represented by a colored box, with similar colors used for interventions within the same domain. The figure also indicates features of the statistical model. For example, interactions are represented with an arrow and star (★). Within a domain, interventions that are nested within a hierarchical model are grouped within a curly bracket. Interventions that are closed to enrollment are indicated by an "X". Table 1.1 is a companion to the current state figure, and provides the mapping of intervention codes to the actual intervention names (e.g. X2 = Lopinavir/ritonavir).

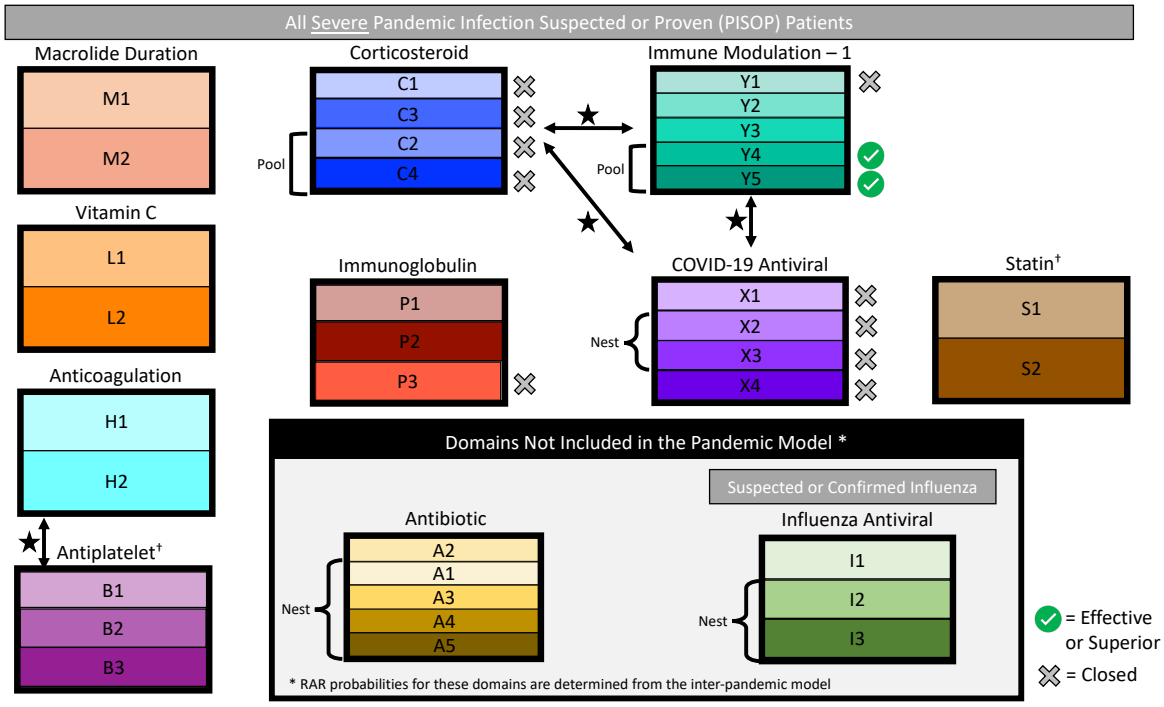


Figure 1.1: Current state of the **Severe State** pandemic domains and interventions. Each colored box represents an intervention, grouped by domain, with similar colors used for interventions within the same domain. Domains connected with an arrow and indicated with a star (★) will have interaction terms fit between the interventions in those domains. Within a domain, interventions that are grouped with a curly bracket are part of a nest whose main effects are estimated with a hierarchical model. Interventions that are closed to enrollment are indicated by a grey "X". Interventions that have met an Efficacy or Superiority trigger are indicated by a green checkmark. Closure of the Antiviral domain occurred simultaneously with the closure of the control arm (Y1) in the Immune Modulation domain and the superiority trigger of tocilizumab (Y4). The superiority trigger for sarilumab (Y5) occurred subsequently and results were publicly disclosed along with tocilizumab. As indicated by the dagger (†), the Statin and Antiplatelet domains are open for randomization but do not contribute data to the model for the current analysis.

Table 1.1: List of all interventions to which a patient may be allocated in **Severe State**.

Code	Intervention	Status
Antibiotic		
A1	Ceftriaxone + Macrolide	
A2	Moxifloxacin or Levofloxacin	
A3	Piperacillin-Tazobactam + Macrolide	
A4	Ceftaroline + Macrolide	
A5	Amoxicillin-Clavulanate + Macrolide	
Macrolide Duration		
M1	Standard course (3 to 5 days)	
M2	Extended course (14 days)	
Corticosteroid		
C1	No corticosteroids	Closed
C2	Hydrocortisone (50mg)	Closed
C3	Shock dependent hydrocortisone	Closed
C4	High-dose hydrocortisone (100mg)	Closed
Influenza Antiviral		
I1	No antiviral	
I2	Oseltamivir 5 days	
I3	Oseltamivir 10 days	
COVID-19 Antiviral		
X1	No antiviral for COVID-19	Closed
X2	Lopinavir/ritonavir	Closed
X3	Hydroxychloroquine	Closed
X4	Hydroxychloroquine + lopinavir/ritonavir	Closed
COVID-19 Immune Modulation		
Y1	No immune modulation for COVID-19	Closed
Y2	Interferon-Beta-1a	
Y3	Anakinra	
Y4	Tocilizumab	Effective
Y5	Sarilumab	Effective
COVID-19 Immunoglobulin		
P1	No Immunoglobulin against COVID-19	
P2	Convalescent plasma	
P3	Delayed convalescent plasma	Closed
COVID-19 Therapeutic Anticoagulation		
H1	Standard practice thromboprophylaxis	
H2	Therapeutic anticoagulation	
Vitamin C		
L1	No vitamin C	
L2	Vitamin C	
Statin Therapy†		
S1	No simvastatin	
S2	Simvastatin	
COVID-19 Antiplatelet†		
B1	No antiplatelet therapy	
B2	Aspirin	
B3	P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor)	

† Domain open for randomization but data not yet available for inclusion in the model

1.6 Analysis Population

This report restricts the analysis population to consented patients with pandemic infection suspected or proven (PISOP) that were randomized for the first time in Severe disease state (excluding patients first randomized in Moderate state that progressed to Severe state) on or before 12:00 UTC on November 19, 2020. This population is defined as the **REMAP-CAP COVID-19 severe state ITT population**. The patient population breakdown is as follows:

- 2328 PISOP consented patients randomized to at least one domain in any disease state (Moderate or Severe) on or before 12:00 UTC on November 19, 2020.
  - 1991 PISOP consented patients randomized initially in Severe disease state (never randomized in Moderate state) to at least one domain on or before 12:00 UTC on November 19, 2020
    - ➔ 1928 PISOP consented patients randomized initially in Severe disease state (never randomized in Moderate state) to at least one domain on or before 12:00 UTC on November 19, 2020 for whom 21 days have elapsed since randomization and there is a known outcome on the 21-day organ-support free-days endpoint
  - 694 PISOP consented patients randomized initially in Severe disease state (never randomized in Moderate state) to the COVID-19 Antiviral domain on or before 12:00 UTC on November 19, 2020
    - ➔ 677 PISOP consented patients randomized initially in Severe disease state (never randomized in Moderate state) to the COVID-19 Antiviral domain on or before 12:00 UTC on November 19, 2020 for whom 21 days have elapsed since randomization and there is a known outcome on the 21-day organ-support free-days endpoint

Thus the analysis model is run on the 1928 PISOP Severe patients for whom 21 days have elapsed since randomization and there is a known outcome on the 21-day OSFD endpoint. This count excludes patients who were initially randomized while in Moderate State and later progressed to Severe State with additional randomized assignments for Severe state domains.

Patients initially randomized in Moderate state are not included in the analysis population and do not contribute to the statistical model. However, Section 7 provides descriptive summaries for patients randomized within the COVID-19 Antiviral domain in Moderate state.

These counts exclude patients that withdrew consent for the use of their data. The patients who withdrew consent do not appear in the SAC data export, so no information is available to the SAC regarding when in the process (e.g. before or after eligibility assessment) consent was withdrawn.

2 Data Summaries

2.1 Overview of Descriptive Data Summaries

Data for the Severe PISOP patient population will be summarized, both across all Severe state PISOP patients (without respect to intervention assignments), and at the intervention level for the interventions in the COVID-19 Antiviral domain. A description of each of the summary tables and figures is provided here.

Summary of the availability of data:

- **Number Eligible:** Eligibility is assessed both at the domain level and the intervention level. We tabulate the number of patients eligible for the domain, and within each category of domain eligibility, the number of patients eligible for each intervention. Eligibility captures both the patient meeting the inclusion criteria, and the domain or intervention being available and active at their site.
- **Number Assigned:** We tabulate the number of patients assigned to each intervention, by eligibility category. No randomized assignment can be given when a patient is ineligible for a domain, or when a patient is eligible for only one intervention within a domain. A patient must be eligible for at least two interventions within a domain to receive a randomized assignment.
- **Number Revealed:** Among the patients eligible and assigned to each intervention, we tabulate the number of patients whose assignment was revealed. Reveal means that the randomization assignment was made known and the patient then commences treatment according to their assigned intervention.

- **Number Past 21 Days:** Among the patients eligible and assigned to each intervention, we tabulate the number of patients who have had the opportunity to complete the 21 days of follow-up for the primary endpoint. A patient must have been in the trial at least 21 days to be included in the analysis.
- **Number Missing:** Among the patients eligible and assigned to each intervention, we tabulate the number of patients who have completed 21 days of follow-up but do not have an outcome available on the primary endpoint.
- **Number Known:** Among the patients eligible and assigned to each intervention, we tabulate the number of patients who have completed 21 days of follow-up and have a known outcome on the primary endpoint.
- For the subjects that are eligible for the domain, a bar chart summarizes the number and percent of patients assigned to each intervention.

Summary of the observed outcomes data:

For patients that are eligible for the domain and assigned to an intervention, we repeat the tabulation of the number of patients assigned to an intervention and with a known outcome on the 21-day endpoint. Additionally, we provide summaries of the following:

- **Number Deaths:** The number of in-hospital deaths, where the death corresponds to -1 on the OSFD endpoint.
- **Mortality Rate:** We calculate the observed in-hospital mortality rate as the number of in-hospital deaths out of the total number of patients with a known 21-day outcome.
- **OSFD median (IQR):** Among the patients with a known 21-day outcome, we compute the 25th, 50th, and 75th percentiles of the Organ-Support Free-Days endpoint. The interquartile range (IQR) is shown in parentheses as the range between the 25th and 75th percentiles.
- **Conditional OSFD:** Among the patients with a known 21-day outcome that were not deceased, we compute the 25th, 50th, and 75th percentiles of the Organ-Support Free-Days endpoint. The interquartile range (IQR) is shown in parentheses as the range between the 25th and 75th percentiles.
- For the subjects that are eligible for the domain, we show a plot of the cumulative distribution function for the OSFD endpoint for each intervention within the domain.
- For the subjects that are eligible for the domain, we show a stacked bar plot for the OSFD outcomes for each intervention within the domain. Red represents worse outcomes and blue represents better outcomes.

2.2 Overall Severe State Summaries

Figure 2.1 displays the distribution of outcomes on the primary endpoint for all patients in the analysis population (across all domains), without respect to treatment assignments. Table 2.1 provides descriptive summaries of the OSFD and in-hospital mortality outcomes for all patients in the analysis population.

Table 2.1: Overall summary of the OSFD and In-Hospital mortality data

Participant Group	Number Assigned (N)	Number Past Day 21	Number Known (n)	Number Deaths (y)	Mortality Rate (y/n)	OSFD median (IQR)	Conditional* OSFD median (IQR)
COVID Severe State	2696	1991	1928	642	0.333	3.00 ($-1.00 - 15.00$)	13.00 ($3.00 - 17.00$)

* Conditional OSFD reports the median and IQR for subjects that did not die.

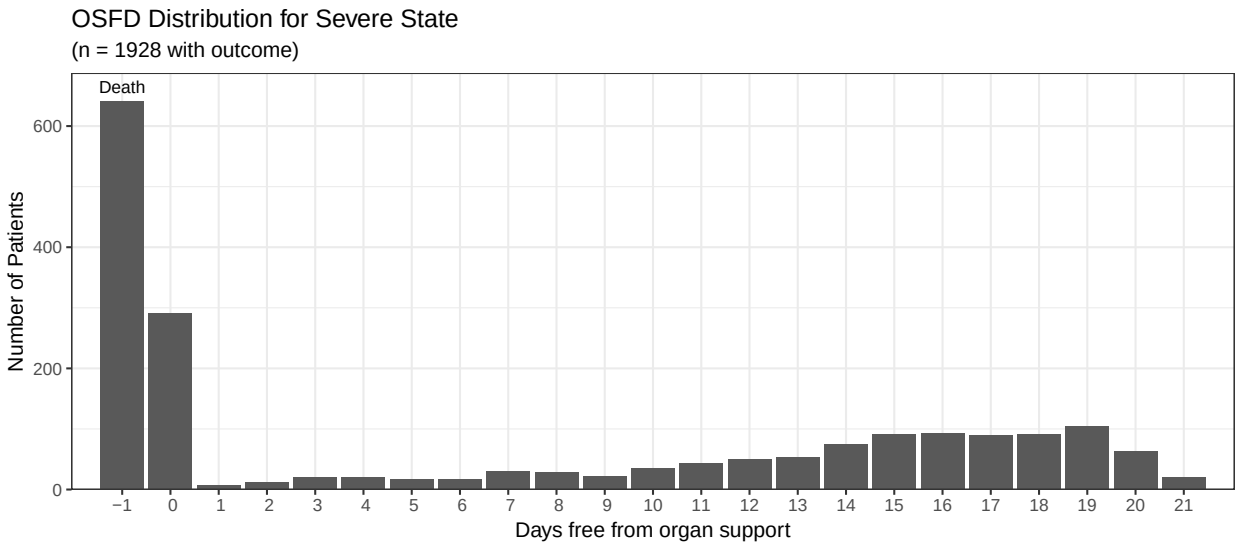


Figure 2.1: Overall distribution of the primary organ support free days endpoint.

2.3 COVID-19 Antiviral Domain

2.3.1 Description of the COVID-19 Antiviral domain

The COVID-19 Antiviral domain includes a total of 4 interventions. This domain:

- started enrollment on April 8, 2020;
- closed randomization in Severe state on November 19, 2020. Interventions X3 (hydroxychloroquine) and X4 (hydroxychloroquine + lopinavir/ritonavir) were closed to randomization prior to meeting any statistical triggers, but in reaction to emerging information from external sources; Intervention X2 (lopinavir/ritonavir) was closed to randomization after meeting a futility trigger at an interim;
- was an immediate reveal domain with immediate initiation of the randomized assignment, unless prospective agreement to participate is required, in which case it was deferred reveal domain;
- has no strata identified as being of interest. Analyses and response adaptive randomization were applied to all randomized patients in Severe State;
- has possible interactions modeled with the corticosteroid domain and with the COVID-19 immune modulation domain;
- includes one intervention that is a combination of the other two active interventions;
- includes a possible interaction effect for the combination of two interventions;
- has one nest, comprised of the two active antiviral interventions when not administered in combination.

2.3.2 Observed data within the COVID-19 Antiviral domain

Table 2.2: Summary of the availability of data in the **COVID-19 Antiviral** domain (**Severe** state)

Intervention	Number Eligible	Number Assigned	Number Revealed	Number Past Day 21	Number Missing	Number Known
Eligible for domain: N=701						
No assignment		7	0	7	2	5
No antiviral for COVID-19	701	362	362	362	9	353
Lopinavir/ritonavir	641	255	255	255	6	249
Hydroxychloroquine	160	50	50	50	1	49
Hydroxychloroquine + lopinavir/ritonavir	98	27	27	27	1	26
Not eligible for domain: N=442						
No assignment		442	0	442	13	429
Domain not active/not available: N=848						
No assignment		848	0	848	31	817

Table 2.3: Summary of the OSFD and In-Hospital mortality data for patients that were eligible for the **COVID-19 Antiviral** domain (**Severe** State)

Intervention	Number Assigned (N)	Number Known (n)	Number of Deaths (y)	Mortality Rate (y/n)	OSFD median (IQR)	Conditional* OSFD median (IQR)
No antiviral for COVID-19	362	353	106	0.300	6.00 (−1.00 – 16.00)	14.00 (3.00 – 18.00)
Lopinavir/ritonavir	255	249	88	0.353	4.00 (−1.00 – 15.00)	14.00 (7.00 – 17.00)
Hydroxychloroquine	50	49	17	0.347	0.00 (−1.00 – 9.00)	4.00 (0.00 – 12.50)
Hydroxychloroquine + lopinavir/ritonavir	27	26	13	0.500	−0.50 (−1.00 – 6.75)	8.00 (0.00 – 13.00)

* Conditional OSFD reports the median and IQR for subjects that did not die.

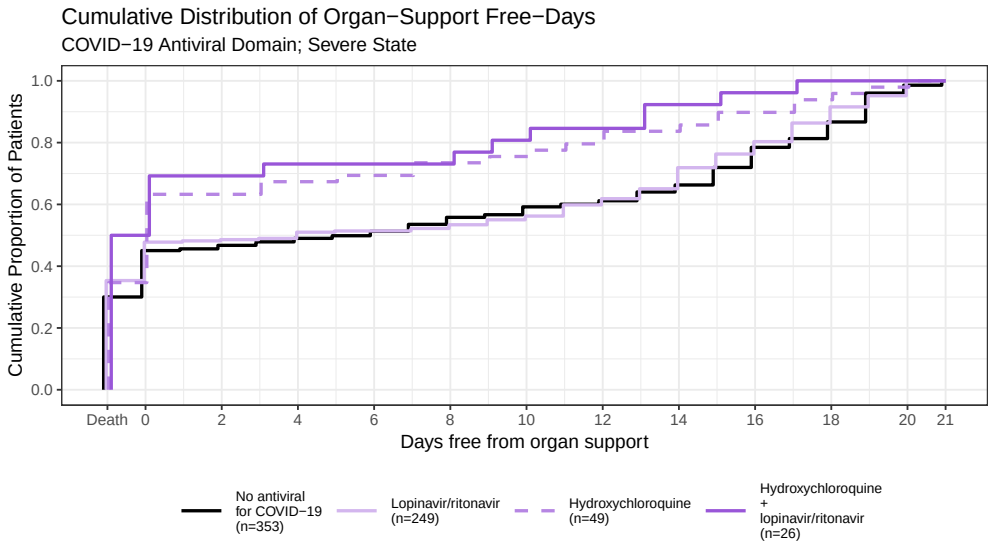


Figure 2.2: Empirical cumulative distribution of organ support free days for the **COVID-19 Antiviral** domain. This plot is restricted to patients who were eligible for the domain in **Severe** State

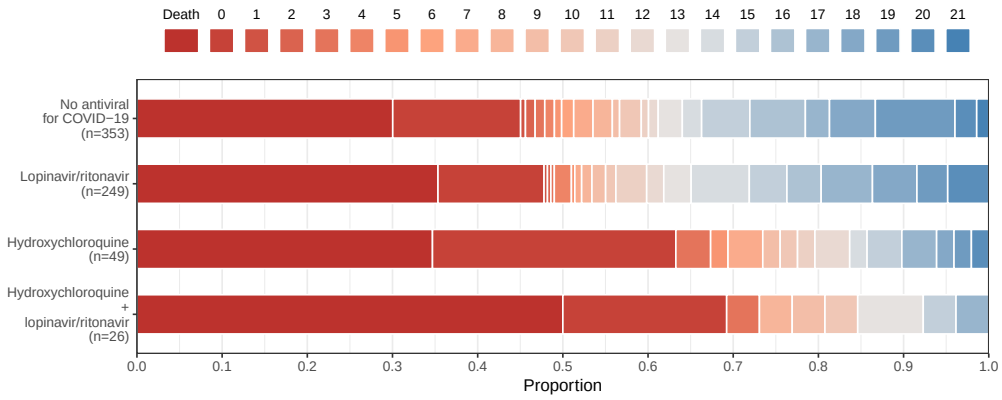


Figure 2.3: Stacked proportion of organ support free days for the IL-6ra and control interventions in the **COVID-19 Antiviral** domain. Red represents worse outcomes and blue represents better outcomes. This plot is restricted to include only patients who were eligible for the domain and received a randomized assignment to the domain in **Severe** State

3 Analysis Results and Conclusions

3.1 Definition of Statistical Triggers

The adpative design defines several statistical triggers within the trial, that at any analysis of the trial would result in public disclosure and declaration of a platform conclusion. The following statistical triggers were defined for the COVID-19 Antiviral domain:

1. **Domain Superiority.** If a single intervention within a domain has at least a 99% posterior probability of being in the best regimen for patients in the severe state of the PISOP stratum, this would trigger superiority of that intervention.

2. **Intervention Efficacy.** If an intervention is deemed to have at least a 99% posterior probability of being superior to the control, then a declaration of efficacy of that intervention would be declared. This statistical trigger is active for each of the non-control arms in the domain.

3. **Intervention Equivalence.** If two non-control interventions have a 90% probability of equivalence — that is, that the odds ratio comparing the two interventions is between 0.83 (inverse of 1/1.2 and 1.2) — then a declaration of intervention equivalence would be made.

4. **Intervention Futility.** If an intervention is deemed to have less than 5% posterior probability of at least a 20% odds ratio improvement compared to the control, then a declaration of futility of that intervention would be declared. This statistical trigger is active for each of the non-control arms in the domain.

5. **Intervention Inferiority.** If an intervention has low posterior probability of being the optimal intervention within a state, then that intervention will be deemed inferior. Specifically, an intervention is considered inferior if the probability of being the optimal intervention is less than $0.01/(J_d - 1)$, where J_d is the number of interventions within the domain. For the COVID-19 Antiviral domain, there were initially $J = 4$ interventions. After the closure of the two hydroxychloroquine arms, there were $J = 2$ interventions in the domain.

3.2 Overview of the model results

The OSFD endpoint is an ordered categorical endpoint that is modeled with a cumulative logistic model. The median and 95% Bayesian credible intervals for the odds-ratios are presented for each intervention,

relative to the control intervention in the domain. The model is structured so that an odds-ratio greater than 1 implies patient benefit. We also present the posterior mean and standard deviation, but caution that the mean tends to be higher than the median due to the skewed nature of the posterior distribution.

3.3 Primary analysis for OSFD

Table 3.1 summarizes the model-estimated odds-ratios for the covariates in the model, including age categories, sex at birth, and time effects.

Table 3.1: Model-estimated Odds-Ratios for the **OSFD** endpoint; REMAP-CAP COVID-19 severe state ITT population

Odds-Ratio Parameter	Median	95% Credible Interval	Mean (SD)
≤ 39	4.02	2.87 – 5.67	4.08 (0.73)
40-49	2.39	1.82 – 3.15	2.41 (0.34)
50-59	1.87	1.50 – 2.34	1.88 (0.21)
60-69 (referent)	1.00	$NA - NA$	1.00 (NA)
70-79	0.53	0.42 – 0.67	0.53 (0.07)
80+	0.37	0.25 – 0.55	0.38 (0.08)
Male (referent)	1.00	$NA - NA$	1.00 (NA)
Female	1.12	0.94 – 1.33	1.12 (0.10)
Time-0 (referent)	1.00	$NA - NA$	1.00 (NA)
Time-1	1.00	0.84 – 1.14	1.00 (0.07)
Time-2	1.04	0.81 – 1.28	1.04 (0.12)
Time-3	1.16	0.88 – 1.55	1.17 (0.17)
Time-4	1.27	0.93 – 1.79	1.29 (0.22)
Time-5	1.35	0.98 – 1.91	1.38 (0.24)
Time-6	1.41	1.00 – 1.97	1.43 (0.25)
Time-7	1.46	1.05 – 2.06	1.49 (0.26)
Time-8	1.52	1.09 – 2.17	1.55 (0.27)
Time-9	1.50	1.07 – 2.15	1.53 (0.28)
Time-10	1.35	0.93 – 1.95	1.37 (0.26)
Time-11	1.22	0.80 – 1.80	1.24 (0.26)
Time-12	1.11	0.71 – 1.71	1.14 (0.26)
Time-13	1.08	0.67 – 1.73	1.11 (0.27)
Time-14	1.10	0.65 – 1.85	1.14 (0.31)
Time-15	1.12	0.59 – 2.16	1.19 (0.40)
Lopinavir/ritonavir	0.73	0.55 – 0.99	0.74 (0.11)
HCQ	0.57	0.35 – 0.83	0.58 (0.13)
Lopinavir/ritonavir + HCQ	0.41	0.24 – 0.72	0.43 (0.12)
Lopinavir/ritonavir * fixed-dose steroids	1.01	0.92 – 1.11	1.01 (0.05)
HCQ * fixed-dose steroids	1.00	0.91 – 1.10	1.00 (0.05)
(Lopinavir/ritonavir + HCQ) * fixed-dose steroids	1.00	0.91 – 1.10	1.00 (0.05)
Lopinavir/ritonavir * IL-6	1.01	0.92 – 1.11	1.01 (0.05)
HCQ * IL-6	1.00	0.91 – 1.11	1.00 (0.05)
(Lopinavir/ritonavir + HCQ) * IL-6	1.00	0.91 – 1.11	1.00 (0.05)

Note: For referent categories, the Odds-Ratio is 1.0 by definition. Time bucket X is the Xth 2-week interval prior to the most recent month, and Odds-Ratios are relative to the most recent month.

Table 3.2: Posterior Probabilities for the **OSFD** endpoint; REMAP-CAP COVID-19 severe state ITT population

Quantity of Interest	Posterior Probability
Prob(in optimal) lopinavir/ritonavir	0.0282
Prob(OR > 1) lopinavir/ritonavir	0.0200
Prob(OR < 1.2) lopinavir/ritonavir	0.9988
Prob(in optimal) HCQ	0.0030
Prob(OR > 1) HCQ	0.0012
Prob(OR < 1.2) HCQ	1.0000
Prob(in optimal) lopinavir/ritonavir + HCQ	0.0014
Prob(OR > 1) lopinavir/ritonavir + HCQ	0.0008
Prob(OR < 1.2) lopinavir/ritonavir + HCQ	1.0000
Prob(OR > 1) lopinavir/ritonavir * fixed-dose corticosteroid	0.6025
Prob(OR > 1) lopinavir/ritonavir * IL-6	0.5669
Prob(OR > 1) HCQ * fixed-dose corticosteroid	0.4984
Prob(OR > 1) HCQ * IL-6	0.5090
Prob(OR > 1) (lopinavir/ritonavir + HCQ) * fixed-dose corticosteroid	0.4928
Prob(OR > 1) (lopinavir/ritonavir + HCQ) * IL-6	0.5258

3.4 Primary analysis for in-hospital mortality

Table 3.3: Model-estimated Odds-Ratios for the **Mortality** endpoint; REMAP-CAP COVID-19 severe state ITT population

Odds-Ratio Parameter	Median	95% Credible Interval	Mean (SD)
≤ 39	11.05	$5.64 - 23.06$	11.90 (4.54)
40-49	4.22	$2.79 - 6.70$	4.34 (0.98)
50-59	3.01	$2.20 - 4.14$	3.05 (0.50)
60-69 (referent)	1.00	$NA - NA$	1.00 (NA)
70-79	0.45	$0.34 - 0.61$	0.46 (0.07)
80+	0.30	$0.20 - 0.47$	0.31 (0.07)
Male (referent)	1.00	$NA - NA$	1.00 (NA)
Female	1.14	$0.90 - 1.46$	1.15 (0.14)
Time-0 (referent)	1.00	$NA - NA$	1.00 (NA)
Time-1	0.99	$0.83 - 1.14$	0.99 (0.08)
Time-2	0.99	$0.74 - 1.27$	0.99 (0.13)
Time-3	1.05	$0.74 - 1.45$	1.06 (0.18)
Time-4	1.13	$0.77 - 1.64$	1.14 (0.22)
Time-5	1.21	$0.80 - 1.82$	1.23 (0.26)
Time-6	1.29	$0.85 - 1.94$	1.31 (0.28)
Time-7	1.37	$0.91 - 2.08$	1.40 (0.30)
Time-8	1.47	$0.98 - 2.25$	1.51 (0.33)
Time-9	1.58	$1.02 - 2.52$	1.63 (0.39)
Time-10	1.58	$1.00 - 2.58$	1.63 (0.41)
Time-11	1.49	$0.90 - 2.49$	1.55 (0.41)
Time-12	1.40	$0.81 - 2.44$	1.46 (0.42)
Time-13	1.38	$0.74 - 2.53$	1.44 (0.46)
Time-14	1.41	$0.69 - 2.84$	1.51 (0.55)
Time-15	1.47	$0.62 - 3.57$	1.64 (0.77)
Lopinavir/ritonavir	0.65	$0.45 - 0.95$	0.67 (0.13)
HCQ	0.56	$0.30 - 0.89$	0.57 (0.15)
Lopinavir/ritonavir + HCQ	0.36	$0.17 - 0.73$	0.38 (0.15)
Lopinavir/ritonavir * fixed-dose steroids	1.00	$0.91 - 1.10$	1.00 (0.05)
HCQ * fixed-dose steroids	1.00	$0.91 - 1.10$	1.00 (0.05)
(Lopinavir/ritonavir + HCQ) * fixed-dose steroids	1.00	$0.90 - 1.10$	1.00 (0.05)
Lopinavir/ritonavir * IL-6	1.00	$0.91 - 1.10$	1.00 (0.05)
HCQ * IL-6	1.00	$0.91 - 1.10$	1.01 (0.05)
(Lopinavir/ritonavir + HCQ) * IL-6	1.00	$0.91 - 1.10$	1.00 (0.05)

Note: For referent categories, the Odds-Ratio is 1.0 by definition. Time bucket X is the Xth 2-week interval prior to the most recent month, and Odds-Ratios are relative to the most recent month.

Table 3.4: Posterior Probabilities for the **Mortality** endpoint; REMAP-CAP COVID-19 severe state ITT population

Quantity of Interest	Posterior Probability
Prob(in optimal) lopinavir/ritonavir	0.0148
Prob(OR $>$ 1) lopinavir/ritonavir	0.0149
Prob(OR $<$ 1.2) lopinavir/ritonavir	0.9992
Prob(in optimal) HCQ	0.0072
Prob(OR $>$ 1) HCQ	0.0061
Prob(OR $<$ 1.2) HCQ	0.9993
Prob(in optimal) lopinavir/ritonavir + HCQ	0.0019
Prob(OR $>$ 1) lopinavir/ritonavir + HCQ	0.0025
Prob(OR $<$ 1.2) lopinavir/ritonavir + HCQ	0.9993
Prob(OR $>$ 1) lopinavir/ritonavir * fixed-dose corticosteroid	0.5191
Prob(OR $>$ 1) lopinavir/ritonavir * IL-6	0.5083
Prob(OR $>$ 1) HCQ * fixed-dose corticosteroid	0.4980
Prob(OR $>$ 1) HCQ * IL-6	0.5332
Prob(OR $>$ 1) (lopinavir/ritonavir + HCQ) * fixed-dose corticosteroid	0.4916
Prob(OR $>$ 1) (lopinavir/ritonavir + HCQ) * IL-6	0.5067

3.5 Sensitivity analysis of OSFD with less informative priors on interaction effects

To assess whether results are strongly influenced by the informative priors on the interaction terms between the antiviral interventions and corticosteroids and between the antiviral interventions and IL-6ra, the model was evaluated with less informative priors on those terms.

Table 3.5: Model-estimated Odds-Ratios for the **OSFD** endpoint; REMAP-CAP COVID-19 severe state ITT population; sensitivity analysis with less informative priors on interaction effects

Odds-Ratio Parameter	Median	95% Credible Interval	Mean (SD)
≤ 39	4.01	2.83 – 5.66	4.07 (0.74)
40-49	2.38	1.82 – 3.14	2.41 (0.34)
50-59	1.87	1.49 – 2.34	1.88 (0.22)
60-69 (referent)	1.00	$NA - NA$	1.00 (NA)
70-79	0.53	0.41 – 0.68	0.53 (0.07)
80+	0.37	0.24 – 0.55	0.37 (0.08)
Male (referent)	1.00	$NA - NA$	1.00 (NA)
Female	1.12	0.93 – 1.33	1.12 (0.10)
Time-0 (referent)	1.00	$NA - NA$	1.00 (NA)
Time-1	1.00	0.85 – 1.14	1.00 (0.07)
Time-2	1.04	0.82 – 1.29	1.04 (0.12)
Time-3	1.16	0.89 – 1.58	1.18 (0.18)
Time-4	1.28	0.94 – 1.81	1.30 (0.22)
Time-5	1.36	0.98 – 1.92	1.39 (0.24)
Time-6	1.41	1.00 – 1.99	1.43 (0.25)
Time-7	1.47	1.06 – 2.08	1.49 (0.26)
Time-8	1.53	1.10 – 2.19	1.56 (0.28)
Time-9	1.50	1.06 – 2.20	1.54 (0.29)
Time-10	1.35	0.93 – 1.97	1.38 (0.26)
Time-11	1.21	0.80 – 1.81	1.24 (0.26)
Time-12	1.11	0.71 – 1.72	1.14 (0.26)
Time-13	1.07	0.67 – 1.72	1.11 (0.27)
Time-14	1.09	0.64 – 1.86	1.13 (0.31)
Time-15	1.11	0.58 – 2.16	1.17 (0.41)
Lopinavir/ritonavir	0.69	0.51 – 0.96	0.70 (0.12)
HCQ	0.55	0.32 – 0.82	0.55 (0.13)
Lopinavir/ritonavir + HCQ	0.37	0.20 – 0.68	0.39 (0.12)
Lopinavir/ritonavir * fixed-dose steroids	1.01	0.92 – 1.11	1.01 (0.05)
HCQ * fixed-dose steroids	1.00	0.91 – 1.10	1.00 (0.05)
(Lopinavir/ritonavir + HCQ) * fixed-dose steroids	1.00	0.91 – 1.10	1.00 (0.05)
Lopinavir/ritonavir * IL-6	1.25	0.73 – 2.12	1.29 (0.35)
HCQ * IL-6	1.05	0.38 – 2.89	1.20 (0.66)
(Lopinavir/ritonavir + HCQ) * IL-6	1.52	0.37 – 6.12	1.94 (1.57)

Note: For referent categories, the Odds-Ratio is 1.0 by definition. Time bucket X is the Xth 2-week interval prior to the most recent month, and Odds-Ratios are relative to the most recent month.

Table 3.6: Posterior Probabilities for the **OSFD** endpoint; REMAP-CAP COVID-19 severe state ITT population; sensitivity analysis with less informative priors on interaction effects

Quantity of Interest	Posterior Probability
Prob(in optimal) lopinavir/ritonavir	0.0785
Prob(OR > 1) lopinavir/ritonavir	0.0131
Prob(OR < 1.2) lopinavir/ritonavir	0.9996
Prob(in optimal) HCQ	0.0394
Prob(OR > 1) HCQ	0.0019
Prob(OR < 1.2) HCQ	1.0000
Prob(in optimal) lopinavir/ritonavir + HCQ	0.2038
Prob(OR > 1) lopinavir/ritonavir + HCQ	0.0006
Prob(OR < 1.2) lopinavir/ritonavir + HCQ	1.0000
Prob(OR > 1) lopinavir/ritonavir * fixed-dose corticosteroid	0.5948
Prob(OR > 1) lopinavir/ritonavir * IL-6	0.7911
Prob(OR > 1) HCQ * fixed-dose corticosteroid	0.4918
Prob(OR > 1) HCQ * IL-6	0.5396
Prob(OR > 1) (lopinavir/ritonavir + HCQ) * fixed-dose corticosteroid	0.4918
Prob(OR > 1) (lopinavir/ritonavir + HCQ) * IL-6	0.7246

3.6 Sensitivity analysis of the proportional odds assumption

An assumption of the ordinal logistic regression model being used to analyze OSFD is that effects have a *proportional* effect on log-odds. That is, a treatment effect that increases the log-odds of OSFD being greater than X is the same for all values of X. In order to assess this modeling assumption, a logistic regression model is fit to dichotomized versions of the OSFD values ($\leq X$ versus $> X$) across the possible range of OSFD values, to see if the estimated treatment effect is nearly constant. The prior distribution for the dichotomized outcomes is constructed in like manner, converting the Dirichlet distribution across OSFD values to a Beta distribution by summing across the parameter values for the corresponding OSFD ranges.

The logistic regression model is subject to poor estimation when categories in the model contain only a single outcome type (e.g. all observations are $\leq X$). With the large number of covariate effects being used in the current model, some categories of these covariate crossings may contain single outcomes, particularly as the dichotomization goes to the higher end of the OSFD values with low frequencies. The Bayesian model uses informative priors and thus a model fit can always be constructed. However, because many of the prior distributions in the model are relatively non-informative, the MCMC fitting algorithms can perform poorly in the more extreme dichotomizations. Some poor MCMC behavior was observed for dichotomizations at ≥ 15 OSFD and higher.

Per the SAP, if a particular dichotomization would lead to cumulative probabilities less than 5% or greater than 95% then these dichotomizations may be ignored. Therefore, the model is only fit for dichotomizations up to >= 19.

Table 3.7: Sensitivity analysis of proportional odds assumption. Values are Odds-Ratio estimates for the **OSFD** endpoint for different dichotomizations of OSFD; REMAP-CAP COVID-19 severe state ITT population (Lopinavir/ritonavir)

OSFD Dichotomization	Lopinavir/ritonavir		
	Median	95% Credible Interval	Mean (SD)
≤-1 vs ≥0	0.65	0.45 – 0.95	0.67 (0.13)
≤0 vs ≥1	0.77	0.55 – 1.09	0.79 (0.14)
≤1 vs ≥2	0.78	0.55 – 1.12	0.79 (0.14)
≤2 vs ≥3	0.80	0.57 – 1.14	0.82 (0.14)
≤3 vs ≥4	0.82	0.58 – 1.18	0.83 (0.15)
≤4 vs ≥5	0.79	0.56 – 1.12	0.80 (0.15)
≤5 vs ≥6	0.82	0.58 – 1.17	0.83 (0.15)
≤6 vs ≥7	0.86	0.61 – 1.23	0.87 (0.16)
≤7 vs ≥8	0.93	0.65 – 1.34	0.95 (0.18)
≤8 vs ≥9	0.98	0.69 – 1.41	1.00 (0.18)
≤9 vs ≥10	0.93	0.65 – 1.33	0.95 (0.17)
≤10 vs ≥11	0.97	0.67 – 1.41	0.99 (0.19)
≤11 vs ≥12	0.86	0.61 – 1.25	0.88 (0.17)
≤12 vs ≥13	0.85	0.59 – 1.24	0.87 (0.17)
≤13 vs ≥14	0.81	0.55 – 1.16	0.82 (0.16)
≤14 vs ≥15	0.64	0.44 – 0.93	0.65 (0.12)
≤15 vs ≥16	0.66	0.44 – 0.98	0.67 (0.14)
≤16 vs ≥17	0.74	0.49 – 1.12	0.75 (0.16)
≤17 vs ≥18	0.55	0.34 – 0.87	0.57 (0.14)
≤18 vs ≥19	0.45	0.26 – 0.81	0.48 (0.14)

Table 3.8: Sensitivity analysis of proportional odds assumption. Values are Odds-Ratio estimates for the **OSFD** endpoint for different dichotomizations of OSFD; REMAP-CAP COVID-19 severe state ITT population (HCQ)

OSFD Dichotomization	HCQ		
	Median	95% Credible Interval	Mean (SD)
≤-1 vs ≥0	0.56	0.30 – 0.89	0.57 (0.15)
≤0 vs ≥1	0.54	0.28 – 0.89	0.55 (0.16)
≤1 vs ≥2	0.57	0.30 – 0.91	0.58 (0.16)
≤2 vs ≥3	0.59	0.31 – 0.95	0.60 (0.17)
≤3 vs ≥4	0.50	0.24 – 0.87	0.52 (0.16)
≤4 vs ≥5	0.55	0.27 – 0.89	0.56 (0.16)
≤5 vs ≥6	0.54	0.28 – 0.91	0.56 (0.17)
≤6 vs ≥7	0.60	0.30 – 0.98	0.61 (0.18)
≤7 vs ≥8	0.54	0.26 – 0.97	0.56 (0.19)
≤8 vs ≥9	0.55	0.27 – 0.98	0.57 (0.19)
≤9 vs ≥10	0.51	0.24 – 0.95	0.53 (0.18)
≤10 vs ≥11	0.47	0.23 – 0.91	0.50 (0.18)
≤11 vs ≥12	0.51	0.23 – 0.92	0.53 (0.18)
≤12 vs ≥13	0.45	0.20 – 0.86	0.47 (0.18)
≤13 vs ≥14	0.41	0.18 – 0.82	0.44 (0.17)
≤14 vs ≥15	0.50	0.22 – 0.83	0.50 (0.16)
≤15 vs ≥16	0.41	0.15 – 0.79	0.43 (0.17)
≤16 vs ≥17	0.55	0.20 – 0.97	0.55 (0.20)
≤17 vs ≥18	0.39	0.10 – 0.75	0.40 (0.17)
≤18 vs ≥19	0.36	0.10 – 0.76	0.38 (0.17)

Table 3.9: Sensitivity analysis of proportional odds assumption. Values are Odds-Ratio estimates for the **OSFD** endpoint for different dichotomizations of OSFD; REMAP-CAP COVID-19 severe state ITT population (Lopinavir/ritonavir + HCQ)

	Lopinavir/ritonavir + HCQ		
OSFD Dichotomization	Median	95% Credible Interval	Mean (SD)
≤-1 vs ≥0	0.36	0.17 − 0.73	0.38 (0.15)
≤0 vs ≥1	0.41	0.20 − 0.80	0.43 (0.15)
≤1 vs ≥2	0.43	0.21 − 0.87	0.46 (0.17)
≤2 vs ≥3	0.47	0.23 − 0.90	0.49 (0.17)
≤3 vs ≥4	0.40	0.19 − 0.80	0.43 (0.16)
≤4 vs ≥5	0.42	0.20 − 0.83	0.45 (0.16)
≤5 vs ≥6	0.44	0.21 − 0.88	0.46 (0.17)
≤6 vs ≥7	0.51	0.23 − 0.98	0.53 (0.19)
≤7 vs ≥8	0.50	0.23 − 1.03	0.53 (0.21)
≤8 vs ≥9	0.54	0.25 − 1.07	0.57 (0.21)
≤9 vs ≥10	0.47	0.21 − 0.99	0.50 (0.20)
≤10 vs ≥11	0.45	0.20 − 0.95	0.49 (0.20)
≤11 vs ≥12	0.43	0.19 − 0.91	0.46 (0.19)
≤12 vs ≥13	0.37	0.16 − 0.82	0.41 (0.17)
≤13 vs ≥14	0.33	0.14 − 0.74	0.36 (0.15)
≤14 vs ≥15	0.31	0.13 − 0.66	0.33 (0.14)
≤15 vs ≥16	0.26	0.09 − 0.64	0.29 (0.14)
≤16 vs ≥17	0.39	0.14 − 0.92	0.42 (0.20)
≤17 vs ≥18	0.21	0.05 − 0.54	0.23 (0.13)
≤18 vs ≥19	0.15	0.04 − 0.51	0.19 (0.13)

4 Other Data Summaries

This section provides summary tables and graphics for variables that are included as covariates in the model, including age, sex at birth, sites within country, and time effects.

Table 4.1: Summary of the number of sites and patients randomized within each country (**Severe** State)

		All Domains			COVID-19 Antiviral Domain		
Region	Country	Number of Sites	Number of Patients Randomized	Number of Patients w/ Outcomes	Number of Sites	Number of Patients Randomized	Number of Patients w/ Outcomes
Americas	Canada	21	148	119	6	42	39
	United States of America	2	94	94	1	8	8
Europe	France	3	11	11			
	Germany	2	4	4			
	Ireland	2	34	34	2	6	6
	Netherlands	7	96	94	3	20	20
	Portugal	1	3	3			
	United Kingdom	121	1405	1378	74	502	491
Middle East	Saudi Arabia	1	114	114	1	100	100
Oceana	Australia	22	73	68	10	14	11
	New Zealand	5	9	9	2	2	2

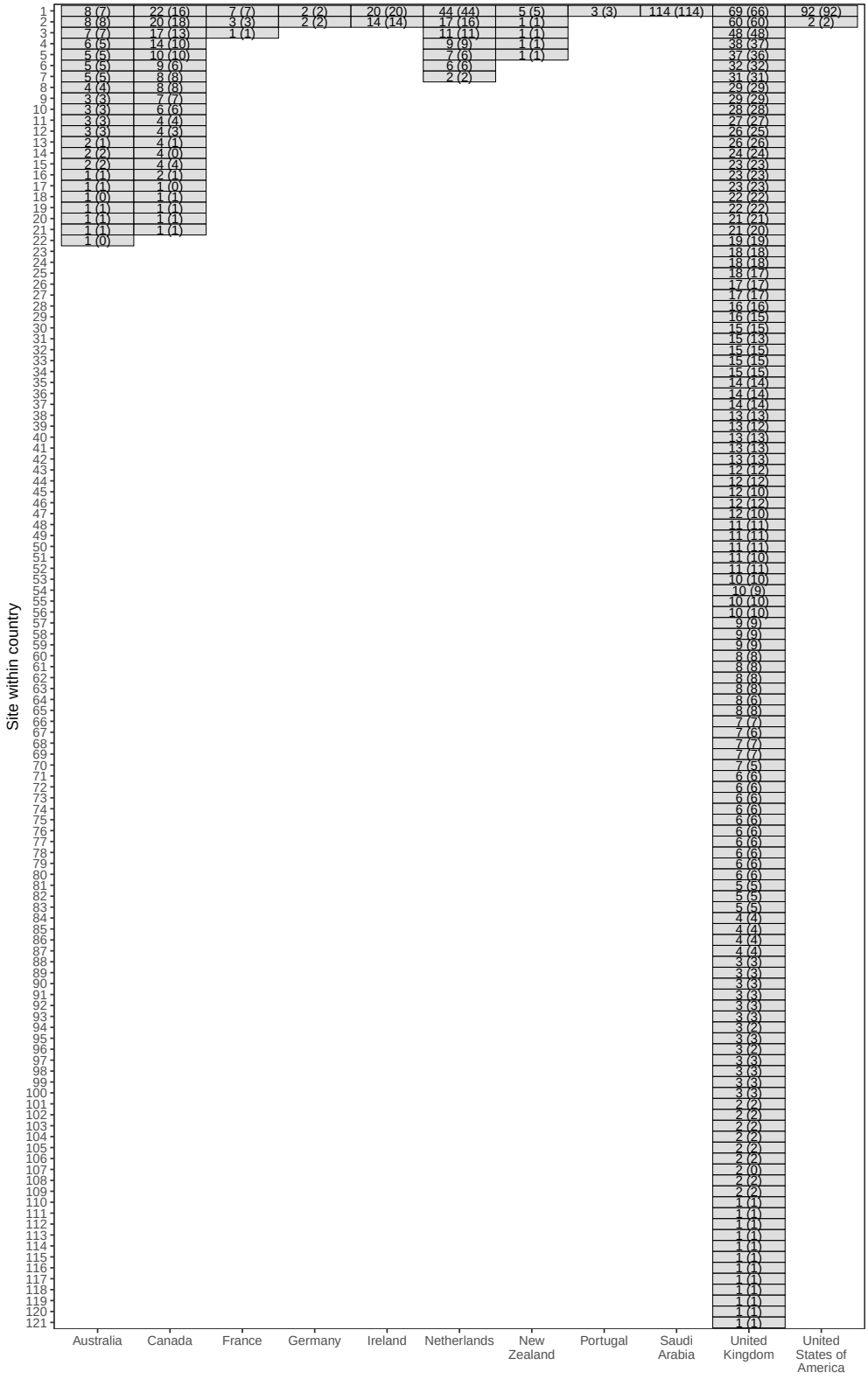


Figure 4.1: Sample size at each site within each country (**Severe** State). The values in each cell represent the number of patients randomized to any domain at that site and, in parentheses, the number of patients for whom the outcome on the 21-day endpoint is known. Within each country, all sites having fewer than 5 randomized patients are combined into a single site for the statistical model.

Table 4.2: Summary of age groups by sex at birth (**Severe** State)

	Age Group (years)						
	≤ 39	$40-49$	$50-59$	$60-69$	$70-79$	≥ 80	Total
Male	76	155	324	416	313	85	1369
Female	52	79	143	166	136	46	622
Total	128	234	467	582	449	131	1991

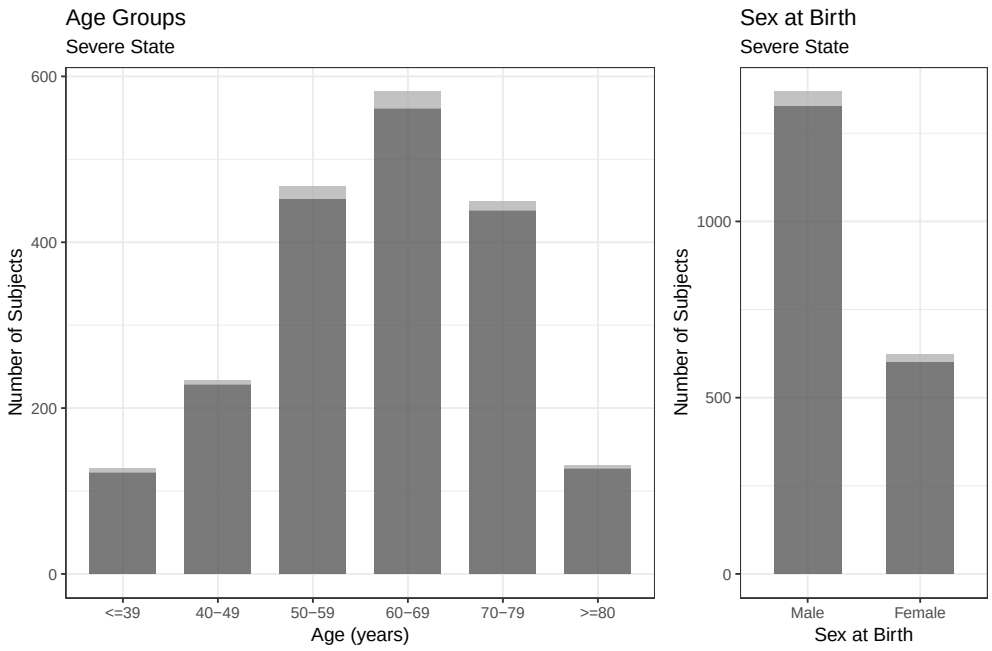


Figure 4.2: Distribution of age groups and sex at birth (**Severe** State). The total height of each bar represents the number of patients in each category. The darker shaded area indicates the number of patients for whom 21 days have elapsed since randomization and have a known OSFD outcome. The lighter shaded area indicates the number of patients who do not have a known OSFD outcome.

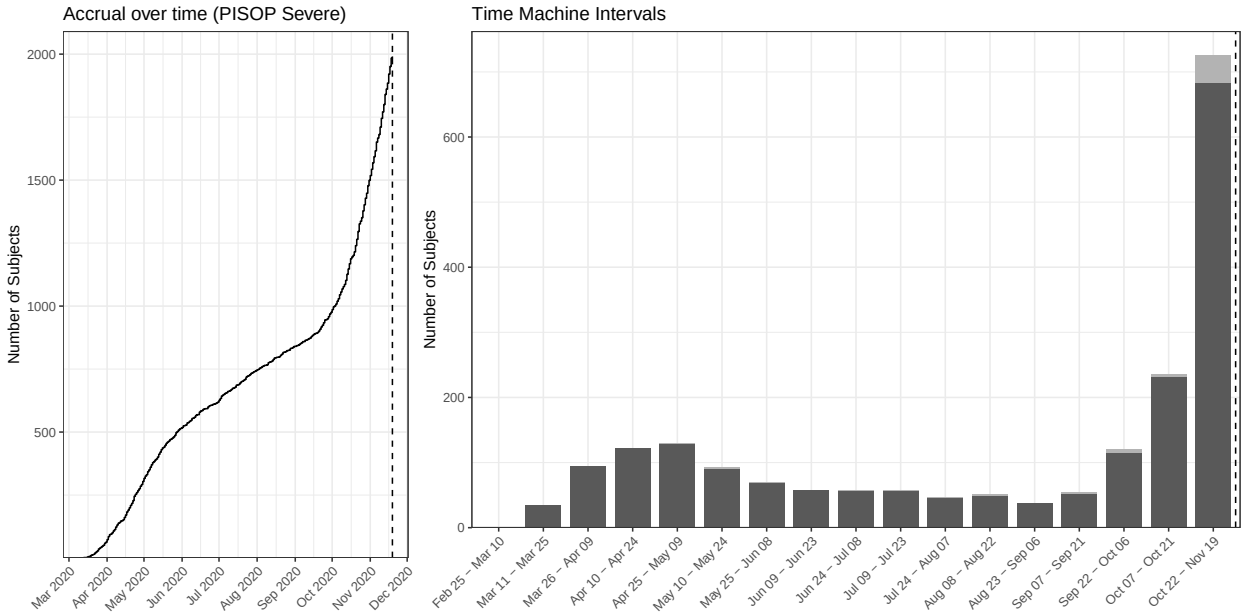


Figure 4.3: Accrual over time and distribution of patients within each of the time buckets used to estimate time trends in the analysis model for **Severe** State. The time buckets are derived so that the first bucket is the most recent month going backwards in time from the most recently randomized patient in the dataset that has an outcome. Thereafter, each bucket is defined as the next two-week interval backwards in time. The total height of each bar represents the number of patients in each category. The darker shaded area indicates the number of patients for whom 21 days have elapsed since randomization and have a known OSFD outcome. The lighter shaded area indicates the number of patients who do not have a known OSFD outcome. The vertical dashed line indicates the randomization date for the last patient who has past 21 days and has a known outcome on the primary endpoint at the time of this analysis.

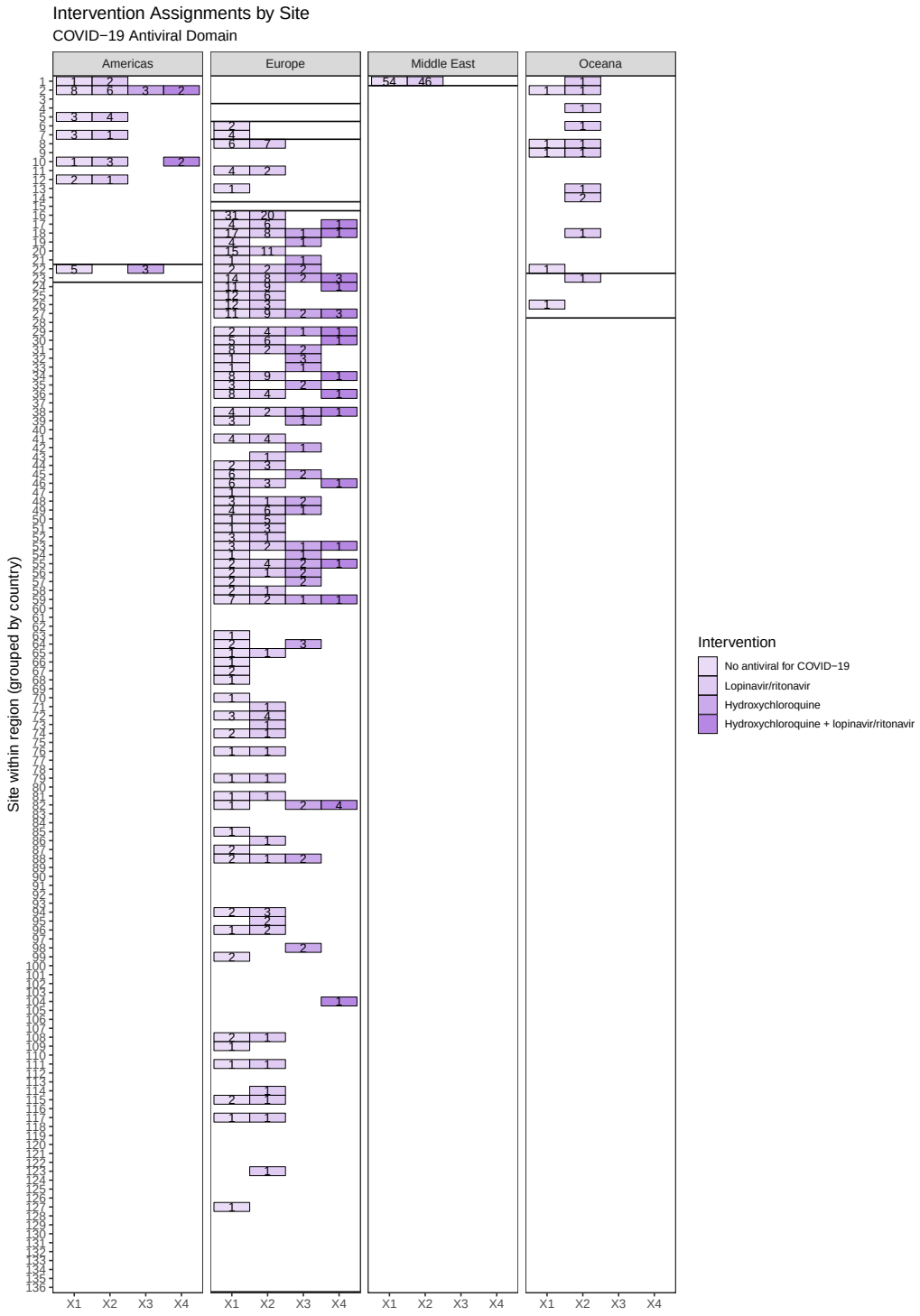


Figure 4.4: Allocation of **Severe State** interventions in the **COVID-19 Antiviral** domain by site. The data are summarized in four panels — one for each geographical region. Each panel is a grid with interventions on the x-axis and sites on the y-axis. Each colored cell corresponds to an intervention that has randomized patients at a site. Cells are colored by intervention, with the number in each cell representing how many patients were randomized to the intervention at that site. The solid black horizontal lines distinguish sites located within the same country in the region.

5 Analysis Conventions

The following conventions were applied to the analyses contained in this report:

- The ITSC closed randomization to the Corticosteroid domain within the PISOP stratum on June 17, 2020. This decision was made following the release of the RECOVERY trial results on June 16, 2020 which reported strong positive effects of dexamethasone. Following this decision, the results from the Corticosteroid domain in REMAP-CAP were publicly disclosed. Patients who are randomized within the PISOP stratum after June 17 receive no randomized assignment within the Corticosteroid domain; however it is asssumed they likely receive fixed duration steroid. Thus, for the statistical model, patients randomized after June 17 are coded identically to patients randomized to fixed duration steroid.
- All sites within a country that have < 5 patients randomized in the analysis population will have their results combined into a single site within that country.
- For the estimation of time trends in the model, time buckets with < 5 patients randomized within the bucket were combined with a neighboring bucket.
- All interactions between the shock-based steroid arm and other domains are dropped (assumed to be zero) per the SAP.
- The two IL-6 receptor agonists, Tocilizumab and Sarilumab, are combined into a single IL-6ra arm, per the SAP.
- Patients with no randomized assignment in any domain were removed from the analysis population.
- Data provided to the SAC only include patients who consented for use of their data.
- Some patients for whom 21 days have elapsed since randomization have missing 21-day OSFD outcomes in the data export. A supplemental file was provided to the SAC in which some additional outcome data was obtained based on a manual review.
- For unique patient identifiers that exist in both the Research Online and Spiral databases, the analysis generally pulls the eligibility and randomization information from the Spiral database and the outcomes from the Research Online database. If outcomes were reported in both places, the reported outcome in Spiral was selected per instructions from the global project manager for the trial (email dated August 6, 2020).

6 Model Stability

The Bayesian model was computed in R version 4.0.3 (2020-10-10), using the rstan package version 2.21.0. This package computes the Markov Chain Monte Carlo (MCMC) using the highly efficient Hamiltonian Monte Carlo method. The MCMC used 5 separate chains, with each chain using a burnin of 500 samples, followed by 2000 samples, for a total of 10000 samples. Convergence diagnostics were assessed, and no concerns regarding mixing or convergence were identified. All $\hat{R}$ values were less than 1.05. All model runs used a random number seed of 1252021 for the MCMC initialization.

7 Descriptive Summaries for Moderate State

This section includes descriptive summaries for patients randomized in the COVID-19 Antiviral domain in the Moderate state. These summaries include 3 patients that were randomized in the COVID-19 Antiviral domain in Moderate state that later met criteria for Severe State and recieved additional randomization assignments in Severe State. These patients were not included in the summaries and model results above.

Table 7.1: Summary of the availability of data in the **COVID-19 Antiviral** domain (**Moderate** state)

Intervention	Number Eligible	Number Assigned	Number Revealed	Number Past Day 21	Number Missing	Number Known
Eligible for domain: N=33						
No assignment		1	0	1	0	1
No antiviral for COVID-19	33	14	14	14	0	14
Lopinavir/ritonavir	7	6	6	6	0	6
Hydroxychloroquine	26	12	12	12	0	12
Not eligible for domain: N=6						
No assignment		6	0	6	0	6

Table 7.2: Summary of the OSFD and In-Hospital mortality data for patients that were eligible for the **COVID-19 Antiviral** domain (**Moderate** State)

Intervention	Number Assigned (N)	Number Known (n)	Number of Deaths (y)	Mortality Rate (y/n)	OSFD median (IQR)	Conditional* OSFD median (IQR)
No antiviral for COVID-19	14	14	2	0.143	22.00 (22.00 – 22.00)	22.00 (22.00 – 22.00)
Lopinavir/ritonavir	6	6	1	0.167	16.00 (12.50 – 19.50)	18.00 (14.00 – 20.00)
Hydroxychloroquine	12	12	2	0.167	22.00 (6.00 – 22.00)	22.00 (22.00 – 22.00)

* Conditional OSFD reports the median and IQR for subjects that did not die.

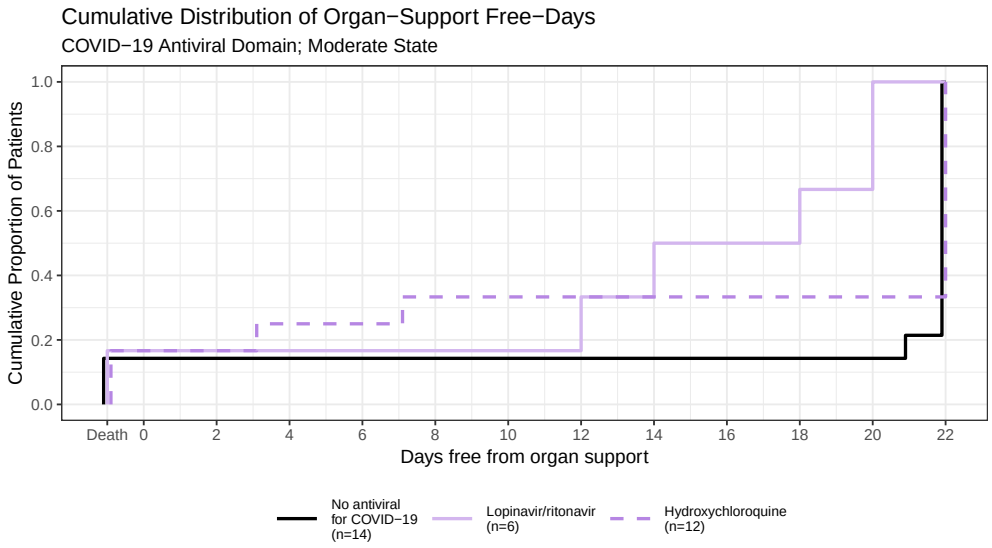


Figure 7.1: Empirical cumulative distribution of organ support free days for the **COVID-19 Antiviral** domain. This plot is restricted to patients who were eligible for the domain in **Moderate** State

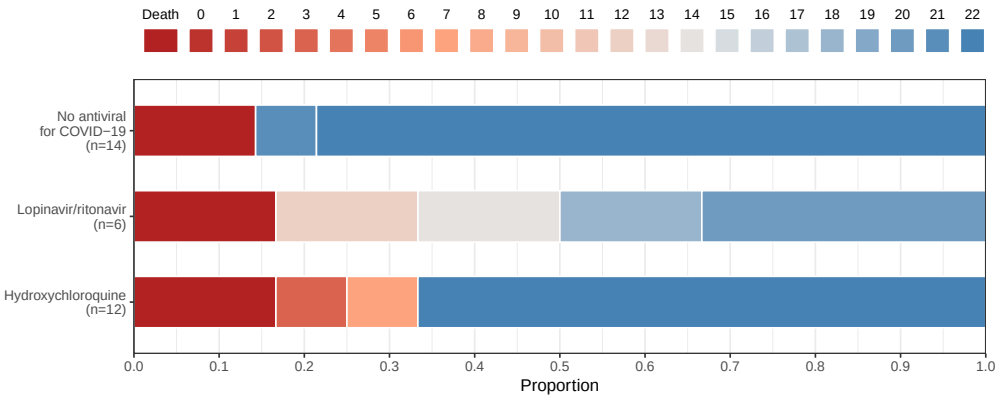


Figure 7.2: Stacked proportion of organ support free days for the IL-6ra and control interventions in the **COVID-19 Antiviral** domain. Red represents worse outcomes and blue represents better outcomes. This plot is restricted to include only patients who were eligible for the domain and received a randomized assignment to the domain in **Moderate** State

8 Report Production

All analyses in this report are based on the following documents:

- Statistical Analysis Appendix for REMAP-COVID, version 1, dated August 18, 2020;
- Statistical Analysis Plan for the COVID-19 Antiviral Therapy Domain for Patients with COVID-19 Pandemic Infection Suspected or Proven (PISOP), version 1, dated January 14, 2021;
- Current State of the Statistical Model: Pandemic Model, version 2.3-AV, dated January 19, 2021;
- Errata Sheet, last updated January 26, 2021.

Berry Consultants performed the analysis using data received from multiple sources. Table 8.1 shows the file names for the data exports from each database along with the names of supplemental files received by the SAC, and the dates on which each file was received by the SAC.

Table 8.1: Summary of data sources.

File Name	Date Received	Description
UPMC_SACDataExport_12132020_1035.csv	December 13, 2020	UPMC data
remapcap_spiral_interimexport_2020-12-18_091609_v10.1.csv	December 18, 2020	Spiral data
RAR_Unscrambled_RO_20201214_v3.csv	December 15, 2020	Research Online data
missingOSFD_PISOPSevereModeling_RandDomainH_2020-12-21_CG.csv	December 22, 2020	Supplemental OSFD outcome data
missingOSFD_PISOPSevereModeling_ExcludingRandDomainH_2020-12-21_CG.csv	December 22, 2020	Supplemental OSFD outcome data

All data summaries were completed using the R[1] statistical computing environment R version 3.5.2 (2018-12-20).

[1]R Development Core Team (2005). R: *A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. URL http://www.R-project.org.

REMAP-CAP Unblinded Analysis Report for the Antiviral Domain

Prepared by the ITSC Analysis Committee

May 11, 2021

Contents

1 Introduction

This report summarizes the data and the results for the antiviral domain analyses run by the ITSC analysis committee. The ITSC analysis committee is blinded to all ongoing domains and interventions in REMAP-CAP.

1.1 Antiviral domain interventions

There are four interventions in the COVID-19 Antiviral Therapy Domain. These are:

1. **Control** (No antiviral for COVID-19)
2. **Lopinavir-ritonavir**
3. **Hydroxychloroquine**
4. **Combination therapy** (Hydroxychloroquine and lopinavir/ritonavir)

These four interventions are mutually exclusive; patients randomized in this domain are assigned to one of the four interventions. The **Lopinavir-ritonavir** intervention refers to patients randomized to lopinavir-

ritonavir alone, and not patients randomized to **Combination therapy**. Similarly, the **Hydroxychloroquine** intervention does not include patients randomized to **Combination therapy**. In some models/tables/figures in this report, the three active antiviral arms are pooled into a single group labeled **Pooled antiviral**.

1.2 Analysis populations

The SAP for the antiviral domain analysis defines five populations in which analyses will be performed. This report includes analysis results for four of the five analysis populations. The analysis results for the **REMAP-CAP COVID-19 severe state intent-to-treat (ITT)** population are not included in this report since the ITSC analysis committee remains blinded to ongoing domains and interventions. Results for the **REMAP-CAP COVID-19 severe state intent-to-treat (ITT)** population are included in a separate report prepared by the fully unblinded Statistical Analysis Committee (SAC). In this report, tables and figures summarize data in the **Antiviral specific ITT population**. In this report, we summarize analysis results from the following four analysis populations:

1. The **Unblinded ITT population** is defined as all severe patients randomized in the Antiviral domain within the pandemic stratum. The unblinded ITT population consists of 1293 patients. There are 22 patients within this population that are missing values of OSFD and in-hospital mortality.

- 362 patients randomized to **Control** of which 353 have known OSFD outcomes
- 255 patients randomized to **Lopinavir-ritonavir** of which 249 have known OSFD outcomes
- 50 patients randomized to **Hydroxychloroquine** of which 49 have known OSFD outcomes
- 27 patients randomized to the **Combination therapy** of which 26 have known OSFD outcomes
- 381 patients randomized to the Corticosteroid domain of which 380 have known OSFD outcomes
- 807 patients randomized to control/tocilizumab/sarilumab in the Immune Modulation Therapy domain of which 796 have known OSFD outcomes.

2. The **Unblinded non-negative COVID-19 population** is defined as all patients in the Unblinded ITT population after removing those with >1 negative test for COVID-19 and no positive tests. The unblinded ITT population restricted to non-negative COVID-19 consists of 1136 patients. There are 21 patients within this population that are missing values of OSFD and in-hospital mortality.

- 322 patients randomized to **Control** of which 313 have known OSFD outcomes
- 227 patients randomized to **Lopinavir-ritonavir** of which 222 have known OSFD outcomes
- 46 patients randomized to **Hydroxychloroquine** of which 45 have known OSFD outcomes

- 24 patients randomized to the **Combination therapy** of which 23 have known OSFD outcomes
- 315 patients randomized to the Corticosteroid domain of which 314 have known OSFD outcomes
- 726 patients randomized to the control/tocilizumab/sarilumab in the Immune Modulation Therapy domain of which 715 have known OSFD outcomes

3. The **Antiviral ITT population** consists of patients in the severe state that were randomized to the antiviral domain within the pandemic stratum. The Antiviral ITT population consists of 694 patients. There are 17 patients within this population that are missing values of OSFD and in-hospital mortality.

- 362 patients randomized to **Control** of which 353 have known OSFD outcomes
- 255 patients randomized to **Lopinavir-ritonavir** of which 249 have known OSFD outcomes
- 50 patients randomized to **Hydroxychloroquine** of which 49 have known OSFD outcomes
- 27 patients randomized to **Combination therapy** of which 26 have known OSFD outcomes

4. The **Antiviral PP population** consists of the patients in the Antiviral ITT population who have been treated as per protocol. The Antiviral specific per protocol population consists of 629 patients. There are 10 patients within this population that are missing values of OSFD and in-hospital mortality.

- 343 patients randomized to **Control** of which 335 have known OSFD outcomes
- 220 patients randomized to **Lopinavir-ritonavir** of which 218 have known OSFD outcomes
- 46 patients randomized to **Hydroxychloroquine** of which 46 have known OSFD outcomes
- 20 patients randomized to **Combination therapy** of which 20 have known OSFD outcomes

1.3 Modeling conventions

- All reported credible intervals (CrIs) are 95% equal-tailed intervals.
- Results from models of ordinal and dichotomous endpoints are reported as odds ratios (ORs). Results from models of time to event endpoints are reported as hazard ratios (HRs). **For consistency of interpretation, all models are parameterized so that an OR/HR greater than 1 indicates patient benefit relative to the reference group and an OR/HR less than 1 indicates patient harm relative to the reference group.**
- The reference group for the age category OR/HRs is the age category from 60-69 years old.
- The reference group for the time epochs OR/HRs is the most recent time epoch consisting of the four-week period preceding Nov 19, 2020. Time epoch 0 is the most recent epoch and the epochs move backwards in time in two-week periods from epoch 1 to 16. The Unblinded ITT and Unblinded

non-negative COVID-19 populations include patients randomized in epochs 0 to 16. The Antiviral ITT and PP populations include patients randomized in epochs 0 to 13.

- The reference group for the sex at birth OR/HRs is the male category.
- **Lopinavir-ritonavir**, **Hydroxychloroquine**, and **Combination therapy** are compared to the **Control** intervention. A posterior probability of at least 99% that the odds ratio is greater than 1 is used as a statistical trigger for efficacy (or superiority to control). Similarly, a probability of harm is reported as the probability that the odds ratio is less than 1 relative to **Control**, or 1 minus the probability of efficacy.
- **Lopinavir-ritonavir**, **Hydroxychloroquine**, and **Combination therapy** are compared to **Control** for futility. A 95% probability of a smaller than 1.2 odds ratio for **Lopinavir-ritonavir**, **Hydroxychloroquine**, or **Combination therapy** relative to **Control** is used as a statistical trigger for futility.
- **Lopinavir-ritonavir** and **Hydroxychloroquine** are compared for equivalence. A 90% probability of equivalence (defined as an odds ratio of **Lopinavir-ritonavir** relative to **Hydroxychloroquine** between 1/1.2 and 1.2) is used as a statistical trigger for intervention equivalence.
- For each intervention in the Antiviral domain, the probability of being in the optimal regimen is calculated and used for statistical triggers of domain superiority and inferiority. A greater than 99% probability of being in the optimal regimen is used as a statistical trigger for superiority for each active antiviral intervention. A less than 0.33% probability of being in the optimal regimen is used as a statistical trigger of inferiority for all antiviral interventions.
- OR/HR effects for pre-specified **combinations** of interventions from the Antiviral domain with the Corticosteroid and Immune Modulation Therapy domain are reported relative to control. These OR/HRs incorporate the effect of each individual intervention and the interaction term for the combination of interventions.
- OR/HR effects for pre-specified **interaction effects** are reported relative to an additive effect. For example, if an interaction effect OR/HR is equal to 1, the combination of interventions is additive (equal to the sum of the effects of the two interventions taken separately). If an interaction OR/HR is greater than 1, the effect of the combination of interventions is synergistic (greater than the sum of the effects of the two interventions taken separately). If the interaction OR/HR is less than 1, the effect of the combination is sub-additive (less than the sum of the effects of the two interventions taken separately).
- Interaction effects are reported for pre-specified interventions from the Antiviral domain with the Immune Modulation Therapy and Corticosteroid domains.

1.4 Overall summaries of OSFD in the Unblinded ITT population

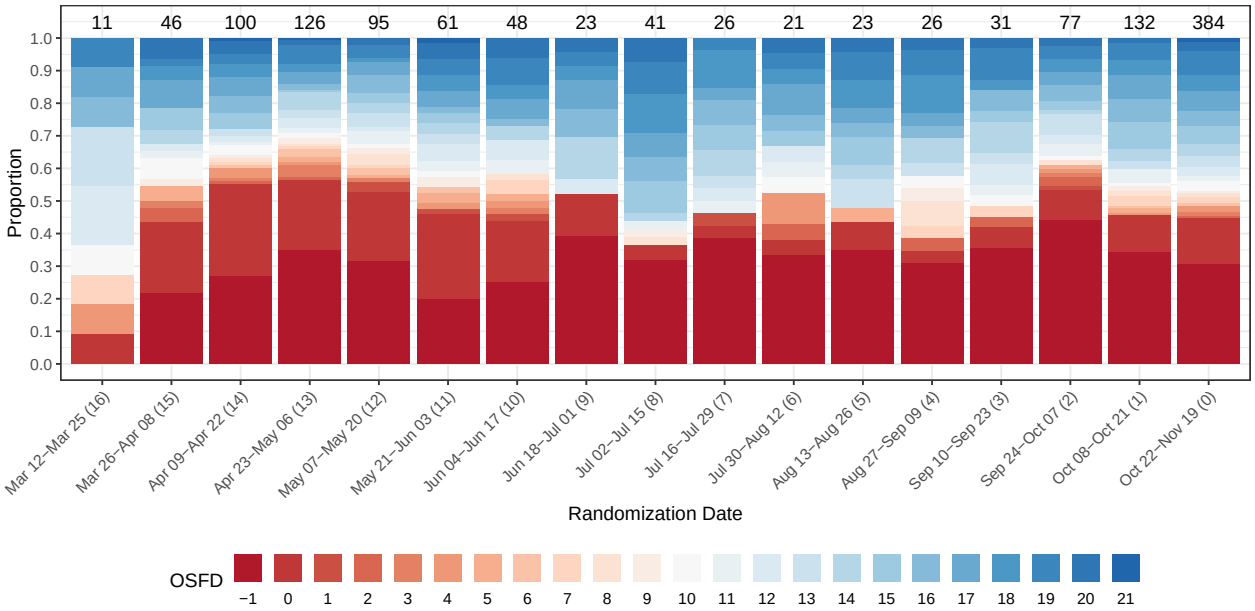


Figure 1: Empirical distribution of organ support free days (OSFD) by time epoch. The Oct 22-Nov 19 category (epoch 0) is the reference time epoch in all models. This plot shows the time epochs defined for the Unblinded ITT population, with the labeled number shown in parentheses. Other analysis populations may have fewer time epochs based on the randomization dates of included patients.

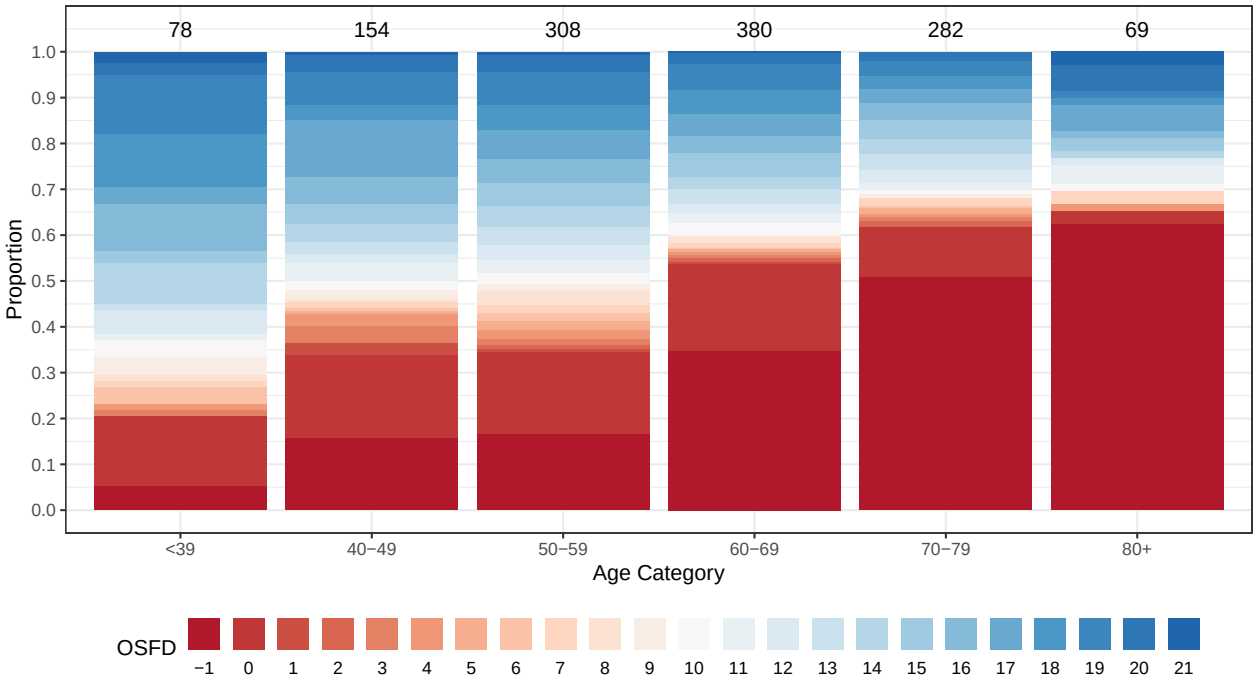


Figure 2: Empirical distribution of organ support free days (OSFD) by age category for the Unblinded ITT population. The 60—69 year age category is the reference group in all models.

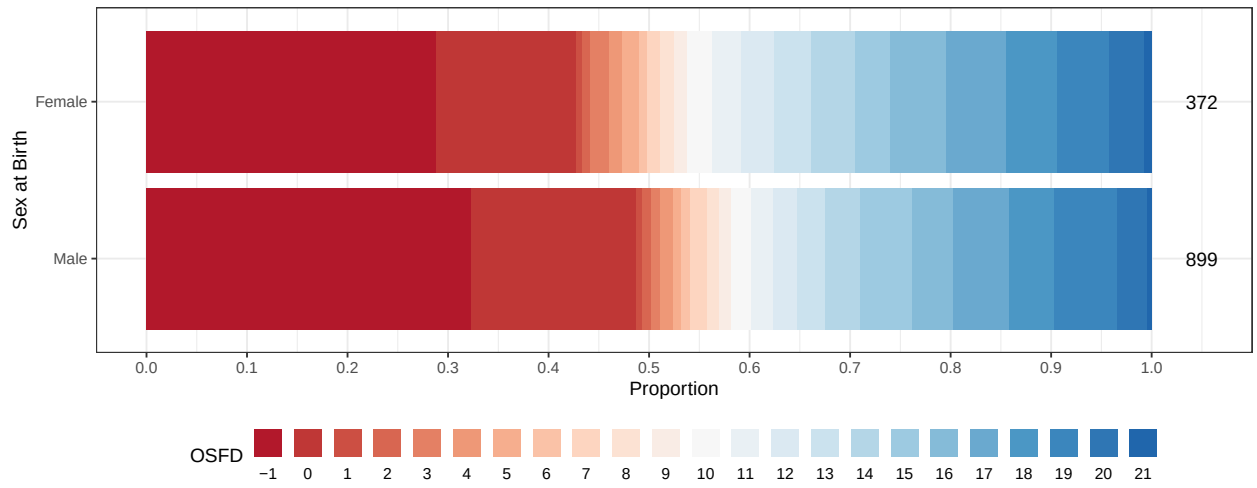


Figure 3: Empirical distribution of organ support free days (OSFD) by sex at birth for the Unblinded ITT population. The male category is the reference group in all models.

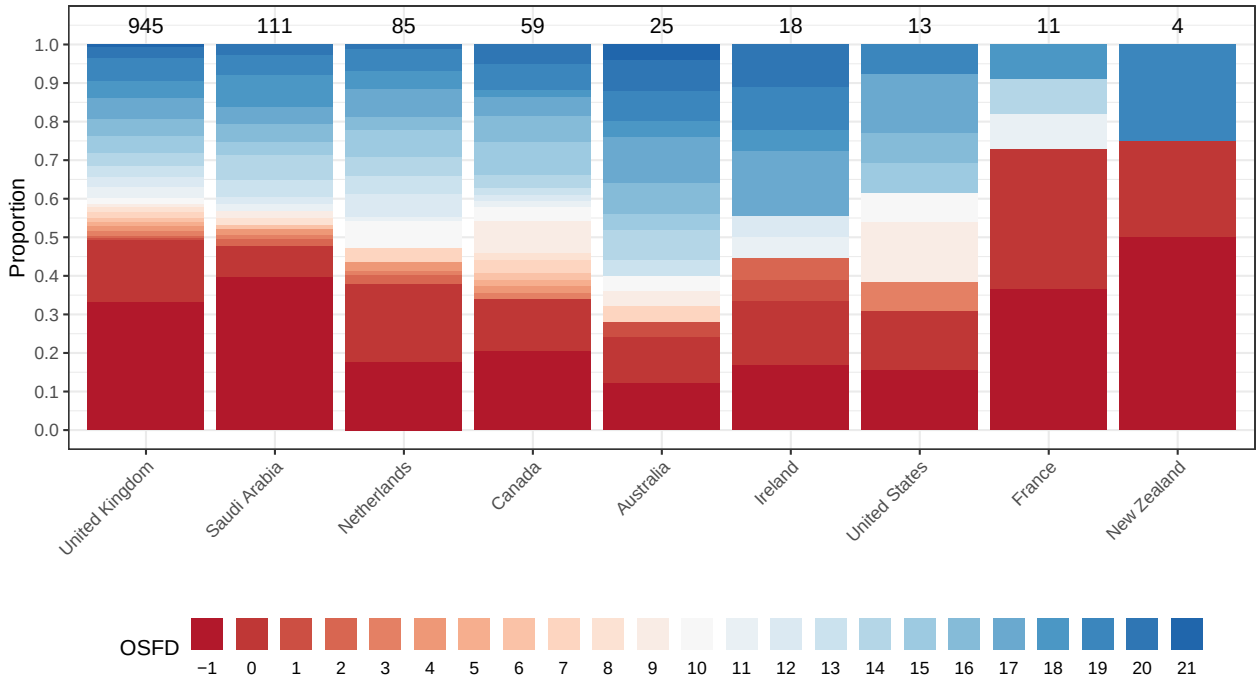


Figure 4: Empirical distribution of organ support free days (OSFD) by country for the Unblinded ITT population.

2 Secondary analyses of OSFD endpoint

2.1 Empirical distribution of OSFD in Antiviral ITT population

Table 1: Summary of OSFD for the Antiviral ITT population

Intervention	# Patients	# Known	OSFD median (IQR)	OSFD in Survivors* median (IQR)
Lopinavir-ritonavir	255	249	4 (-1, 15)	14 (7, 17)
Hydroxychloroquine	50	49	0 (-1, 9)	4 (0, 12.5)
Combination therapy	27	26	-0.5 (-1, 6.75)	8 (0, 13)
Control	362	353	6 (-1, 16)	14 (3, 18)
Pooled Antiviral	332	324	0 (-1, 14)	13 (2.25, 17)

* Days Free of Organ Support in Survivors within 21 days

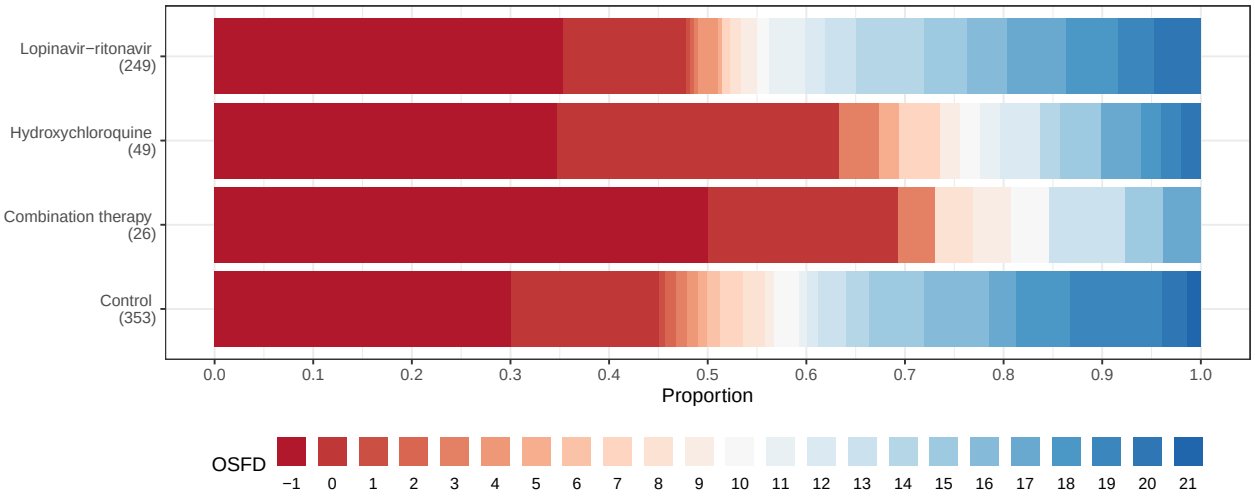


Figure 5: Empirical distribution of organ support free days (OSFD) for lopinavir−ritonavir, hydroxychloroquine, the combination therapy, and control. This plot is restricted to the Antiviral ITT population.

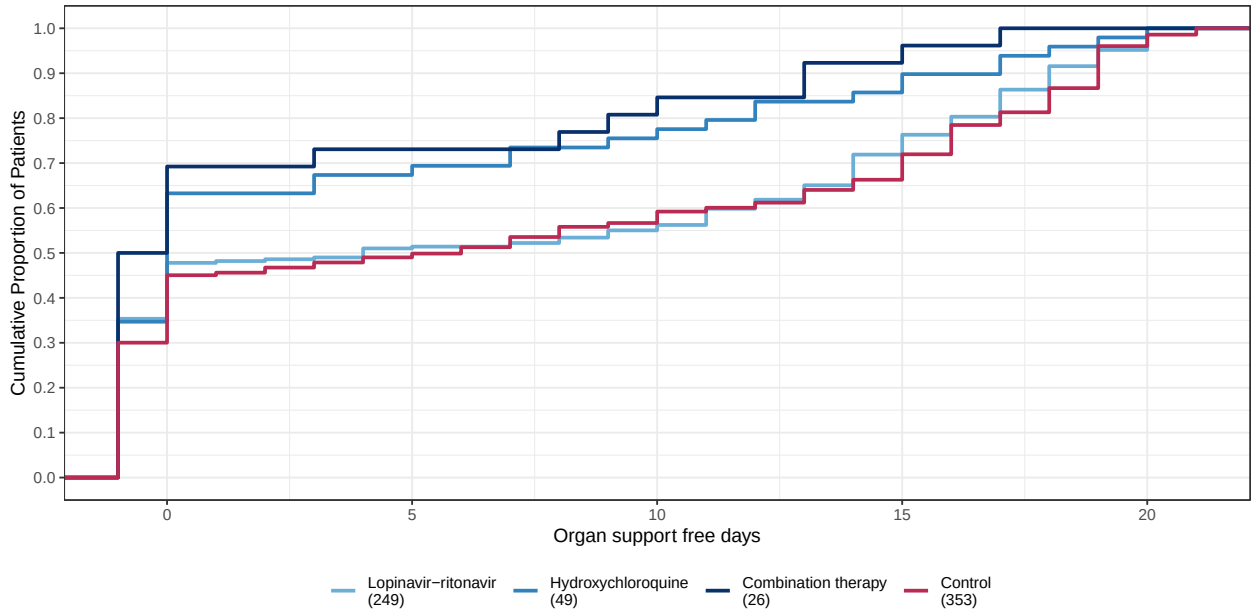


Figure 6: Empirical cumulative distribution of organ support free days (OSFD) for lopinavir−ritonavir, hydroxychloroquine, the combination therapy, and control. This plot is restricted to the Antiviral ITT population.

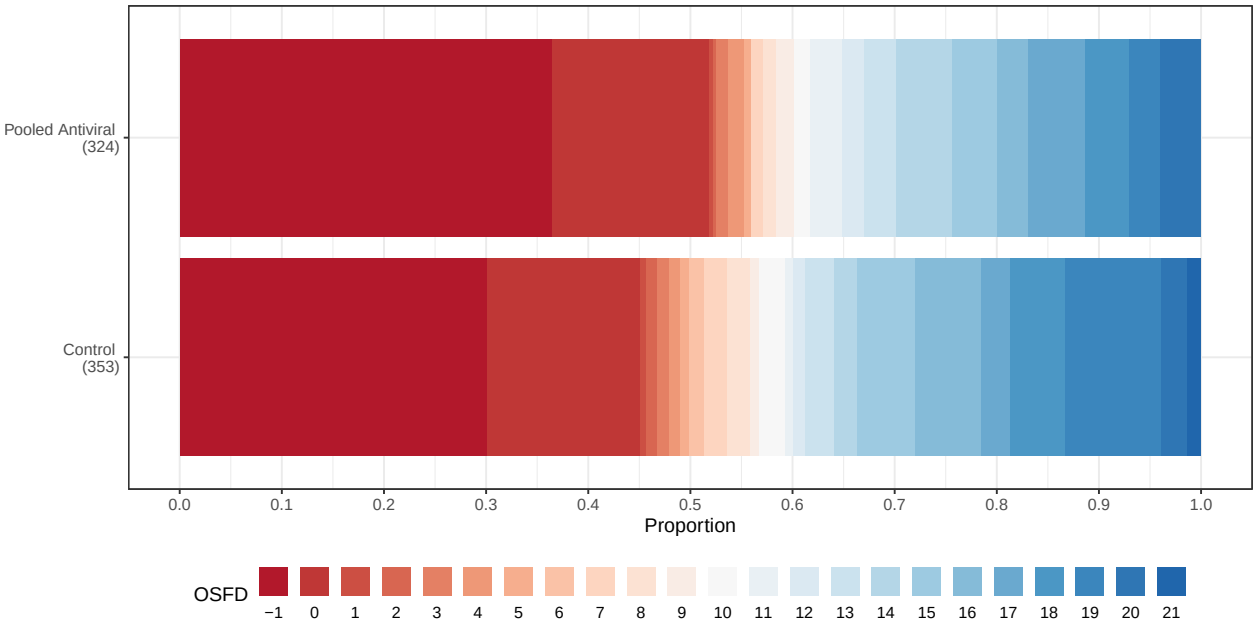


Figure 7: Empirical cumulative distribution of organ support free days (OSFD) for antiviral interventions and control. This plot is restricted to the Antiviral ITT population.

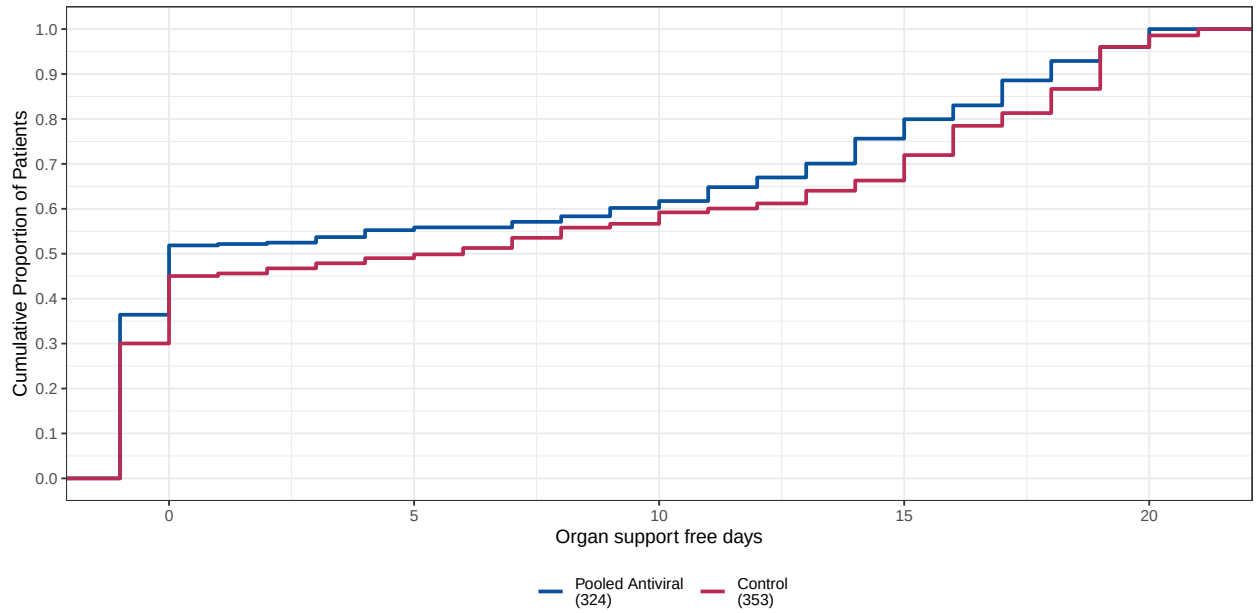


Figure 8: Empirical cumulative distribution of organ support free days (OSFD) for antiviral and control interventions. This plot is restricted to the Antiviral ITT population.

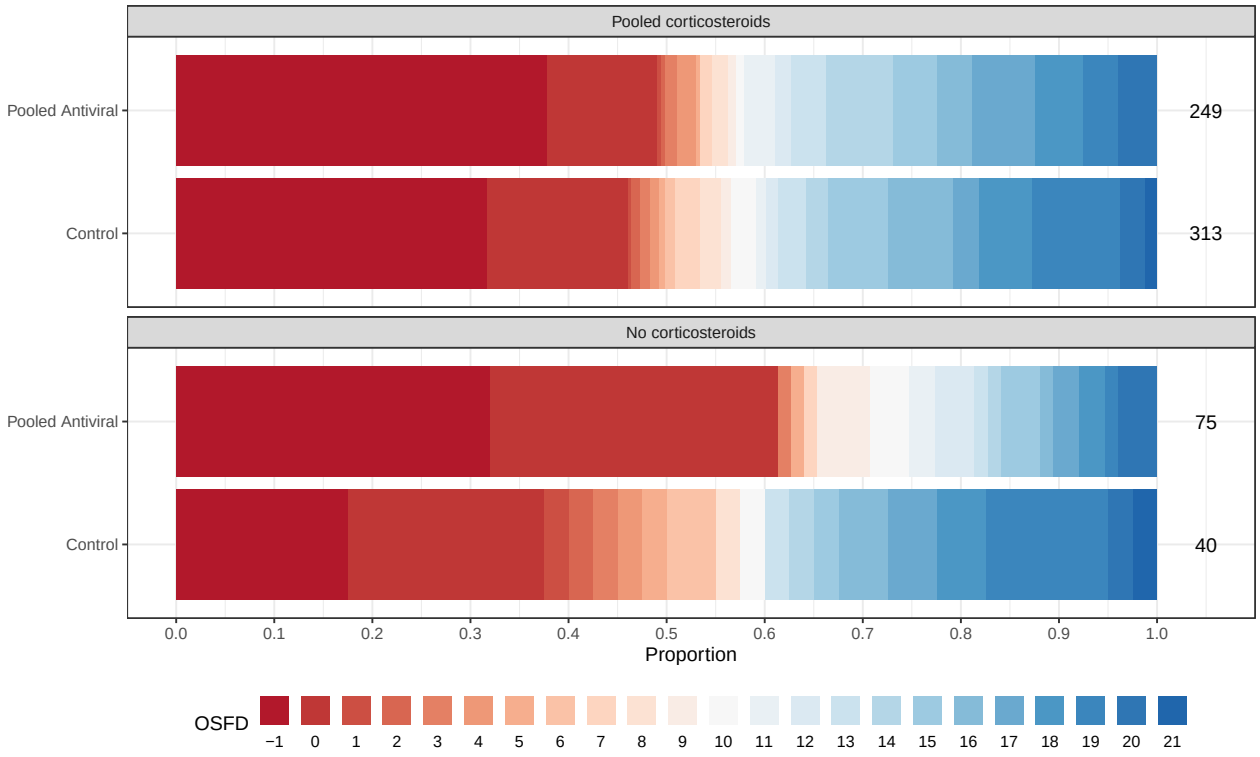


Figure 9: Empirical cumulative distribution of organ support free days (OSFD) for pooled antiviral and control interventions, separated by patients who received no corticosteroid interventions and patients who received a corticosteroid intervention. This plot is restricted to the Antiviral ITT population.

2.2 Secondary analysis of OSFD endpoint for Unblinded ITT population

- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.

Table 2: Odds ratio parameters for secondary analysis of OSFD endpoint for Unblinded ITT population

	Mean	SD	Median	CrI
Age<39	4.09	0.91	3.99	(2.62, 6.11)
Age 40-49	2.11	0.36	2.08	(1.50, 2.91)
Age 50-59	1.96	0.28	1.93	(1.48, 2.56)
Age 70-79	0.52	0.08	0.51	(0.38, 0.69)
Age 80+	0.34	0.09	0.32	(0.19, 0.55)
Female	1.17	0.13	1.16	(0.93, 1.45)
Time epoch 1	0.95	0.08	0.95	(0.79, 1.11)
Time epoch 2	0.90	0.13	0.90	(0.65, 1.16)
Time epoch 3	0.95	0.17	0.94	(0.66, 1.31)
Time epoch 4	1.06	0.22	1.03	(0.70, 1.56)
Time epoch 5	1.16	0.27	1.13	(0.74, 1.82)
Time epoch 6	1.22	0.29	1.18	(0.76, 1.92)
Time epoch 7	1.26	0.30	1.22	(0.79, 1.95)
Time epoch 8	1.29	0.30	1.25	(0.82, 2.00)
Time epoch 9	1.23	0.27	1.19	(0.79, 1.86)
Time epoch 10	1.12	0.24	1.09	(0.73, 1.67)
Time epoch 11	0.96	0.20	0.94	(0.62, 1.41)
Time epoch 12	0.85	0.19	0.83	(0.54, 1.26)
Time epoch 13	0.84	0.19	0.83	(0.54, 1.27)
Time epoch 14	0.93	0.21	0.91	(0.58, 1.42)
Time epoch 15	1.10	0.32	1.05	(0.61, 1.85)
Time epoch 16	1.40	0.63	1.27	(0.60, 2.98)
Lopinavir−ritonavir	0.77	0.12	0.76	(0.57, 1.02)
Hydroxychloroquine	0.60	0.14	0.59	(0.35, 0.88)
Pooled IL-6ra	1.68	0.23	1.67	(1.28, 2.17)
Fixed-dose corticosteroids	1.44	0.33	1.41	(0.91, 2.19)
Shock-dependent corticosteroids	1.14	0.27	1.11	(0.71, 1.75)
Combination therapy	0.46	0.14	0.45	(0.25, 0.78)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.32	0.27	1.29	(0.86, 1.93)
Hydroxychloroquine*Pooled IL-6ra combination	1.01	0.27	0.98	(0.56, 1.61)
Combination therapy*Pooled IL-6ra combination	0.78	0.26	0.74	(0.39, 1.42)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	1.13	0.31	1.09	(0.65, 1.85)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.87	0.29	0.83	(0.42, 1.55)
Combination therapy*Fixed-dose corticosteroids combination	0.67	0.26	0.63	(0.30, 1.31)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	0.99	(0.90, 1.10)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.02	0.05	1.02	(0.92, 1.12)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 3: Posterior probabilities for secondary analysis of OSFD endpoint for Unblinded ITT population

	Posterior Probability
Lopinavir–ritonavir is optimal	0.050
Lopinavir–ritonavir is superior to control	0.037
Lopinavir–ritonavir is futile (OR < 1.2)	0.999
Lopinavir–ritonavir is harmful (OR < 1)	0.963
Hydroxychloroquine is optimal	0.006
Hydroxychloroquine is superior to control	0.004
Hydroxychloroquine is futile (OR < 1.2)	1.000
Hydroxychloroquine is harmful (OR < 1)	0.996
Combination therapy is optimal	0.003
Combination therapy OR > 1	0.002
Combination therapy is futile (OR < 1.2)	1.000
Combination therapy is harmful (OR < 1)	0.998
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.892
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.474
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.628
Hydroxychloroquine*Fixed-dose combination OR > 1	0.272
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.419

2.3 Secondary analysis of OSFD endpoint for Unblinded ITT population restricted to non-negative COVID-19

- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.

Table 4: Odds ratio parameters for secondary analysis of OSFD endpoint for Unblinded ITT population restricted to non-negative COVID-19

	Mean	SD	Median	CrI
Age<39	4.47	1.10	4.35	(2.72, 6.97)
Age 40-49	2.10	0.38	2.06	(1.44, 2.94)
Age 50-59	1.95	0.29	1.93	(1.45, 2.57)
Age 70-79	0.50	0.08	0.50	(0.36, 0.68)
Age 80+	0.27	0.08	0.26	(0.14, 0.45)
Female	1.12	0.14	1.11	(0.88, 1.41)
Time epoch 1	0.96	0.08	0.95	(0.81, 1.12)
Time epoch 2	0.93	0.13	0.93	(0.68, 1.19)
Time epoch 3	0.97	0.18	0.96	(0.67, 1.35)
Time epoch 4	1.07	0.24	1.04	(0.69, 1.62)
Time epoch 5	1.14	0.30	1.09	(0.70, 1.86)
Time epoch 6	1.17	0.32	1.12	(0.70, 1.93)
Time epoch 7	1.15	0.31	1.10	(0.69, 1.88)
Time epoch 8	1.11	0.29	1.07	(0.67, 1.77)
Time epoch 9	1.04	0.25	1.00	(0.64, 1.62)
Time epoch 10	0.95	0.22	0.92	(0.60, 1.44)
Time epoch 11	0.85	0.19	0.82	(0.53, 1.28)
Time epoch 12	0.79	0.19	0.77	(0.47, 1.20)
Time epoch 13	0.82	0.19	0.80	(0.50, 1.25)
Time epoch 14	0.92	0.23	0.89	(0.55, 1.44)
Time epoch 15	1.05	0.33	1.00	(0.56, 1.83)
Time epoch 16	1.28	0.58	1.15	(0.53, 2.78)
Lopinavir−ritonavir	0.84	0.14	0.83	(0.61, 1.15)
Hydroxychloroquine	0.55	0.15	0.53	(0.30, 0.87)
Pooled IL-6ra	1.73	0.25	1.71	(1.29, 2.28)
Fixed-dose corticosteroids	1.29	0.31	1.25	(0.79, 2.01)
Shock-dependent corticosteroids	0.97	0.24	0.94	(0.58, 1.52)
Combination therapy	0.46	0.15	0.44	(0.23, 0.81)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.47	0.33	1.43	(0.93, 2.22)
Hydroxychloroquine*Pooled IL-6ra combination	0.95	0.29	0.92	(0.48, 1.61)
Combination therapy*Pooled IL-6ra combination	0.80	0.29	0.75	(0.38, 1.49)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	1.10	0.33	1.06	(0.60, 1.88)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.71	0.26	0.67	(0.32, 1.34)
Combination therapy*Fixed-dose corticosteroids combination	0.59	0.25	0.55	(0.25, 1.22)
Hydroxychloroquine and Lopinavir−ritonavir interaction	0.99	0.05	0.99	(0.90, 1.09)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.02	0.05	1.02	(0.92, 1.12)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.90, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.90, 1.10)

Table 5: Posterior probabilities for secondary analysis of OSFD endpoint for Unblinded ITT population restricted to non-negative COVID-19

	Posterior Probability
Lopinavir–ritonavir is optimal	0.158
Lopinavir–ritonavir is superior to control	0.129
Lopinavir–ritonavir is futile (OR < 1.2)	0.985
Lopinavir–ritonavir is harmful (OR < 1)	0.871
Hydroxychloroquine is optimal	0.002
Hydroxychloroquine is superior to control	0.003
Hydroxychloroquine is futile (OR < 1.2)	1.000
Hydroxychloroquine is harmful (OR < 1)	0.997
Combination therapy is optimal	0.004
Combination therapy OR > 1	0.004
Combination therapy is futile (OR < 1.2)	0.999
Combination therapy is harmful (OR < 1)	0.996
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.949
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.392
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.575
Hydroxychloroquine*Fixed-dose combination OR > 1	0.132
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.231

2.4 Secondary analysis of OSFD endpoint for Antiviral ITT population

- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and control interventions

Table 6: Odds ratio parameters for sensitivity analysis of OSFD in Antiviral ITT population

	Mean	SD	Median	CrI
Age<39	3.60	1.07	3.45	(1.95, 6.12)
Age 40-49	2.62	0.59	2.56	(1.66, 3.91)
Age 50-59	2.04	0.38	2.01	(1.40, 2.86)
Age 70-79	0.56	0.12	0.55	(0.36, 0.83)
Age 80+	0.42	0.16	0.40	(0.19, 0.80)
Female	0.97	0.15	0.96	(0.71, 1.30)
Time epoch 1	0.96	0.08	0.95	(0.79, 1.13)
Time epoch 2	0.92	0.14	0.91	(0.65, 1.21)
Time epoch 3	0.95	0.19	0.94	(0.63, 1.35)
Time epoch 4	1.02	0.24	0.99	(0.64, 1.57)
Time epoch 5	1.06	0.28	1.02	(0.64, 1.72)
Time epoch 6	1.08	0.29	1.03	(0.64, 1.77)
Time epoch 7	1.06	0.28	1.02	(0.63, 1.75)
Time epoch 8	1.03	0.27	0.99	(0.62, 1.68)
Time epoch 9	0.97	0.24	0.94	(0.59, 1.53)
Time epoch 10	0.89	0.21	0.86	(0.56, 1.37)
Time epoch 11	0.79	0.17	0.77	(0.51, 1.19)
Time epoch 12	0.69	0.14	0.67	(0.45, 1.01)
Time epoch 13	0.62	0.14	0.61	(0.40, 0.93)
Time epoch 14	0.58	0.15	0.56	(0.34, 0.93)
Time epoch 15	0.56	0.22	0.51	(0.25, 1.10)
Lopinavir-ritonavir	0.80	0.12	0.80	(0.61, 1.06)
Hydroxychloroquine	0.68	0.14	0.67	(0.42, 0.97)
Combination	0.55	0.15	0.53	(0.30, 0.90)
Combination interaction	1.00	0.05	1.00	(0.90, 1.10)

Table 7: Posterior probabilities for sensitivity analysis of OSFD in Antiviral ITT population

	Posterior Probability
Lopinavir-ritonavir is optimal	0.052
Lopinavir-ritonavir is superior to control	0.057
Lopinavir-ritonavir is futile (OR < 1.2)	0.997
Lopinavir-ritonavir is harmful (OR < 1)	0.943
Hydroxychloroquine is optimal	0.012
Hydroxychloroquine is superior to control	0.016
Hydroxychloroquine is futile (OR < 1.2)	0.999
Hydroxychloroquine is harmful (OR < 1)	0.984
Combination therapy is optimal	0.005
Combination therapy is superior to control	0.009
Combination therapy is futile (OR < 1.2)	0.998
Combination therapy is harmful (OR < 1)	0.991
Lopinavir-ritonavir and hydroxychloroquine are equivalent	0.547

3 Secondary analyses of in-hospital mortality

For consistency of interpretation, all models are parameterized so that an OR/HR greater than 1 indicates patient benefit relative to the reference group and an OR/HR less than 1 indicates patient harm relative to the reference group. In this section, the ORs can be interpreted for the outcome of in-hospital survival.

3.1 Empirical distribution of in-hospital mortality in Antiviral ITT population

Table 8: Summary of in-hospital mortality for the Antiviral ITT population

Intervention	# Patients (N)	# Known (n)	Deaths (y)	Mortality Rate (y/n)
Lopinavir-ritonavir	255	249	88	0.353
Hydroxychloroquine	50	49	17	0.347
Combination therapy	27	26	13	0.500
Control	362	353	106	0.300
Pooled Antiviral	332	324	118	0.364

3.2 Secondary analysis of in-hospital mortality for Unblinded ITT population

- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Ther-

apy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.

Table 9: Odds ratio parameters for secondary analysis of in-hospital mortality for Unblinded ITT population

	Mean	SD	Median	CrI
Age<39	12.95	6.50	11.44	(5.03, 29.83)
Age 40-49	3.33	0.87	3.21	(1.97, 5.39)
Age 50-59	2.98	0.60	2.92	(1.99, 4.31)
Age 70-79	0.41	0.07	0.41	(0.29, 0.58)
Age 80+	0.23	0.07	0.22	(0.12, 0.40)
Female	1.19	0.19	1.18	(0.87, 1.60)
Time epoch 1	0.93	0.08	0.93	(0.78, 1.10)
Time epoch 2	0.86	0.13	0.86	(0.61, 1.13)
Time epoch 3	0.85	0.17	0.84	(0.55, 1.22)
Time epoch 4	0.87	0.20	0.84	(0.53, 1.32)
Time epoch 5	0.89	0.23	0.86	(0.52, 1.40)
Time epoch 6	0.89	0.24	0.87	(0.52, 1.44)
Time epoch 7	0.90	0.24	0.87	(0.52, 1.46)
Time epoch 8	0.94	0.24	0.90	(0.55, 1.48)
Time epoch 9	0.97	0.25	0.94	(0.59, 1.56)
Time epoch 10	1.01	0.27	0.97	(0.60, 1.63)
Time epoch 11	1.00	0.26	0.97	(0.59, 1.61)
Time epoch 12	0.98	0.26	0.95	(0.56, 1.58)
Time epoch 13	0.99	0.27	0.95	(0.55, 1.63)
Time epoch 14	1.07	0.33	1.02	(0.56, 1.86)
Time epoch 15	1.22	0.49	1.13	(0.55, 2.45)
Time epoch 16	1.50	0.98	1.27	(0.51, 3.96)
Lopinavir−ritonavir	0.67	0.13	0.66	(0.46, 0.96)
Hydroxychloroquine	0.59	0.15	0.58	(0.32, 0.91)
Pooled IL-6ra	1.71	0.31	1.69	(1.18, 2.37)
Fixed-dose corticosteroids	0.99	0.30	0.95	(0.53, 1.70)
Shock-dependent corticosteroids	1.21	0.39	1.16	(0.62, 2.15)
Combination therapy	0.40	0.15	0.38	(0.18, 0.76)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.16	0.31	1.12	(0.67, 1.86)
Hydroxychloroquine*Pooled IL-6ra combination	1.01	0.33	0.97	(0.49, 1.76)
Combination therapy*Pooled IL-6ra combination	0.69	0.30	0.63	(0.28, 1.42)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	0.67	0.24	0.63	(0.32, 1.25)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.58	0.24	0.54	(0.24, 1.16)
Combination therapy*Fixed-dose corticosteroids combination	0.40	0.20	0.36	(0.14, 0.91)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	1.00	(0.90, 1.10)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.01	0.05	1.00	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.11)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 10: Posterior probabilities for secondary analysis of in-hospital mortality for Unblinded ITT population

	Posterior Probability
Lopinavir−ritonavir is optimal	0.016
Lopinavir−ritonavir is superior to control	0.015
Lopinavir−ritonavir is futile (OR < 1.2)	0.999
Lopinavir−ritonavir is harmful (OR < 1)	0.985
Hydroxychloroquine is optimal	0.009
Hydroxychloroquine is superior to control	0.009
Hydroxychloroquine is futile (OR < 1.2)	0.999
Hydroxychloroquine is harmful (OR < 1)	0.992
Combination therapy is optimal	0.002
Combination therapy OR > 1	0.003
Combination therapy is futile (OR < 1.2)	0.999
Combination therapy is harmful (OR < 1)	0.997
Lopinavir−ritonavir*Pooled IL-6ra combination OR > 1	0.671
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.463
Lopinavir−ritonavir*Fixed-dose combination OR > 1	0.096
Hydroxychloroquine*Fixed-dose combination OR > 1	0.059
Lopinavir−ritonavir and Hydroxychloroquine are equivalent	0.570

3.3 Secondary analysis of in-hospital mortality for Unblinded ITT population restricted to non-negative COVID-19

- Model: Primary dichotomous model
- Factors: Age, sex, site, time, tocilizumab, sarilumab, and control interventions, corticosteroid interventions (control, fixed-duration, shock-dependent) and antiviral interventions (control, Hydroxychloroquine, Lopinavir−ritonavir, Lopinavir−ritonavir + Hydroxychloroquine), and interactions between tocilizumab, sarilumab, corticosteroids, and antivirals

Table 11: Odds ratio parameters for secondary analysis of in-hospital mortality for Unblinded ITT population restricted to non-negative COVID-19

	Mean	SD	Median	CrI
Age<39	12.76	7.29	10.95	(4.67, 31.90)
Age 40-49	3.09	0.86	2.97	(1.79, 5.14)
Age 50-59	2.82	0.58	2.77	(1.87, 4.14)
Age 70-79	0.42	0.08	0.42	(0.29, 0.61)
Age 80+	0.21	0.07	0.20	(0.11, 0.37)
Female	1.18	0.20	1.16	(0.84, 1.61)
Time epoch 1	0.94	0.08	0.94	(0.79, 1.10)
Time epoch 2	0.88	0.13	0.87	(0.63, 1.16)
Time epoch 3	0.85	0.17	0.84	(0.56, 1.23)
Time epoch 4	0.85	0.21	0.83	(0.52, 1.34)
Time epoch 5	0.86	0.23	0.83	(0.49, 1.40)
Time epoch 6	0.85	0.24	0.82	(0.47, 1.43)
Time epoch 7	0.84	0.24	0.81	(0.46, 1.43)
Time epoch 8	0.85	0.24	0.82	(0.47, 1.41)
Time epoch 9	0.88	0.25	0.85	(0.49, 1.45)
Time epoch 10	0.91	0.25	0.88	(0.51, 1.50)
Time epoch 11	0.92	0.25	0.89	(0.53, 1.52)
Time epoch 12	0.94	0.26	0.90	(0.53, 1.53)
Time epoch 13	0.99	0.29	0.94	(0.54, 1.67)
Time epoch 14	1.09	0.36	1.04	(0.55, 1.96)
Time epoch 15	1.26	0.53	1.16	(0.55, 2.58)
Time epoch 16	1.53	0.97	1.30	(0.50, 3.83)
Lopinavir−ritonavir	0.69	0.14	0.68	(0.46, 1.01)
Hydroxychloroquine	0.53	0.16	0.52	(0.25, 0.87)
Pooled IL-6ra	1.70	0.33	1.67	(1.15, 2.42)
Fixed-dose corticosteroids	0.92	0.30	0.87	(0.46, 1.62)
Shock-dependent corticosteroids	1.07	0.37	1.02	(0.53, 1.95)
Combination therapy	0.37	0.15	0.34	(0.16, 0.74)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.19	0.34	1.14	(0.65, 1.99)
Hydroxychloroquine*Pooled IL-6ra combination	0.90	0.33	0.86	(0.39, 1.69)
Combination therapy*Pooled IL-6ra combination	0.63	0.29	0.57	(0.24, 1.37)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	0.64	0.25	0.59	(0.28, 1.25)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.48	0.22	0.44	(0.17, 1.04)
Combination therapy*Fixed-dose corticosteroids combination	0.34	0.19	0.30	(0.11, 0.83)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	0.99	(0.90, 1.10)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.91, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.90, 1.10)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.11)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.90, 1.10)

Table 12: Posterior probabilities for secondary analysis of in-hospital mortality for Unblinded ITT population restricted to non-negative COVID-19

	Posterior Probability
Lopinavir–ritonavir is optimal	0.033
Lopinavir–ritonavir is superior to control	0.029
Lopinavir–ritonavir is futile (OR < 1.2)	0.998
Lopinavir–ritonavir is harmful (OR < 1)	0.971
Hydroxychloroquine is optimal	0.005
Hydroxychloroquine is superior to control	0.005
Hydroxychloroquine is futile (OR < 1.2)	1.000
Hydroxychloroquine is harmful (OR < 1)	0.995
Combination therapy is optimal	0.002
Combination therapy OR > 1	0.003
Combination therapy is futile (OR < 1.2)	1.000
Combination therapy is harmful (OR < 1)	0.997
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.680
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.333
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.091
Hydroxychloroquine*Fixed-dose combination OR > 1	0.030
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.428

3.4 Secondary analysis of in-hospital mortality for Antiviral ITT population

- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, lopinavir–ritonavir, hydroxychloroquine, combination therapy and control interventions

Table 13: Odds ratio parameters for sensitivity analysis of in hospital mortality in Antiviral ITT population

	Mean	SD	Median	CrI
Age<39	10.13	6.10	8.62	(3.34, 25.81)
Age 40-49	5.10	1.92	4.71	(2.45, 10.00)
Age 50-59	3.29	0.87	3.17	(1.94, 5.31)
Age 70-79	0.49	0.12	0.48	(0.30, 0.76)
Age 80+	0.34	0.13	0.32	(0.15, 0.65)
Female	0.98	0.21	0.96	(0.65, 1.46)
Time epoch 1	0.97	0.09	0.96	(0.79, 1.16)
Time epoch 2	0.92	0.16	0.92	(0.63, 1.25)
Time epoch 3	0.93	0.21	0.91	(0.57, 1.39)
Time epoch 4	0.96	0.26	0.93	(0.55, 1.56)
Time epoch 5	0.98	0.30	0.93	(0.52, 1.66)
Time epoch 6	0.97	0.31	0.93	(0.50, 1.70)
Time epoch 7	0.97	0.32	0.93	(0.49, 1.73)
Time epoch 8	0.99	0.32	0.95	(0.51, 1.75)
Time epoch 9	1.02	0.33	0.97	(0.54, 1.78)
Time epoch 10	1.05	0.33	0.99	(0.57, 1.83)
Time epoch 11	1.03	0.30	0.98	(0.57, 1.74)
Time epoch 12	0.98	0.28	0.94	(0.55, 1.64)
Time epoch 13	0.94	0.29	0.90	(0.50, 1.60)
Time epoch 14	0.93	0.36	0.87	(0.41, 1.78)
Time epoch 15	0.95	0.55	0.85	(0.30, 2.19)
Lopinavir-ritonavir	0.72	0.13	0.70	(0.49, 1.01)
Hydroxychloroquine	0.61	0.16	0.60	(0.31, 0.96)
Combination	0.44	0.17	0.41	(0.19, 0.84)
Combination interaction	1.00	0.05	1.00	(0.90, 1.10)

Table 14: Posterior probabilities for sensitivity analysis of in-hospital mortality in Antiviral ITT population

	Posterior Probability
Lopinavir-ritonavir is optimal	0.026
Lopinavir-ritonavir is superior to control	0.029
Lopinavir-ritonavir is futile (OR < 1.2)	0.998
Lopinavir-ritonavir is harmful (OR < 1)	0.971
Hydroxychloroquine is optimal	0.013
Hydroxychloroquine is superior to control	0.016
Hydroxychloroquine is futile (OR < 1.2)	0.998
Hydroxychloroquine is harmful (OR < 1)	0.984
Combination therapy is optimal	0.004
Combination therapy is superior to control	0.007
Combination therapy is futile (OR < 1.2)	0.999
Combination therapy is harmful (OR < 1)	0.993
Lopinavir-ritonavir and hydroxychloroquine are equivalent	0.534

4 Safety analyses

4.1 Empirical distribution of any serious adverse event in Antiviral ITT population

Table 15: Summary of any serious adverse event (SAE) for the Antiviral ITT population. Note that this table shows the number of patients with any serious adverse event rather than the total number of serious adverse events observed.

Intervention	# Patients (N)	# Known (n)	Any serious adverse event (y)	Rate of any serious adverse event (y/n)
Lopinavir-ritonavir	255	255	13	0.051
Hydroxychloroquine	50	50	3	0.060
Combination therapy	27	27	1	0.037
Control	362	362	12	0.033

4.2 Primary safety analysis of any serious adverse event in Antiviral ITT population

- Model: Primary dichotomous model
- Factors: Age, sex, site, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir–ritonavir

Table 16: Odds ratio parameters for the primary safety analysis of any serious adverse event in the Antiviral ITT population

	Mean	SD	Median	CrI
Age<39	10.16	11.29	6.64	(1.33, 39.71)
Age 40-49	4.56	3.71	3.51	(1.04, 14.34)
Age 50-59	1.28	0.62	1.16	(0.48, 2.86)
Age 70-79	0.82	0.43	0.73	(0.29, 1.93)
Age 80+	1.05	0.95	0.77	(0.20, 3.54)
Female	1.05	0.47	0.95	(0.43, 2.23)
Lopinavir−ritonavir	0.60	0.26	0.55	(0.24, 1.22)
Hydroxychloroquine	0.81	0.60	0.65	(0.20, 2.38)
Combination therapy	1.35	1.25	0.97	(0.24, 4.79)

Table 17: Posterior probabilities for the primary safety analysis of any serious adverse event in the Antiviral ITT population

	Posterior Probability
Lopinavir−ritonavir is superior to control	0.070
Hydroxychloroquine is superior to control	0.252
Combination therapy is superior to control	0.481

4.3 Empirical distribution of serious ventricular arrhythmia or sudden unexpected death in Antiviral ITT population

Table 18: Summary of serious ventricular arrythmia (SVA) or sudden unexpected death for the Antiviral ITT population

Intervention	# Patients (N)	# Known (n)	Serious ventricular arrythmia or sudden unexpected death (y)	Rate of serious ventricular arrythmia or sudden unexpected death (y/n)
Lopinavir-ritonavir	255	239	6	0.025
Hydroxychloroquine	50	49	2	0.041
Combination therapy	27	26	2	0.077
Control	362	345	10	0.029

4.4 Primary safety analysis of serious ventricular arrhythmia or sudden unexpected death in Antiviral ITT population

- Model: Primary dichotomous model
- Factors: Age, sex, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir–ritonavir
- This model was fit without a site effect due to the small number of events observed.

Table 19: Odds ratio parameters for the primary safety analysis of serious ventricular arrythmia or sudden unexpected death in the Antiviral ITT population

	Mean	SD	Median	CrI
Age<39	4.48	4.68	3.06	(0.72, 16.37)
Age 40-49	5.25	4.90	3.82	(1.04, 18.36)
Age 50-59	1.35	0.72	1.19	(0.48, 3.17)
Age 70-79	1.08	0.58	0.95	(0.39, 2.56)
Age 80+	2.48	2.51	1.78	(0.45, 8.74)
Female	1.50	0.80	1.32	(0.55, 3.51)
Lopinavir–ritonavir	1.46	0.73	1.30	(0.56, 3.28)
Hydroxychloroquine	1.14	0.93	0.88	(0.27, 3.55)
Combination therapy	0.83	0.73	0.62	(0.18, 2.60)

Table 20: Posterior probabilities for the primary safety analysis of serious ventricular arrythmia or sudden unexpected death in the Antiviral ITT population

	Posterior Probability
Lopinavir–ritonavir is superior to control	0.718
Hydroxychloroquine is superior to control	0.418
Combination therapy is superior to control	0.250

5 Analyses of secondary endpoints

5.1 Secondary analysis of mortality

- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no

steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation

- Population: Unblinded ITT

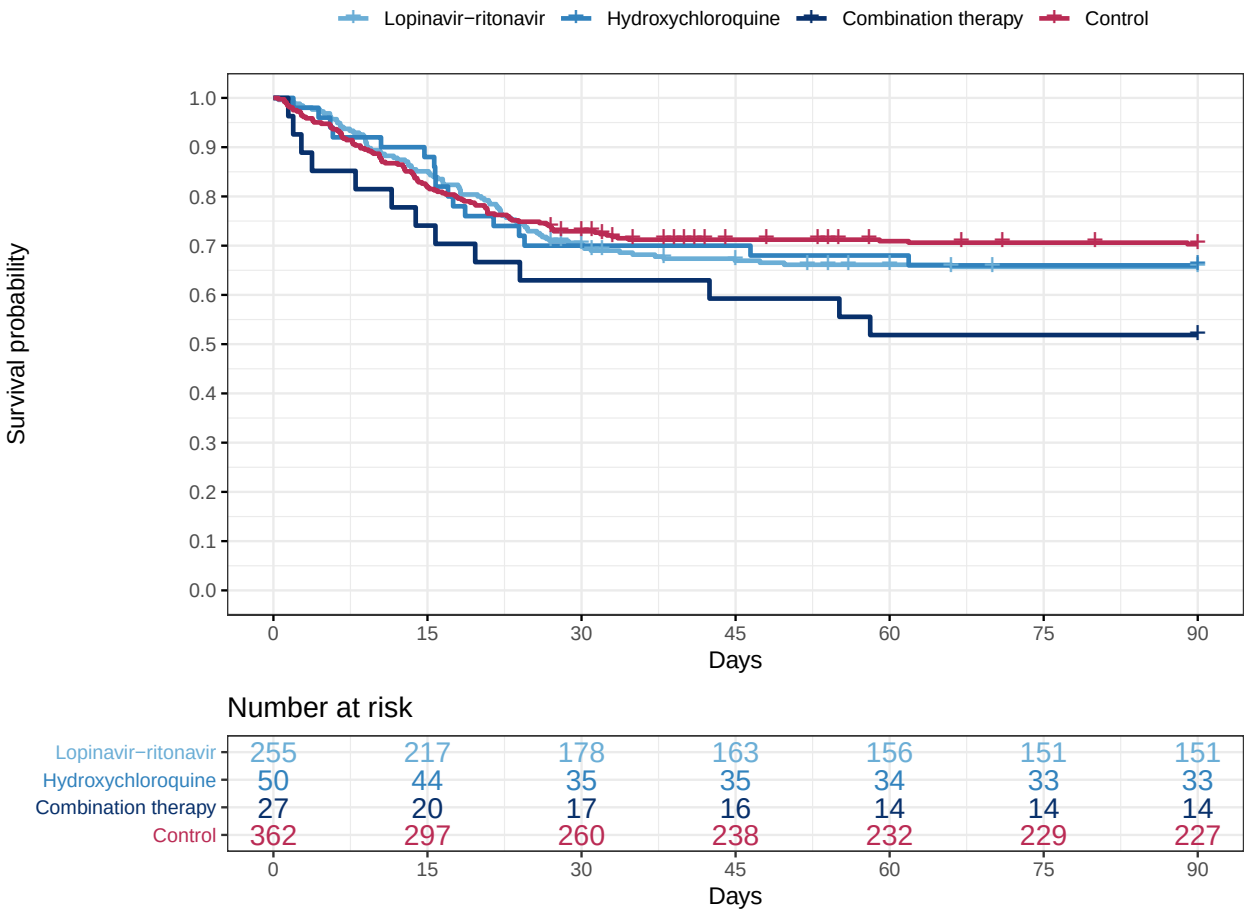


Figure 10: Empirical distribution of mortality for Lopinavir−ritonavir, Hydroxychloroquine, Combination therapy and control. This plot is restricted to the Antiviral ITT population.

Table 21: Summary of 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates for mortality (in days). Displaying the observed percentiles for this outcome.

	2.5	10.0	25.0	50.0	75.0	90.0	97.5
Lopinavir-ritonavir	4.54	9.17	23.58	-	-	-	-
Hydroxychloroquine	4.4	12.59	21.44	-	-	-	-
Combination therapy	1.45	2.72	13.85	-	-	-	-
Control	2.3	8.48	23.88	-	-	-	-

Table 22: Hazard ratio parameters for secondary analysis of mortality

	Mean	SD	Median	CrI
Age<39	5.80	2.26	5.36	(2.83, 11.24)
Age 40-49	2.33	0.51	2.28	(1.52, 3.46)
Age 50-59	2.28	0.38	2.25	(1.61, 3.12)
Age 70-79	0.49	0.06	0.49	(0.38, 0.62)
Age 80+	0.32	0.06	0.31	(0.22, 0.45)
Female	1.08	0.13	1.07	(0.86, 1.34)
Time epoch 1	0.96	0.08	0.96	(0.82, 1.11)
Time epoch 2	0.92	0.11	0.91	(0.71, 1.15)
Time epoch 3	0.92	0.14	0.91	(0.67, 1.22)
Time epoch 4	0.93	0.17	0.92	(0.64, 1.31)
Time epoch 5	0.94	0.20	0.92	(0.62, 1.39)
Time epoch 6	0.92	0.20	0.90	(0.59, 1.36)
Time epoch 7	0.89	0.19	0.87	(0.57, 1.31)
Time epoch 8	0.90	0.18	0.88	(0.59, 1.33)
Time epoch 9	0.92	0.19	0.91	(0.62, 1.36)
Time epoch 10	0.96	0.19	0.94	(0.64, 1.41)
Time epoch 11	0.94	0.18	0.92	(0.63, 1.34)
Time epoch 12	0.90	0.17	0.89	(0.62, 1.26)
Time epoch 13	0.90	0.17	0.89	(0.61, 1.27)
Time epoch 14	0.98	0.20	0.96	(0.64, 1.42)
Time epoch 15	1.13	0.34	1.07	(0.64, 1.94)
Time epoch 16	1.42	0.93	1.23	(0.62, 3.30)
Lopinavir−ritonavir	0.84	0.11	0.83	(0.65, 1.07)
Hydroxychloroquine	0.71	0.13	0.71	(0.45, 0.97)
Pooled IL-6ra	1.62	0.20	1.61	(1.26, 2.07)
Fixed-dose corticosteroids	0.87	0.15	0.85	(0.62, 1.19)
Shock-dependent corticosteroids	1.03	0.23	1.00	(0.66, 1.54)
Combination therapy	0.59	0.14	0.58	(0.36, 0.92)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.37	0.26	1.34	(0.95, 1.95)
Hydroxychloroquine*Pooled IL-6ra combination	1.15	0.27	1.13	(0.70, 1.73)
Combination therapy*Pooled IL-6ra combination	0.97	0.27	0.94	(0.55, 1.61)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	0.73	0.15	0.71	(0.48, 1.10)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.61	0.16	0.59	(0.34, 0.98)
Combination therapy*Fixed-dose corticosteroids combination	0.52	0.16	0.49	(0.27, 0.92)
Hydroxychloroquine and Lopinavir−ritonavir interaction	0.99	0.05	0.99	(0.90, 1.10)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.01	0.05	1.00	(0.91, 1.11)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.92, 1.10)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.90, 1.10)

Table 23: Posterior probabilities for secondary analysis of mortality

	Posterior Probability
Lopinavir–ritonavir is optimal	0.077
Lopinavir–ritonavir is superior to control	0.080
Lopinavir–ritonavir is futile (OR < 1.2)	0.998
Lopinavir–ritonavir is harmful (OR < 1)	0.920
Hydroxychloroquine is optimal	0.018
Hydroxychloroquine is superior to control	0.017
Hydroxychloroquine is futile (OR < 1.2)	0.998
Hydroxychloroquine is harmful (OR < 1)	0.984
Combination therapy is optimal	0.009
Combination therapy OR > 1	0.013
Combination therapy is futile (OR < 1.2)	0.997
Combination therapy is harmful (OR < 1)	0.987
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.953
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.702
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.058
Hydroxychloroquine*Fixed-dose combination OR > 1	0.021
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.547

5.2 Secondary analysis of progression to intubation, ECMO, or death

- Model: Primary dichotomous model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation
- Population: Unblinded ITT not on ventilation or ECMO at baseline. There are 453 patients that meet this criterion.

Table 24: Summary of progression to intubation, ECMO, or death for the Unblinded ITT population restricted to patients not on mechanical ventilation or ECMO at baseline

Intervention	# Patients (N)	# Progressors (y)	Progression Rate (y/N)
Lopinavir-ritonavir	176	89	0.506
Hydroxychloroquine	24	17	0.708
Combination therapy	14	11	0.786
Control	239	107	0.448

Table 25: Summary of progression to intubation, ECMO, or death by component for the Unblinded ITT population restricted to patients not on mechanical ventilation or ECMO at baseline. Note that a patient may progress on more than one component of the composite endpoint, so the sum of events in this table will not match the total number of progressors.

Intervention	# Patients (N)	Death, n (%)	Intubation, n (%)	ECMO, n (%)
Lopinavir-ritonavir	176	52 (29.5)	73 (41.5)	1 (0.6)
Hydroxychloroquine	24	9 (37.5)	14 (58.3)	2 (8.3)
Combination therapy	14	6 (42.9)	10 (71.4)	1 (7.1)
Control	239	61 (25.5)	79 (33.1)	3 (1.3)

Table 26: Odds ratio parameters for secondary analysis of progression to intubation, ECMO, or death

	Mean	SD	Median	CrI
Age<39	5.35	2.10	4.96	(2.48, 10.50)
Age 40-49	1.88	0.47	1.83	(1.14, 2.96)
Age 50-59	1.70	0.35	1.66	(1.12, 2.50)
Age 70-79	0.80	0.17	0.78	(0.52, 1.18)
Age 80+	0.51	0.16	0.49	(0.26, 0.89)
Female	1.10	0.19	1.09	(0.78, 1.50)
Time epoch 1	0.93	0.08	0.93	(0.78, 1.11)
Time epoch 2	0.84	0.13	0.84	(0.60, 1.11)
Time epoch 3	0.80	0.16	0.78	(0.51, 1.14)
Time epoch 4	0.78	0.18	0.76	(0.47, 1.19)
Time epoch 5	0.78	0.20	0.75	(0.45, 1.24)
Time epoch 6	0.77	0.21	0.74	(0.43, 1.26)
Time epoch 7	0.77	0.21	0.74	(0.44, 1.26)
Time epoch 8	0.78	0.21	0.76	(0.45, 1.27)
Time epoch 9	0.80	0.22	0.77	(0.46, 1.31)
Time epoch 10	0.83	0.24	0.79	(0.46, 1.38)
Time epoch 11	0.84	0.26	0.80	(0.45, 1.45)
Time epoch 12	0.86	0.28	0.82	(0.44, 1.53)
Time epoch 13	0.91	0.32	0.86	(0.44, 1.66)
Time epoch 14	1.01	0.41	0.94	(0.45, 2.01)
Time epoch 15	1.19	0.66	1.04	(0.42, 2.79)
Lopinavir−ritonavir	0.77	0.16	0.75	(0.50, 1.12)
Hydroxychloroquine	0.58	0.20	0.58	(0.24, 1.00)
Pooled IL-6ra	1.72	0.32	1.69	(1.18, 2.42)
Fixed-dose corticosteroids	2.92	1.17	2.70	(1.31, 5.78)
Shock-dependent corticosteroids	1.34	0.53	1.24	(0.59, 2.66)
Combination therapy	0.45	0.20	0.42	(0.16, 0.95)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.33	0.39	1.27	(0.73, 2.23)
Hydroxychloroquine*Pooled IL-6ra combination	1.00	0.40	0.96	(0.37, 1.91)
Combination therapy*Pooled IL-6ra combination	0.78	0.39	0.70	(0.26, 1.75)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	2.24	1.04	2.03	(0.89, 4.83)
Hydroxychloroquine*Fixed-dose corticosteroids combination	1.69	0.90	1.52	(0.50, 4.00)
Combination therapy*Fixed-dose corticosteroids combination	1.31	0.81	1.11	(0.35, 3.42)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	1.00	(0.90, 1.10)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.91, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.01	0.05	1.00	(0.91, 1.11)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.11)

Table 27: Posterior probabilities for secondary analysis of progression to intubation, ECMO, or death

	Posterior Probability
Lopinavir–ritonavir is optimal	0.078
Lopinavir–ritonavir is superior to control	0.080
Lopinavir–ritonavir is futile (OR < 1.2)	0.988
Lopinavir–ritonavir is harmful (OR < 1)	0.920
Hydroxychloroquine is optimal	0.018
Hydroxychloroquine is superior to control	0.024
Hydroxychloroquine is futile (OR < 1.2)	0.997
Hydroxychloroquine is harmful (OR < 1)	0.976
Combination therapy is optimal	0.012
Combination therapy OR > 1	0.018
Combination therapy is futile (OR < 1.2)	0.993
Combination therapy is harmful (OR < 1)	0.982
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.808
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.457
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.953
Hydroxychloroquine*Fixed-dose combination OR > 1	0.783
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.434

5.3 Secondary analysis of days free of vasopressors/inotropes

- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation
- Population: Unblinded ITT
- There are 25 missing values of days free of vasopressors/inotropes in the Unblinded ITT population due to missing daily data. These patients are removed from this analysis.

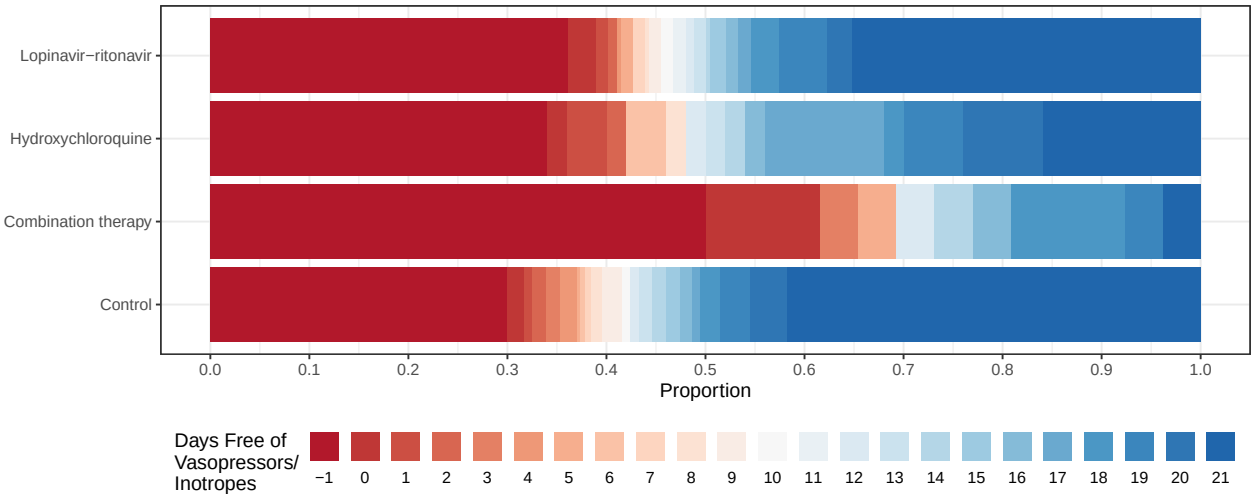


Figure 11: Empirical distribution of days-free of vasopressors and inotropes for lopinavir−ritonavir, hydroxychloroquine, combination therapy, and control. This plot is restricted to the Antiviral ITT population.

Table 28: Summary of Days Free of Vasopressors/Inotropes for the Antiviral ITT population

Intervention	# Patients	# Known	Days Free Vasopressors/Inotropes median (IQR)	Days Free of Vasopressors/Inotropes in Survivors* median (IQR)
Lopinavir-ritonavir	255	244	13.5 (-1, 21)	21 (16, 21)
Hydroxychloroquine	50	50	12.5 (-1, 19)	17 (12.75, 20.25)
Combination therapy	27	26	-0.5 (-1, 13.5)	14 (3, 18)
Control	362	354	18 (-1, 21)	21 (15.5, 21)

* Days Free of vasopressors/inotropes in survivors within 21 days

Table 29: Odds ratio parameters for secondary analysis of days free of vasopressors/inotropes

	Mean	SD	Median	CrI
Age<39	3.88	0.92	3.77	(2.42, 5.94)
Age 40-49	2.46	0.44	2.42	(1.72, 3.42)
Age 50-59	2.02	0.29	2.00	(1.52, 2.66)
Age 70-79	0.50	0.08	0.49	(0.36, 0.67)
Age 80+	0.29	0.08	0.28	(0.16, 0.47)
Female	1.17	0.14	1.16	(0.91, 1.47)
Time epoch 1	0.95	0.08	0.95	(0.80, 1.10)
Time epoch 2	0.90	0.13	0.90	(0.66, 1.16)
Time epoch 3	0.93	0.16	0.92	(0.65, 1.26)
Time epoch 4	0.99	0.21	0.96	(0.66, 1.44)
Time epoch 5	1.03	0.24	1.00	(0.66, 1.59)
Time epoch 6	1.04	0.24	1.00	(0.65, 1.59)
Time epoch 7	1.02	0.23	1.00	(0.65, 1.56)
Time epoch 8	1.02	0.23	0.99	(0.65, 1.53)
Time epoch 9	0.99	0.21	0.96	(0.64, 1.47)
Time epoch 10	0.94	0.20	0.91	(0.61, 1.39)
Time epoch 11	0.85	0.18	0.83	(0.56, 1.25)
Time epoch 12	0.78	0.17	0.77	(0.51, 1.16)
Time epoch 13	0.75	0.17	0.73	(0.48, 1.12)
Time epoch 14	0.76	0.18	0.73	(0.47, 1.16)
Time epoch 15	0.80	0.23	0.77	(0.45, 1.33)
Time epoch 16	0.90	0.36	0.83	(0.41, 1.78)
Lopinavir−ritonavir	0.67	0.10	0.66	(0.49, 0.89)
Hydroxychloroquine	0.61	0.12	0.60	(0.39, 0.86)
Pooled IL-6ra	1.68	0.25	1.66	(1.25, 2.21)
Fixed-dose corticosteroids	1.46	0.33	1.42	(0.92, 2.20)
Shock-dependent corticosteroids	1.16	0.27	1.14	(0.73, 1.78)
Combination therapy	0.41	0.12	0.39	(0.22, 0.69)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.13	0.24	1.10	(0.73, 1.68)
Hydroxychloroquine*Pooled IL-6ra combination	1.02	0.26	1.00	(0.60, 1.60)
Combination therapy*Pooled IL-6ra combination	0.69	0.23	0.65	(0.34, 1.23)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	0.98	0.27	0.94	(0.55, 1.60)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.89	0.28	0.85	(0.46, 1.54)
Combination therapy*Fixed-dose corticosteroids combination	0.60	0.23	0.56	(0.27, 1.15)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	0.99	(0.90, 1.09)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.01	0.05	1.00	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.01	0.05	1.01	(0.91, 1.11)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.01	0.05	1.00	(0.91, 1.11)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 30: Posterior probabilities for secondary analysis of days free of vasopressors/inotropes

	Posterior Probability
Lopinavir–ritonavir is optimal	0.004
Lopinavir–ritonavir is superior to control	0.003
Lopinavir–ritonavir is futile (OR < 1.2)	1.000
Lopinavir–ritonavir is harmful (OR < 1)	0.997
Hydroxychloroquine is optimal	0.005
Hydroxychloroquine is superior to control	0.004
Hydroxychloroquine is futile (OR < 1.2)	1.000
Hydroxychloroquine is harmful (OR < 1)	0.996
Combination therapy is optimal	0.001
Combination therapy OR > 1	0.000
Combination therapy is futile (OR < 1.2)	1.000
Combination therapy is harmful (OR < 1)	1.000
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.681
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.496
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.412
Hydroxychloroquine*Fixed-dose combination OR > 1	0.302
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.653

5.4 Secondary analysis of days free of ventilation

- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation
- Population: Unblinded ITT
- There are 25 missing values of days free of ventilation in the Unblinded ITT population due to missing daily data. These patients are removed from this analysis.

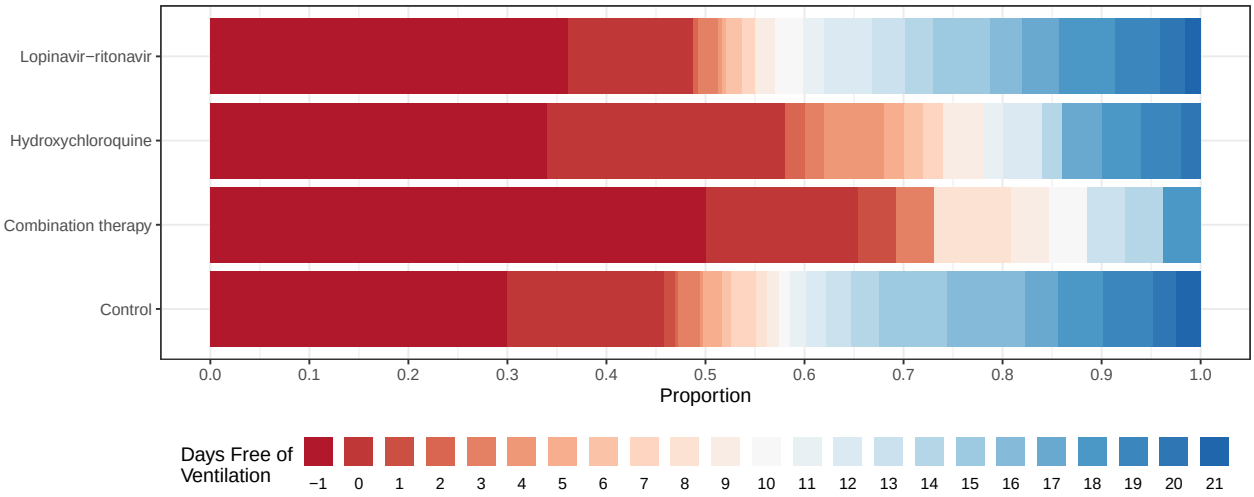


Figure 12: Empirical distribution of days-free of ventilation for lopinavir−ritonavir, hydroxychloroquine, combination therapy, and control. This plot is restricted to the Antiviral ITT population.

Table 31: Summary of Days Free of Ventilation for the Antiviral ITT population

Intervention	# Patients	# Known	Days Free of Ventilation median (IQR)	Days Free of Ventilation in Survivors* median (IQR)
Lopinavir-ritonavir	255	244	3 (-1, 15)	13 (4.75, 17)
Hydroxychloroquine	50	50	0 (-1, 8.5)	4 (0, 12)
Combination therapy	27	26	-0.5 (-1, 6.75)	8 (0, 10)
Control	362	354	5 (-1, 16)	14 (3, 17)

* Days Free of ventilation in survivors within 21 days

Table 32: Odds ratio parameters for secondary analysis of days free of ventilation

	Mean	SD	Median	CrI
Age<39	4.11	0.91	4.01	(2.62, 6.17)
Age 40-49	2.11	0.37	2.08	(1.48, 2.91)
Age 50-59	1.89	0.26	1.87	(1.43, 2.44)
Age 70-79	0.50	0.08	0.49	(0.36, 0.66)
Age 80+	0.33	0.09	0.32	(0.19, 0.54)
Female	1.20	0.14	1.19	(0.95, 1.49)
Time epoch 1	0.96	0.08	0.96	(0.80, 1.12)
Time epoch 2	0.91	0.14	0.91	(0.66, 1.19)
Time epoch 3	0.98	0.18	0.97	(0.67, 1.36)
Time epoch 4	1.09	0.23	1.07	(0.71, 1.61)
Time epoch 5	1.22	0.29	1.18	(0.76, 1.90)
Time epoch 6	1.29	0.32	1.24	(0.80, 2.04)
Time epoch 7	1.32	0.32	1.27	(0.83, 2.06)
Time epoch 8	1.35	0.32	1.31	(0.85, 2.11)
Time epoch 9	1.28	0.29	1.24	(0.82, 1.94)
Time epoch 10	1.15	0.25	1.12	(0.75, 1.71)
Time epoch 11	0.98	0.20	0.96	(0.63, 1.43)
Time epoch 12	0.86	0.19	0.85	(0.55, 1.27)
Time epoch 13	0.85	0.19	0.84	(0.54, 1.27)
Time epoch 14	0.93	0.21	0.91	(0.58, 1.42)
Time epoch 15	1.08	0.31	1.04	(0.60, 1.81)
Time epoch 16	1.35	0.60	1.22	(0.57, 2.88)
Lopinavir−ritonavir	0.76	0.11	0.75	(0.56, 0.99)
Hydroxychloroquine	0.65	0.13	0.64	(0.40, 0.92)
Pooled IL-6ra	1.77	0.25	1.75	(1.33, 2.32)
Fixed-dose corticosteroids	1.46	0.33	1.42	(0.92, 2.22)
Shock-dependent corticosteroids	1.22	0.28	1.19	(0.77, 1.87)
Combination therapy	0.49	0.14	0.47	(0.27, 0.83)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.36	0.28	1.33	(0.88, 1.99)
Hydroxychloroquine*Pooled IL-6ra combination	1.15	0.30	1.13	(0.66, 1.81)
Combination therapy*Pooled IL-6ra combination	0.88	0.29	0.83	(0.44, 1.58)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	1.12	0.30	1.08	(0.64, 1.83)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.95	0.30	0.91	(0.48, 1.64)
Combination therapy*Fixed-dose corticosteroids combination	0.72	0.27	0.67	(0.32, 1.40)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	1.00	(0.90, 1.10)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.90, 1.10)

Table 33: Posterior probabilities for secondary analysis of days free of ventilation

	Posterior Probability
Lopinavir–ritonavir is optimal	0.032
Lopinavir–ritonavir is superior to control	0.023
Lopinavir–ritonavir is futile (OR < 1.2)	1.000
Lopinavir–ritonavir is harmful (OR < 1)	0.977
Hydroxychloroquine is optimal	0.009
Hydroxychloroquine is superior to control	0.009
Hydroxychloroquine is futile (OR < 1.2)	1.000
Hydroxychloroquine is harmful (OR < 1)	0.992
Combination therapy is optimal	0.003
Combination therapy OR > 1	0.003
Combination therapy is futile (OR < 1.2)	0.999
Combination therapy is harmful (OR < 1)	0.997
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.920
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.677
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.615
Hydroxychloroquine*Fixed-dose combination OR > 1	0.376
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.577

5.5 Secondary analysis of length of ICU stay

- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation
- Population: Unblinded ITT

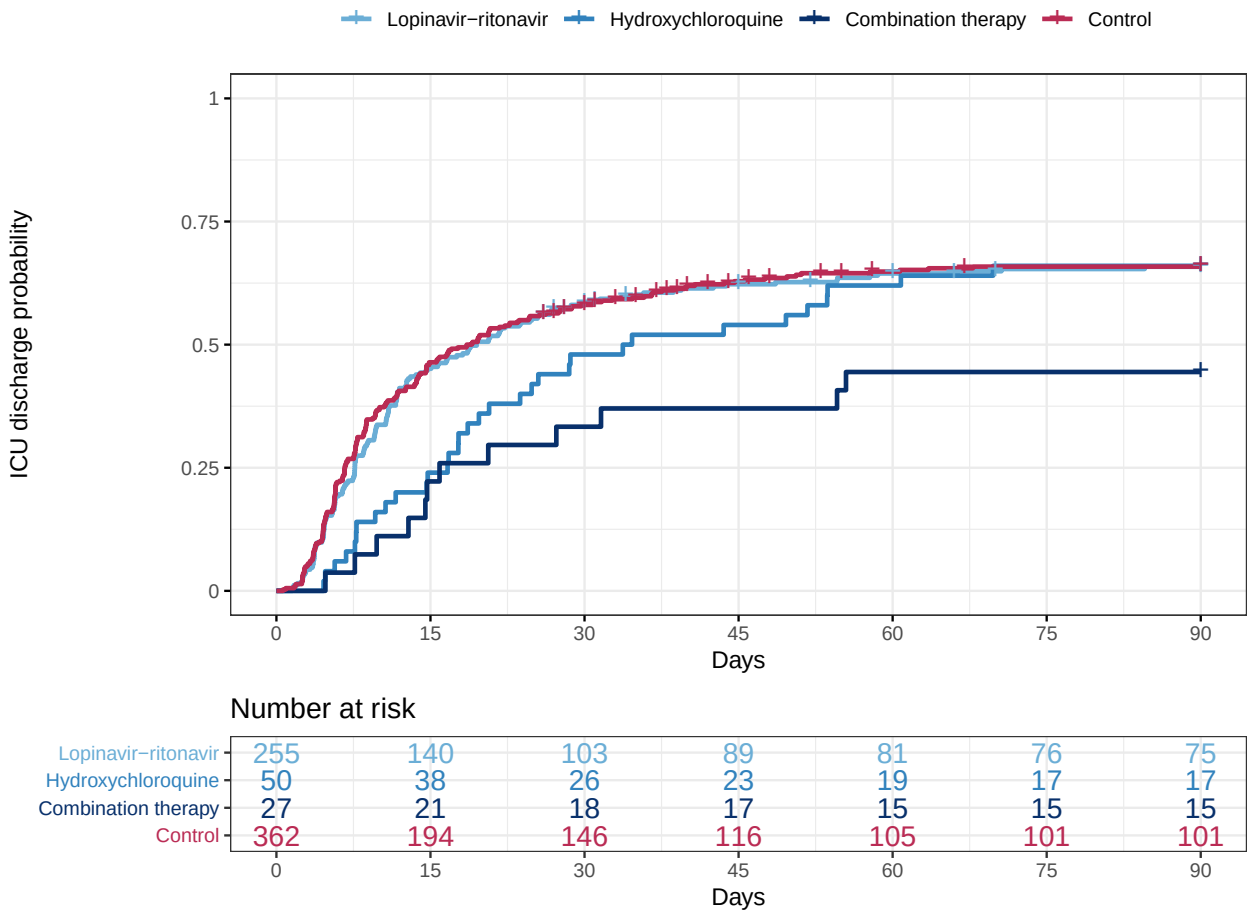


Figure 13: Empirical distribution of length of ICU stay for lopinavir−ritonavir, hydroxychloroquine, combination therapy, and control. This plot is restricted to the Antiviral ITT population.

Table 34: Summary of 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates for length of ICU stay (in days). Displaying the observed percentiles for this outcome.

	2.5	10.0	25.0	50.0	75.0	90.0	97.5
Lopinavir-ritonavir	2.57	4.42	7.63	19.5	-	-	-
Hydroxychloroquine	4.75	7.71	16.67	34.18	-	-	-
Combination therapy	4.77	9.76	15.88	-	-	-	-
Control	2.54	4.39	6.67	18.77	-	-	-

Table 35: Hazard ratio parameters for secondary analysis of length of ICU stay

	Mean	SD	Median	CrI
Age<39	2.53	0.35	2.51	(1.90, 3.23)
Age 40-49	1.69	0.19	1.68	(1.34, 2.10)
Age 50-59	1.62	0.15	1.61	(1.35, 1.93)
Age 70-79	0.68	0.07	0.67	(0.54, 0.83)
Age 80+	0.71	0.13	0.71	(0.49, 1.00)
Female	1.18	0.09	1.18	(1.02, 1.37)
Time epoch 1	1.00	0.06	1.00	(0.87, 1.12)
Time epoch 2	1.02	0.10	1.02	(0.83, 1.22)
Time epoch 3	1.08	0.13	1.07	(0.85, 1.37)
Time epoch 4	1.16	0.17	1.14	(0.89, 1.53)
Time epoch 5	1.19	0.19	1.17	(0.89, 1.61)
Time epoch 6	1.17	0.17	1.15	(0.87, 1.54)
Time epoch 7	1.14	0.16	1.13	(0.84, 1.48)
Time epoch 8	1.14	0.16	1.13	(0.86, 1.47)
Time epoch 9	1.13	0.15	1.12	(0.85, 1.44)
Time epoch 10	1.10	0.15	1.09	(0.84, 1.42)
Time epoch 11	1.06	0.14	1.05	(0.80, 1.36)
Time epoch 12	1.02	0.14	1.02	(0.76, 1.30)
Time epoch 13	1.03	0.14	1.03	(0.77, 1.32)
Time epoch 14	1.12	0.16	1.11	(0.83, 1.43)
Time epoch 15	1.25	0.22	1.23	(0.88, 1.71)
Time epoch 16	1.46	0.39	1.40	(0.87, 2.43)
Lopinavir−ritonavir	0.88	0.09	0.87	(0.72, 1.07)
Hydroxychloroquine	0.74	0.11	0.74	(0.52, 0.94)
Pooled IL-6ra	1.44	0.13	1.43	(1.19, 1.72)
Fixed-dose corticosteroids	0.91	0.11	0.90	(0.72, 1.14)
Shock-dependent corticosteroids	0.95	0.13	0.94	(0.73, 1.21)
Combination therapy	0.64	0.12	0.63	(0.44, 0.89)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.28	0.18	1.27	(0.97, 1.67)
Hydroxychloroquine*Pooled IL-6ra combination	1.06	0.19	1.06	(0.73, 1.43)
Combination therapy*Pooled IL-6ra combination	0.94	0.20	0.91	(0.61, 1.37)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	0.81	0.13	0.81	(0.59, 1.08)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.67	0.13	0.66	(0.44, 0.95)
Combination therapy*Fixed-dose corticosteroids combination	0.59	0.13	0.58	(0.37, 0.89)
Hydroxychloroquine and Lopinavir−ritonavir interaction	0.99	0.05	0.99	(0.90, 1.09)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.02	0.05	1.02	(0.92, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.02	0.05	1.02	(0.92, 1.13)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 36: Posterior probabilities for secondary analysis of length of ICU stay

	Posterior Probability
Lopinavir–ritonavir is optimal	0.126
Lopinavir–ritonavir is superior to control	0.087
Lopinavir–ritonavir is futile (OR < 1.2)	0.999
Lopinavir–ritonavir is harmful (OR < 1)	0.912
Hydroxychloroquine is optimal	0.005
Hydroxychloroquine is superior to control	0.006
Hydroxychloroquine is futile (OR < 1.2)	1.000
Hydroxychloroquine is harmful (OR < 1)	0.994
Combination therapy is optimal	0.006
Combination therapy OR > 1	0.003
Combination therapy is futile (OR < 1.2)	1.000
Combination therapy is harmful (OR < 1)	0.997
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.953
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.607
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.081
Hydroxychloroquine*Fixed-dose combination OR > 1	0.012
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.556

5.6 Secondary analysis of length of hospital stay

- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation
- Population: Unblinded ITT

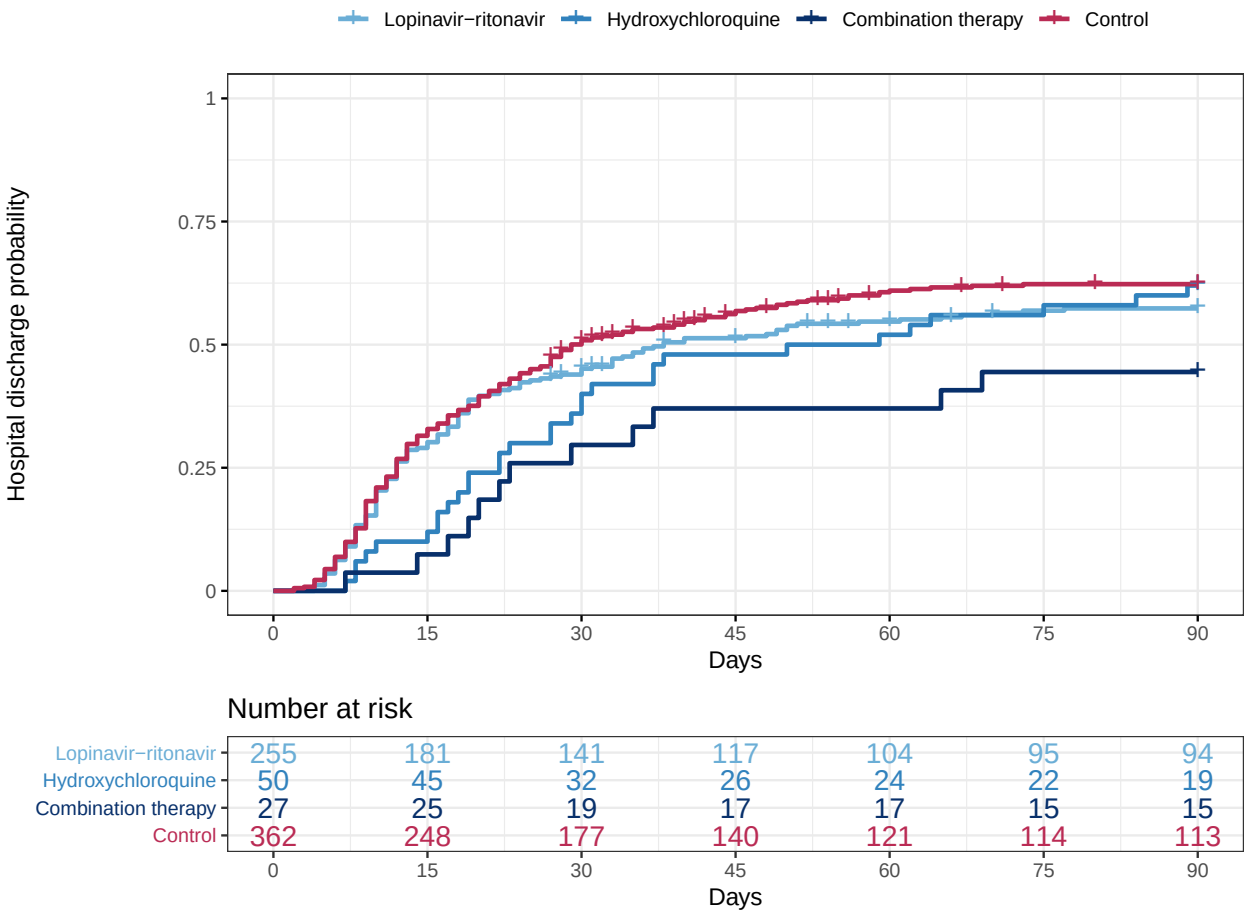


Figure 14: Empirical distribution of length of hospital stay for lopinavir−ritonavir, hydroxychloroquine, combination therapy, and control. This plot is restricted to the Antiviral ITT population.

Table 37: Summary of 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates for length of hospital stay (in days). Displaying the observed percentiles for this outcome.

	2.5	10.0	25.0	50.0	75.0	90.0	97.5
Lopinavir-ritonavir	5	8	12	38	-	-	-
Hydroxychloroquine	8	12.5	22	54.5	-	-	-
Combination therapy	7	17	23	-	-	-	-
Control	5	8	12	29	-	-	-

Table 38: Hazard ratio parameters for secondary analysis of length of hospital stay

	Mean	SD	Median	CrI
Age<39	2.83	0.39	2.82	(2.13, 3.67)
Age 40-49	1.81	0.22	1.80	(1.43, 2.26)
Age 50-59	1.72	0.17	1.71	(1.41, 2.06)
Age 70-79	0.62	0.07	0.62	(0.49, 0.77)
Age 80+	0.46	0.10	0.45	(0.28, 0.66)
Female	1.13	0.09	1.12	(0.96, 1.32)
Time epoch 1	0.99	0.07	0.99	(0.86, 1.12)
Time epoch 2	1.00	0.11	0.99	(0.78, 1.21)
Time epoch 3	1.05	0.14	1.04	(0.80, 1.35)
Time epoch 4	1.12	0.17	1.10	(0.83, 1.50)
Time epoch 5	1.16	0.19	1.14	(0.86, 1.57)
Time epoch 6	1.17	0.19	1.15	(0.86, 1.58)
Time epoch 7	1.17	0.18	1.16	(0.85, 1.57)
Time epoch 8	1.19	0.17	1.18	(0.88, 1.56)
Time epoch 9	1.19	0.17	1.18	(0.90, 1.58)
Time epoch 10	1.18	0.16	1.17	(0.89, 1.53)
Time epoch 11	1.12	0.16	1.11	(0.85, 1.46)
Time epoch 12	1.06	0.15	1.05	(0.80, 1.38)
Time epoch 13	1.05	0.15	1.03	(0.79, 1.36)
Time epoch 14	1.11	0.16	1.09	(0.82, 1.48)
Time epoch 15	1.25	0.23	1.22	(0.86, 1.77)
Time epoch 16	1.49	0.44	1.42	(0.87, 2.59)
Lopinavir−ritonavir	0.83	0.08	0.83	(0.68, 0.99)
Hydroxychloroquine	0.76	0.10	0.76	(0.56, 0.97)
Pooled IL-6ra	1.42	0.13	1.41	(1.19, 1.69)
Fixed-dose corticosteroids	0.91	0.12	0.90	(0.70, 1.15)
Shock-dependent corticosteroids	0.93	0.13	0.93	(0.71, 1.20)
Combination therapy	0.63	0.12	0.63	(0.42, 0.89)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.19	0.17	1.18	(0.89, 1.56)
Hydroxychloroquine*Pooled IL-6ra combination	1.09	0.19	1.08	(0.76, 1.48)
Combination therapy*Pooled IL-6ra combination	0.91	0.20	0.89	(0.58, 1.35)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	0.76	0.13	0.75	(0.54, 1.03)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.70	0.14	0.68	(0.46, 1.00)
Combination therapy*Fixed-dose corticosteroids combination	0.58	0.14	0.57	(0.35, 0.89)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	1.00	(0.91, 1.09)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 39: Posterior probabilities for secondary analysis of length of hospital stay

	Posterior Probability
Lopinavir–ritonavir is optimal	0.035
Lopinavir–ritonavir is superior to control	0.019
Lopinavir–ritonavir is futile (OR < 1.2)	1.000
Lopinavir–ritonavir is harmful (OR < 1)	0.981
Hydroxychloroquine is optimal	0.017
Hydroxychloroquine is superior to control	0.015
Hydroxychloroquine is futile (OR < 1.2)	1.000
Hydroxychloroquine is harmful (OR < 1)	0.985
Combination therapy is optimal	0.004
Combination therapy OR > 1	0.004
Combination therapy is futile (OR < 1.2)	1.000
Combination therapy is harmful (OR < 1)	0.996
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.880
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.665
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.035
Hydroxychloroquine*Fixed-dose combination OR > 1	0.027
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.744

5.7 Secondary analysis of WHO scale at 14 days

- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation
- Population: Unblinded ITT
- There are 19 missing values of WHO scale at day 14 due to missing daily data. These patients are removed from this analysis.

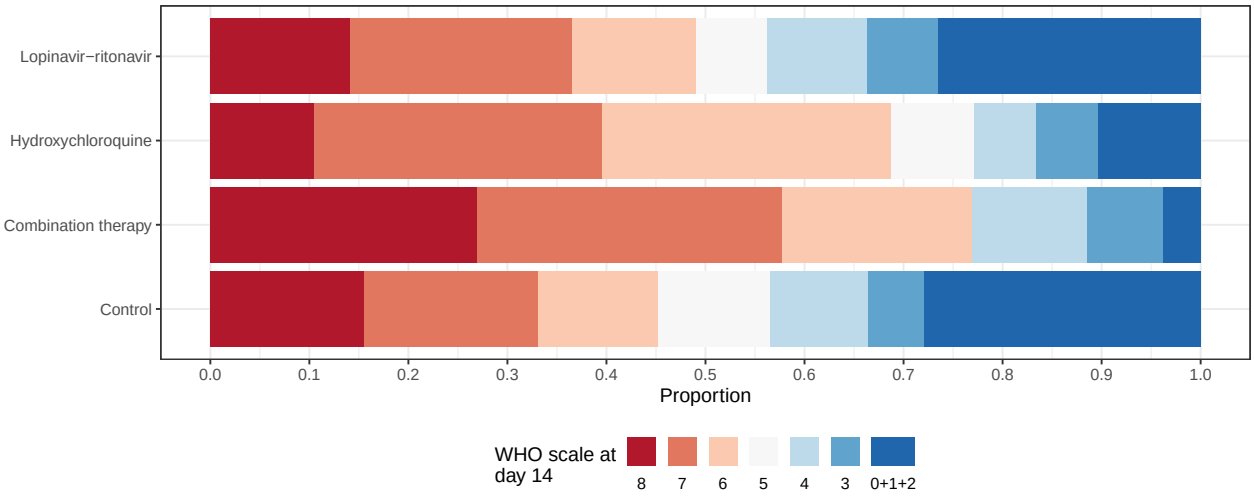


Figure 15: Empirical distribution of modified WHO scale at day 14 for lopinavir−ritonavir, hydroxychloroquine, combination therapy, and control. This plot is restricted to the Antiviral ITT population.

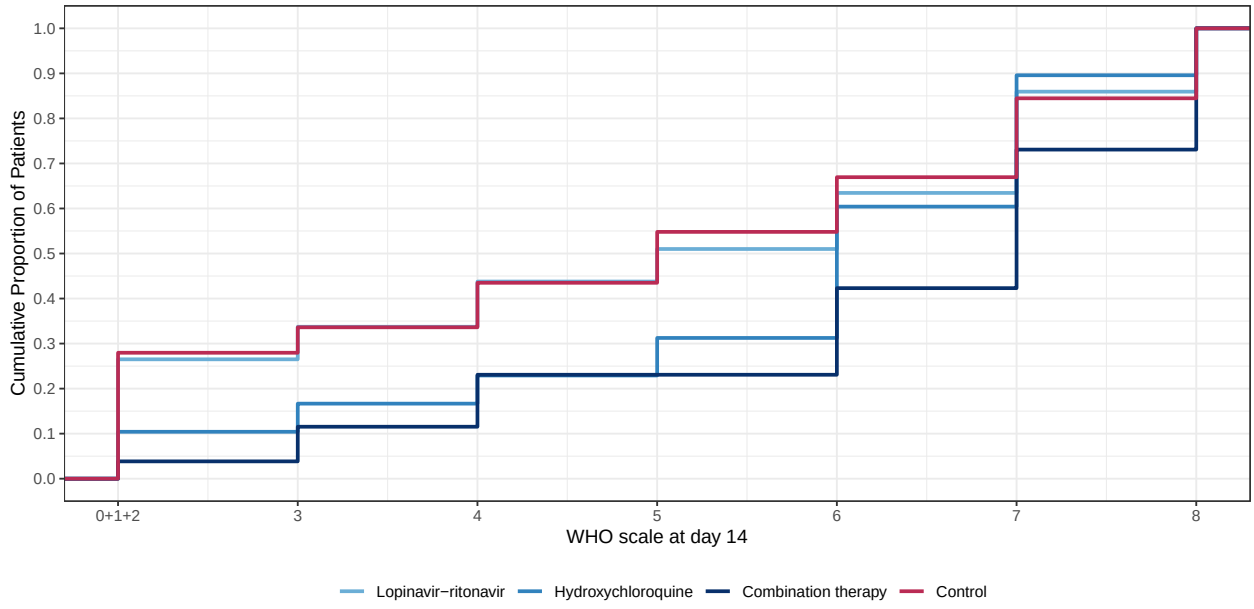


Figure 16: Empirical cumulative distribution of WHO scale for lopinavir−ritonavir, hydroxychloroquine, the combination therapy, and control. This plot is restricted to the Antiviral ITT population.

Table 40: Odds ratio parameters for secondary analysis of WHO scale

	Mean	SD	Median	CrI
Age<39	4.17	0.97	4.07	(2.56, 6.38)
Age 40-49	2.01	0.36	1.98	(1.40, 2.80)
Age 50-59	1.76	0.25	1.74	(1.32, 2.28)
Age 70-79	0.59	0.09	0.58	(0.44, 0.77)
Age 80+	0.33	0.08	0.32	(0.19, 0.51)
Female	1.06	0.12	1.05	(0.84, 1.31)
Time epoch 1	1.04	0.08	1.04	(0.88, 1.22)
Time epoch 2	1.10	0.14	1.09	(0.85, 1.41)
Time epoch 3	1.20	0.21	1.18	(0.84, 1.66)
Time epoch 4	1.33	0.29	1.28	(0.88, 2.00)
Time epoch 5	1.40	0.35	1.34	(0.88, 2.22)
Time epoch 6	1.35	0.33	1.30	(0.84, 2.12)
Time epoch 7	1.26	0.29	1.22	(0.79, 1.92)
Time epoch 8	1.17	0.25	1.14	(0.76, 1.75)
Time epoch 9	1.05	0.22	1.03	(0.70, 1.54)
Time epoch 10	0.95	0.19	0.93	(0.63, 1.38)
Time epoch 11	0.85	0.17	0.83	(0.55, 1.23)
Time epoch 12	0.80	0.17	0.78	(0.51, 1.17)
Time epoch 13	0.82	0.17	0.80	(0.52, 1.20)
Time epoch 14	0.94	0.21	0.91	(0.59, 1.42)
Time epoch 15	1.17	0.34	1.13	(0.66, 1.99)
Time epoch 16	1.60	0.75	1.43	(0.67, 3.49)
Lopinavir−ritonavir	0.86	0.12	0.85	(0.65, 1.13)
Hydroxychloroquine	0.76	0.14	0.76	(0.49, 1.07)
Pooled IL-6ra	1.86	0.26	1.84	(1.39, 2.41)
Fixed-dose corticosteroids	1.35	0.30	1.31	(0.85, 2.03)
Shock-dependent corticosteroids	0.99	0.22	0.96	(0.62, 1.49)
Combination therapy	0.66	0.18	0.63	(0.38, 1.08)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.62	0.33	1.59	(1.08, 2.34)
Hydroxychloroquine*Pooled IL-6ra combination	1.42	0.34	1.39	(0.84, 2.18)
Combination therapy*Pooled IL-6ra combination	1.23	0.38	1.18	(0.66, 2.15)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	1.19	0.32	1.15	(0.68, 1.89)
Hydroxychloroquine*Fixed-dose corticosteroids combination	1.03	0.31	0.99	(0.54, 1.76)
Combination therapy*Fixed-dose corticosteroids combination	0.89	0.33	0.84	(0.42, 1.68)
Hydroxychloroquine and Lopinavir−ritonavir interaction	0.99	0.05	0.99	(0.90, 1.09)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.02	0.05	1.02	(0.93, 1.12)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.90, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 41: Posterior probabilities for secondary analysis of WHO scale

	Posterior Probability
Lopinavir−ritonavir is optimal	0.147
Lopinavir−ritonavir is superior to control	0.134
Lopinavir−ritonavir is futile (OR < 1.2)	0.992
Lopinavir−ritonavir is harmful (OR < 1)	0.867
Hydroxychloroquine is optimal	0.038
Hydroxychloroquine is superior to control	0.056
Hydroxychloroquine is futile (OR < 1.2)	0.996
Hydroxychloroquine is harmful (OR < 1)	0.944
Combination therapy is optimal	0.035
Combination therapy OR > 1	0.045
Combination therapy is futile (OR < 1.2)	0.993
Combination therapy is harmful (OR < 1)	0.955
Lopinavir−ritonavir*Pooled IL-6ra combination OR > 1	0.990
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.905
Lopinavir−ritonavir*Fixed-dose combination OR > 1	0.698
Hydroxychloroquine*Fixed-dose combination OR > 1	0.485
Lopinavir−ritonavir and Hydroxychloroquine are equivalent	0.622

5.8 Secondary analysis of SARS-CoV-2 RNA Clearance

- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control and antiviral interventions (lopinavir−ritonavir, hydroxychloroquine, combination therapy), corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation
- Population: The Unblinded ITT restricted to patients with at least one follow-up rRT-PCR test performed after confirmatory test of SARS-CoV-2. There are 422 patients in this population.
- Note: The pre-specified secondary analysis model of SARS-CoV RNA clearance was run but low sample sizes resulting in an unstable model fit. Due to this instability, the model results were not deemed to be appropriate to report and interpret and have been omitted from this report.

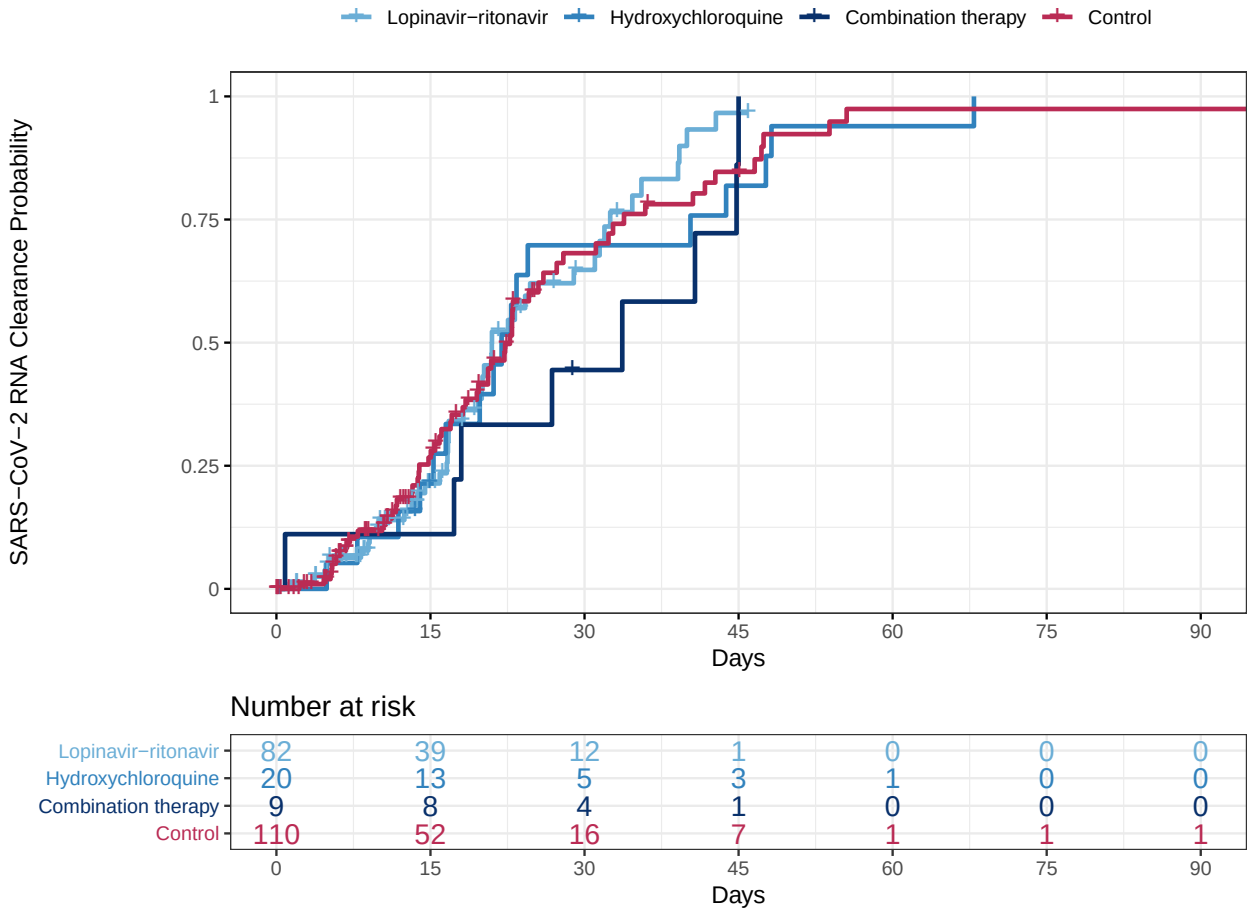


Figure 17: Empirical distribution of SARS-CoV-2 RNA Clearance for Lopinavir−ritonavir, Hydroxychloroquine, Combination therapy and control. This plot is restricted to the Antiviral ITT population.

Table 42: Summary of 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates for time to SARS-CoV-2 RNA Clearance (in days). Displaying the observed percentiles for this outcome.

	2.5	10.0	25.0	50.0	75.0	90.0	97.5
Lopinavir-ritonavir	4.7	9.07	16.59	20.99	32.5	39.97	-
Hydroxychloroquine	4.89	7.88	15.29	21.93	40.32	48.2	67.91
Combination therapy	0.84	0.84	18	33.67	44.8	45	45
Control	5.27	7.15	13.91	22.74	33.84	47.43	98.36

6 Sensitivity analyses

6.1 Sensitivity analyses of OSFD

6.1.1 Sensitivity analysis of OSFD endpoint for Antiviral specific per protocol population

- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, lopinavir−ritonavir, hydroxychloroquine, combination therapy andcontrol interventions
- Population: Antiviral specific per protocol

Table 43: Odds ratio parameters for sensitivity analysis of OSFD in Antiviral Per Protocol population

	Mean	SD	Median	CrI
Age<39	3.39	1.06	3.24	(1.76, 5.85)
Age 40-49	2.31	0.54	2.25	(1.43, 3.55)
Age 50-59	1.99	0.39	1.95	(1.33, 2.84)
Age 70-79	0.49	0.11	0.48	(0.31, 0.74)
Age 80+	0.37	0.14	0.35	(0.16, 0.71)
Female	0.97	0.16	0.96	(0.70, 1.31)
Time epoch 1	0.93	0.08	0.93	(0.76, 1.09)
Time epoch 2	0.86	0.14	0.86	(0.59, 1.15)
Time epoch 3	0.87	0.17	0.86	(0.57, 1.24)
Time epoch 4	0.92	0.22	0.89	(0.58, 1.42)
Time epoch 5	0.96	0.26	0.92	(0.57, 1.57)
Time epoch 6	0.96	0.27	0.92	(0.56, 1.61)
Time epoch 7	0.94	0.26	0.90	(0.55, 1.56)
Time epoch 8	0.91	0.25	0.87	(0.53, 1.49)
Time epoch 9	0.86	0.23	0.83	(0.51, 1.39)
Time epoch 10	0.81	0.20	0.78	(0.49, 1.27)
Time epoch 11	0.74	0.17	0.72	(0.46, 1.12)
Time epoch 12	0.66	0.14	0.65	(0.42, 0.97)
Time epoch 13	0.61	0.14	0.60	(0.39, 0.91)
Time epoch 14	0.58	0.16	0.56	(0.33, 0.94)
Time epoch 15	0.57	0.24	0.53	(0.25, 1.12)
Lopinavir-ritonavir	0.75	0.11	0.74	(0.56, 0.99)
Hydroxychloroquine	0.69	0.14	0.68	(0.43, 0.99)
Combination	0.52	0.15	0.50	(0.28, 0.87)
Combination interaction	1.00	0.05	1.00	(0.90, 1.10)

Table 44: Posterior probabilities for sensitivity analysis of OSFD in Antiviral Per Protocol population

	Posterior Probability
Lopinavir-ritonavir is optimal	0.018
Lopinavir-ritonavir is superior to control	0.021
Lopinavir-ritonavir is futile (OR < 1.2)	0.999
Lopinavir-ritonavir is harmful (OR < 1)	0.980
Hydroxychloroquine is optimal	0.019
Hydroxychloroquine is superior to control	0.021
Hydroxychloroquine is futile (OR < 1.2)	0.998
Hydroxychloroquine is harmful (OR < 1)	0.979
Combination therapy is optimal	0.003
Combination therapy is superior to control	0.007
Combination therapy is futile (OR < 1.2)	0.999
Combination therapy is harmful (OR < 1)	0.993
Lopinavir-ritonavir and hydroxychloroquine are equivalent	0.664

6.1.2 Sensitivity analysis of OSFD endpoint for Unblinded ITT population with site and time factors removed

- Model: Primary analysis ordinal model
- Factors: Age, sex, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir−ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation

Table 45: Odds ratio parameters for sensitivity analysis of OSFD with site and time factors removed

	Mean	SD	Median	CrI
Age<39	3.60	0.76	3.53	(2.33, 5.24)
Age 40-49	2.04	0.34	2.02	(1.46, 2.78)
Age 50-59	1.87	0.25	1.85	(1.43, 2.42)
Age 70-79	0.57	0.08	0.56	(0.42, 0.75)
Age 80+	0.40	0.11	0.39	(0.23, 0.64)
Female	1.14	0.13	1.14	(0.91, 1.40)
Lopinavir−ritonavir	0.81	0.12	0.80	(0.59, 1.08)
Hydroxychloroquine	0.52	0.12	0.51	(0.31, 0.79)
Pooled IL-6ra	1.59	0.22	1.58	(1.21, 2.05)
Fixed-dose corticosteroids	1.61	0.31	1.58	(1.09, 2.29)
Shock-dependent corticosteroids	1.29	0.28	1.26	(0.81, 1.92)
Combination therapy	0.42	0.12	0.40	(0.23, 0.70)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.29	0.27	1.27	(0.85, 1.89)
Hydroxychloroquine*Pooled IL-6ra combination	0.84	0.23	0.81	(0.47, 1.38)
Combination therapy*Pooled IL-6ra combination	0.67	0.22	0.64	(0.34, 1.20)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	1.31	0.32	1.28	(0.81, 2.04)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.85	0.28	0.81	(0.41, 1.49)
Combination therapy*Fixed-dose corticosteroids combination	0.68	0.26	0.64	(0.31, 1.29)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	1.00	(0.90, 1.10)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.02	0.05	1.01	(0.92, 1.12)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 46: Posterior probabilities for sensitivity analysis of OSFD with site and time factors removed

	Posterior Probability
Lopinavir–ritonavir is optimal	0.083
Lopinavir–ritonavir is superior to control	0.065
Lopinavir–ritonavir is futile (OR < 1.2)	0.997
Lopinavir–ritonavir is harmful (OR < 1)	0.935
Hydroxychloroquine is optimal	0.001
Hydroxychloroquine is superior to control	0.001
Hydroxychloroquine is futile (OR < 1.2)	1.000
Hydroxychloroquine is harmful (OR < 1)	0.999
Combination therapy is optimal	0.001
Combination therapy OR > 1	0.000
Combination therapy is futile (OR < 1.2)	1.000
Combination therapy is harmful (OR < 1)	1.000
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.877
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.220
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.848
Hydroxychloroquine*Fixed-dose combination OR > 1	0.261
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.191

6.1.3 Sensitivity analysis of OSFD endpoint for Unblinded ITT population with alternative coding of corticosteroid interventions

- Model: Primary analysis ordinal model
- Factors: Age, sex, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation
- Patients randomized after the closure of the corticosteroid domain (June 17, 2020) will be coded as receiving steroids if they received steroids prior to randomization or within the first two study days. There are 803 patients randomized after the closure of the corticosteroid domain. Of those patients, 55 patients did not receive steroids prior to randomization or within the first two study days. In the model, the patients that received steroids post-closure of the corticosteroid domain will be pooled with the patients randomized to a corticosteroid intervention. The patients that did not receive steroids post-closure of the corticosteroid domain will be pooled with patients randomized to no corticosteroid intervention.

Table 47: Odds ratio parameters for sensitivity analysis of OSFD endpoint for Unblinded ITT population with alternative coding of corticosteroid interventions

	Mean	SD	Median	CrI
Age<39	4.03	0.87	3.94	(2.59, 5.98)
Age 40-49	2.10	0.36	2.07	(1.48, 2.86)
Age 50-59	1.96	0.27	1.94	(1.47, 2.53)
Age 70-79	0.52	0.08	0.51	(0.38, 0.68)
Age 80+	0.33	0.09	0.32	(0.19, 0.54)
Female	1.17	0.13	1.16	(0.93, 1.45)
Time epoch 1	0.95	0.08	0.95	(0.79, 1.12)
Time epoch 2	0.90	0.14	0.90	(0.65, 1.18)
Time epoch 3	0.97	0.18	0.95	(0.66, 1.36)
Time epoch 4	1.09	0.24	1.06	(0.70, 1.63)
Time epoch 5	1.20	0.29	1.16	(0.75, 1.86)
Time epoch 6	1.26	0.31	1.21	(0.78, 1.97)
Time epoch 7	1.29	0.31	1.25	(0.80, 2.01)
Time epoch 8	1.32	0.32	1.27	(0.82, 2.05)
Time epoch 9	1.22	0.27	1.19	(0.79, 1.85)
Time epoch 10	1.08	0.21	1.06	(0.73, 1.56)
Time epoch 11	0.90	0.16	0.89	(0.61, 1.26)
Time epoch 12	0.78	0.15	0.77	(0.52, 1.11)
Time epoch 13	0.77	0.15	0.76	(0.52, 1.09)
Time epoch 14	0.85	0.17	0.83	(0.57, 1.23)
Time epoch 15	0.99	0.26	0.96	(0.57, 1.61)
Time epoch 16	1.24	0.54	1.13	(0.54, 2.65)
Lopinavir−ritonavir	0.78	0.12	0.78	(0.59, 1.04)
Hydroxychloroquine	0.61	0.14	0.61	(0.36, 0.90)
Pooled IL-6ra	1.68	0.23	1.67	(1.27, 2.18)
Steroids	1.36	0.23	1.34	(0.98, 1.87)
Combination therapy	0.48	0.14	0.46	(0.26, 0.81)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.33	0.28	1.31	(0.87, 1.96)
Hydroxychloroquine*Pooled IL-6ra combination	1.03	0.28	1.01	(0.57, 1.65)
Combination therapy*Pooled IL-6ra combination	0.82	0.27	0.77	(0.41, 1.45)
Lopinavir−ritonavir*Steroids combination	1.08	0.25	1.05	(0.69, 1.65)
Hydroxychloroquine*Steroids combination	0.83	0.24	0.81	(0.44, 1.38)
Combination therapy*Steroids combination	0.66	0.23	0.62	(0.31, 1.22)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	1.00	(0.90, 1.10)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Lopinavir−ritonavir*Steroids interaction	1.01	0.05	1.01	(0.92, 1.12)
Hydroxychloroquine*Steroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Steroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 48: Posterior probabilities for sensitivity analysis of OSFD endpoint for Unblinded ITT population with alternative coding of corticosteroid interventions

	Posterior Probability
Lopinavir−ritonavir is optimal	0.064
Lopinavir−ritonavir is superior to control	0.044
Lopinavir−ritonavir is futile (OR < 1.2)	0.998
Lopinavir−ritonavir is harmful (OR < 1)	0.956
Hydroxychloroquine is optimal	0.005
Hydroxychloroquine is superior to control	0.006
Hydroxychloroquine is futile (OR < 1.2)	1.000
Hydroxychloroquine is harmful (OR < 1)	0.994
Combination therapy is optimal	0.003
Combination therapy OR > 1	0.004
Combination therapy is futile (OR < 1.2)	1.000
Combination therapy is harmful (OR < 1)	0.996
Lopinavir−ritonavir*Pooled IL-6ra combination OR > 1	0.904
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.509
Lopinavir−ritonavir*Fixed-dose combination OR > 1	0.593
Hydroxychloroquine*Fixed-dose combination OR > 1	0.221
Lopinavir−ritonavir and Hydroxychloroquine are equivalent	0.429

6.2 Sensitivity analyses of in-hospital mortality

6.2.1 Sensitivity analysis of in-hospital mortality for Antiviral specific per protocol population

- Model: Primary dichotomous model
- Factors: Age, sex, site, time, lopinavir−ritonavir, hydroxychloroquine, combination therapy and control interventions
- Population: Antiviral specific per protocol

Table 49: Odds ratio parameters for sensitivity analysis of in-hospital mortality in Antiviral Per Protocol population

	Mean	SD	Median	CrI
Age<39	8.16	5.09	6.88	(2.61, 21.17)
Age 40-49	4.94	1.91	4.60	(2.31, 9.50)
Age 50-59	3.28	0.90	3.16	(1.89, 5.36)
Age 70-79	0.45	0.11	0.44	(0.27, 0.70)
Age 80+	0.32	0.13	0.30	(0.14, 0.64)
Female	1.00	0.22	0.98	(0.65, 1.50)
Time epoch 1	0.95	0.09	0.95	(0.78, 1.14)
Time epoch 2	0.90	0.15	0.90	(0.63, 1.23)
Time epoch 3	0.89	0.20	0.87	(0.55, 1.33)
Time epoch 4	0.90	0.24	0.87	(0.52, 1.45)
Time epoch 5	0.90	0.27	0.86	(0.49, 1.52)
Time epoch 6	0.89	0.28	0.85	(0.46, 1.55)
Time epoch 7	0.88	0.28	0.84	(0.45, 1.56)
Time epoch 8	0.89	0.29	0.85	(0.45, 1.55)
Time epoch 9	0.92	0.29	0.87	(0.48, 1.60)
Time epoch 10	0.95	0.29	0.91	(0.51, 1.65)
Time epoch 11	0.97	0.28	0.93	(0.54, 1.65)
Time epoch 12	0.97	0.27	0.93	(0.55, 1.62)
Time epoch 13	0.97	0.30	0.93	(0.52, 1.68)
Time epoch 14	1.00	0.38	0.93	(0.46, 1.93)
Time epoch 15	1.07	0.59	0.94	(0.35, 2.49)
Lopinavir-ritonavir	0.68	0.13	0.67	(0.47, 0.97)
Hydroxychloroquine	0.64	0.17	0.63	(0.35, 1.02)
Combination	0.45	0.17	0.42	(0.20, 0.87)
Combination interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 50: Posterior probabilities for sensitivity analysis of in-hospital mortality in Antiviral Per Protocol population

	Posterior Probability
Lopinavir-ritonavir is optimal	0.014
Lopinavir-ritonavir is superior to control	0.017
Lopinavir-ritonavir is futile (OR < 1.2)	0.999
Lopinavir-ritonavir is harmful (OR < 1)	0.983
Hydroxychloroquine is optimal	0.025
Hydroxychloroquine is superior to control	0.029
Hydroxychloroquine is futile (OR < 1.2)	0.994
Hydroxychloroquine is harmful (OR < 1)	0.971
Combination therapy is optimal	0.004
Combination therapy is superior to control	0.011
Combination therapy is futile (OR < 1.2)	0.998
Combination therapy is harmful (OR < 1)	0.989
Lopinavir-ritonavir and hydroxychloroquine are equivalent	0.634

6.2.2 Sensitivity analysis of in-hospital mortality for Unblinded ITT population with site and time factors removed

- Model: Primary dichotomous model
- Factors: Age, sex, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (as a combined IL-6 arm) and no immune modulation

Table 51: Odds ratio parameters for sensitivity analysis of in-hospital mortality with site and time factors removed

	Mean	SD	Median	CrI
Age<39	10.38	5.34	9.15	(4.11, 24.12)
Age 40-49	3.15	0.77	3.05	(1.93, 4.93)
Age 50-59	2.73	0.51	2.69	(1.87, 3.88)
Age 70-79	0.51	0.08	0.51	(0.37, 0.70)
Age 80+	0.32	0.09	0.31	(0.18, 0.52)
Female	1.16	0.17	1.15	(0.86, 1.54)
Lopinavir−ritonavir	0.70	0.12	0.69	(0.49, 0.98)
Hydroxychloroquine	0.57	0.14	0.57	(0.32, 0.87)
Pooled IL-6ra	1.60	0.27	1.58	(1.13, 2.18)
Fixed-dose corticosteroids	1.06	0.27	1.03	(0.64, 1.68)
Shock-dependent corticosteroids	1.43	0.43	1.37	(0.78, 2.43)
Combination therapy	0.40	0.14	0.38	(0.19, 0.73)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.13	0.28	1.09	(0.68, 1.78)
Hydroxychloroquine*Pooled IL-6ra combination	0.92	0.28	0.89	(0.45, 1.56)
Combination therapy*Pooled IL-6ra combination	0.65	0.26	0.61	(0.28, 1.27)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	0.75	0.23	0.71	(0.39, 1.27)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.61	0.23	0.58	(0.26, 1.16)
Combination therapy*Fixed-dose corticosteroids combination	0.44	0.20	0.40	(0.17, 0.92)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	1.00	(0.90, 1.09)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.01	0.05	1.00	(0.91, 1.10)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 52: Posterior probabilities for sensitivity analysis of in-hospital mortality with site and time factors removed

	Posterior Probability
Lopinavir–ritonavir is optimal	0.020
Lopinavir–ritonavir is superior to control	0.019
Lopinavir–ritonavir is futile (OR < 1.2)	0.999
Lopinavir–ritonavir is harmful (OR < 1)	0.981
Hydroxychloroquine is optimal	0.005
Hydroxychloroquine is superior to control	0.005
Hydroxychloroquine is futile (OR < 1.2)	1.000
Hydroxychloroquine is harmful (OR < 1)	0.995
Combination therapy is optimal	0.001
Combination therapy OR > 1	0.002
Combination therapy is futile (OR < 1.2)	1.000
Combination therapy is harmful (OR < 1)	0.998
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.641
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.353
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.132
Hydroxychloroquine*Fixed-dose combination OR > 1	0.062
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.502

6.2.3 Sensitivity analysis of in-hospital mortality for Unblinded ITT population with alternative coding of corticosteroid interventions

- Model: Primary analysis dichotomous model
- Factors: Age, sex, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (as a combined IL-6 arm) and no immune modulation
- Patients randomized after the closure of the corticosteroid domain (June 17, 2020) will be coded as receiving steroids if they received steroids prior to randomization or within the first two study days. There are 803 patients randomized after the closure of the corticosteroid domain. Of those patients, 55 patients did not receive steroids prior to randomization or within the first two study days. In the model, the patients that received steroids post-closure of the corticosteroid domain will be pooled with the patients randomized to a corticosteroid intervention. The patients that did not receive steroids post-closure of the corticosteroid domain will be pooled with patients randomized

to no corticosteroid intervention.

Table 53: Odds ratio parameters for sensitivity analysis of in-hospital mortality for Unblinded ITT population with alternative coding of corticosteroid interventions

	Mean	SD	Median	CrI
Age<39	13.03	6.64	11.47	(5.04, 29.81)
Age 40-49	3.33	0.90	3.20	(1.95, 5.40)
Age 50-59	2.96	0.60	2.90	(1.99, 4.26)
Age 70-79	0.41	0.07	0.41	(0.29, 0.58)
Age 80+	0.23	0.07	0.22	(0.12, 0.38)
Female	1.19	0.19	1.18	(0.87, 1.59)
Time epoch 1	0.94	0.08	0.93	(0.78, 1.11)
Time epoch 2	0.87	0.14	0.86	(0.61, 1.14)
Time epoch 3	0.86	0.17	0.85	(0.55, 1.23)
Time epoch 4	0.88	0.21	0.86	(0.53, 1.34)
Time epoch 5	0.91	0.24	0.88	(0.53, 1.46)
Time epoch 6	0.93	0.25	0.90	(0.52, 1.51)
Time epoch 7	0.95	0.26	0.92	(0.53, 1.53)
Time epoch 8	1.00	0.25	0.97	(0.58, 1.59)
Time epoch 9	1.06	0.26	1.03	(0.64, 1.65)
Time epoch 10	1.12	0.27	1.08	(0.69, 1.75)
Time epoch 11	1.12	0.26	1.09	(0.71, 1.70)
Time epoch 12	1.09	0.24	1.06	(0.68, 1.62)
Time epoch 13	1.10	0.25	1.07	(0.68, 1.68)
Time epoch 14	1.19	0.31	1.15	(0.70, 1.91)
Time epoch 15	1.37	0.48	1.28	(0.68, 2.57)
Time epoch 16	1.70	1.08	1.44	(0.61, 4.29)
Lopinavir−ritonavir	0.68	0.13	0.67	(0.47, 0.97)
Hydroxychloroquine	0.59	0.15	0.58	(0.32, 0.92)
Pooled IL-6ra	1.71	0.31	1.68	(1.18, 2.40)
Steroids	1.24	0.27	1.21	(0.78, 1.84)
Combination therapy	0.41	0.15	0.38	(0.18, 0.78)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.17	0.32	1.13	(0.68, 1.90)
Hydroxychloroquine*Pooled IL-6ra combination	1.02	0.33	0.98	(0.50, 1.80)
Combination therapy*Pooled IL-6ra combination	0.71	0.31	0.65	(0.28, 1.46)
Lopinavir−ritonavir*Steroids combination	0.84	0.25	0.81	(0.45, 1.42)
Hydroxychloroquine*Steroids combination	0.73	0.26	0.70	(0.34, 1.34)
Combination therapy*Steroids combination	0.51	0.23	0.47	(0.19, 1.11)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	0.99	(0.90, 1.10)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Lopinavir−ritonavir*Steroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Hydroxychloroquine*Steroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Steroids interaction	1.00	0.05	1.00	(0.90, 1.10)

Table 54: Posterior probabilities for sensitivity analysis of in-hospital mortality for Unblinded ITT population with alternative coding of corticosteroid interventions

	Posterior Probability
Lopinavir–ritonavir is optimal	0.019
Lopinavir–ritonavir is superior to control	0.015
Lopinavir–ritonavir is futile (OR < 1.2)	0.999
Lopinavir–ritonavir is harmful (OR < 1)	0.985
Hydroxychloroquine is optimal	0.013
Hydroxychloroquine is superior to control	0.012
Hydroxychloroquine is futile (OR < 1.2)	0.999
Hydroxychloroquine is harmful (OR < 1)	0.988
Combination therapy is optimal	0.003
Combination therapy OR > 1	0.004
Combination therapy is futile (OR < 1.2)	0.999
Combination therapy is harmful (OR < 1)	0.996
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.677
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.472
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.235
Hydroxychloroquine*Fixed-dose combination OR > 1	0.138
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.573

7 Subgroup analyses

7.1 Subgroup analyses by baseline mechanical ventilation status

7.1.1 Data summaries of baseline mechanical ventilation status in the Antiviral ITT population

Table 55: Summary of baseline mechanical ventilation by intervention

Intervention	Patients	No mechanical ventilation at baseline	Mechanical ventilation at baseline
Lopinavir-ritonavir	255	183 (71.8%)	72 (28.2%)
Hydroxychloroquine	50	27 (54%)	23 (46%)
Combination therapy	27	14 (51.9%)	13 (48.1%)
Control	362	253 (69.9%)	109 (30.1%)
Pooled Antiviral	332	224 (67.5%)	108 (32.5%)
Pooled antiviral and control	694	477 (68.7%)	217 (31.3%)

Table 56: Summary of subjects by baseline mechanical ventilation status in the Antiviral ITT population

Intervention	Patients	Known	Deaths (%)	OSFD median (IQR)	OSFD in Survivors* median (IQR)
No mechanical ventilation at baseline					
Lopinavir-ritonavir	183	180	53 (29.4%)	11 (-1, 17)	14 (10.5, 18)
Hydroxychloroquine	27	26	9 (34.6%)	0 (-1, 11.25)	7 (0, 17)
Combination therapy	14	14	6 (42.9%)	0 (-1, 12.25)	11.5 (6.75, 13.5)
Control	253	247	64 (25.9%)	10 (-1, 16)	15 (7, 18)
Pooled Antiviral	224	220	68 (30.9%)	9 (-1, 16)	14 (8, 17)
Mechanical ventilation at baseline					
Lopinavir-ritonavir	72	69	35 (50.7%)	-1 (-1, 9)	9 (0, 14)
Hydroxychloroquine	23	23	8 (34.8%)	0 (-1, 1.5)	0 (0, 10.5)
Combination therapy	13	12	7 (58.3%)	-1 (-1, 0)	0 (0, 3)
Control	109	106	42 (39.6%)	0 (-1, 8)	7 (0, 16)
Pooled Antiviral	108	104	50 (48.1%)	0 (-1, 4.25)	4 (0, 12)

* Days Free of Organ Support in Survivors measured within 21 days.

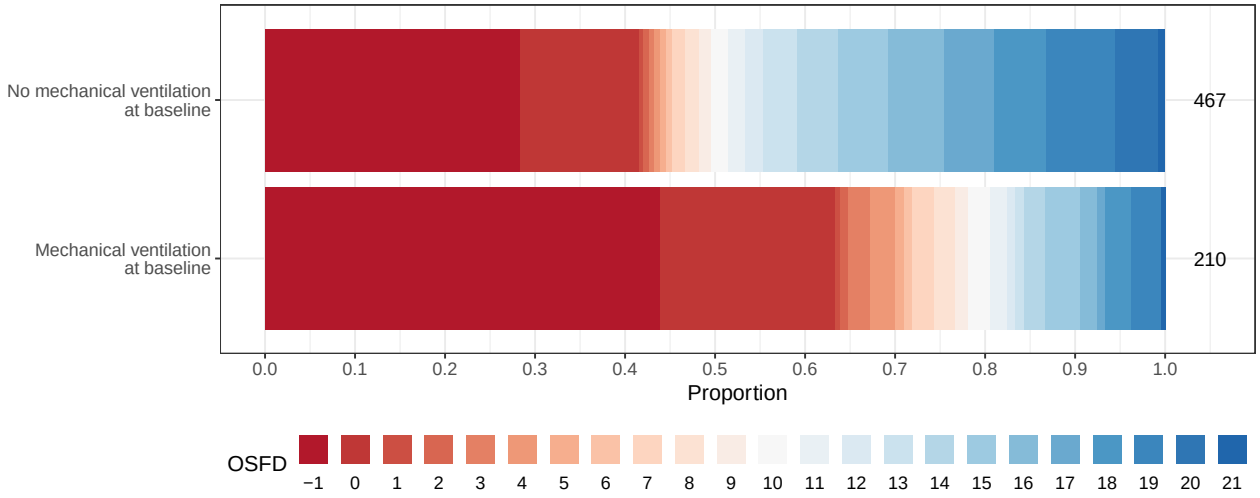


Figure 18: Empirical distribution of organ support free days (OSFD) by baseline mechanical ventilation status. This plot is restricted to the Antiviral ITT population.

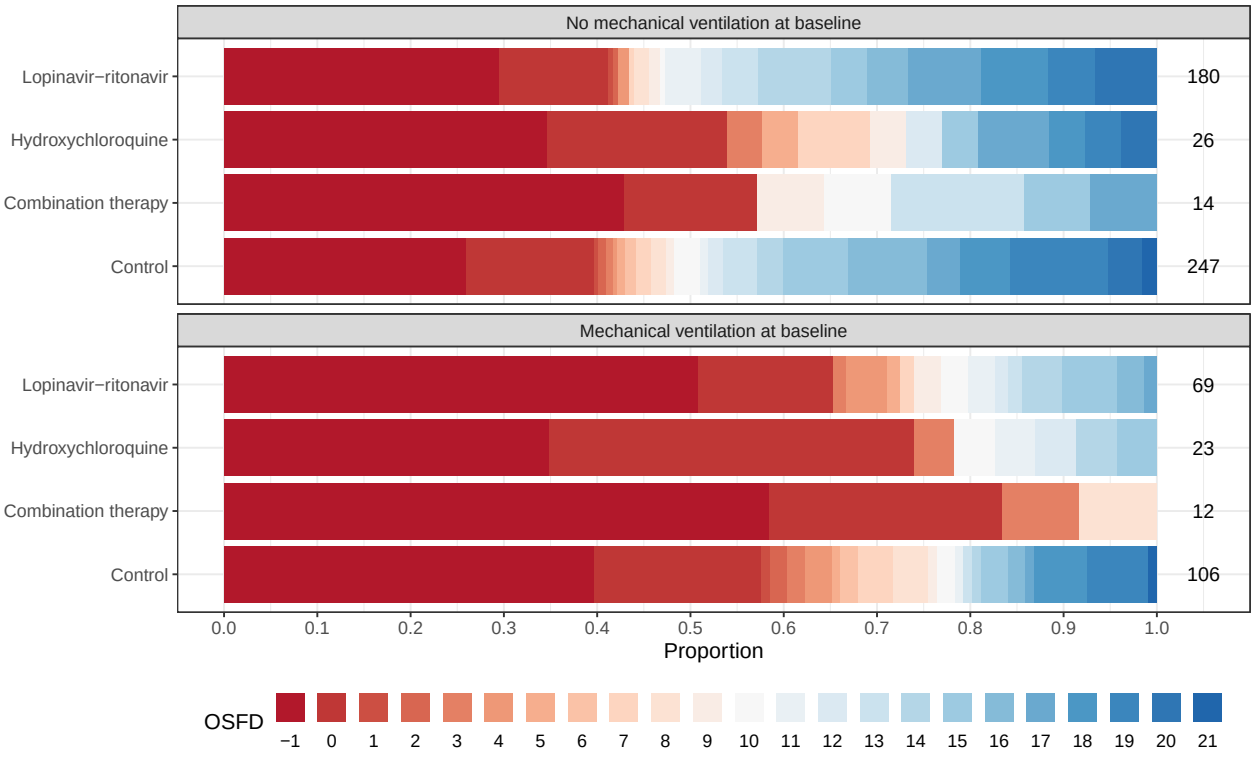


Figure 19: Empirical distribution of organ support free days (OSFD) for Lopinavir−ritonavir, Hydroxychloroquine, combination therapy, and control by baseline mechanical ventilation status. This plot is restricted to the Antiviral ITT population.

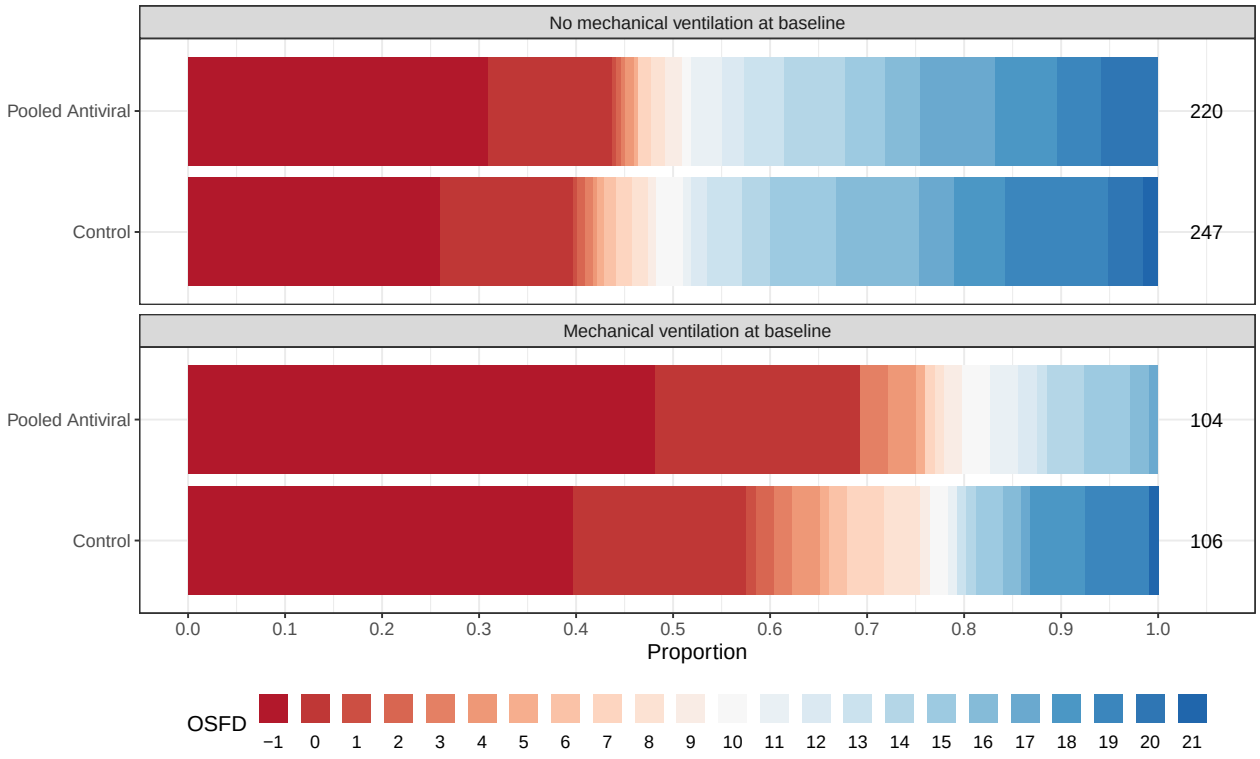


Figure 20: Empirical distribution of organ support free days (OSFD) for pooled antiviral and control interventions by baseline mechanical ventilation status. This plot is restricted to the Antiviral ITT population.

7.1.2 Subgroup analysis with differential effect on OSFD by baseline mechanical ventilation status

- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Differential treatment effects for antiviral interventions by baseline invasive mechanical ventilation status will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy for each subgroup.
- Population: Unblinded ITT
- Note: The prespecified subgroup analysis included each individual antiviral intervention. However, due to low sample sizes within each subgroup, the active antiviral interventions have been pooled

for this subgroup analysis.

Table 57: Odds ratio parameters for subgroup analysis with differential effect on OSFD endpoint by mechanical ventilation with antiviral interventions

	Mean	SD	Median	CrI
Age<39	4.61	0.99	4.51	(2.97, 6.83)
Age 40-49	1.98	0.33	1.95	(1.41, 2.71)
Age 50-59	2.01	0.28	1.99	(1.52, 2.60)
Age 70-79	0.51	0.08	0.51	(0.38, 0.68)
Age 80+	0.33	0.09	0.31	(0.18, 0.54)
Female	1.16	0.13	1.15	(0.92, 1.44)
Time epoch 1	0.95	0.08	0.95	(0.79, 1.12)
Time epoch 2	0.90	0.13	0.89	(0.65, 1.17)
Time epoch 3	0.95	0.17	0.94	(0.65, 1.33)
Time epoch 4	1.07	0.22	1.04	(0.69, 1.57)
Time epoch 5	1.18	0.28	1.15	(0.75, 1.83)
Time epoch 6	1.25	0.30	1.21	(0.77, 1.95)
Time epoch 7	1.29	0.30	1.25	(0.80, 1.99)
Time epoch 8	1.34	0.31	1.30	(0.85, 2.04)
Time epoch 9	1.31	0.29	1.28	(0.85, 1.98)
Time epoch 10	1.27	0.28	1.24	(0.83, 1.91)
Time epoch 11	1.15	0.24	1.13	(0.75, 1.69)
Time epoch 12	1.07	0.23	1.05	(0.68, 1.57)
Time epoch 13	1.10	0.25	1.08	(0.69, 1.65)
Time epoch 14	1.30	0.30	1.27	(0.82, 1.99)
Time epoch 15	1.66	0.48	1.59	(0.91, 2.81)
Time epoch 16	2.29	1.05	2.06	(0.95, 5.00)
Mechanical ventilation	0.38	0.05	0.37	(0.28, 0.49)
Pooled Antiviral, no MV	0.82	0.13	0.81	(0.59, 1.11)
Pooled Antiviral, MV	0.59	0.13	0.58	(0.38, 0.88)
Pooled IL-6ra	1.68	0.23	1.67	(1.27, 2.17)
Fixed-dose corticosteroid	1.52	0.35	1.49	(0.95, 2.29)
Shock-dependent corticosteroid	1.10	0.26	1.07	(0.69, 1.68)
Pooled Antiviral*Pooled IL-6ra combination, no MV	1.40	0.31	1.37	(0.89, 2.10)
Pooled Antiviral*Pooled IL-6ra combination, MV	1.00	0.25	0.96	(0.59, 1.57)
Pooled Antiviral*Fixed-dose combination, no MV	1.27	0.35	1.22	(0.71, 2.07)
Pooled Antiviral*Fixed-dose combination, MV	0.90	0.29	0.86	(0.45, 1.59)
Pooled Antiviral*Pooled IL-6ra interaction, no MV	1.01	0.05	1.01	(0.92, 1.11)
Pooled Antiviral*Pooled IL-6ra interaction, MV	1.00	0.05	1.00	(0.91, 1.10)
Pooled Antiviral*Fixed-dose interaction, no MV	1.01	0.05	1.01	(0.92, 1.12)
Pooled Antiviral*Fixed-dose interaction, MV	1.00	0.05	1.00	(0.90, 1.10)

Table 58: Posterior probabilities for subgroup analysis with differential effect on OSFD endpoint by mechanical ventilation with antiviral interventions

	Posterior Probability
Pooled antiviral is superior to control with no MV	0.098
Pooled antiviral is futile to control with no MV	0.993
Pooled antiviral is superior to control with MV	0.006
Pooled antiviral is futile to control with MV	1.000
Pooled antiviral*Pooled IL-6ra combination is superior to control with no MV	0.926
Pooled antiviral*Pooled IL-6ra combination is superior to control MV	0.445
Pooled antiviral*Fixed-dose combination is superior to control no MV	0.771
Pooled antiviral*Fixed-dose combination is superior to control MV	0.309
Pooled antiviral with no MV > Pooled antiviral with MV	0.906

7.1.3 Subgroup analysis with differential effect on in-hospital mortality by baseline mechanical ventilation status

- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir−ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Differential treatment effects for antiviral interventions by baseline invasive mechanical ventilation status will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy for each subgroup.
- Population: Unblinded ITT
- Note: The prespecified subgroup analysis included each individual antiviral intervention. However, due to low sample sizes within each subgroup, the active antiviral interventions have been pooled for this subgroup analysis.

Table 59: Odds ratio parameters for subgroup analysis with differential effect on in hospital moratlity endpoint by mechanical ventilation with pooled antiviral interventions

	Mean	SD	Median	CrI
Age<39	14.80	7.57	13.01	(5.71, 33.52)
Age 40-49	3.23	0.84	3.12	(1.91, 5.19)

Table 59: Odds ratio parameters for subgroup analysis with differential effect on in hospital moratlity endpoint by mechanical ventilation with pooled antiviral interventions *(continued)*

	Mean	SD	Median	CrI
Age 50-59	3.07	0.64	3.01	(2.03, 4.56)
Age 70-79	0.42	0.08	0.41	(0.29, 0.59)
Age 80+	0.23	0.07	0.22	(0.12, 0.38)
Female	1.19	0.19	1.17	(0.86, 1.61)
Time epoch 1	0.94	0.09	0.93	(0.77, 1.11)
Time epoch 2	0.86	0.14	0.85	(0.59, 1.15)
Time epoch 3	0.85	0.18	0.84	(0.53, 1.24)
Time epoch 4	0.87	0.22	0.85	(0.52, 1.36)
Time epoch 5	0.90	0.25	0.87	(0.52, 1.48)
Time epoch 6	0.91	0.26	0.88	(0.51, 1.50)
Time epoch 7	0.92	0.26	0.90	(0.51, 1.50)
Time epoch 8	0.96	0.26	0.94	(0.55, 1.55)
Time epoch 9	1.03	0.27	1.00	(0.60, 1.66)
Time epoch 10	1.11	0.30	1.07	(0.65, 1.81)
Time epoch 11	1.14	0.31	1.10	(0.66, 1.87)
Time epoch 12	1.15	0.31	1.11	(0.65, 1.85)
Time epoch 13	1.19	0.33	1.14	(0.66, 1.96)
Time epoch 14	1.33	0.41	1.27	(0.71, 2.30)
Time epoch 15	1.60	0.66	1.48	(0.72, 3.20)
Time epoch 16	2.12	1.80	1.74	(0.68, 5.89)
Mechanical ventilation	0.46	0.09	0.45	(0.32, 0.65)
Pooled Antiviral, no MV	0.84	0.18	0.82	(0.54, 1.27)
Pooled Antiviral, MV	0.48	0.14	0.46	(0.27, 0.80)
Pooled IL-6ra	1.74	0.32	1.71	(1.19, 2.46)
Fixed-dose corticosteroid	1.00	0.31	0.96	(0.54, 1.74)
Shock-dependent corticosteroid	1.22	0.40	1.17	(0.62, 2.18)
Pooled Antiviral*Pooled IL-6ra combination, no MV	1.47	0.43	1.41	(0.81, 2.47)
Pooled Antiviral*Pooled IL-6ra combination, MV	0.84	0.29	0.79	(0.41, 1.52)
Pooled Antiviral*Fixed-dose combination, no MV	0.85	0.32	0.79	(0.39, 1.63)
Pooled Antiviral*Fixed-dose combination, MV	0.48	0.21	0.44	(0.19, 1.00)
Pooled Antiviral*Pooled IL-6ra interaction, no MV	1.00	0.05	1.00	(0.91, 1.11)
Pooled Antiviral*Pooled IL-6ra interaction, MV	1.00	0.05	1.00	(0.91, 1.11)
Pooled Antiviral*Fixed-dose interaction, no MV	1.00	0.05	1.00	(0.91, 1.10)
Pooled Antiviral*Fixed-dose interaction, MV	1.00	0.05	1.00	(0.90, 1.10)

Table 60: Posterior probabilities for subgroup analysis with differential effect on in-hospital mortality by mechanical ventilation for pooled antiviral interventions.

	Posterior Probability
Pooled antiviral is superior to control with no MV	0.183
Pooled antiviral is futile to control with no MV	0.957
Pooled antiviral is harmful with no MV	0.817
Pooled antiviral is superior to control with MV	0.003
Pooled antiviral is futile to control with MV	1.000
Pooled antiviral is harmful with MV	0.997
Pooled antiviral*Pooled IL-6ra combination is superior to control with no MV	0.886
Pooled antiviral*Pooled IL-6ra combination is superior to control MV	0.238
Pooled antiviral*Fixed-dose combination is superior to control no MV	0.259
Pooled antiviral*Fixed-dose combination is superior to control MV	0.025
Pooled antiviral with no MV > Pooled antiviral with MV	0.959

7.2 Subgroup analyses by baseline shock status

7.2.1 Data summaries of baseline shock status in the Antiviral ITT population

Table 61: Summary of baseline shock status by intervention

Intervention	Patients	No shock at baseline	Shock at baseline
Lopinavir-ritonavir	255	208 (81.6%)	47 (18.4%)
Hydroxychloroquine	50	37 (74%)	13 (26%)
Combination therapy	27	22 (81.5%)	5 (18.5%)
Control	362	290 (80.1%)	72 (19.9%)
Pooled Antiviral	332	267 (80.4%)	65 (19.6%)
Pooled antiviral and control	694	557 (80.3%)	137 (19.7%)

Table 62: Summary of subjects by baseline shock status in the Antiviral ITT population

Intervention	Patients	Known	Deaths (%)	OSFD median (IQR)	OSFD in Survivors* median (IQR)
No shock at baseline					
Lopinavir-ritonavir	208	204	62 (30.4%)	11 (-1, 16)	14 (9, 17)
Hydroxychloroquine	37	36	11 (30.6%)	0 (-1, 11.25)	5 (0, 14)
Combination therapy	22	21	11 (52.4%)	-1 (-1, 8)	8.5 (0.75, 12.25)
Control	290	281	74 (26.3%)	8 (-1, 16)	14 (4.5, 18)
Pooled Antiviral	267	261	84 (32.2%)	5 (-1, 15)	14 (4, 17)
Shock at baseline					
Lopinavir-ritonavir	47	45	26 (57.8%)	-1 (-1, 0)	4 (0, 12.5)
Hydroxychloroquine	13	13	6 (46.2%)	0 (-1, 0)	0 (0, 9.5)
Combination therapy	5	5	2 (40%)	0 (-1, 0)	0 (0, 8.5)
Control	72	72	32 (44.4%)	0 (-1, 11.25)	8.5 (2.75, 18)
Pooled Antiviral	65	63	34 (54%)	-1 (-1, 0)	4 (0, 11)

* Days Free of Organ Support in Survivors measured within 21 days.

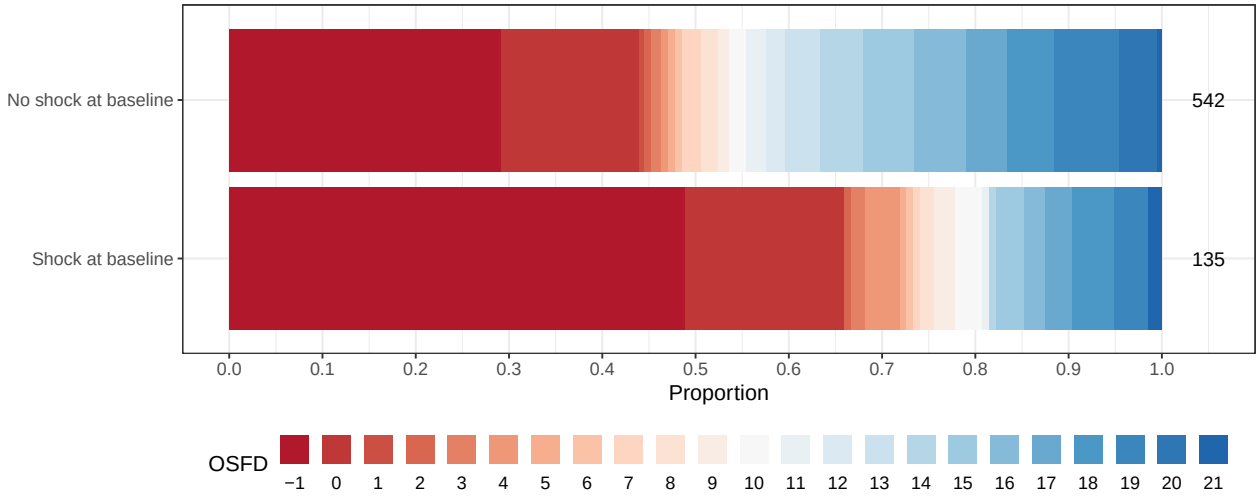


Figure 21: Empirical distribution of organ support free days (OSFD) by baseline shock status. This plot is restricted to the Antiviral ITT population.

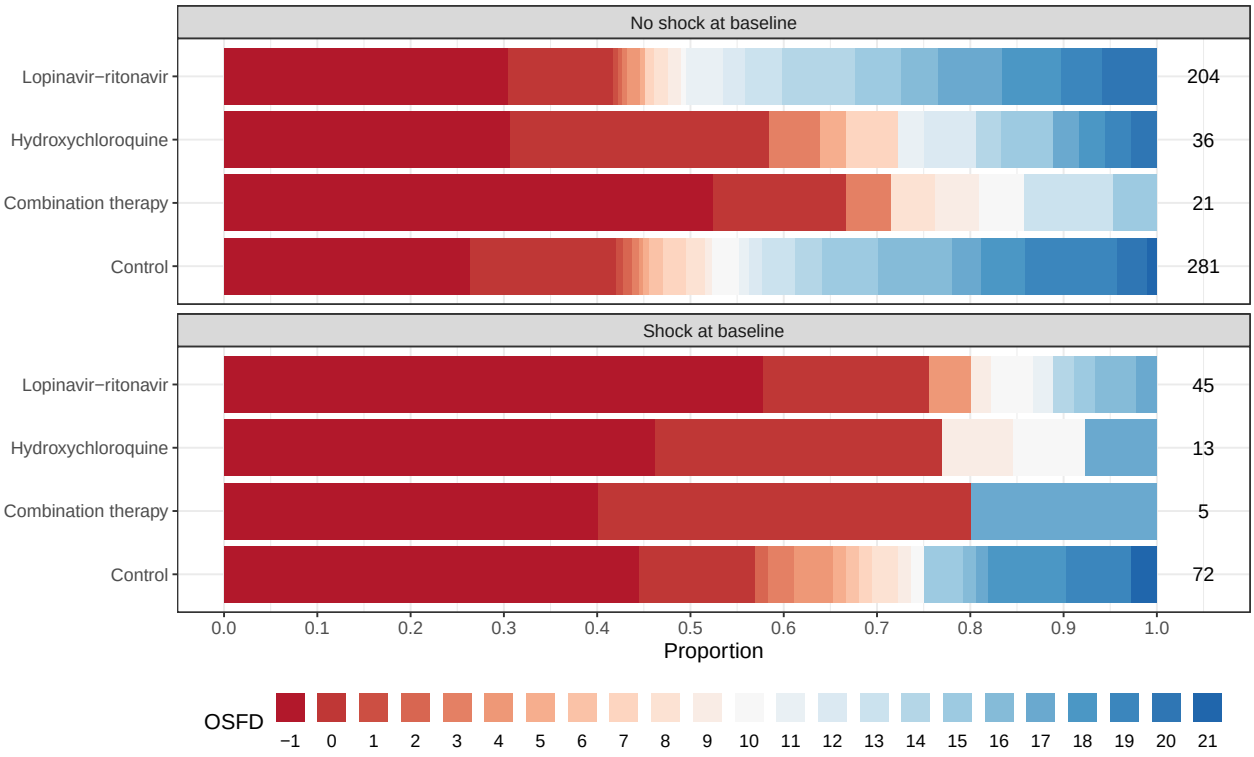


Figure 22: Empirical distribution of organ support free days (OSFD) for Lopinavir−ritonavir, Hydroxychloroquine, combination therapy, and control by baseline shock status. This plot is restricted to the Antiviral ITT population.

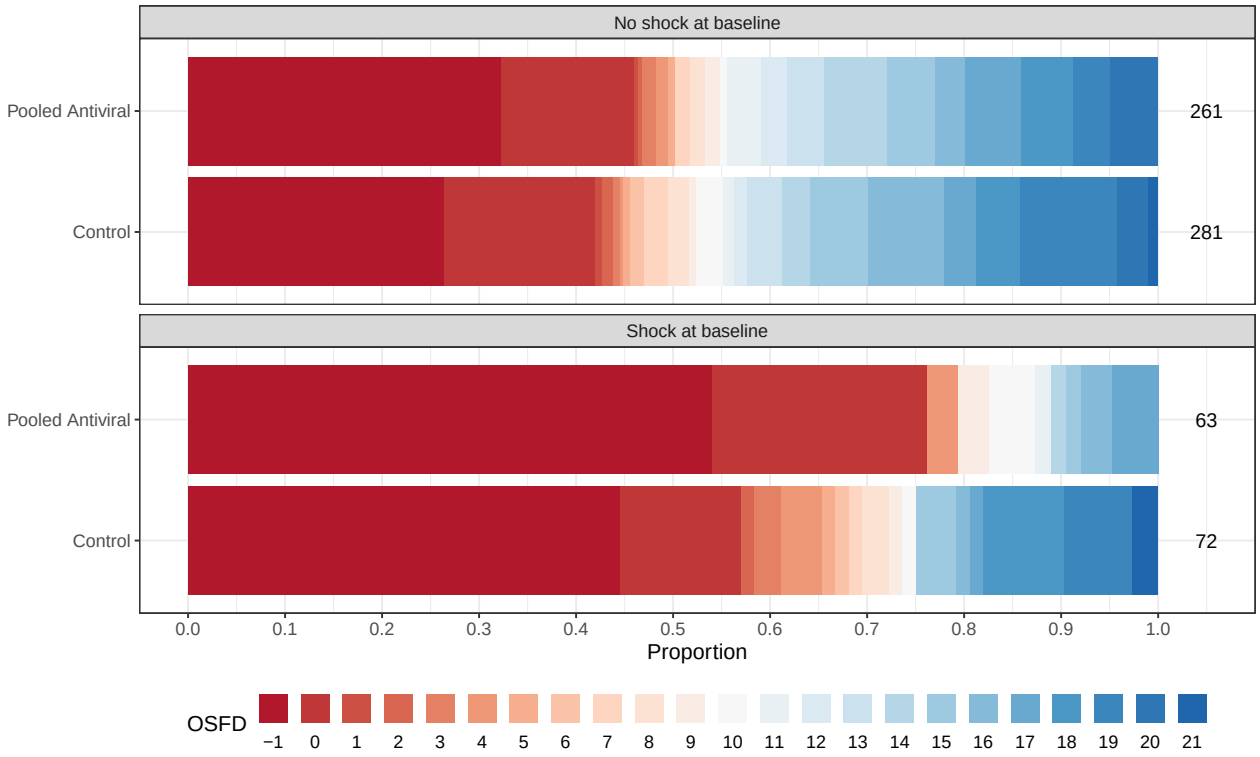


Figure 23: Empirical distribution of organ support free days (OSFD) for pooled antiviral and control interventions by baseline shock status. This plot is restricted to the Antiviral ITT population.

7.2.2 Subgroup analysis with differential effect on OSFD by baseline shock status

- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Differential treatment effects for antiviral interventions by baseline shock status will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy for each subgroup.
- Population: Unblinded ITT
- Note: The prespecified subgroup analysis included each individual antiviral intervention. However, due to low sample sizes within each subgroup, the active antiviral interventions have been pooled

for this subgroup analysis.

Table 63: Odds ratio parameters for subgroup analysis with differential effect on OSFD endpoint by shock status with pooled antiviral interventions

	Mean	SD	Median	CrI
Age<39	4.19	0.91	4.10	(2.65, 6.19)
Age 40-49	2.04	0.35	2.01	(1.45, 2.79)
Age 50-59	1.99	0.27	1.97	(1.50, 2.57)
Age 70-79	0.52	0.08	0.51	(0.38, 0.69)
Age 80+	0.33	0.09	0.32	(0.19, 0.55)
Female	1.17	0.13	1.17	(0.93, 1.44)
Time epoch 1	0.93	0.09	0.93	(0.77, 1.11)
Time epoch 2	0.85	0.14	0.85	(0.60, 1.13)
Time epoch 3	0.91	0.18	0.90	(0.60, 1.30)
Time epoch 4	1.06	0.24	1.03	(0.67, 1.61)
Time epoch 5	1.21	0.31	1.16	(0.73, 1.94)
Time epoch 6	1.27	0.33	1.23	(0.76, 2.05)
Time epoch 7	1.32	0.33	1.28	(0.79, 2.09)
Time epoch 8	1.39	0.34	1.34	(0.85, 2.17)
Time epoch 9	1.31	0.31	1.28	(0.83, 2.03)
Time epoch 10	1.20	0.28	1.17	(0.77, 1.86)
Time epoch 11	0.97	0.21	0.95	(0.62, 1.45)
Time epoch 12	0.83	0.19	0.81	(0.52, 1.25)
Time epoch 13	0.87	0.20	0.85	(0.54, 1.33)
Time epoch 14	1.10	0.26	1.07	(0.68, 1.69)
Time epoch 15	1.51	0.45	1.45	(0.83, 2.55)
Time epoch 16	2.31	1.10	2.07	(0.91, 5.01)
Shock at baseline (relative to no shock at baseline)	0.44	0.06	0.44	(0.34, 0.58)
Pooled Antiviral, no shock	0.84	0.12	0.83	(0.62, 1.11)
Pooled Antiviral, shock	1.64	2.09	1.00	(0.14, 6.98)
Pooled IL-6ra	1.66	0.23	1.64	(1.25, 2.16)
Fixed-dose corticosteroid	1.56	0.35	1.53	(0.99, 2.36)
Shock-dependent corticosteroid	1.15	0.26	1.12	(0.71, 1.75)
Pooled Antiviral*Pooled IL-6ra combination, no shock	1.40	0.29	1.37	(0.93, 2.05)
Pooled Antiviral*Pooled IL-6ra combination, shock	2.72	3.53	1.64	(0.23, 11.58)
Pooled Antiviral*Fixed-dose combination, no shock	1.34	0.35	1.29	(0.78, 2.13)
Pooled Antiviral*Fixed-dose combination, shock	2.56	3.37	1.52	(0.21, 11.04)
Pooled Antiviral*Pooled IL-6ra interaction, no shock	1.01	0.05	1.01	(0.91, 1.11)
Pooled Antiviral*Pooled IL-6ra interaction, shock	1.00	0.05	1.00	(0.91, 1.10)
Pooled Antiviral*Fixed-dose interaction, no shock	1.02	0.05	1.02	(0.92, 1.12)
Pooled Antiviral*Fixed-dose interaction, shock	1.00	0.05	1.00	(0.91, 1.11)

Table 64: Posterior probabilities for subgroup analysis with differential effect on OSFD endpoint by mechanical ventilation with pooled antiviral interventions

	Posterior Probability
Pooled antiviral is superior to control with no shock	0.104
Pooled antiviral is futile to control with no shock	0.994
Pooled antiviral is harmful with no shock	0.896
Pooled antiviral is superior to control with shock	0.499
Pooled antiviral is futile to control with shock	0.572
Pooled antiviral is harmful with shock	0.501
Pooled antiviral*Pooled IL-6ra combination is superior to control with no shock	0.939
Pooled antiviral*Pooled IL-6ra combination is superior to control shock	0.684
Pooled antiviral*Fixed-dose combination is superior to control no shock	0.834
Pooled antiviral*Fixed-dose combination is superior to control shock	0.658
Pooled antiviral with no shock > Pooled antiviral with shock	0.430

7.2.3 Subgroup analysis with differential effect on in-hospital mortality by baseline shock status

- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Differential treatment effects for antiviral interventions by baseline shock status will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy for each subgroup.
- Population: Unblinded ITT
- Note: The prespecified subgroup analysis included each individual antiviral intervention. However, due to low sample sizes within each subgroup, the active antiviral interventions have been pooled for this subgroup analysis.

Table 65: Odds ratio parameters for subgroup analysis with differential effect on in-hospital mortality endpoint by baseline shock status with pooled antiviral interventions

	Mean	SD	Median	CrI
Age<39	13.44	6.84	11.90	(5.25, 30.92)
Age 40-49	3.26	0.88	3.14	(1.91, 5.35)

Table 65: Odds ratio parameters for subgroup analysis with differential effect on in-hospital mortality endpoint by baseline shock status with pooled antiviral interventions *(continued)*

	Mean	SD	Median	CrI
Age 50-59	3.03	0.61	2.97	(2.01, 4.38)
Age 70-79	0.42	0.07	0.41	(0.29, 0.59)
Age 80+	0.23	0.07	0.22	(0.12, 0.39)
Female	1.20	0.19	1.18	(0.87, 1.60)
Time epoch 1	0.92	0.09	0.92	(0.76, 1.10)
Time epoch 2	0.82	0.14	0.82	(0.54, 1.10)
Time epoch 3	0.81	0.18	0.80	(0.50, 1.20)
Time epoch 4	0.85	0.22	0.83	(0.50, 1.35)
Time epoch 5	0.90	0.26	0.86	(0.50, 1.51)
Time epoch 6	0.91	0.27	0.88	(0.50, 1.54)
Time epoch 7	0.92	0.27	0.89	(0.51, 1.54)
Time epoch 8	0.97	0.27	0.93	(0.55, 1.60)
Time epoch 9	1.04	0.29	1.00	(0.59, 1.72)
Time epoch 10	1.11	0.33	1.06	(0.63, 1.88)
Time epoch 11	1.09	0.31	1.05	(0.62, 1.83)
Time epoch 12	1.05	0.29	1.02	(0.59, 1.70)
Time epoch 13	1.11	0.31	1.06	(0.61, 1.82)
Time epoch 14	1.32	0.41	1.27	(0.70, 2.29)
Time epoch 15	1.76	0.77	1.61	(0.77, 3.76)
Time epoch 16	2.73	2.59	2.05	(0.77, 8.82)
Shock at baseline (relative to no shock at baseline)	0.41	0.08	0.40	(0.28, 0.58)
Pooled Antiviral, no shock	0.82	0.16	0.80	(0.55, 1.18)
Pooled Antiviral, shock	1.65	2.20	1.00	(0.14, 7.05)
Pooled IL-6ra	1.71	0.32	1.68	(1.18, 2.40)
Fixed-dose corticosteroid	1.08	0.33	1.03	(0.58, 1.85)
Shock-dependent corticosteroid	1.21	0.39	1.15	(0.63, 2.16)
Pooled Antiviral*Pooled IL-6ra combination, no shock	1.40	0.39	1.35	(0.79, 2.32)
Pooled Antiviral*Pooled IL-6ra combination, shock	2.83	3.91	1.67	(0.22, 12.34)
Pooled Antiviral*Fixed-dose combination, no shock	0.89	0.32	0.83	(0.42, 1.64)
Pooled Antiviral*Fixed-dose combination, shock	1.79	2.57	1.03	(0.13, 7.99)
Pooled Antiviral*Pooled IL-6ra interaction, no shock	1.00	0.05	1.00	(0.91, 1.10)
Pooled Antiviral*Pooled IL-6ra interaction, shock	1.00	0.05	1.00	(0.91, 1.10)
Pooled Antiviral*Fixed-dose interaction, no shock	1.00	0.05	1.00	(0.91, 1.11)
Pooled Antiviral*Fixed-dose interaction, shock	1.00	0.05	1.00	(0.91, 1.10)

Table 66: Posterior probabilities for subgroup analysis with differential effect on in-hospital mortality endpoint by baseline shock status with pooled antiviral interventions

	Posterior Probability
Pooled antiviral is superior to control with no shock	0.133
Pooled antiviral is futile to control with no shock	0.981
Pooled antiviral is harmful with no shock	0.867
Pooled antiviral is superior to control with shock	0.499
Pooled antiviral is futile to control with shock	0.573
Pooled antiviral is harmful with shock	0.501
Pooled antiviral*Pooled IL-6ra combination is superior to control with no shock	0.860
Pooled antiviral*Pooled IL-6ra combination is superior to control shock	0.696
Pooled antiviral*Fixed-dose combination is superior to control no shock	0.301
Pooled antiviral*Fixed-dose combination is superior to control shock	0.509
Pooled antiviral with no shock > Pooled antiviral with shock	0.411

8 Post hoc analyses

8.1 Post hoc analysis of OSFD restricted to patients randomized concurrently with hydroxychloroquine interventions

Table 67: Summary of OSFD and in-hospital mortality for the Antiviral ITT population restricted to patients randomized concurrently with hydroxychloroquine interventions

Intervention	# Patients	# Known	# Deaths	OSFD median (IQR)
Lopinavir-ritonavir	34	33	8 (24.2%)	8 (0, 13)
Hydroxychloroquine	50	49	17 (34.7%)	0 (-1, 9)
Combination therapy	27	26	13 (50%)	-0.5 (-1, 6.75)
Control	78	77	21 (27.3%)	1 (-1, 13)
Pooled Antiviral	111	108	38 (35.2%)	0 (-1, 10.25)

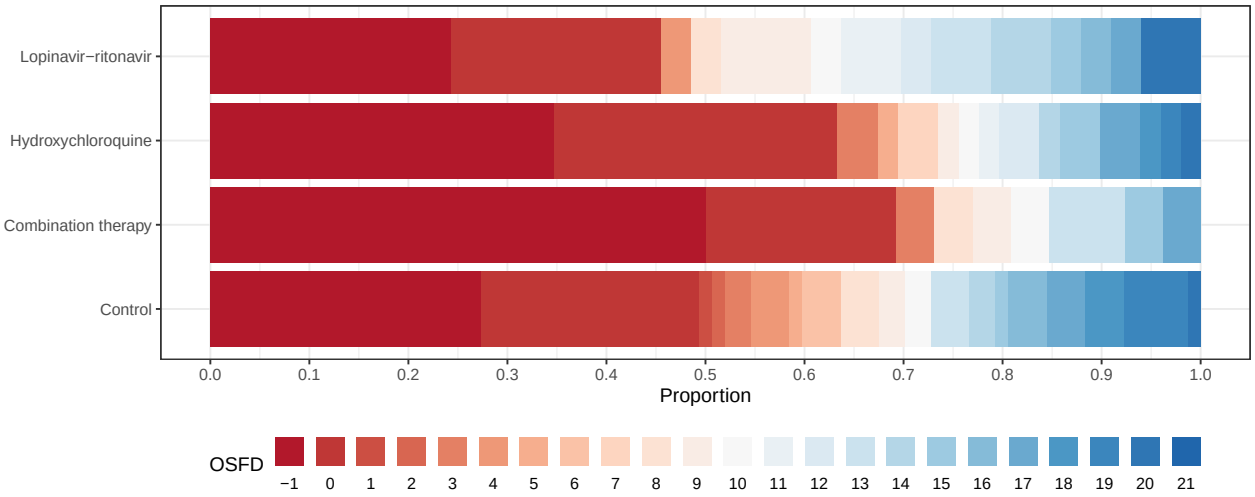


Figure 24: Empirical distribution of organ support free days (OSFD) for lopinavir−ritonavir, hydroxychloroquine, the combination therapy, and control. This plot is the Antiviral ITT population restricted to patients randomized concurrently with hydroxychloroquine interventions.

- Model: Primary analysis ordinal model
- Factors: Age, sex, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir−ritonavir, hydroxychloroquine, combination therapy
  - This model uses the pre-specified prior for the interaction between lopinavir-ritonavir and hydroxychloroquine from the primary analysis model that has a strong assumption of an additive effect on the log odds-ratio scale ($N(0, 0.05^2)$ on the interaction log odds ratio).
- Population: Antiviral ITT restricted to patients randomized concurrently with hydroxychloroquine interventions
  - Randomization to hydroxychloroquine interventions was initially halted on May 23, 2020. The ITSC later decided that any region that wanted to recommence hydroxychloroquine interventions could re-open them at sites that had equipoise. REMAP-CAP ITSC decided to finally close hydroxychloroquine interventions at all sites, and this was communicated to sites and the DSMB on the 13th of July. In this analysis, the concurrent population is defined as patients randomized thru May 23rd at all sites except one site with additional randomizations to hydroxychloroquine interventions after this date. For this one site, the "concurrent" population is all patients randomized through July 13, 2020. At this site, there are a total of 8 patients randomized in the antiviral domain after May 23, and 6 patients with complete

primary outcomes. Of these 8 patients, 2 were randomized to control, 3 were randomized to lopinavir-ritonavir, 2 were randomized to hydroxychloroquine, and 1 was randomized to combination therapy.

- Notes on model fit: Small sample sizes in this population resulted in an unstable fit due to low counts for certain covariate groups. The Antiviral Domain SAP specifies that the statisticians running the statistical model may make changes to the model to stabilize model fit provided that the changes do not have a large impact on the interpretation of the model. The following changes have been implemented for this analysis:
  - This population included one patient older than 80, so a "Age > 70" category has replaced the "Age 70-79" and "Age > 80" categories.
  - The site effects have been removed from the model.
  - Following the conventions outlined in the Current State document, the time buckets have been collapsed into four buckets: Bucket 0 (reference group) from May 18, 2020 to July 13, 2020 includes 28 patients; Bucket 1 from May 4, 2020 to May 17, 2020 includes 63 patients; Bucket 2 from April 20, 2020 to May 3, 2020 includes 68 patients; Bucket 3 from April 6, 2020 to April 19, 2020 includes 26 patients.
  - This population did not include any outcomes of 21 OSFD. The ordinal outcome has been modeled as a 22-level outcome from -1 to 20 rather than the full 23-level scale from -1 to 21.

Table 68: Odds ratio parameters for the analysis of OSFD restricted to patients randomized concurrently with hydroxychloroquine interventions

	Mean	SD	Median	CrI
Age<39	4.36	2.17	3.89	(1.54, 9.97)
Age 40-49	3.44	1.43	3.18	(1.46, 6.89)
Age 50-59	2.43	0.76	2.32	(1.27, 4.23)
Age 70+	0.38	0.17	0.34	(0.14, 0.80)
Female	1.41	0.40	1.36	(0.79, 2.35)
Time epoch 1	1.00	0.12	0.99	(0.78, 1.25)
Time epoch 2	1.02	0.24	0.99	(0.63, 1.55)
Time epoch 3	1.10	0.41	1.03	(0.51, 2.11)
Lopinavir−ritonavir	0.80	0.21	0.76	(0.48, 1.31)
Hydroxychloroquine	0.63	0.16	0.62	(0.37, 0.98)
Combination therapy	0.51	0.21	0.47	(0.22, 1.02)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	1.00	(0.90, 1.10)

Table 69: Posterior probabilities for the analysis of OSFD restricted to patients randomized concurrently with hydroxychloroquine interventions

	Posterior Probability
Lopinavir–ritonavir is optimal	0.140
Lopinavir–ritonavir is superior to control	0.151
Lopinavir–ritonavir is futile (OR < 1.2)	0.951
Lopinavir–ritonavir is harmful (OR < 1)	0.849
Hydroxychloroquine is optimal	0.010
Hydroxychloroquine is superior to control	0.019
Hydroxychloroquine is futile (OR < 1.2)	0.998
Hydroxychloroquine is harmful (OR < 1)	0.981
Combination therapy is optimal	0.011
Combination therapy OR > 1	0.028
Combination therapy is futile (OR < 1.2)	0.991
Combination therapy is harmful (OR < 1)	0.972
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.498

8.2 Post hoc analysis of OSFD restricted to patients randomized concurrently with hydroxychloroquine interventions with a weaker prior on the interaction term for combination therapy

- Model: Primary analysis ordinal model
- Factors: Age, sex, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy
  - The prior for the interaction between lopinavir-ritonavir and hydroxychloroquine is a standard normal prior to relax the assumption that there is an additive interaction between the two interventions.
- Population: Antiviral ITT restricted to patients randomized concurrently with hydroxychloroquine interventions
  - Randomization to hydroxychloroquine interventions was initially halted on May 23, 2020. The ITSC later decided that any region that wanted to recommence hydroxychloroquine interventions could re-open them at sites that had equipoise. REMAP-CAP ITSC decided to finally close hydroxychloroquine interventions at all sites, and this was communicated to sites and the DSMB on the 13th of July. In this analysis, the concurrent population is defined as patients randomized thru May 23rd at all sites except one site with additional randomizations to hydroxychloroquine

interventions after this date. For this one site, the "concurrent" population is all patients randomized through July 13, 2020. At this site, there are a total of 8 patients randomized in the antiviral domain after May 23.

- Notes on model fit: Small sample sizes in this population resulted in an unstable fit due to low counts for certain covariate groups. The Antiviral Domain SAP specifies that the statisticians running the statistical model may make changes to the model to stabilize model fit provided that the changes do not have a large impact on the interpretation of the model. The following changes have been implemented for this analysis:
  - This population included one patient older than 80, so a "Age > 70" category has replaced the "Age 70-79" and "Age > 80" categories.
  - The site effects have been removed from the model.
  - Following the conventions outlined in the Current State document, the time buckets have been collapsed into four buckets: Bucket 0 (reference group) from May 18, 2020 to July 13, 2020 includes 28 patients; Bucket 1 from May 4, 2020 to May 17, 2020 includes 63 patients; Bucket 2 from April 20, 2020 to May 3, 2020 includes 68 patients; Bucket 3 from April 6, 2020 to April 19, 2020 includes 26 patients.
  - This population did not include any outcomes of 21 OSFD. The ordinal outcome has been modeled as a 22-level outcome from -1 to 20 rather than the full 23-level scale from -1 to 21.

Table 70: Odds ratio parameters for the analysis of OSFD restricted to patients randomized concurrently with hydroxychloroquine interventions with a weaker prior on the interaction term for combination therapy

	Mean	SD	Median	CrI
Age<39	4.24	2.11	3.78	(1.50, 9.60)
Age 40-49	3.42	1.41	3.18	(1.46, 6.87)
Age 50-59	2.44	0.78	2.33	(1.27, 4.27)
Age 70+	0.38	0.18	0.35	(0.14, 0.83)
Female	1.43	0.41	1.38	(0.79, 2.36)
Time epoch 1	1.00	0.12	0.99	(0.78, 1.26)
Time epoch 2	1.02	0.24	1.00	(0.63, 1.56)
Time epoch 3	1.12	0.42	1.04	(0.52, 2.14)
Lopinavir−ritonavir	0.91	0.31	0.85	(0.47, 1.66)
Hydroxychloroquine	0.71	0.22	0.68	(0.37, 1.21)
Combination therapy	0.47	0.21	0.43	(0.18, 0.99)
Hydroxychloroquine and Lopinavir−ritonavir interaction	0.84	0.46	0.74	(0.27, 1.98)

Table 71: Posterior probabilities for the analysis of OSFD restricted to patients randomized concurrently with hydroxychloroquine interventions with a weaker prior on the interaction term for combination therapy

	Posterior Probability
Lopinavir–ritonavir is optimal	0.293
Lopinavir–ritonavir is superior to control	0.318
Lopinavir–ritonavir is futile (OR < 1.2)	0.845
Lopinavir–ritonavir is harmful (OR < 1)	0.682
Hydroxychloroquine is optimal	0.040
Hydroxychloroquine is superior to control	0.095
Hydroxychloroquine is futile (OR < 1.2)	0.974
Hydroxychloroquine is harmful (OR < 1)	0.905
Combination therapy is optimal	0.013
Combination therapy OR > 1	0.024
Combination therapy is futile (OR < 1.2)	0.992
Combination therapy is harmful (OR < 1)	0.976
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.473

8.3 Post hoc analysis of in-hospital mortality restricted to patients randomized concurrently with hydroxychloroquine interventions

- Model: Primary analysis dichotomous model
- Factors: Age, sex, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy
  - This model uses the pre-specified prior for the interaction between lopinavir-ritonavir and hydroxychloroquine from the primary analysis model that has a strong assumption of an additive effect on the log odds-ratio scale ($N(0, 0.05^2)$ on the interaction log odds ratio).
- Population: Antiviral ITT restricted to patients randomized concurrently with hydroxychloroquine interventions
  - Randomization to hydroxychloroquine interventions was initially halted on May 23, 2020. The ITSC later decided that any region that wanted to recommence hydroxychloroquine interventions could re-open them at sites that had equipoise. REMAP-CAP ITSC decided to finally close hydroxychloroquine interventions at all sites, and this was communicated to sites and the DSMB on the 13th of July. In this analysis, the concurrent population is defined as patients randomized thru May 23rd at all sites except one site with additional randomizations to hydroxychloroquine interventions after this date. For this one site, the "concurrent" population is all patients ran-

domized through July 13, 2020. At this site, there are a total of 8 patients randomized in the antiviral domain after May 23.

- Notes on model fit: Small sample sizes in this population resulted in an unstable fit due to low counts for certain covariate groups. The Antiviral Domain SAP specifies that the statisticians running the statistical model may make changes to the model to stabilize model fit provided that the changes do not have a large impact on the interpretation of the model. The following changes have been implemented for this analysis:
  - This population included one patient older than 80, so a "Age > 70" category has replaced the "Age 70-79" and "Age > 80" categories.
  - The site effects have been removed from the model.
  - Following the conventions outlined in the Current State document, the time buckets have been collapsed into four buckets: Bucket 0 (reference group) from May 18, 2020 to July 13, 2020 includes 28 patients; Bucket 1 from May 4, 2020 to May 17, 2020 includes 63 patients; Bucket 2 from April 20, 2020 to May 3, 2020 includes 68 patients; Bucket 3 from April 6, 2020 to April 19, 2020 includes 26 patients.

Table 72: Odds ratio parameters for the analysis of in-hospital mortality restricted to patients randomized concurrently with hydroxychloroquine interventions

	Mean	SD	Median	CrI
Age<39	8.56	7.45	6.44	(1.74, 28.37)
Age 40-49	6.05	3.94	5.07	(1.78, 16.10)
Age 50-59	4.11	1.81	3.74	(1.70, 8.56)
Age 70+	0.29	0.14	0.27	(0.11, 0.64)
Female	1.46	0.57	1.35	(0.66, 2.85)
Time epoch 1	1.04	0.13	1.04	(0.80, 1.33)
Time epoch 2	1.14	0.31	1.09	(0.65, 1.86)
Time epoch 3	1.32	0.65	1.18	(0.51, 2.92)
Lopinavir−ritonavir	0.69	0.22	0.65	(0.37, 1.22)
Hydroxychloroquine	0.61	0.18	0.58	(0.31, 1.02)
Combination therapy	0.43	0.23	0.38	(0.14, 1.02)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	1.00	(0.90, 1.10)

Table 73: Posterior probabilities for the analysis of OSFD restricted to patients randomized concurrently with hydroxychloroquine interventions

	Posterior Probability
Lopinavir–ritonavir is optimal	0.070
Lopinavir–ritonavir is superior to control	0.082
Lopinavir–ritonavir is futile (OR < 1.2)	0.972
Lopinavir–ritonavir is harmful (OR < 1)	0.918
Hydroxychloroquine is optimal	0.017
Hydroxychloroquine is superior to control	0.029
Hydroxychloroquine is futile (OR < 1.2)	0.993
Hydroxychloroquine is harmful (OR < 1)	0.971
Combination therapy is optimal	0.012
Combination therapy OR > 1	0.028
Combination therapy is futile (OR < 1.2)	0.989
Combination therapy is harmful (OR < 1)	0.972
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.577

8.4 Post hoc analysis of OSFD without borrowing between antiviral interventions

- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Population: Unblinded ITT
- The nesting of lopinavir–ritonavir and hydroxychloroquine has been removed from this model. The log odds ratio for each intervention is modeled with independent standard normal prior distributions.

Table 74: Odds ratio parameters for exploratory analysis of OSFD endpoint without borrowing between antiviral interventions

	Mean	SD	Median	CrI
Age<39	4.12	0.91	4.01	(2.63, 6.23)
Age 40-49	2.11	0.36	2.08	(1.50, 2.89)
Age 50-59	1.96	0.27	1.94	(1.49, 2.55)
Age 70-79	0.52	0.08	0.51	(0.38, 0.68)
Age 80+	0.34	0.09	0.33	(0.19, 0.55)
Female	1.17	0.13	1.16	(0.93, 1.44)
Time epoch 1	0.95	0.08	0.95	(0.80, 1.11)
Time epoch 2	0.90	0.13	0.90	(0.66, 1.16)
Time epoch 3	0.95	0.17	0.94	(0.65, 1.32)
Time epoch 4	1.05	0.22	1.03	(0.69, 1.54)
Time epoch 5	1.15	0.27	1.12	(0.73, 1.76)
Time epoch 6	1.21	0.29	1.17	(0.76, 1.87)
Time epoch 7	1.24	0.29	1.20	(0.78, 1.90)
Time epoch 8	1.27	0.29	1.24	(0.81, 1.95)
Time epoch 9	1.22	0.27	1.18	(0.79, 1.82)
Time epoch 10	1.13	0.24	1.10	(0.74, 1.68)
Time epoch 11	0.98	0.21	0.96	(0.64, 1.44)
Time epoch 12	0.88	0.19	0.87	(0.56, 1.31)
Time epoch 13	0.88	0.20	0.86	(0.56, 1.31)
Time epoch 14	0.97	0.23	0.95	(0.60, 1.48)
Time epoch 15	1.13	0.33	1.08	(0.63, 1.91)
Time epoch 16	1.41	0.64	1.28	(0.60, 2.99)
Lopinavir−ritonavir	0.82	0.12	0.81	(0.60, 1.09)
Hydroxychloroquine	0.52	0.13	0.51	(0.31, 0.80)
Pooled IL-6ra	1.69	0.23	1.67	(1.27, 2.19)
Fixed-dose corticosteroids	1.45	0.33	1.41	(0.91, 2.19)
Shock-dependent corticosteroids	1.14	0.26	1.11	(0.71, 1.73)
Combination therapy	0.43	0.13	0.41	(0.23, 0.72)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.40	0.29	1.37	(0.92, 2.05)
Hydroxychloroquine*Pooled IL-6ra combination	0.88	0.25	0.85	(0.49, 1.44)
Combination therapy*Pooled IL-6ra combination	0.73	0.24	0.69	(0.36, 1.30)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	1.20	0.34	1.16	(0.68, 1.98)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.76	0.26	0.72	(0.37, 1.37)
Combination therapy*Fixed-dose corticosteroids combination	0.62	0.24	0.58	(0.27, 1.22)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	1.00	(0.90, 1.10)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.01	0.05	1.00	(0.91, 1.10)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.11)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 75: Posterior probabilities for exploratory analysis of OSFD endpoint without borrowing between antiviral interventions

	Posterior Probability
Lopinavir–ritonavir is optimal	0.102
Lopinavir–ritonavir is superior to control	0.084
Lopinavir–ritonavir is futile (OR < 1.2)	0.997
Lopinavir–ritonavir is harmful (OR < 1)	0.916
Hydroxychloroquine is optimal	0.002
Hydroxychloroquine is superior to control	0.002
Hydroxychloroquine is futile (OR < 1.2)	1.000
Hydroxychloroquine is harmful (OR < 1)	0.998
Combination therapy is optimal	0.001
Combination therapy OR > 1	0.001
Combination therapy is futile (OR < 1.2)	1.000
Combination therapy is harmful (OR < 1)	0.999
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.938
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.282
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.708
Hydroxychloroquine*Fixed-dose combination OR > 1	0.160
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.142

8.5 Post hoc analysis of in-hospital mortality without borrowing between antiviral interventions

- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Population: Unblinded ITT
- The nesting of lopinavir–ritonavir and hydroxychloroquine has been removed from this model. The log odds ratio for each intervention is modeled with independent standard normal prior distributions.

Table 76: Odds ratio parameters for exploratory analysis of in-hospital mortality without borrowing between antiviral interventions

	Mean	SD	Median	CrI
Age<39	13.11	6.93	11.44	(5.07, 30.03)
Age 40-49	3.35	0.87	3.22	(1.97, 5.42)
Age 50-59	2.98	0.60	2.91	(2.00, 4.34)
Age 70-79	0.41	0.07	0.41	(0.29, 0.57)
Age 80+	0.23	0.07	0.22	(0.12, 0.39)
Female	1.19	0.19	1.18	(0.87, 1.61)
Time epoch 1	0.93	0.08	0.93	(0.77, 1.10)
Time epoch 2	0.86	0.14	0.85	(0.60, 1.13)
Time epoch 3	0.84	0.17	0.83	(0.54, 1.21)
Time epoch 4	0.85	0.20	0.83	(0.52, 1.31)
Time epoch 5	0.88	0.23	0.85	(0.52, 1.40)
Time epoch 6	0.89	0.24	0.86	(0.51, 1.45)
Time epoch 7	0.90	0.24	0.87	(0.52, 1.45)
Time epoch 8	0.93	0.24	0.90	(0.55, 1.49)
Time epoch 9	0.98	0.25	0.94	(0.59, 1.56)
Time epoch 10	1.02	0.27	0.98	(0.60, 1.66)
Time epoch 11	1.02	0.27	0.98	(0.60, 1.66)
Time epoch 12	1.00	0.27	0.97	(0.58, 1.63)
Time epoch 13	1.02	0.29	0.98	(0.58, 1.70)
Time epoch 14	1.11	0.35	1.05	(0.59, 1.94)
Time epoch 15	1.28	0.52	1.18	(0.57, 2.59)
Time epoch 16	1.60	1.06	1.34	(0.53, 4.18)
Lopinavir−ritonavir	0.73	0.14	0.71	(0.48, 1.04)
Hydroxychloroquine	0.52	0.17	0.50	(0.26, 0.93)
Pooled IL-6ra	1.71	0.31	1.68	(1.19, 2.40)
Fixed-dose corticosteroids	0.99	0.30	0.95	(0.53, 1.68)
Shock-dependent corticosteroids	1.21	0.40	1.15	(0.62, 2.15)
Combination therapy	0.38	0.15	0.35	(0.17, 0.73)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.25	0.34	1.20	(0.71, 2.03)
Hydroxychloroquine*Pooled IL-6ra combination	0.90	0.35	0.84	(0.40, 1.75)
Combination therapy*Pooled IL-6ra combination	0.65	0.29	0.60	(0.26, 1.37)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	0.72	0.26	0.68	(0.34, 1.34)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.52	0.24	0.47	(0.20, 1.13)
Combination therapy*Fixed-dose corticosteroids combination	0.38	0.20	0.34	(0.13, 0.89)
Hydroxychloroquine and Lopinavir−ritonavir interaction	1.00	0.05	1.00	(0.90, 1.10)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Hydroxychloroquine*Pooled IL-6ra interaction	1.01	0.05	1.00	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.90, 1.10)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.90, 1.10)

Table 77: Posterior probabilities for exploratory analysis of in-hospital mortality endpoint without borrowing between antiviral interventions

	Posterior Probability
Lopinavir–ritonavir is optimal	0.044
Lopinavir–ritonavir is superior to control	0.042
Lopinavir–ritonavir is futile (OR < 1.2)	0.997
Lopinavir–ritonavir is harmful (OR < 1)	0.958
Hydroxychloroquine is optimal	0.017
Hydroxychloroquine is superior to control	0.017
Hydroxychloroquine is futile (OR < 1.2)	0.997
Hydroxychloroquine is harmful (OR < 1)	0.983
Combination therapy is optimal	0.001
Combination therapy OR > 1	0.002
Combination therapy is futile (OR < 1.2)	1.000
Combination therapy is harmful (OR < 1)	0.998
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.760
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.327
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.131
Hydroxychloroquine*Fixed-dose combination OR > 1	0.046
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.243

8.6 Post hoc analysis of OSFD with a weaker prior on the interaction term for combination therapy

- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Population: Unblinded ITT
- A less informative (standard normal) prior has been specified on the interaction term for the combination therapy.

Table 78: Odds ratio parameters for exploratory analysis of OSFD endpoint with a weaker prior on the combination therapy interaction term

	Mean	SD	Median	CrI
Age<39	4.10	0.92	3.99	(2.58, 6.18)
Age 40-49	2.11	0.36	2.08	(1.48, 2.89)
Age 50-59	1.96	0.27	1.95	(1.49, 2.56)
Age 70-79	0.52	0.08	0.51	(0.38, 0.69)
Age 80+	0.34	0.09	0.33	(0.19, 0.55)
Female	1.17	0.13	1.16	(0.93, 1.45)
Time epoch 1	0.95	0.08	0.95	(0.79, 1.11)
Time epoch 2	0.90	0.13	0.90	(0.66, 1.17)
Time epoch 3	0.95	0.17	0.94	(0.65, 1.32)
Time epoch 4	1.05	0.22	1.03	(0.69, 1.55)
Time epoch 5	1.15	0.27	1.12	(0.73, 1.77)
Time epoch 6	1.20	0.28	1.17	(0.75, 1.86)
Time epoch 7	1.24	0.29	1.20	(0.78, 1.91)
Time epoch 8	1.27	0.29	1.23	(0.82, 1.93)
Time epoch 9	1.21	0.27	1.18	(0.79, 1.81)
Time epoch 10	1.11	0.24	1.09	(0.73, 1.66)
Time epoch 11	0.96	0.20	0.94	(0.62, 1.40)
Time epoch 12	0.86	0.19	0.84	(0.54, 1.26)
Time epoch 13	0.85	0.19	0.83	(0.54, 1.27)
Time epoch 14	0.94	0.22	0.92	(0.59, 1.43)
Time epoch 15	1.10	0.32	1.05	(0.61, 1.83)
Time epoch 16	1.39	0.62	1.25	(0.59, 2.96)
Lopinavir−ritonavir	0.81	0.13	0.80	(0.58, 1.10)
Hydroxychloroquine	0.66	0.16	0.65	(0.36, 1.00)
Pooled IL-6ra	1.69	0.23	1.67	(1.29, 2.19)
Fixed-dose corticosteroids	1.46	0.33	1.42	(0.92, 2.22)
Shock-dependent corticosteroids	1.15	0.26	1.12	(0.72, 1.74)
Combination therapy	0.38	0.15	0.36	(0.17, 0.75)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.38	0.30	1.34	(0.89, 2.04)
Hydroxychloroquine*Pooled IL-6ra combination	1.12	0.32	1.09	(0.58, 1.84)
Combination therapy*Pooled IL-6ra combination	0.92	0.35	0.86	(0.40, 1.77)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	1.20	0.34	1.15	(0.68, 2.00)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.97	0.34	0.92	(0.45, 1.75)
Combination therapy*Fixed-dose corticosteroids combination	0.79	0.34	0.73	(0.31, 1.64)
Hydroxychloroquine and Lopinavir−ritonavir interaction	0.77	0.35	0.70	(0.30, 1.63)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.01	0.05	1.01	(0.91, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.10)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.01	0.05	1.01	(0.92, 1.11)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 79: Posterior probabilities for exploratory analysis of OSFD endpoint with a weaker prior on the combination therapy interaction term

	Posterior Probability
Lopinavir–ritonavir is optimal	0.093
Lopinavir–ritonavir is superior to control	0.078
Lopinavir–ritonavir is futile (OR < 1.2)	0.994
Lopinavir–ritonavir is harmful (OR < 1)	0.922
Hydroxychloroquine is optimal	0.025
Hydroxychloroquine is superior to control	0.025
Hydroxychloroquine is futile (OR < 1.2)	0.998
Hydroxychloroquine is harmful (OR < 1)	0.975
Combination therapy is optimal	0.004
Combination therapy OR > 1	0.004
Combination therapy is futile (OR < 1.2)	0.999
Combination therapy is harmful (OR < 1)	0.997
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.919
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.609
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.693
Hydroxychloroquine*Fixed-dose combination OR > 1	0.402
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.492

8.7 Post hoc analysis of in-hospital mortality with a weaker prior on the interaction term for combination therapy

- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir–ritonavir, hydroxychloroquine, combination therapy, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-dependent steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Population: Unblinded ITT
- A less informative (standard normal) prior has been specified on the interaction term for the combination therapy.

Table 80: Odds ratio parameters for exploratory analysis of in-hospital mortality with a weaker prior on the combination therapy interaction term

	Mean	SD	Median	CrI
Age<39	12.86	6.54	11.33	(5.00, 29.55)
Age 40-49	3.31	0.88	3.20	(1.94, 5.35)
Age 50-59	2.98	0.62	2.92	(1.96, 4.37)
Age 70-79	0.41	0.07	0.41	(0.29, 0.58)
Age 80+	0.23	0.07	0.22	(0.13, 0.39)
Female	1.19	0.19	1.18	(0.86, 1.61)
Time epoch 1	0.93	0.08	0.93	(0.78, 1.10)
Time epoch 2	0.86	0.13	0.86	(0.61, 1.14)
Time epoch 3	0.84	0.17	0.83	(0.54, 1.22)
Time epoch 4	0.86	0.20	0.84	(0.52, 1.32)
Time epoch 5	0.88	0.23	0.85	(0.51, 1.40)
Time epoch 6	0.89	0.24	0.86	(0.51, 1.44)
Time epoch 7	0.90	0.24	0.87	(0.52, 1.46)
Time epoch 8	0.93	0.24	0.90	(0.55, 1.49)
Time epoch 9	0.97	0.25	0.94	(0.58, 1.56)
Time epoch 10	1.01	0.27	0.97	(0.60, 1.65)
Time epoch 11	1.01	0.27	0.97	(0.60, 1.64)
Time epoch 12	0.99	0.26	0.95	(0.57, 1.60)
Time epoch 13	1.00	0.28	0.96	(0.56, 1.66)
Time epoch 14	1.08	0.34	1.03	(0.57, 1.89)
Time epoch 15	1.24	0.50	1.14	(0.56, 2.44)
Time epoch 16	1.53	0.99	1.29	(0.52, 4.05)
Lopinavir−ritonavir	0.72	0.14	0.71	(0.48, 1.04)
Hydroxychloroquine	0.66	0.19	0.65	(0.34, 1.08)
Pooled IL-6ra	1.71	0.32	1.69	(1.18, 2.42)
Fixed-dose corticosteroids	1.00	0.30	0.95	(0.53, 1.69)
Shock-dependent corticosteroids	1.21	0.39	1.15	(0.62, 2.14)
Combination therapy	0.31	0.16	0.28	(0.11, 0.71)
Lopinavir−ritonavir*Pooled IL-6ra combination	1.24	0.34	1.20	(0.70, 2.06)
Hydroxychloroquine*Pooled IL-6ra combination	1.14	0.40	1.09	(0.52, 2.08)
Combination therapy*Pooled IL-6ra combination	0.85	0.41	0.77	(0.30, 1.86)
Lopinavir−ritonavir*Fixed-dose corticosteroids combination	0.72	0.27	0.67	(0.33, 1.37)
Hydroxychloroquine*Fixed-dose corticosteroids combination	0.66	0.29	0.62	(0.26, 1.38)
Combination therapy*Fixed-dose corticosteroids combination	0.49	0.27	0.43	(0.15, 1.19)
Hydroxychloroquine and Lopinavir−ritonavir interaction	0.71	0.39	0.62	(0.22, 1.73)
Lopinavir−ritonavir*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Hydroxychloroquine*Pooled IL-6ra interaction	1.01	0.05	1.00	(0.91, 1.11)
Combination therapy*Pooled IL-6ra interaction	1.00	0.05	1.00	(0.91, 1.11)
Lopinavir−ritonavir*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.90, 1.10)
Hydroxychloroquine*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)
Combination therapy*Fixed-dose corticosteroids interaction	1.00	0.05	1.00	(0.91, 1.10)

Table 81: Posterior probabilities for exploratory analysis of in-hospital mortality with a weaker prior on the combination therapy interaction term

	Posterior Probability
Lopinavir–ritonavir is optimal	0.037
Lopinavir–ritonavir is superior to control	0.042
Lopinavir–ritonavir is futile (OR < 1.2)	0.997
Lopinavir–ritonavir is harmful (OR < 1)	0.958
Hydroxychloroquine is optimal	0.044
Hydroxychloroquine is superior to control	0.045
Hydroxychloroquine is futile (OR < 1.2)	0.988
Hydroxychloroquine is harmful (OR < 1)	0.955
Combination therapy is optimal	0.003
Combination therapy OR > 1	0.003
Combination therapy is futile (OR < 1.2)	0.999
Combination therapy is harmful (OR < 1)	0.997
Lopinavir–ritonavir*Pooled IL-6ra combination OR > 1	0.747
Hydroxychloroquine*Pooled IL-6ra combination OR > 1	0.605
Lopinavir–ritonavir*Fixed-dose combination OR > 1	0.140
Hydroxychloroquine*Fixed-dose combination OR > 1	0.118
Lopinavir–ritonavir and Hydroxychloroquine are equivalent	0.610

9 Report production and data sources

All analyses in this report are based on the following documents:

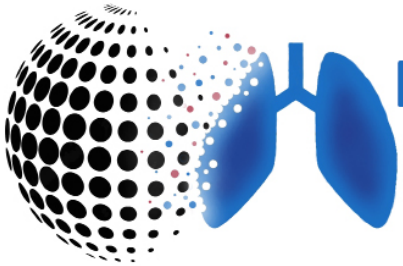
- Statistical Analysis Appendix for REMAP-COVID, version 1, dated August 18, 2020;
- Statistical Analysis Plan for the COVID-19 Antiviral Therapy Domain for Patients with COVID-19 Pandemic Infection Suspected or Proven (PISOP), version 1, dated January 14, 2021;
- Current State of the Statistical Model: Pandemic Model, version 2.3-AV, dated January 19, 2021;
- Errata Sheet, last updated January 26, 2021.

The blinded ITSC analysis team at Berry Consultants performed the analyses in this report using data received from multiple sources. The OSFD outcomes and treatment assignments for patients in unblinded domains were sent from the unblinded Statistical Analysis Committee (SAC) with all blinded information removed. The baseline/discharge, daily, and medication data for patients randomized in unblinded domains were sent from an unblinded data coordination team at Monash University. The table below shows the file names for the data exports from each data source and the date each file was received by the blinded

ITSC analysis committee. All merging and summarization of data was done using the R statistical computing environment. This report was generated from an Rmarkdown document in the Rstudio software.

Table 82: Summary of data sources

Filename	Date received	Description
merged_REMAP_PISOPSevere_CXY_2020-12-22.csv	December 22, 2020	OSFD and treatment assignments from unblinded SAC
Immune modulation baseline discharge compliance data_Dec27_Designteam.csv	December 27, 2020	Baseline and discharge data for unblinded ITT
Antiviral baseline and discharge data_Jan20_Designteam.csv	January 20, 2021	Baseline and discharge data for unblinded ITT with added compliance variables
Immune Modulation daily data_Dec21_Designteam.csv	December 21, 2020	Daily ICU data for unblinded ITT
Immune Modulation_medication_blinded_Dec27_Designteam.csv	December 27, 2020	Medication data for unblinded ITT
UPMC_cs_antiviral_testresults.csv	February 1, 2021	COVID-19 test results for UPMC patients



Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP): CORE PROTOCOL

REMAP-CAP Core Protocol Version 3 dated 10 July 2019

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1. ABBREVIATIONS AND GLOSSARY

1.1. Abbreviations

ANZ	Australia and New Zealand
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
BHM	Bayesian Hierarchical Model
CAP	Community-Acquired Pneumonia
CIHR	Canadian Institutes of Health Research
CIHR-SPOR	Canadian Institutes of Health Research Strategy for Patient-Oriented Research
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCIS	Electronic Clinical Information System
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EU	European
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
HDU	High Dependency Unit
HRC	Health Research Council
HRQoL	Health Related Quality of Life
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IEIG	International Embedding Interest Group
IIG	International Interest Group
ILTOHEIG	International Long-term Outcomes and Health Economics Interest Group
IPWG	International Pandemic Working Group
ISIG	International Statistics Interest Group

ITSC	International Trial Steering Committee
ITT	Intention-To-Treat
LOS	Length of Stay
NHMRC	National Health and Medical Research Council
OFFD	Organ Failure Free Days
P:F Ratio	Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration
PEEP	Positive End-Expiratory Pressure
PREPARE	Platform for European Preparedness Against (Re-)emerging Epidemics
RAR	Response Adaptive Randomization
REMAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RCC	Regional Coordinating Center
RCT	Randomized Controlled Trial
RMC	Regional Management Committee
RSA	Region-Specific Appendix
SAC	Statistical Analysis Committee
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SOPs	Standard Operating Procedures
VFD	Ventilator Free Days
WG	Working Group
WHODAS	World Health Organization Disability Assessment Schedule

1.2. Glossary

Borrowing is the process within the statistical model, whereby, when the treatment effect is similar in different strata, evidence relating to the effectiveness of an intervention in one stratum contributes to the estimation of the posterior probability in another stratum.

Core Protocol is a module of the protocol that contains all information that is generic to the Randomized, Embedded, Multifactorial, Adaptive Platform trial (REMAP), irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested.

Domain-Specific Appendix is an appendix to the Core Protocol. These appendices are modules of the protocol that contain all information about the interventions, which are nested within a domain that will be a subject of this REMAP. Each domain will have its own Domain-Specific Appendix (DSA). The information contained in each DSA includes criteria that determine eligibility of patients to that domain, the features of the interventions and how they are delivered, and any additional endpoints and data collection that are not covered in the Core Protocol.

Domain-Specific Working Group is a sub-committee involved in trial management, the members of which take responsibility for the development and management of a current or proposed new domain.

Domain consists of a specific set of competing alternative interventions within a common clinical mode, which, for the purposes of the platform, are mutually exclusive and exhaustive. Where there is only a single intervention option within a domain the comparator is all other usual care in the absence of the intervention. Where multiple interventions exist within a domain, comparators are the range of interventions either with or without a no intervention option, depending on whether an intervention, within the domain, is provided to all patients as part of standard care. Within the REMAP every patient will be assigned to receive one and only one of the available interventions within every domain for which they are eligible.

International Trial Steering Committee is the committee that takes overall responsibility for the management and conduct of the REMAP with oversight over all regions and all domains.

Intervention is a treatment option that is subject to variation in clinical practice (comparative effectiveness intervention) or has been proposed for introduction into clinical practice (experimental intervention) and also is being subjected to experimental manipulation within the design of a

REMAP. For the purposes of the REMAP an intervention can include an option in which no treatment is provided.

Monte-Carlo Simulations are computational algorithms that employ repeated random sampling to obtain a probability distribution. They are used in the design of the study to anticipate trial performance under a variety of potential states of 'truth' (e.g., to test the way in which a particular trial design feature will help or hinder the ability to determine whether a 'true' treatment effect will be discovered by the trial). Monte Carlo methods are also used to provide updated posterior probability distributions for the ongoing analyses of the trial.

Pandemic Appendix describes an appendix to the Core Protocol that includes the modifications to the Core Protocol that will occur during a pandemic of respiratory infection that results in severe CAP.

Platform Conclusion describes when a Statistical Trigger has been reached and, following evaluation by the Data Safety and Monitoring Board (DSMB) +/- the International Trial Steering Committee (ITSC), there is a *decision* to conclude that superiority, inferiority or equivalence has been demonstrated. Under all circumstances a Platform Conclusion leads to implementation of the result within the REMAP and under almost all circumstances a Platform Conclusion leads, immediately, to Public Disclosure of the result by presentation and publication. Where the Statistical Trigger is for superiority or inferiority, so long as the DSMB is satisfied that the Statistical Trigger has truly been met a Platform Conclusion will be automatic in almost all circumstances. Where the Statistical Trigger is for equivalence the DSMB, in conjunction with the ITSC, may decide to not reach a Platform Conclusion at that time but, rather, to continue recruitment, for example, to allow a conclusion to be reached regarding clinically important secondary endpoints. There are situations in which the need to evaluate interactions may also result in a Statistical Trigger not leading, immediately, to a Platform Conclusion, although if superiority or inferiority has been demonstrated all patients in the REMAP will receive the superior intervention or no longer be exposed to inferior intervention(s), respectively.

Platform Trial is a type of clinical trial that studies multiple interventions simultaneously. Common features of a platform trial include frequent adaptive analyses using Bayesian statistical analysis, Response Adaptive Randomization (RAR), evaluation of treatment effect in pre-specified strata, and evaluation of multiple research questions simultaneously that can be perpetual with substitution of answered research questions with new questions as the trial evolves.

Public Disclosure is the communication of a Platform Conclusion to the broad medical community by means of presentation, publication or both.

Regimen consists of the unique combination of interventions, within multiple domains, (including no treatment options) that a patient receives within a REMAP.

Region-Specific Appendix is an appendix to the Core Protocol. These appendices are modules of the protocol that contain all information about the trial specific to the conduct of the trial in that region. Each region will have its own Regional-Specific Appendix (RSA). A region is defined as a country or collection of countries with study sites for which a Regional Management Committee (RMC) is responsible.

Regional Management Committee is a sub-committee involved in trial management. The members of the RMC take responsibility for the management of trial activities in a specified region. The role, responsibilities, and composition of each RMC are specified in each region's RSA.

REMAP is a variant of a platform trial that targets questions that are relevant to routine care and relies heavily on embedding the trial in clinical practice. Like other platform trials, the focus is on a particular disease or condition, rather than a particular intervention, and it is capable of running perpetually, adding new questions sequentially.

Response Adaptive Randomization is a dynamic process in which the analysis of accrued trial data is used to determine the proportion of future patients who are randomized to each intervention within a domain.

State a state is a set of mutually exclusive and exhaustive categories, defined by characteristics of a patient within the REMAP, that are capable of changing over time for a single patient at different time-points during the patient's participation in the REMAP (i.e. they can be dynamic). States are used to define eligibility for domains and this can include defining eligibility that occurs after the time of enrollment. State is used as an additive covariate within the Bayesian statistical model.

Statistical Analysis Committee takes responsibility for the conduct of the preplanned adaptations in the trial. This task generally consists of running predetermined statistical models at each adaptive analysis and providing this output to the DSMB. It is not a trial sub-committee. Rather, it will usually comprise individuals who are employed by the organization that undertakes statistical analysis, and from a trial governance perspective is under the supervision of the DSMB.

Statistical Model is a computational algorithm that is used to estimate the posterior probability of the superiority, inferiority or equivalence of the regimens and interventions that are being evaluated within the REMAP.

Statistical Trigger within the REMAP two or more interventions within a domain are evaluated and statistical models are used to determine if one or more interventions are superior, inferior or equivalent. A Statistical Trigger occurs when the statistical models used to analyze the REMAP indicate that the *threshold* for declaring superiority, inferiority, or equivalence for one or more interventions within a domain has been crossed. A Statistical Trigger applies to a stratum but may be reached in more than one stratum for the same intervention at the same adaptive analysis.

Strata comprise a set of mutually exclusive and exhaustive categories (stratum), defined by baseline characteristics of a patient within the REMAP, in which the relative effects of interventions may be differential. These possibly differential effects of interventions are reflected in the statistical model, the randomization probabilities, and the Platform Conclusions. The criteria that define a stratum must be present at or before the time of enrollment.

Unit-of-analysis is the group of patients who are analyzed together within the model for a particular domain. The unit-of-analysis can be all patients who have received an allocation status in that domain or a sub-group of patients who received an allocation status determined by their status with respect to one or more strata. Within a domain, the RAR is applied to the unit-of-analysis.

2. INTRODUCTION

2.1. Synopsis

Background: Community-acquired pneumonia (CAP) that is of sufficient severity to require admission to an Intensive Care Unit (ICU) is associated with substantial mortality. All patients with severe pneumonia who are treated in an ICU will receive therapy that consists of a combination of multiple different treatments. For many of these treatments, different options are available currently. For example, several antibiotics exist that are active against the microorganisms that cause pneumonia commonly but it is not known if one antibiotic strategy is best or whether all suitable antibiotic strategies have similar levels of effectiveness. Of all the treatments that clinicians use for patients with severe CAP, only a small minority have been tested in randomized controlled trials to determine their comparative effectiveness. As a consequence, the standard treatments that are administered vary between and within countries. Current conventional clinical trials methods to assess the efficacy of treatments for pneumonia generally compare two treatment options (either two options for the same treatment modality, where both are in common use; or a new treatment against no treatment or placebo where the effectiveness of the new treatment is not known). Using this approach, in a series of separate and sequential trials, it will take an inordinate length of time to study all the treatment options. Additionally, with conventional trial designs it is not possible to evaluate interactions between treatment options.

Aim: The primary objective of this REMAP is, for patients with severe CAP who are admitted to an ICU, to identify the effect of a range of interventions to improve outcome as defined by all-cause mortality at 90 days.

Methods: The study will enroll adult patients with severe CAP who are admitted to ICUs using a design known as a REMAP, which is a type of platform trial. Within this REMAP, eligible participants will be randomized to receive one intervention in each of one or more domains (a domain is a category of treatment that contains one or more options, termed interventions, with each intervention option being mutually exclusive). The primary outcome is all-cause mortality at 90 days. There will also be both general and domain-specific secondary outcome measures.

In a conventional trial, enrollment continues until a pre-specified sample size is obtained, at which time enrollment ceases, and the trial data are analyzed to obtain a result. The possible results are

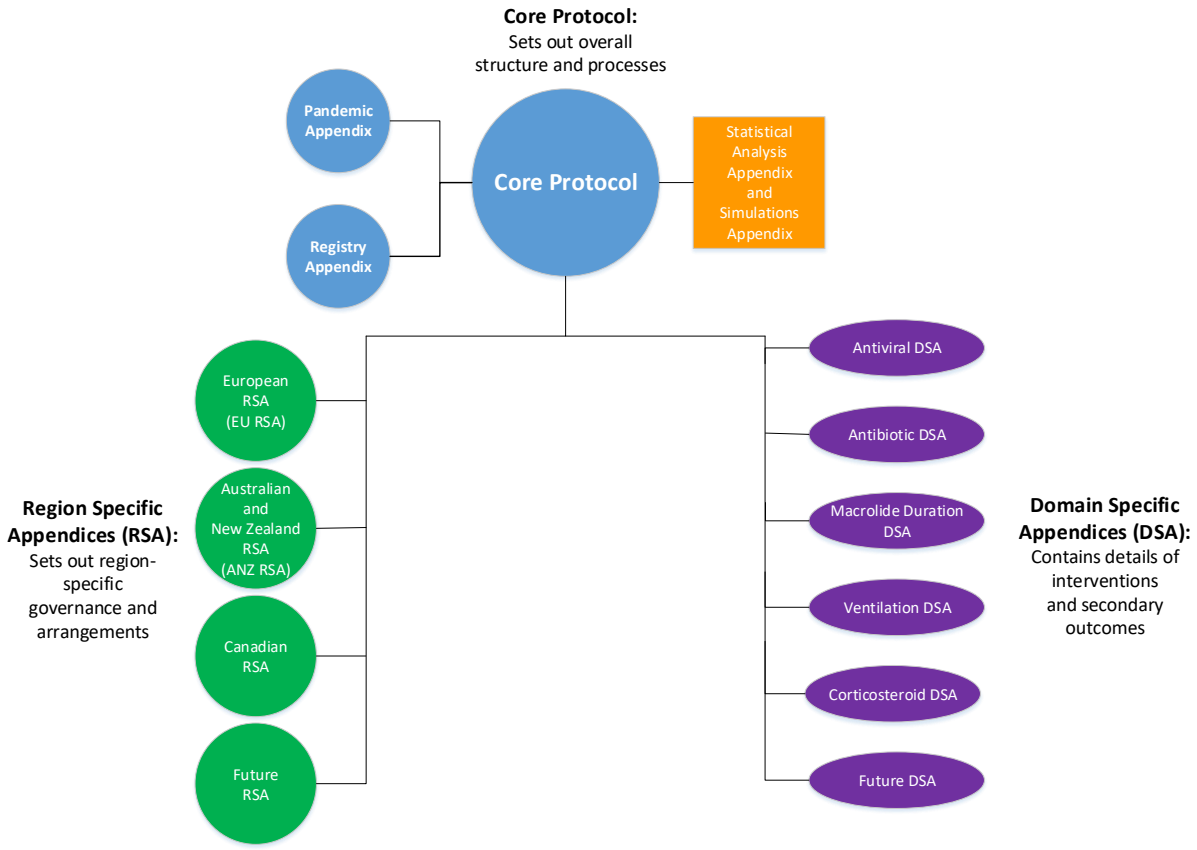
that a difference is detected or no that no difference is detected. However, when the conclusion of the statistical test is “no difference”, this could be that there truly is no meaningful difference, or that the result is indeterminate (i.e. it is possible that if more patients had been enrolled a clinically relevant difference may have been detected).

In comparison to a conventional trial, this REMAP uses an adaptive design, relying on pre-specified criteria for adaptation, that: avoids indeterminate results; concludes an answer to a question when sufficient data have accrued (not when a pre-specified sample is reached); evaluates the effect of treatment options in pre-defined subgroups of patients (termed strata); utilizes already accrued data to increase the likelihood that patients within the trial are randomized to treatments that are more likely to be beneficial; is multifactorial, evaluating multiple questions simultaneously; is intended to be perpetual (or at least open-ended), substituting new questions in series as initial questions are answered; and can evaluate the interaction between interventions in different domains. Bayesian statistical methods will be used to establish the superiority, inferiority, or equivalence of interventions within a domain. Interventions determined to be superior will be incorporated into standard care within the ongoing REMAP. Interventions determined to be inferior will be discontinued. While a limited number of initial treatments and treatment domains have been specified at initiation, it is planned that this REMAP will continue to evaluate other treatments in the future. Furthermore, in the event of a future epidemic of a novel or re-emerging respiratory pathogen (which typically present as severe CAP), this REMAP would be adapted to evaluate the most relevant treatment options. Each new treatment that is proposed to be evaluated within the REMAP will be submitted for prospective ethical review.

2.2. Protocol Structure

The structure of this protocol is different to that used for a conventional trial 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 for definitions of these terms), by changing aspects of the trial during a pandemic, and commencement of the trial in new regions. The structure of the protocol is outlined in Figure 1.

Figure 1: Protocol Structure



The protocol has multiple modules, comprising a Core Protocol, Pandemic Appendix to the Core Protocol, multiple DSAs, multiple RSAs, and a Statistical Analysis Appendix. A Pandemic Appendix to the Core Protocol is intended to be added subsequently. A Simulations Appendix is updated periodically as an operational document.

2.2.1. Core Protocol

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 has the following structure:

- The background and rationale for studying severe CAP
- The background and rationale for the research approach
- The trial design including study setting, the criteria that define eligibility for the REMAP, treatment allocation, strata (see glossary for a definition of this term), principles of application of trial interventions, trial endpoints, methods to control bias, principles of statistical analysis, and criteria for termination of the trial

- The trial conduct including recruitment methods, time-lines for sites, delivery of trial interventions, data collection, data management, and management of participant safety
- The overall / international trial governance structures and ethical considerations

2.2.2. Domain-Specific Appendices

DSAs contain all information about the interventions that will be the subject of the REMAP, which are nested within domains. As such, the Core Protocol does not include information about the intervention(s) that will be evaluated within the REMAP, but rather provides the framework on which multiple different interventions, within domains, can exist within this trial. Each new DSA or addition of one or more interventions to an existing DSA will be submitted for ethical approval prior to commencement. It is anticipated that the DSAs will change over time with removal and addition of interventions within an existing domain, as well as removal and addition of entire domains. Each DSA has the following structure:

- background on the interventions within that domain
- criteria that determine eligibility of patients to that domain
- the features of the interventions and how they are delivered
- any endpoints and data collection that are specific to the domain and additional to those specified in the Core Protocol
- any ethical issues specific to the domain
- the organization of management of the domain

2.2.3. Region-Specific Appendices

This REMAP is intended to be a global trial, conducted in multiple different geographical regions. The RSAs contain all information about the REMAP that is specific to the conduct of the trial in a particular region. This allows additional regions to be added or changes to each region to be made without needing to make major amendments to the Core Protocol in other regions. It is planned that, within each region, the documents submitted for ethical review will comprise the Core Protocol, DSAs, and the RSA for that region (but not other regions). Each RSA has the following structure:

- the definition of the region
- the organization of trial management and administration within the region
- information about availability of domains and interventions
- data management and randomization procedures

- ethical issues that are specific to a region.

If there is information that applies to one or more sub-areas of a region (e.g. a country within Europe or a state or territory within a country) and it is necessary to incorporate this information in the protocol, this information will be included within the RSA. Unless otherwise specified, the RSA will apply to all locations within that region.

2.2.4. Statistical Analysis Appendix and Simulations Appendix

The Statistical Analysis Appendix contains a detailed description of how the statistical analysis will be conducted for reporting treatment effects and reporting interaction between treatments, as well as the RAR. The Statistical Analysis Appendix will be amended when new interventions are added to a domain or when a new domain is added, but will not be updated when interventions are removed from a domain because of inferiority.

The Simulations Appendix is an operational document that contains the results of Monte Carlo simulations that are conducted to describe and understand the operating characteristics of the REMAP across a range of plausible assumptions regarding outcomes, treatment effects, and interactions between interventions in different domains. The statistical power of the study (likelihood of type II error) and the likelihood of type I error are evaluated using these simulations. As the trial adapts, with, for example, the introduction of new interventions, the trial simulations are updated and the Simulations Appendix is amended. The Simulations Appendix is not part of the formal protocol but the conclusions from the Simulations Appendix will be included in protocol documents which will be updated as required. The Simulations Appendix will be maintained as a publicly accessible document on the study website.

2.2.5. Pandemic Appendix

The Pandemic Appendix (to the Core Protocol) contains information about how the core elements of the REMAP will be modified during a pandemic of severe acute respiratory infection that results in CAP. The Pandemic Appendix has the following structure:

- The background and rationale for studying severe CAP caused by a pandemic
- The procedure that will determine activation of the Pandemic Appendix
- How the trial design adapts during a pandemic, including changes to one or more of study setting, treatment allocation, strata, trial endpoints, and principles of statistical analysis that

will operate during a pandemic, as well as how the platform resets following a resolution of a pandemic

2.2.6. Version History

Version 1: Approved by the ITSC on 20 November 2016

Version 1.1: Approved by the ITSC on 10 April 2017

Version 2: Approved by the ITSC on 12 December 2017

Version 2.1: Approved by the ITSC on 26 March 2019

Version 3: Approved by the ITSC on 10 July 2019

2.3. Lay Description

Pneumonia, or infection involving the lungs, is a common reason for admission to an ICU. Severe pneumonia is associated not only with failure of lungs supplying oxygen to the body, but also failure of other organ systems that is due to an uncontrolled immune response to infection.

Patients with severe pneumonia routinely receive multiple treatments at the same time – medications to treat the infection (antibiotics), medications that may modify the immune system (immunomodulators) and supportive treatments to support failing organs, such as mechanical ventilation (organ support) and prevention of complications of critical illness or its treatment. For many categories of treatment there are many treatment options that are in widespread use, are believed or known to be safe and effective, but it is not known which option is best. This REMAP aims to determine the best treatment in each category of treatment, for example, the best antibiotic, the best immunomodulation strategy, and the best method to support each failing organ system.

In a conventional clinical trial, selected patients are allocated to receive one treatment from a short list of alternatives, typically one or two. This trial differs from conventional clinical trials by being randomized, embedded, multifactorial, adaptive, and a platform (a “REMAP”). (Angus, 2015) In this type of trial, we will test many alternative treatments (“multifactorial”) by replacing *ad hoc* treatment decisions with “randomized” treatment allocation (“embedded”). Although treatments will be allocated randomly, patients will preferentially be allocated to treatments that statistical models derived from trial data indicate are more likely to be the most effective treatments. The trial will “adapt” in multiple ways including answering questions as soon as sufficient data have accrued

to answer the question of the effectiveness of each treatment and by changing the treatments that are being tested over-time so as to progressively determine the best package of treatments for pre-defined categories of patients with severe pneumonia. Once a treatment is identified as being optimal it is subsequently routinely provided to all eligible patients within the REMAP. The REMAP is also designed to adapt to test relevant interventions during a pandemic caused by lung infection that results in severe pneumonia.

2.4. Trial registration

This is a single trial conducted in multiple regions, but will, as a minimum, be registered with ClinicalTrials.gov. The trial registration number is: NCT02735707.

The Universal Trial Number is: U1111-1189-1653.

2.5. Funding of the trial

At initiation, the trial had funding from the following sources.

The Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) consortium is funded by the European Union (FP7-HEALTH-2013-INNOVATION-1, grant number 602525). Within the PREPARE consortium, the trial has funding for the recruitment of approximately 4000 patients.

In Australia, the trial has been funded by the National Health and Medical Research Council (NHMRC) (APP1101719) for AUD $4,413,145, for the recruitment of 2000 patients.

In New Zealand, the trial has been funded by the Health Research Council (HRC) (16/631) for NZD $4,814,924, for the recruitment of 800 patients.

In Canada, the trial has been funded by the Canadian Institute of Health Research, Strategy for Patient-Oriented Research (CIHR-SPOR) Innovative Clinical Trials Program Grant (no. 158584) for CAD $1,497,200, for the recruitment of 300 patients.

Funding is being sought for other regions and countries.

3. STUDY ADMINISTRATION STRUCTURE

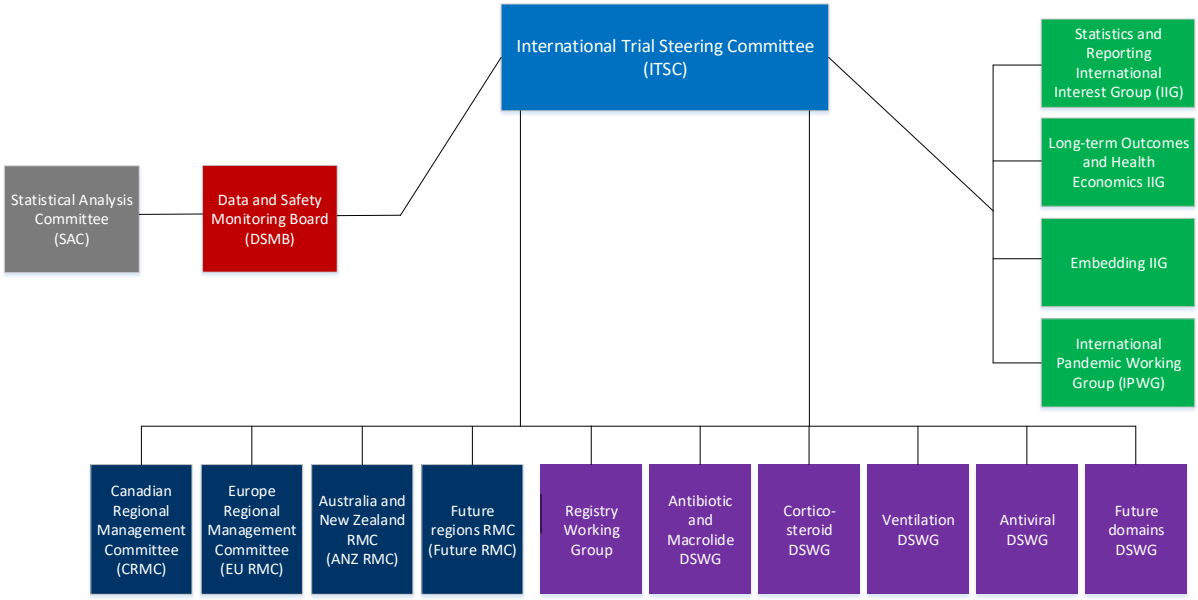
The study administration structure is designed to provide appropriate management of all aspects of the study, taking into account multiple factors including representation from regions that are participating in the trial, availability of skills and expertise related to trial conduct and statistical

analysis, and content knowledge regarding pneumonia and the interventions that are being evaluated. The administration model is designed to provide effective operational and strategic management of the REMAP that operates in multiple regions, is supported by multiple funding bodies and sponsors, and will evolve with addition of further regions and funding bodies as well as changes in the domains and interventions that are being evaluated.

The ITSC takes overall responsibility for the trial design and conduct. Each participating region has a RMC that takes primary responsibility for trial execution in that region. An internationally based Domain-Specific Working Group (DSWG) exists for each domain (or for several domains that are closely related) and has responsibility for design and oversight of each domain. Internationally based Interest Groups exist to allow discussion and development of particular aspects of the REMAP related to statistical analysis, embedding, and health economic analysis of results from the trial.

The organizational chart for REMAP-CAP is outlined in Figure 2.

Figure 2: REMAP-CAP Organization Chart



3.1. International Trial Steering Committee

The ITSC comprises the investigators who initially conceived and designed the trial (Foundation members) and representatives from each (funded and active) region. The intent of the ITSC is to have both theoretical and practical experience and knowledge regarding overall design, domain-specific expertise, and regional-specific expertise. As such, the ITSC will include clinical trialists, biostatisticians, regional lead investigators, domain lead investigators, and regional project managers, and must include one individual who is a Research Coordinator.

3.1.1. Responsibilities

The responsibilities of the ITSC are:

- development and amendment of the Core Protocol
- recruitment and approval of new regions to the REMAP
- liaison with the DSMB including, where appropriate, decisions regarding Platform Conclusions
- consideration of requests and approval of the addition of domains and their nested interventions to the REMAP including prioritization of new domains, new interventions within a domain or both
- liaison with the academic community including the International Committee of Medical Journal Editors (ICMJE) regarding issues such as data sharing and reporting of platform trials including REMAPs
- in conjunction with DSWGs, the analysis and reporting of results from domains
- approval of manuscripts reporting results that are submitted by DSWGs
- coordination of the REMAP during a pandemic
- obtaining funding for the REMAP
- determine the strategic direction of the REMAP

3.1.2. Members

Membership of the ITSC comprises at least 3 investigators from each funded location, the project manager or trial physician in each funded location, at least 1 investigator from Berry Consultants, at least one individual who is a research coordinator, and the chairs of active DSWGs. The operation of the ITSC will be specified by Terms of Reference that will be developed and modified, as required, by the ITSC. The members of the ITSC are:

Professor Derek Angus, Chair Corticosteroid DSWG and Foundation member

Ms. Wilma van Bentum-Puijk, European (EU) Project Manager

Dr. Scott Berry, President and Senior Statistical Scientist of Berry Consultants, and Foundation member

Ms. Zahra Bhimani, Canadian Project Manager

Professor Marc Bonten, European Executive Director, Chair European RMC, and PREPARE Work Package 5 co-lead (specific issues)

Professor Frank Brunkhorst, member EU RMC

Professor Allen Cheng, Chair Antibiotic Domain and Macrolide Duration DSWG

Professor Menno De Jong, member Antiviral DSWG

Dr. Lennie Derde, European Coordinating Investigator, PREPARE Work Package 5 co-lead (specific issues)

Professor Herman Goossens, Principal Investigator for PREPARE

Professor Anthony Gordon, member EU RMC

Mr. Cameron Green, Global Project Manager

Professor Roger Lewis, Foundation member (will step down when SAC is convened)

Dr. Ed Litton, member Australian and New Zealand (ANZ) RMC

Professor John Marshall, Canadian Executive Director

Dr. Colin McArthur, ANZ Deputy Executive Director and Chair Registry WG

Dr. Shay McGuinness, Chair ANZ RMC

Associate Professor Srinivas Murthy, Canadian Deputy Executive Director and Chair Antiviral DSWG

Professor Alistair Nichol, Chair Ventilation DSWG

Associate Professor Rachael Parke, member ANZ RMC

Ms. Jane Parker, Australian Project Manager

Professor Kathy Rowan, member EU RMC

Ms. Anne Turner, New Zealand Project Manager

Professor Steve Webb, ANZ Executive Director and Foundation member

3.1.3. Contact Details

The secretariat functions of the ITSC will rotate among the Regional Coordinating Centers (RCC).

3.2. Regional Management Committees

The operation of the REMAP in each region is undertaken by that region's RMC, the composition of which is be determined by investigators in each region with membership listed in each RSA. Cross-representation between RMCs is strongly encouraged.

3.2.1. Responsibilities

The responsibilities of each RMC are:

- development and amendment of the RSA for that region
- identification and management of sites in that region
- obtaining funding for that region
- liaison with regional funding bodies
- consideration of the feasibility and suitability of interventions (and domains) for that region
- liaison with the sponsor(s) for that region
- management of systems for randomization and data management for that region

3.3. Domain-Specific Working Groups

Each active and future planned domain (or closely related set of domains) will be administered by a DSWG.

3.3.1. Responsibilities

The responsibilities of each DSWG are:

- development and amendment of the DSA
- proposal and development of new interventions within a domain
- in conjunction with the ITSC, analyzing and reporting results from the domain
- obtaining funding to support the domain, with a requirement that, if such funds are obtained, that an appropriate contribution to the conduct of the REMAP is also made.

3.3.2. Members

Membership of each DSWG is set out in the corresponding DSA but should comprise individuals that provide broad international representation, content knowledge of the domain, and expertise of trial conduct and design.

3.4. International Interest Groups

The following International Interest Groups (IIG) contribute to the trial:

- REMAP-CAP International Statistics Interest Group (ISIG)
- REMAP-CAP International Embedding Interest Group (IEIG)

- REMAP-CAP International Long-term Outcomes and Health Economics Interest Group (ILTOHEIG)
- REMAP-CAP International Pandemic Working Group (IPWG)

3.4.1. Role

The role of the interest groups is to provide advice to the ITSC and DSWGs about trial design and conduct as well as advance academic aspects of the conduct, analysis, and reporting of platform trials including REMAPs.

3.5. Sponsors

In relation to recruitment that occurs in:

- countries in Europe the sponsor is University Medical Center Utrecht.
- Australia the sponsor is Monash University.
- New Zealand the sponsor is the Medical Research Institute of New Zealand.
- Canada the sponsor is Unity Health Toronto.

3.5.1. Role of sponsor

The role of the sponsor in each region is specified in each RSA.

3.5.2. Insurance

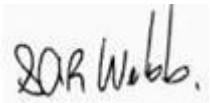
The provision of insurance is specified in each RSA.

4. INTERNATIONAL TRIAL STEERING COMMITTEE AUTHORIZATION

The ITSC have read the appendix and authorize it as the official Core Protocol for the study entitled REMAP-CAP. Signed by the ITSC,

EU Executive Director
Marc Bonten

ANZ Executive Director
Steve Webb



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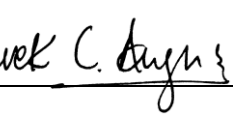
Colin McArthur

ITSC Member
Derek Angus



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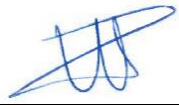
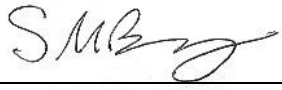


ITSC Member
Scott Berry



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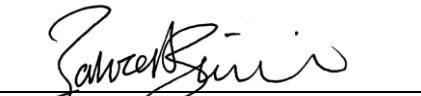
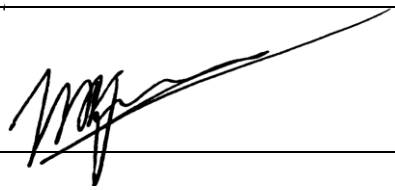
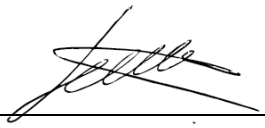


ITSC Member
Frank Brunkhorst

ITSC Member
Allen Cheng



ITSC Member
Menno De Jong



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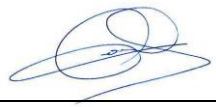

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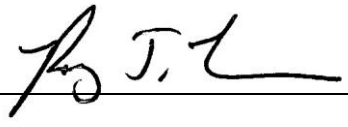

ITSC Member
Roger Lewis

ITSC Member
Ed Litton

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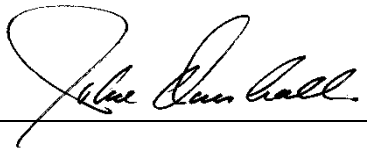
John Marshall



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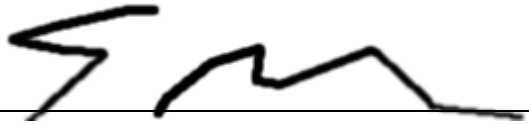

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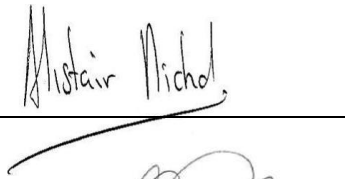

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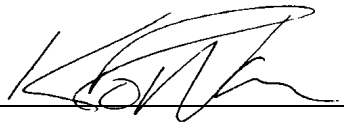

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Kathy Rowan

ITSC Member
Anne Turner

5. BACKGROUND & RATIONALE

5.1. Severe Community-Acquired Pneumonia

5.1.1. Introduction

This section, within the Core Protocol, provides background on the epidemiology, causes, treatment categories, and evidence base for the management of patients with severe community pneumonia. Detailed information regarding the rationale for specific interventions to which patients will be

randomized within the REMAP can be found in a corresponding DSA. As the trial is intended to be perpetual, if background information changes, appropriate amendments to the protocol documents will occur periodically, but it is anticipated that this will occur predominantly by amendment of DSAs.

5.1.2. Epidemiology

CAP is a syndrome in which acute infection of the lungs develops in persons who have neither been hospitalized recently nor had regular exposure to the healthcare system. (Musher and Thorner, 2014) A wide range of micro-organisms are capable of causing pneumonia but bacteria and viruses are responsible for the vast majority of cases where a cause is identified. Severe CAP is defined as pneumonia of sufficient severity to be an immediate threat to life. In developed countries, patients with severe CAP are often admitted to an ICU or a High Dependency Unit (HDU). Throughout the remainder of this protocol, we will use the term ICU for units that provide specialized care for critically ill patients, including HDU, Critical Care Units, and Intensive Treatment Units. Although admission criteria may vary, the occurrence of admission to an ICU or a HDU can be used as an operational definition of severe CAP.

CAP is an important health problem and a common cause of death from infection globally, with lower respiratory tract infection, implicated in 3.1 million deaths in 2012, ranked as the 4th most common cause of death, although most of these deaths occur in low and middle-income countries. (Bjerre et al., 2009, Musher et al., 2013, Singanayagam et al., 2009) In developed countries, around half of patients with CAP are treated successfully without admission to hospital. (Almirall et al., 2000) Among patients who are admitted to hospital around 10 to 20% are admitted to an ICU. (Alvarez-Lerma and Torres, 2004, Ewig et al., 2011) The population incidence of CAP that involves admission to an ICU is about 0.4 cases per 1000 per year. (Finfer et al., 2004) Among patients admitted to an ICU with CAP, case-fatality is reported to be in the range from 20 to 50%. (Alvarez-Lerma and Torres, 2004, Leroy et al., 1995, Sligl and Marrie, 2013) In low and middle-income countries, the overlapping syndromes of CAP, bronchiolitis, and bronchitis are a major public health problem and represent the world's most important cause of disability-adjusted life years lost and the third most important cause of death. (World Health Organization, 2008)

5.1.3. Standard care for patients with severe CAP

All patients admitted to an ICU with severe CAP will receive multiple different component therapies and many of these therapies will be administered concurrently. These therapies can be grouped into the following categories: treatment of the underlying infection (including antibacterial and antiviral

agents); the optional use of agents, such as corticosteroids, that modulate the host immune response to infection; and multiple supportive therapies that are used to manage organ systems that have failed or prevent complications of critical illness and its treatment (Table 1).

The choice of empiric antimicrobial therapy is generally made before a microbiologic etiology is established, both because of the lag between collection of specimens and the availability of results from microbiological tests, and because microbiological tests lack sensitivity, particularly when samples are collected after initiation of antimicrobial therapy. It is recommended that antimicrobial treatment be initiated promptly and at the point of care where the diagnosis of pneumonia is first made. (Musher and Thorner, 2014)

Examples of commonly used therapies that support failed organ systems or prevent the complications of critical illness and its treatment include oxygen therapy, invasive and non-invasive mechanical ventilation, intravenous fluid resuscitation, vasoactive drugs, dialysis, provision of nutrition, sedation, physiotherapy including mobilization, diuretic medications, suppression of gastric acid production, and mechanical or pharmacological interventions to prevent venous thromboembolism. The exact combination of supportive therapies is influenced by the spectrum of organ failures that occurs in any individual patient. (Dellinger et al., 2013)

Table 1: Potential targets of interventions to reduce mortality in patients with CAP

Target of intervention	Examples
Eradication of pathogens	Antibiotics (agents, route, dose) Antivirals (agents, route, dose) Microbiological diagnostic strategies
Modulation of the host immune response	Corticosteroid Macrolides
Methods to support failing organ systems and prevention of complications	Lung ventilation strategies and respiratory salvage modalities (e.g. extra-corporeal membrane oxygen, prone positioning) Renal replacement therapy Inotropic/vasopressor support Fluid resuscitation strategies

	Nutrition Mobilization Sedation Venous thromboembolism prophylaxis Stress ulcer prophylaxis

5.1.4. Treatment guidelines

A range of different guidelines have been published that are relevant to the care of critically ill patients with CAP. (Eccles et al., 2014, Lim et al., 2009, Mandell et al., 2007, Wiersinga et al., 2012, Wilkinson and Woodhead, 2004, Woodhead et al., 2011) These guidelines generally focus on recommendations related to assessment of severity, diagnostic evaluation, and empiric and guided antimicrobial therapy. Guidelines from the Surviving Sepsis Campaign are relevant to many aspects of the supportive care of the critically ill patients with CAP. (Dellinger et al., 2013)

There is a stark contrast between the substantial public health impact of severe CAP and the low quality of evidence that guides therapy. The number of treatment recommendations in guidelines that are supported by high quality randomized controlled trial (RCT) evidence is 4 of 44 for treatment recommendations in the European guidelines (Eccles et al., 2014, Lim et al., 2009, Woodhead et al., 2011), 11 of 43 in the United States guidelines (Mandell et al., 2007), and 7 of 93 in the Surviving Sepsis Campaign Guidelines. (Rhodes et al., 2017) As a consequence of the limited evidence-base there are a number of inconsistencies and even complete contradictions among international guidelines.

5.1.5. Variation in care and compliance with guidelines

Several observational studies report substantial variation in care with, for example, compliance with administration of antibiotics recommended by guidelines occurring in between 40% and 75% of patients. (Bodi et al., 2005, Frei et al., 2010, Lee et al., 2014, Shorr et al., 2006) These and other studies also report better clinical outcomes for patients who received antibiotics that were recommended by guidelines. (McCabe et al., 2009, Mortensen et al., 2004, Mortensen et al., 2005) However, it remains unclear if adherence to guideline recommendations is due to a direct causal link, or whether it is a surrogate for better quality care generally. There is also widely reported variation in compliance with many supportive therapies for patients with severe CAP, such as use of

low tidal volume ventilation, type of resuscitation fluid, and thresholds for the administration of transfusion for anemia. (Bellani et al., 2016, Finfer et al., 2010, Blood Observational Study Investigators of Anzics-Clinical Trials Group et al., 2010, Cecconi et al., 2015)

5.1.6. An unmet need for better evidence

Many factors contribute to the substantial unmet need for better evidence to determine the optimal treatment for patients with severe CAP. Severe CAP is common, case-fatality is high, the strength of current evidence is limited, and there is evidence of substantial variation in existing standard care. The combination of these factors provides a strong rationale for the need for better quality evidence about the impact of the different treatment options that are in existing practice, the impact of different combinations of treatment options, and the timely and effective evaluation of new candidate interventions to improve outcomes.

5.2. Influenza pandemics and emerging pathogens

A pandemic of severe CAP caused by a known (e.g., influenza) or unknown virus, as occurred during the Severe Acute Respiratory Syndrome (SARS) outbreak, can rapidly change the etiological spectrum of severe CAP in patients who require admission to an ICU. This necessitates adaptation of empiric treatment protocols or diagnostic procedures or both. Naturally, there will be no evidence base for the medical management of such a disease at the time of its emergence, and medical decisions will be mostly based on expert opinion with extrapolation from evidence derived from the treatment of analogous clinical syndromes. There is substantial unmet need to generate evidence about the most effective treatment approaches during a pandemic or regional outbreak. Furthermore, to have impact on patient outcomes during an outbreak, evidence must be available during the pandemic. As a consequence, such evidence must be capable of being generated, disseminated, and implemented rapidly. More detailed background information about pandemics of respiratory infection, together with challenges associated with the clinical research response are outlined in the Pandemic Appendix.

5.3. Randomized Embedded Multifactorial Adaptive Platform Trials

5.3.1. Generating clinical evidence

Angus has noted several problems encountered when generating robust clinical evidence, including barriers to conducting clinical trials, the generalizability of data from populations that are too broad or too narrow, the issue of equipoise especially when comparing different types of existing care, and

the delay in translating results into clinical practice. (Angus, 2015) A REMAP provides a strategy to address many of these problems by gaining economies of scale from a common platform, which allows for broad enrollment but retaining the ability to examine for heterogeneity of treatment effects between defined subgroups. A REMAP focuses predominantly on the evaluation of treatment options for the disease of interest that are variations within the spectrum of standard care (although testing of novel or experimental therapies is not precluded) and does so by embedding the trial within routine healthcare delivery. In this regard the REMAP seeks to replace random variation in treatment with randomized variation in treatment allowing causal inference to be generated about the comparative effectiveness of different existing treatment options. The use of RAR, which allows the allocation ratios to change over time based on accruing outcomes data, maximizes the chance of good outcomes for trial participants. The embedding of such a platform within the day-to-day activities of ICUs facilitates the translation of outcomes to clinical practice as a "self-learning" system. As such, it also functions as an embedded and automated continuous quality-improvement program. A final advantage of a REMAP for pneumonia is the ability to rapidly adapt to generate evidence if new respiratory pathogens emerge, avoiding the inevitable delays associated with conventional trials in an outbreak of a new infectious diseases. (Burns et al., 2011)

5.3.2. Underlying Principles of the Study Design

A REMAP applies novel and innovative trial adaptive design and statistical methods to evaluate a range of treatment options as efficiently as possible. The broad objective of a REMAP is, over time, to determine and continuously update the optimal set of treatments for the disease of interest. The set of treatments that may be tested within a REMAP comprise the set of all treatments that are used currently or may be developed in the future and used or considered for use in the disease of interest. The design maximizes the efficiency with which available sample size is applied to evaluate treatment options as rapidly as possible. A REMAP has the capacity to identify differential treatment effects in defined sub-groups (termed strata), address multiple questions simultaneously, and can evaluate interactions among selected treatment options. Throughout the platform, patients who are enrolled in the trial are treated as effectively as possible. (Angus, 2015, Berry et al., 2015, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016)

A conventional RCT (i.e. a non-platform trial) makes a wide range of assumptions at the time of design. These assumptions include the plausible size of the treatment effect, the incidence of the primary outcome, the planned sample size, the (typically, small number of) treatments to be tested, and that treatment effects are not influenced by concomitant treatment options. These assumptions are held constant until the trial completes recruitment and is analyzed. (Barker et al., 2009, Berry,

2012, Connor et al., 2013) Participants who are enrolled in a conventional RCT are not able to benefit from knowledge accrued by the trial because no results are made available until the trial completes. A REMAP uses five approaches to minimize the impact of assumptions on trial efficiency and also maximizes the benefit of participation for individuals who are enrolled in the trial. (Angus, 2015, Berry et al., 2015, Aikman et al., 2013, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016)

These design features are:

- frequent adaptive analyses using Bayesian statistical methods
- RAR
- evaluation of differential treatment effects in pre-specified sub-groups (strata)
- evaluation of specified intervention-intervention interactions
- testing of multiple interventions in parallel and, subsequently, in series

This creates a 'perpetual trial' with no pre-defined sample size, the objective of which is to define and continuously update best treatment over the life-time of the REMAP. The design aspects, including the risk of type I and type II error, are optimized prior to the commencement of the trial by the conduct of extensive pre-trial Monte Carlo simulations, modification of the trial design, and re-simulation in an iterative manner. The methods related to the application of the design features and the statistical analysis of this trial are outlined in the methods section of the protocol (Section 7). The following sections describe the background, rationale, and potential advantages of each of the design features of a REMAP (Section 5.3.4).

5.3.3. Nomenclature

A specific set of nomenclature is used to categorize potential treatments evaluated and populations within a REMAP as well as other aspects of the trial design and statistical analysis. A detailed glossary can be found in Section 1.2. Please see the glossary for the definition and explanations for the following terms: domain, intervention, regimen, stratum, state, Statistical Trigger, Platform Conclusion, and Public Disclosure.

5.3.4. Randomization and Response Adaptive Randomization

The study will randomly allocate participants to one or more interventions, with each intervention nested within a domain. In this regard, a platform trial is no different to other forms of RCT in that randomization provides the basis for causal inference. However, unlike a conventional RCT, the proportion of participants who are randomized to each available intervention within a domain will

not be fixed. Rather, the trial will incorporate RAR. RAR utilizes random allocation with a weighted probability for each intervention, with the weighted probability being proportional to the extent to which similar participants recruited earlier in the trial benefited or not from each particular intervention. (Angus, 2015, Berry, 2012, Connor et al., 2013, Aikman et al., 2013, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) RAR will result in participants in each particular stratum being randomized with greater probability to interventions that are performing better within that stratum. At the initiation of a new domain or when a new intervention is added to a domain the randomization proportion of all new interventions is balanced and only changes, with the application of RAR, that takes into account uncertainty about treatment effect so as to avoid excessive variability in proportions generated by RAR until sufficient sample size has accrued.

The major consequence of RAR is that better therapies move through the evaluation process faster, resulting in trial efficiency gains. (Berry, 2012, Connor et al., 2013) The platform “learns” more quickly about the treatments we ultimately care about, i.e. those that work best. Moreover, as data accrues, newly randomized participants are more likely to receive interventions from which they benefit. (Berry, 2012, Connor et al., 2013, Meurer et al., 2012, Angus, 2015, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) This is a highly ethical fusion of trial science with continuous quality improvement and a learning healthcare system. (Institute of Medicine, 2013) Assuming at least some interventions are better than others, the total mortality within the trial population will be lower than would have occurred with a fixed randomization proportion. It is also particularly relevant to the ethical conduct of trials that enroll critically ill patients where unanticipated increases in mortality have been seen (Dellinger et al., 2013) and to the conduct of trials during a pandemic in which there is in-built implementation of the therapies that are more likely to be beneficial during the trial. The simulations underpinning REMAP-CAP demonstrate that, in instances where particular interventions are indeed superior to others, the use of RAR will, on average, increase the odds of discovering the superiority not only with lower sample size, but with fewer participants exposed to the less efficacious therapies and, thus, fewer deaths.

There are potential disadvantages associated with RAR. It is intended that participating sites and trial investigators will be blind to the RAR proportions. One disadvantage is that, for interventions that are provided without blinding, the treating clinicians may be able to draw inference about the RAR proportions and, as a consequence, draw inference about the interim standing of interventions that are being tested in the REMAP. This could have adverse consequences including that clinicians are influenced to not enroll participants within a domain but rather directly prescribe the treatment that

they believe to be doing better outside the trial. However, a number of factors mitigate this potential concern. First, it can be difficult to distinguish between patterns of sequential allocation status that are derived from fixed versus RAR. Second, extreme proportions will not be used (except where a Statistical Trigger but not a Platform Conclusion has been reached, see later). Finally, for many conditions, team-based management means that an individual clinician will directly observe only a small proportion of all participants enrolled within the trial at each participating site. Another disadvantage of RAR is that, under certain allocation rules, statistical power can be reduced. This concern is mitigated via pre-trial simulation to test the effects of different allocation rules. Furthermore, a REMAP that comprises multiple domains with multiple interventions within each domain will generally have higher, rather than lower, power as a consequence of the use of RAR. Finally, by deploying RAR rules to minimize the odds of exposure to inferior interventions, the design is intended to motivate embedding in clinical practice, thereby resulting in more rapid recruitment.

Within each domain, RAR will be implemented for participants who are eligible to receive two or more interventions within a domain. Where a participant is eligible for only one option within a domain, this will be the treatment allocation for such a participant. In these circumstances, the provision of a treatment allocation status is made, predominantly, so as to provide a process that enhances the effectiveness of embedding, i.e. wherever possible the platform provides the treatment allocation.

5.3.5. Embedding

A trial is most efficient when all eligible participants are recognized and enrolled. Achieving universal enrollment of eligible participants increases the speed with which new knowledge is generated, maximizes internal and external validity, and minimizes operational complexity at the bedside (there is no need to distinguish between trial and non-trial patients, because all patients are trial patients). A number of strategies will be utilized to very tightly “nest” or embed trial processes in daily clinical care operations. The effectiveness of strategies to achieve embedding will be evaluated, updated, and shared with sites, taking into account different clinical processes at different sites. Wherever possible trial treatment allocations will be integrated with electronic customized order sets, produced at the point of delivery of care that also includes each site’s local care standards for concomitant therapies. This allows clinical staff to follow their typical workflow using protocolized order sheets to govern many aspects of patient care and serves to enhance compliance with the interventions allocated by the trial. The intention of embedding is that recruitment occurs 24/7 and is dependent on the usual medical staff who are responsible for patient care. Where possible electronic health records will be utilized to enhance screening and recruitment and specify the

'order set' for participants, including those orders that are determined by allocation status within the REMAP. While screening and recruitment for a REMAP can be conducted by research staff, it is not intended that recruitment should be dependent on research staff, particularly as such staff are typically only present during office hours. In addition to the facilitation of recruitment and high-fidelity delivery of the intervention, a further advantage is that the results of the trial can be translated rapidly within the ongoing REMAP so that all appropriate participants receive a treatment declared to be superior with continued allocation to that treatment option within the REMAP used to ensure implementation.

5.3.6. Multifactorial

If the trial randomizes in more than one domain of care it is multifactorial. The number of domains, at any time, is determined by a combination of the interventions that are appropriate and amenable for evaluation within the REMAP and the available statistical power, as determined by the conduct of simulations. It is intended that this REMAP will increase the number of domains, progressively, as the number of sites and rate of recruitment increases over time. The Bayesian models evaluate treatment effects (superiority, inferiority, equivalence) within each regimen but then, by isolating the effect of each intervention across all regimens in which that intervention is included, the independent effect of each intervention is estimated. The capacity to evaluate interventions within multiple domains, in parallel, increases trial efficiency substantially.

An additional advantage of the trial being multifactorial is the capacity to evaluate interactions between selected interventions in different domains. Where pre-specified, on the basis of clinical plausibility, statistical models will evaluate whether there is interaction between interventions in different domains. Where no interaction is suspected, interactions will not be evaluated as part of the *a priori* statistical model.

Although participants within a REMAP will, typically, receive treatment allocations for multiple domains the decision-making regarding concomitant therapies will be made by the treating clinician in other domains of care. Treatment decisions in other domains of care will be recorded and may be analyzed, using observational methods, to evaluate candidate interventions for evaluation by randomization within the REMAP.

5.3.7. Adaptive

5.3.7.1. *Frequent adaptive analyses*

Frequent adaptive analyses using Bayesian statistical methods will be undertaken using Markov Chain Monte Carlo (MCMC) estimates of the Bayesian posterior probability distributions. The trial will utilize a set of pre-specified rules to reach conclusions regarding the effectiveness of interventions that are being evaluated. It is these pre-specified rules that determines how the trial "adapts" to the information contained in accumulating participant data. An analogy is that the 'routes' that a trial can take are pre-specified, within the protocol, but the exact route that the trial takes is determined by the data that accrues. Such adaptation improves statistical efficiency substantially.

5.3.7.2. *Analysis of data to reach conclusions*

The following structure and sequence of events will be used to reach conclusions from data as it accrues and is analyzed. This document, the Core Protocol, sets out the pre-specified rules for interpreting the results of analyses. These rules include pre-specified threshold levels of probability for achieving superiority, inferiority or equivalence of interventions within a domain. At each adaptive analysis the Statistical Analysis Committee (SAC) evaluates whether one or more probability thresholds that are derived from the trial's statistical model have been exceeded. When the model indicates one or more of superiority, inferiority, or equivalence has occurred this is termed a Statistical Trigger. A Statistical Trigger may be reached for one or more strata at any given adaptive analysis.

The occurrence of a Statistical Trigger is communicated immediately to the trial DSMB by the SAC. The DSMB has primary responsibility for determining if a Statistical Trigger should lead to a Platform Conclusion. The declaration of a Platform Conclusion results in the removal of inferior intervention from randomization options or removal of all other interventions if an intervention is declared as superior. A Platform Conclusion will be communicated to the ITSC who have responsibility for immediate dissemination of the result by presentation and publication of the result.

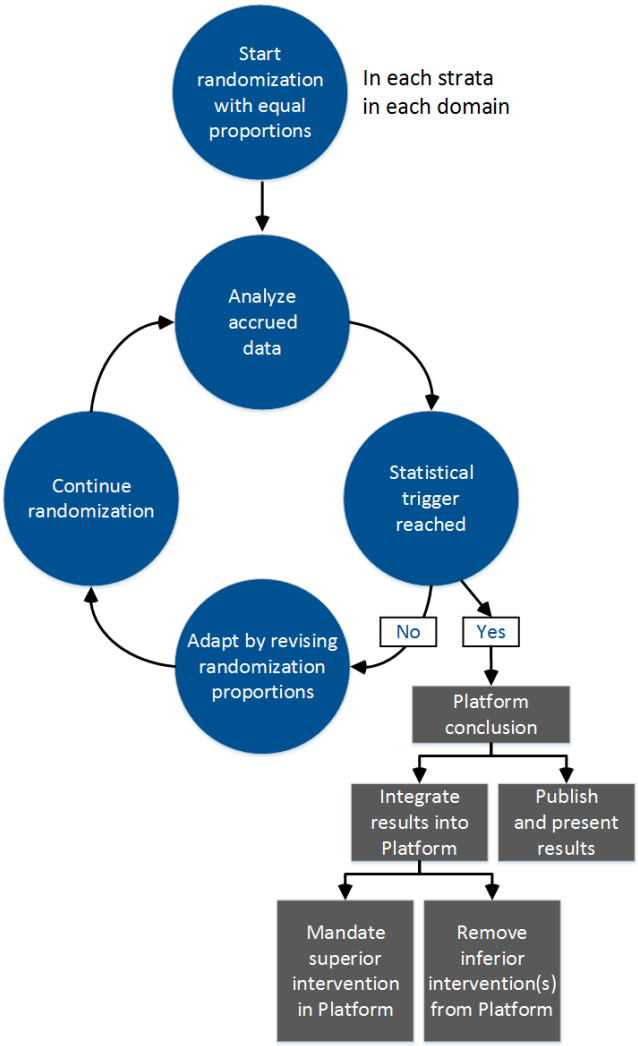
The algorithm by which a Platform Conclusion is reached is different for Statistical Triggers of superiority or inferiority, compared to those triggers that arise because of equivalence. Where the Statistical Trigger is for superiority or inferiority, so long as the DSMB is satisfied that the Statistical Trigger has been met validly, the default position is that the DSMB will declare this result as a Platform Conclusion. The only exception to this situation is if there is a need to evaluate potential interactions between treatments in different domains. In this circumstance the randomization

schedule will be adapted (all participants receive the superior intervention or randomization to one or more inferior interventions is removed) but Public Disclosure may be delayed until evaluation of the interaction is completed.

Where the Statistical Trigger is for equivalence the DSMB will evaluate clinically relevant secondary endpoints. The results, in relation to both primary and secondary endpoints, will be communicated to the ITSC. The DSMB, in conjunction with the ITSC, may declare a Platform Conclusion (for equivalence) or may opt to continue recruitment and randomization to the 'equivalent' interventions, for example, to allow a conclusion to be reached regarding clinically important secondary endpoints, to allow additional accrual to narrow the margin of equivalence (for example where health economic issues are relevant), or to allow evaluation of an interaction).

The pathway for and potential outcomes from each adaptive analysis is displayed in Figure 3.

Figure 3: Adaptive Analyses



5.3.7.3. *Probability thresholds*

In this REMAP the pre-specified rules are that, at any adaptive analysis, an intervention will be declared "superior," if it is has at least a 0.99 posterior probability of being the best intervention within its domain. An intervention will be declared "inferior" if it has a less than 0.01 probability of being the best intervention within its domain. Intervention equivalence is declared between two factors when there is at least a 0.90 posterior probability of the rate of the primary endpoint falls within a pre-specified delta.

5.3.7.4. *Analysis within and between strata*

The frequent adaptive analyses will evaluate the primary endpoint, *within one or more stratum*. Where specified, the statistical models for each strata will be able to 'borrow' information from adjacent strata leading to the declaration of a Statistical Trigger in one, more, or all strata. The

extent to which borrowing occurs is dependent on the pre-specified structure of the model and the degree of statistical congruence of treatment effect between stratum. Where treatment effects are divergent between stratum there is less 'borrowing'. The capacity to evaluate strata is particularly important for interventions that might plausibly have differential, including opposite, treatment effects in different strata. (Dellinger et al., 2013, Finfer et al., 2004, The Acute Respiratory Distress Syndrome Network, 2000) In traditional trial designs, divergent treatment effects among sub-groups may cancel each other out and this is one plausible explanation for the trials that report no overall difference in outcome. It should be noted that strata can be different for different domains and that strata can be changed over time (in conjunction with amendment of the protocol).

If a Platform Conclusion is reached just within a single stratum, this leads to cessation of randomization within that stratum, while continuing to randomize in other strata. It is acknowledged that a Platform Conclusion in one strata may rely on 'borrowing' from adjacent strata and that analysis just within a strata may yield a result that is different. Nevertheless, a Platform Conclusion is still regarded as valid if it relies upon borrowing from adjacent strata and will be reported and published including the extent to which it relies on borrowing.

5.3.7.5. *Frequency of adaptive analyses*

Adaptive analyses will occur frequently, with the frequency being approximately proportional to the rate of recruitment, and will be a largely automatic process; the frequency is chosen to balance logistical demands with the goal of learning rapidly from accumulating data. While this process will be overseen by an independent DSMB, the DSMB will not make design decisions unless the trial's algorithms are no longer acceptable from an ethical, safety, or scientific point of view. The DSMB, in conjunction with the ITSC, having reached a Platform Conclusion, and in deciding to terminate an intervention or domain (in conjunction with a Public Disclosure), may take into account one or more issues such as the value of continuing randomization so as to evaluate additional clinically relevant endpoints or to evaluate potential interactions, as well as take into account the opportunity cost associated with not moving to introduce new domains or interventions.

5.3.7.6. *Advantages of adaptive analysis*

The major advantage of this type of analysis approach is that a conclusion is reached when there is sufficient information to support the conclusion, rather than when enrollment reaches a predetermined sample size. This approach allows a result to be obtained as quickly as possible with appropriate sample size. It also avoids indeterminate results by continuing randomization until either superiority, inferiority, or equivalence is concluded. (Barker et al., 2009, Berry, 2012, Connor

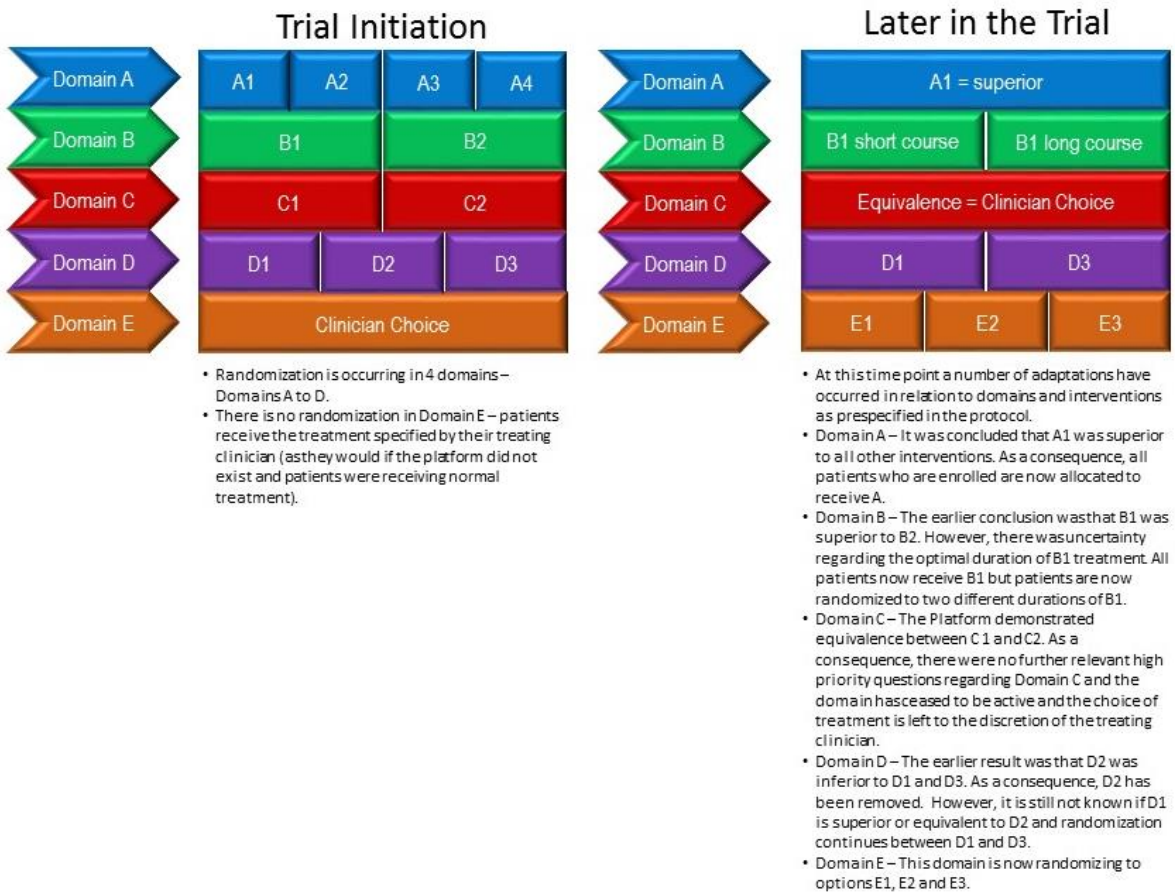
et al., 2013, Meurer et al., 2012, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016) An additional advantage is that dissemination of such results does not interrupt the conduct of the platform. In a single REMAP, there is no need for the "start-and-stop" periods that would typically occur under the alternative approach of multiple separate trials. These "downtime" periods can be quite extensive and carry a number of disadvantages. First, there is a lot of duplicative effort every time a near-identical treatment protocol goes through the appropriate development and approval processes. Second, clinical investigation units must maintain a certain infrastructure, and that infrastructure can be expensive to maintain during periods when participants are not being enrolled or expensive to recreate if the infrastructure degrades. Third, downtime is simply one more contributor to delay in the production of scientific knowledge. Participants at large benefit from earlier production of knowledge regardless of whether new information demonstrates a therapy is effective or ineffective. Finally, the inevitable start up delay before a trial can "go live" can wipe out any possibility of conducting effective research during time-critical situations such as a pandemic.

5.3.7.7. *Substitution of new domains and interventions within the REMAP*

It is intended that the REMAP will be 'perpetual'. In conjunction with a Platform Conclusion being reached, the ITSC takes responsibility for determining what new questions will be introduced to the REMAP including adding one or more new interventions to a domain or adding one or more new domains. In a REMAP, the sample size is not fixed, rather maximum use is made of the available sample and more questions may be asked for the same monetary investment. (Barker et al., 2009, Berry, 2012, Connor et al., 2013, Meurer et al., 2012, Aikman et al., 2013, Bhatt and Mehta, 2016, Park et al., 2016) The only limit on the duration of a platform trial is the availability of ongoing funding, the availability of new interventions to evaluate, and that the disease continues to be a public health problem. The ITSC responsible for the REMAP will develop appropriate processes for identifying and prioritizing the selection of new interventions and domains that are introduced progressively into the REMAP over time.

How the domains and interventions within a REMAP might evolve over time is depicted in Figure 4.

Figure 4: REMAP Evolution Over Time



5.3.8. Nesting of the REMAP within a Registry

The REMAP can also be nested within a registry, with the registry recording information (typically a subset of the trial Case Report Form (CRF)) in all participants who met the REMAP entry criteria, or an expanded set of entry criteria, but who, for any reason, were not randomized. Information obtained from eligible but not randomized participants can be useful for evaluating the external validity of results and optimizing recruitment. Evaluation of non-randomized treatments received by all participants, both randomized and non-randomized, can be used to identify the consequences of natural variation in care so as to identify interventions that should be prioritized for evaluation by randomization within the REMAP. (Byrne and Kastrati, 2013) The design features of the trial and the conceptual advantages associated with each design feature are summarized in Table 2.

If a registry component is included the operation of the registry will be specified in a DSA that applies only to the registry aspects of the study.

5.3.9. Platform

Platform trials simultaneously evaluate multiple potential therapies, where the focus is on finding the best treatment for the disease, rather than precisely characterizing the effect of each intervention in isolation. (Angus, 2015, Berry et al., 2015, Bhatt and Mehta, 2016, Carey and Winer, 2016, Park et al., 2016, Rugo et al., 2016, Harrington and Parmigiani, 2016) Thus the goals of a platform trial are much more aligned with the goals of clinical care than a traditional, narrowly focused phase III RCT of a single agent. All of the component design features of a REMAP have been used previously and have accepted validity. What is innovative and novel, for a REMAP, is the combination of all of these design features within a single platform combined with their use for phase III evaluations and by using embedding to integrate the trial within routine clinical care.

Table 2: Features of a REMAP that contribute to advantages of the design

	Efficient use of information	Safety of trial participants	Avoiding trial down-time	Fusing research with care	Determining optimal disease management	Self-learning healthcare system
Multifactorial	✓		✓	✓	✓	
Response Adaptive Randomization	✓	✓		✓		✓
Embedding				✓		✓
Frequent adaptive analyses	✓	✓			✓	✓
Analysis of strata	✓	✓			✓	
Evaluation of interaction		✓			✓	
Substitution of new interventions	✓		✓		✓	

6. OBJECTIVES

6.1. Primary objective

The primary objective of this REMAP is, for adult patients with severe CAP who are admitted to an ICU, to identify the effect of a range of interventions to improve outcome as defined by all-cause mortality at 90 days.

6.2. Secondary objectives

The secondary objectives are to determine, for adult patients with severe CAP who are admitted to an ICU, the effect of interventions on ICU mortality, ICU length of stay (LOS), hospital LOS, ventilator free days (VFDs) censored at 28 days, organ failure free days (OFFDs) censored at 28 days, other endpoints as indicated for specific domains, and, where feasible or specified in a DSA, survival at 6 months, health related quality of life (HRQoL) assessed after 6 months using the EQ5D and disability assessed after 6 months using the World Health Organization Disability Assessment Schedule (WHODAS).

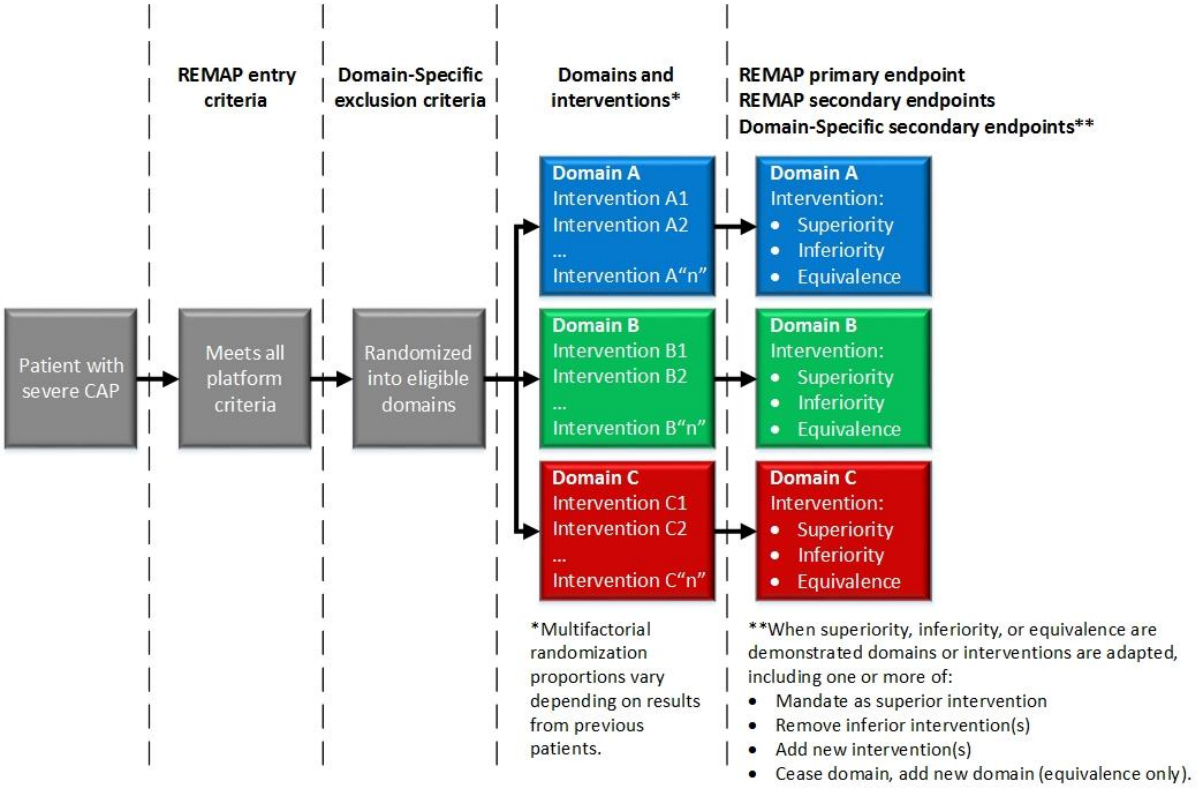
7. SUMMARY OF TRIAL DESIGN

7.1. Introduction

This is a REMAP that aims to test many interventions in a number of domains with the primary outcome being the all-cause mortality at 90 days. Frequent adaptive analyses will be performed to determine if an intervention is superior, inferior, or equivalent to one or more other interventions to which it is being compared, within a domain. A Bayesian analysis method will be used to evaluate superiority, inferiority, or equivalence, as well as to inform the adaptive randomization strategy within each domain. Where it is anticipated that interactions between interventions in different domains may be likely the statistical models will allow evaluation of such interactions. Where the statistical models evaluate such an interaction the models can incorporate the relative likelihood of such interactions, but with possibly low prior probability in cases where it is biologically implausible for interactions to occur. Each intervention within each domain will be evaluated within prospectively defined and mutually exclusive strata (sub-groups) of participants but information from one stratum may be used (via 'borrowing') to contribute to the analysis of the effect of that intervention in other strata. Interventions that are found to be inferior, for a specific stratum, are removed from use in that stratum, and will, typically, be removed from the REMAP allowing new interventions or domains or both to be introduced. An RAR algorithm will be used to preferentially randomize participants to interventions that appear to be performing better. Extensive simulation studies have been performed to define the type I error, power to detect specified differences, and demonstration of equivalence as well as a broad range of operating characteristics. It is planned that further simulation studies will be conducted in conjunction with consideration of the introduction of new interventions or domains or both into the REMAP. The intention-to-treat (ITT) principle will be used for all primary analyses.

The key structure of the REMAP is outlined in Figure 5.

Figure 5: REMAP Structure



7.2. Nomenclature

A specific set of nomenclature is used to categorize potential treatments evaluated and populations within a platform trial as well as other aspects of the trial design and statistical analysis. A detailed glossary can be found in Section 1.2. Please see the glossary for the definition and explanations for the following terms: domain, intervention, regimen, stratum, state, Statistical Trigger, Platform Conclusion, and Public Disclosure. The following section can only be understood in the context of an understanding of the definition and meaning of these specific terms.

7.3. Study setting and participating regions

The trial will recruit only participants who are admitted to an ICU. An ICU is defined as a location that identifies itself as an ICU (or HDU) and is able to provide at least non-invasive ventilation and continuous administration of vasoactive medications. By agreement with the RMC, the definition of an ICU may include a general ward in which a patient is under the care of an Intensive Care Specialist (Intensivist), but resource limitations prevent the immediate delivery of care occurring in the ICU. It is intended that the trial will be conducted in multiple regions. A region is defined as a country or

collection of countries with study sites for which a RMC is responsible. The country or countries for which a RMC are responsible, as well as all aspects of trial conduct that are specific to each region, are described in the RSAs.

Participating ICUs will be selected by a RMC based on response to an expression of interest and fulfilling pre-specified criteria including number of beds in the ICU, annual admissions for severe CAP, resources available to support research activities, and track record in conducting investigator-initiated multicenter trials.

The current regions are:

- Europe, with funding from a European Union FP7 grant (FP7-HEALTH-2013-INNOVATION-1, grant number 602525), to support the enrollment of 4000 participants. This funding terminates in 2021.
- Australia and New Zealand. In Australia the project has received funding from a NHMRC Project Grant (APP1101719), to support the enrollment of 2000 participants. This funding terminates in December 2021, although some extension may be feasible. In New Zealand the project has received funding from a HRC Programme Grant (16/631), to support the enrollment of 800 participants. This funding terminates in November 2021.
- Canada. In Canada the project has received funding for a CIHR grant (158584), to support the enrollment of 300 participants. This funding terminates in 2022.

It is intended that additional regions will be added if funding can be secured in other locations. It is desirable that the REMAP is active in as many locations as possible. There is no upper limit to the number of regions and the number of participating sites.

7.4. Eligibility criteria

The eligibility criteria for the REMAP are applied at two levels. One level is that there are inclusion and exclusion criteria that determine eligibility for randomization within the REMAP. The other level is that, once eligible for inclusion within the REMAP, additional criteria, typically exclusion criteria, are applied that are specific to the level of the domain. A patient is eligible for inclusion within a domain when:

- all REMAP inclusion criteria are present
- none of the REMAP exclusion criteria are present
- Domain-Specific criteria are met

As such, the key “inclusion criteria” for being eligible for a domain are that the patient is eligible for the REMAP. Criteria for inclusion in the registry, in which patients do not receive any randomized intervention, may be broader than the entry criteria for the REMAP (i.e. it is only a subset of registry eligible patients who are eligible for randomization within the REMAP).

7.4.1. REMAP Inclusion Criteria

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

1. Adult patient admitted to an ICU for acute severe CAP within 48 hours of hospital admission with
    a. symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain) AND
    b. Radiological evidence of new onset infiltrate of infective origin (in patients with pre-existing radiological changes, evidence of new infiltrate)
2. Up to 48 hours after ICU admission, receiving organ support with one or more of:
    a. Non-invasive or invasive ventilatory support;
    b. Receiving infusion of vasopressor or inotropes or both

7.4.2. REMAP Exclusion Criteria

A potentially eligible patient who meets any of the following criteria will be excluded from participation in this trial:

1. Healthcare-associated pneumonia:
    a. Prior to this illness, is known to have been an inpatient in any healthcare facility within the last 30 days
    b. Resident of a nursing home or long-term care facility.
2. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment.
3. Previous participation in this REMAP within the last 90 days

7.4.3. Domain-Specific Entry criteria

Each domain may have additional, domain-specific eligibility criteria, typically just exclusion criteria, although a combination of inclusion and exclusion criteria can be specified. Patients who fulfill the Overall REMAP Eligibility Criteria will be assessed for enrollment into all domains that are active at a

site. A participant enrolled in the trial will receive the number of REMAP-specific interventions equivalent to the number of Domains to which they are enrolled. The additional eligibility criteria that are specific to a domain are provided in each DSA.

Where a participant has an exclusion criterion to one or more interventions within a domain, but there are at least two interventions within that domain to which the participant is eligible the patient will be randomized to receive one of the interventions to which the participant is eligible.

7.5. Interventions

7.5.1. Domain-Specific Information

All information related to the background, rationale, and specification of interventions that will be administered within the trial are located in the DSAs. The minimum number of interventions within a domain is two and the maximum number is limited only by statistical power. Each RMC will select the interventions that will be available within a domain that will be offered to participating sites in that region but the default position is that all interventions that are available and feasible in that region or country should be offered to sites. Individual participating sites will select the interventions within a domain that will be available at their site with the default position being all available interventions. The randomization program will only provide treatment allocations that are permitted at each participating site. This allows interventions that are not necessarily available in all regions, for example because of licensing reasons, to be included within the REMAP. Within the context of comparative effectiveness research, this also allows sites to determine the interventions that are within their usual or reasonable spectrum of care. However, the viability of a domain is dependent on at least one intervention being available in all regions and being available at a substantial majority of participating sites. This level of 'connectedness' is necessary for the validity of the statistical models that are used to analyze trial results.

7.5.2. Treatment allocation and Response Adaptive Randomization

Random allocation of treatment status forms the basis of all evaluations of causal inference. RAR will be used to vary the proportion of participants who are allocated randomly to each available intervention. Randomization is done at the regimen level, where a regimen is a selection of one intervention from each domain. The proportion of participants who receive a specified regimen will be determined by a weighted probability, with that probability being determined by the probability, taking into account all accrued data, of that regimen being the optimal regimen. RAR will result in participants being randomized with higher probability to interventions that are performing better.

The proportions that are specified by RAR are determined only by analysis of the primary outcome measure in participants who have completed 90 days of follow-up from the time of enrollment. Although outcome may be known before 90 days (death in hospital) the time at which these alternate events occur may be different. By only including participants in the analysis models that determine the RAR proportions potential bias that arises from different events occurring with different patterns of timing within the 90 day follow up period is avoided. The same statistical model will be used to both analyze the results of the REMAP as well as specify the randomization proportions.

RAR weights reflect the probability each particular regimen is the most effective over all possible regimens within each stratum. The probability a regimen is optimal reflects not just the point estimate of difference in outcomes, but also the uncertainty around that estimate. At initiation of a new domain, the proportion of participants allocated to each intervention is balanced (i.e. all interventions have equal proportions). The RAR proportions are then updated at the first adaptive analysis and at all subsequent adaptive analyses. When sample sizes are small, such as at the initiation of a domain, credible (probability) intervals are wide, and therefore randomization proportions remain close to being balanced among all regimens (i.e. randomization weights are weak and allocation remains close to balanced). When a new intervention is added to an existing domain it will commence with balanced randomization and the randomization weights will be updated with each adaptive analysis but will remain weak until sample size for the new intervention accrues.

As the data accrues and sample sizes increase, if the probability an intervention is part of the optimal regimen becomes large, but not large enough to claim superiority, the randomization proportions will be capped. This is done because interventions are provided on an open-label basis and extreme ratios would be at risk of allowing clinicians who recruit participants to draw inference about the effectiveness of individual interventions or regimens.

Some domains may have more than two interventions and it is possible that participant- or site-level characteristics may result in one or more interventions within a domain not being appropriate for an individual participant (for example, known intolerance to one of the interventions or a machine that is necessary to deliver an intervention not being available). Where a participant is unable to receive one or more interventions, but there are still two or more available interventions, random allocation will still be performed using RAR. However, interventions that are not available will be ‘blocked’ and the remaining RAR proportions will be divided by one minus the sum of the unavailable proportions and applied to the available interventions.

A detailed description of the statistical models and the application of RAR is outlined in the Statistical Analysis Appendix.

7.5.3. Adaptation of Domains and Interventions

Over the lifetime of this REMAP, it is anticipated that new interventions will be added to the starting domains and new domains initiated, including domains that are planned for activation in the event of a pandemic. The addition of interventions within existing domains, and the creation of new domains, will be considered according to a set of priorities and contingencies developed by the ITSC and are dependent on existing or new clinical need and there being sufficient statistical power available within the REMAP. All new interventions and domains will be subject to ethics and regulatory approval prior to initiation.

A domain in which an intervention is identified as being superior and for which there are no new interventions that are appropriate to be introduced will continue as a domain within the REMAP but with all participants allocated to receive the superior intervention. Interventions that are identified as being inferior will be removed from a domain, with or without replacement, as appropriate. If all interventions are identified to have equivalence the ITSC will consider options that include cessation of the domain or continuation of the domain with a smaller delta.

The implementation of adaptations that occurs as a consequence of declaration of a Platform Conclusion may be limited by availability of an intervention in some locations. For example, if a superior intervention was not available (for licensing or site-specific reasons) all inferior options would be removed only at the sites where the superior option is available. Randomization to remaining interventions would likely continue at those sites until the superior intervention is available at those sites.

7.6. Endpoints

The primary outcome for this REMAP will apply to all domains. Secondary outcomes generic to all Domains are provided in this Core Protocol below. Secondary outcomes specific to individual domains are provided in the relevant DSAs. The Primary Endpoint (or the end-point that is used for RAR) may be modified during a pandemic and will be outlined in the Pandemic Appendix.

7.6.1. Primary Endpoint

The primary endpoint for all domains will be all-cause mortality at 90 days.

7.6.2. Secondary Endpoints

A set of generic secondary endpoints will be evaluated in all domains. Additional secondary endpoints may be specified for a domain within the DSA. Some domain-specific secondary endpoints may be specified as Key Domain-Specific Endpoints and will be interpreted in conjunction with the primary endpoint in determining the overall effectiveness of interventions.

The generic secondary endpoints for the trial are:

ICU outcomes:

- ICU mortality censored at 90 days;
- ICU LOS censored at 90 days;
- VFDs censored at 28 days;
- OFFDs censored at 28 days;
- Proportion of intubated participants who receive a tracheostomy censored at 28 days;

Ventilator- and organ failure-free days will be calculated by counting the number of days that the participant is not ventilated or has no organ failure. If a participant dies during the hospitalization during which enrollment occurred, the number of VFDs or OFFDs will be set to zero. If the participant is discharged alive from hospital, the remainder of days censored at 90 days are counted as ventilator- or organ failure-free days.

Hospital outcomes:

- Hospital LOS censored 90 days after enrollment;
- Destination at time of hospital discharge (characterized as home, rehabilitation hospital, nursing home or long-term care facility, or another acute hospital);
- Readmission to the index ICU during the index hospitalization in the 90 days following enrollment;

The index hospital admission is defined as continuing while the participant is admitted to any healthcare facility or level of residence that provides a higher level of care than that corresponding to where the participant was residing prior to the hospital admission. (Huang et al., 2016) This definition is used commonly in ICU trials. Participants who have been and still are admitted to a healthcare facility 90 days after enrollment are coded as being alive.

Day 90 all-cause mortality will be collected in all regions. Additional outcomes will be collected, where feasible, may be mandated in a DSA or a RSA, may be collected by central trial staff or site staff, and will comprise:

- Survival at 6 months after enrollment (where feasible, refer to relevant regional RSA)
- HRQoL at 6 months after enrollment using the EQ5D-5L (where feasible, refer to relevant regional RSA)
- Disability status measured at 6 months after enrollment using the WHODAS 2.0, 12-item instrument (where feasible, refer to relevant regional RSA)

7.7. Bias Control

7.7.1. Randomization

Randomization will be conducted through a password-protected, secure website using a central, computer-based randomization program. Randomization will be at the patient level and occur after data necessary to implement the inclusion and exclusion criteria have been entered into the secure randomization website. The RAR will occur centrally as part of the computerized randomization process. Sites will receive the allocation status and will not be informed of the randomization proportions. Each region will maintain its own computer-based randomization program that is accessed by sites in that region but the RAR proportions will be determined by a SAC and provided monthly to the administrator of each region's randomization program who will update the RAR proportions.

7.7.2. Allocation concealment

Allocation concealment will be maintained by using centralized randomization that is remote from study sites.

7.7.3. Blinding of treatment allocation

The default position within the REMAP is that treatments determined by randomization will be provided on an open-label basis. However, the blinding of treatment status is not precluded within the REMAP. If required, details related to blinding of interventions will be specified in the DSAs.

7.7.4. Blinding of outcome adjudication

The primary outcome of all-cause mortality censored at 90 days is not subject to ascertainment bias. Wherever possible, trial management personnel, who are blinded to allocation status, will conduct any follow up after discharge.

7.7.5. Follow up and missing data

Regional trial management personnel will perform timely validation of data, queries and corrections. Any common patterns of errors found during quality control checks will be fed back to all sites. Data management center study personnel performing site checks will be blind to the study allocation. Missing data will be minimized through a clear and comprehensive data dictionary with online data entry including logical consistency rules. If values necessary for the Bayesian modelling of the primary endpoint and the RAR are missing they may be imputed, using available data. For example, if strata or state is missing, it will be multiply imputed based on the available variables and a prior distribution on the relative prevalence of each strata or state. Values for the primary endpoint will not be imputed. Additional details are provided in the Statistical Analysis Appendix.

7.8. Principles of Statistical Analysis

7.8.1. Preface

The purpose of this section of the protocol is to introduce and summarize the statistical methods that will be used to analyze data within the REMAP. This section duplicates some of the information provided in the Statistical Analysis Appendix but this section is intended to be accessible to individuals with an understanding of common clinical trial designs and classical frequentist analytical methods but without necessarily having training in Bayesian statistics. Interpretation of this section also requires an understanding of the meaning of specific terms for which definitions are provided in the glossary (see Section 1.2).

A formal description of the adaptive Bayesian data analysis methods fundamental to the REMAP design, which assumes substantial familiarity with Bayesian calculation of posterior distributions conditioned on observed data, is located in the Statistical Analysis Appendix. There is some limited overlap between these two sections of the protocol so that each may serve an appropriate audience as a standalone description of the statistical methods.

7.8.2. Introduction

Within the REMAP, two or more interventions within a domain are evaluated and sequential Bayesian statistical analyses are used over time to incorporate new trial outcome information to determine if an intervention is superior, if one or more interventions are inferior in comparison to all other interventions, or if one or more pairs of interventions are equivalent, with respect to the primary endpoint. Every participant will be assigned a set of interventions, comprising one intervention from each domain for which the participant is eligible. The combination of interventions to which a participant is assigned comprises the regimen and the regimens are the available arms in the trial. Participants will be classified by membership in different populations defined by one or more strata. The unit-of-analysis for a domain is the most granular level, defined by one or more stratum, or a state, within which the treatment effect of interventions within that domain may vary in the statistical model. Participants are also classified by the criteria that determine eligibility for each domain.

Inference in this REMAP is determined by analyses using pre-specified statistical models that incorporate region, country, time periods, age, and disease severity to adjust for heterogeneity of enrolled participants that might influence risk of death. These models incorporate variables that represent each intervention assigned to participants and possible interactions between interventions in different domains. The efficacy of each intervention within a domain may be modeled as not varying in any of the strata, or possibly varying in one or more of the different strata in the REMAP. Where the efficacy of each intervention within a domain is modeled as possibly varying, borrowing between strata is permitted. The unit-of-analysis that will be modeled may comprise the entire population (i.e. no categorization by strata is applied) or may be defined by one or more stratum. The unit-of-analysis and whether borrowing can occur between strata is pre-specified for each domain. At each analysis the current active statistical model (or models) is (are) used, and may include patients who were enrolled when previous versions of the model were being used. The current model is described in an operational document, maintained by the SAC. Unless otherwise specified (see Section 8.12) modifications and implementation of modifications to the model require the approval of the ITSC and do not require a protocol amendment.

Whenever a model hits a predefined threshold for any of superiority, inferiority, or equivalence for an intervention with respect to the primary endpoint, this is termed a Statistical Trigger. At any given adaptive analysis, a Statistical Trigger may be reached for all participants or for one or more stratum and will be reviewed immediately by the DSMB. When a Statistical Trigger is confirmed by the DSMB, based on a thorough review of the data including an evaluation of the proportion of patients

for whom monitoring of variables that contribute to the model has been completed, and totality of evidence, and where no compelling reason exists not to reach a conclusion (see Section 7.8.9) regarding that question the result that has led to a Statistical Trigger will be specified to be a Platform Conclusion. The declaration of a Platform Conclusion will lead to appropriate modification of the interventions available within that domain and a Public Disclosure of the result. A Statistical Trigger can be considered as a mathematical threshold, whereas a Platform Conclusion is a decision regarding one or more interventions within a domain.

7.8.3. Target populations (strata and states) and implications for evaluation of treatment-by-treatment and treatment-by-strata interactions

7.8.3.1. *Introduction*

In a clinical trial there are many different potential participant-level covariates. A covariate can be a demographic variable that remains unchanged throughout the trial (i.e. age or gender) or a variable representing the severity or course of the disease that can vary over time (i.e. it can be assessed at the time of enrollment and at other times after enrollment during the course of the illness). In this REMAP, there are two special roles for a subset of these potentially time-varying covariates.

First, covariates determined at the time of enrollment that are identified in the design as possibly having differential treatment effect (i.e. interventions may have differential efficacy for the different levels of the covariate) are referred to as strata. Strata are used to define the unit-of-analysis for a domain within a model. Strata are a recognized element in Platform Trials.

Second, within this REMAP, there is interest in studying domains that are relevant for a target population or defined disease state that, while it may be present at the time of enrollment for some participants, may only occur after enrollment for other participants and may never occur for another set of participants. This disease state could be identified by the same covariate that might also have been used to define a strata (but doesn't have to have been). In this regard, the concept of 'state' is used to define participants with characteristics that define a target population that will be evaluated by a domain, analyzed within the REMAP, and for which the characteristics can be present at the time of enrollment or may develop after the time of enrollment. State can also be used to define the unit-of-analysis for a domain within the model.

The appropriate statistical handling of the analysis of patients who become eligible for a domain as a consequence of entering a state, after the time of enrollment, requires the use of models that take into account that the likelihood of entering the state after enrollment may have been influenced by

the allocation status for other domains that specified the initiation of interventions that commenced at the time prior to entry into the state.

This evolution of Platform Trial design, to include 'state' is a new extension that has not been considered within Platform Trials conducted previously.

7.8.3.2. *Stratum*

A covariate in the REMAP that can be used as a unit-of-analysis within a Bayesian statistical model that allows for the possibility of differential treatment effects for different levels of the variable is referred to as a strata. The covariate is classified into mutually exclusive and exhaustive sets for analysis of treatment effect, as well as for defining separate RAR. The criteria that define a stratum are based on a characteristic that is present at or before the time of enrollment.

The simplest structure for strata is a single dichotomous stratum variable, which divides participants in the REMAP into two stratum. More complex arrangements are possible, such as a single strata variable that is ordinal or two (or more) dichotomous or ordinal strata variables the combination of which defines a single stratum (i.e. there are 2^N stratum when there are N dichotomous stratum variables).

The number of strata variables and the number of strata within the REMAP may be varied, depending on the impact of such decisions on statistical power, as determined by simulations. The modeling of strata may assume no differential effect for some domains. This may occur in two ways. Firstly, when the strata structure defines the entry criteria for a domain. Secondly, when two or more stratum are combined within a single unit-of-analysis (i.e. the unit-of-analysis comprises two or more stratum). If the unit-of-analysis comprises less than all available strata the analysis that is performed assumes that treatment effect does not vary between stratum combined within a common unit-of-analysis. The RAR is applied according to the model. So, the RAR applies to the patients that comprise the unit-of-analysis, irrespective of whether the unit-of-analysis comprises a single stratum or two or more stratum.

A strata variable can be set that is maintained as a silent or 'sleeping' strata which becomes active under pre-defined circumstances, such as the occurrence of a pandemic. In this situation, during the inter-pandemic period, all participants are categorized as non-pandemic but, during a pandemic, a distinction is made between patient with proven or suspected pandemic infection and patients in whom pandemic infection is neither proven nor suspected.

The *a priori* defined strata that are used for determination of results and for RAR may be changed during the life of the REMAP as knowledge is accumulated and, if this occurs, will result in amendment of one or both of the Core Protocol and DSAs. Data from patients enrolled before the change in the strata can be used to determine priors that are incorporated into the model at the outset of the incorporation of the new strata into the model.

7.8.3.3. *Treatment-by-strata interactions: borrowing between strata*

Where specified in the statistical model, the treatment effect of an intervention is allowed to vary between different strata. A Bayesian Hierarchical Model (BHM) is used for all treatment-by-strata interactions. In the BHM a hyperprior is used for the differing treatment effects across strata. The standard deviation of the hyperprior, gamma, is a modeling starting estimate for the variation in the magnitude of the difference in treatment effects between strata. By default, the starting estimate of the difference is zero. The gamma parameter influences the extent to which the treatment effect of different interventions is permitted to vary between strata. At the commencement of a model, the gamma parameter must be set, for each domain-strata pair.

In this REMAP, only three options are permitted with respect to specifying the gamma parameter for each domain-strata pair. Firstly, gamma may be set to zero. The effect of this is that treatment effect of an intervention is not permitted to differ between specified strata. The unit-of-analysis is not sub-divided according to the stratum variable. If gamma is set to zero for all strata for a domain, the unit of analysis is all patients randomized in that domain. Secondly, and at the opposite extreme, gamma can be set to infinity. In this situation treatment effect is evaluated separately and independently in each stratum (with no borrowing between stratum). Thirdly, gamma may be set to a defined number between zero and infinity. This parameter value cannot be varied for different domain-strata pairs, a global REMAP value has been selected. This specified value for gamma places a constraint on the variance of the difference in treatment effect in different stratum but permits the model to estimate treatment effect in one stratum by borrowing from other stratum. Borrowing occurs to the extent that it is supported by the accumulated data, but the setting of gamma influences the amount of borrowing and how quickly borrowing is able to occur. The value of gamma that has been chosen has been determined by simulations to achieve a compromise between type I and type II error in baseline scenarios that assume either equivalence or superiority. Where a value for gamma is specified in the model, in this REMAP the value of gamma will be 0.15.

The specification of gamma determines the unit of analysis in the model and the extent of borrowing. For each domain-strata pair, the unit of analysis can be all patients (gamma = zero), each stratum with borrowing (gamma = 0.15), or each stratum separately (gamma = infinity).

The gamma that will be set, and hence the unit-of-analysis, for each domain-strata pair is specified in each DSA.

7.8.3.4. *Analysis set for strata, timing of enrollment and timing of information regarding strata membership*

It has already been specified that the criteria that define a stratum must be present at or before the time of enrollment. In some situations, the information necessary to determine membership of a stratum may become available after the time of enrollment or may be acquired from information derived after enrollment where the understanding of biology of a disease makes it reasonable to assume that the criteria was met at the time of enrollment. This situation might apply to status with respect to a particular pathogen where results of microbiological testing are not available until after enrollment or when the sample that is tested is not collected until after enrollment.

In this situation randomization is permitted within patients where the criteria is suspected or proven at the time of randomization. With regards to possible infection with a specified pathogen, suspected or proven infection at the time of randomization is sufficient to allow an allocation status to be made. For a patient with suspected infection, membership within the strata is defined by the final test results, but a patient who is suspected but is never tested is analyzed as a positive. If a Platform Conclusion is reached for one or more stratum, analyses will also be done on patients with suspected infection who receive the intervention but who turn out to be negative. Whether borrowing between strata is permitted will be specified in the DSA.

7.8.3.5. *State*

A state is a clinical condition of a participant that may change during the course of their treatment. The different states within the REMAP are used to define possible eligibility of the participant for different domains at different times in the trial. A state is a set of mutually exclusive categories, defined by characteristics of a participant, that are dynamic in that they can change for a single participant, at different time-points, during the participant's participation in the REMAP.

The number of state variables and the number of states within the REMAP may be varied, depending on the impact of such decisions on statistical power, as determined by simulations. The same state may be shared by one or more domains but may be different in different domains. The *a priori*

defined states that are used for determination of results and for RAR may be changed during the life of the REMAP as knowledge is accumulated or as domains change and, if this occurs, will result in amendment of one or both of the Core Protocol or DSAs. Data from patients enrolled before the change in the state can be used to determine priors that are incorporated into the model at the outset of the incorporation of the new state into the model.

7.8.3.6. *Timing of randomization and revealing of allocation status*

Several different scenarios are recognized that represent different combinations of randomization within a stratum or a state and by the options for the time (at enrollment or later) at which administration of the allocated intervention is commenced.

At the time of enrollment, all participants, are randomized to one intervention in every domain for which the participant is eligible for at enrollment or might become eligible for depending on the progression of the state of their illness (i.e. randomization occurs once and only once at the time of enrollment).

For participants, who at the time of enrollment are eligible for a domain and for which the intervention will be commenced immediately, the allocation status is revealed immediately and the participant then commences treatment according to their allocated intervention. This is referred to as **Randomization with Immediate Reveal and Initiation**.

In circumstances where the participant is eligible for inclusion in the REMAP but is not eligible for a domain at the time of enrollment but might become eligible if the participant's state changes, the participant's allocation status is revealed only if and when the patient enters the state that confers eligibility. This is referred to as **Randomization with Delayed Reveal**.

Another situation applies when eligibility is determined by information that relates to the condition of the patient at the time of initial assessment of eligibility and is relevant to determination of eligibility but is not known until later. In this circumstance, the participant's allocation status can be revealed when the additional information becomes available. Examples of this type of information include the results of microbiological tests and the outcome of a request for consent. Information related to the safety of an intervention in individuals that may change between the time of initial assessment of eligibility and initiation of an intervention may also be reassessed and be used to determine if an allocation status will be revealed. Where initiation of the intervention is deferred pending availability of this additional information, this is referred to as **Randomization with**

Deferred Reveal. It is noted that submission of information regarding microbiological results, consent, or safety information occurs without knowledge of allocation status.

Variation in relation to the timing of revealing and initiation of an intervention has implications to the treatment-by-treatment interactions that are potentially evaluable. Analysis of participants who are enrolled in one or more domains on the basis of Randomization with Immediate Reveal can be conducted within a state, for which membership occurs for at least some participants at the time of enrollment. However, the analysis within this state will also include participants who are enrolled in the same domain on the basis of Randomization with Delayed Reveal with their eligibility for the act of revealing allocation status being defined by progression to the same state at some time-point after enrollment. Participants who are randomized within such a domain, at time of enrollment, but never enter a state that corresponds to eligibility for a domain never have their allocation status revealed and do not contribute to the analysis of treatment effect for interventions in that domain. In this regard, the ITT principle is not violated as the allocation status of such participants is never revealed. The models that are used to provide statistical analysis of the effect of an intervention within a domain that is contained wholly within one state are not able to evaluate interactions with interventions in domains that are defined in different states.

The final scenario to consider involves participants who are enrolled in one or more domains on the basis of Randomization with Deferred Reveal within a stratum. For such participants, their allocation status is revealed at, or close to, the time of deferred initiation of the intervention, when additional information necessary to establish eligibility has become available but relates to information that applies at baseline. Participants in this category are analyzed within baseline stratum in an ITT fashion. As such, the model allows evaluation of interactions with treatments in other domains that share the same stratum. Within such a domain, it can be assumed that there will be some participants who are never eligible to commence receiving the intervention (for example, due to death, or never reaching the defined criteria for the intervention to be commenced) and do not receive the intervention. However, all participants who have an allocation status revealed, even if the intervention is never administered, are analyzed according to and in compliance with the ITT principle.

7.8.3.7. *Treatment-by-treatment interactions*

Where specified in the statistical model, the treatment effect of an intervention is allowed to vary depending on treatment allocation in another domain (i.e. allow evaluation of treatment-by-treatment interaction). A BHM is used for all treatment-by-treatment interactions. In the BHM, a

hyperprior is used for the differing treatment-by-treatment interaction effects. The standard deviation of the hyperprior, lambda, is a modeling starting estimate for the variation in the magnitude of the difference in treatment effect dependent on an intervention assignment in another domain. By default, the starting estimate of the difference is zero (i.e. no interaction). The lambda parameter influences the extent to which the treatment effect of different interventions is permitted to vary dependent on intervention assignment in other domains. At the commencement of a model, the lambda parameter must be set, for each domain by domain pair.

In this REMAP, only three options are permitted with respect to specifying the lambda parameter for each domain-domain pair. Firstly, lambda may be set to zero. The effect of this is that there are no treatment-by-treatment interactions being evaluated between interventions in those two domains. Alternatively, lambda may be set to a defined number between zero and infinity. This parameter value cannot be varied for different domain-domain pairs; a global REMAP value has been selected. This specified value for lambda places a constraint on the variance of the difference in treatment-by-treatment interaction. Borrowing occurs to the extent that it is supported by the accumulated data, but the setting of lambda influences the initial amount of borrowing and the degree of borrowing as data accumulates. The value of lambda that has been chosen has been determined by simulations to achieve a compromise between type I and type II error in baseline scenarios that assume either no interactions or moderate interactions exist. Where a value for gamma is specified in the model, in this REMAP the value of gamma will be 0.075. The third choice is to allow no borrowing of the treatment-by-treatment interactions. This is equivalent to selecting a lambda of infinity. This choice would be the most aggressive choice in estimating treatment-by-treatment interactions.

The lambda that will be set for each domain-domain pair is specified in each DSA.

7.8.3.8. *Nested analysis of interventions within a domain*

Within domains in which there are three or more interventions, some interventions may be more likely to have a similar treatment effect. There are several examples of such similarity. For example, the interventions within a domain may comprise a no intervention option and two doses or strategy of administration of the same intervention, or two or more interventions within a domain may belong to the same class of drug than one or more other interventions in that domain.

In situations in which interventions may be more similar than others, the model may nest the more similar interventions within a higher-level intervention category that comprises all the interventions deemed similar. In this situation, and to evaluate the occurrence of a Statistical Trigger, there are two models for analysis. Firstly, all patients receiving the nested interventions, treated as a single

combined intervention, are compared with all other interventions in the domain. Secondly, all interventions are modeled individually. In this analysis, the interventions within a nest are modeled using a BHM incorporating the nesting structure. The BHM has a hyperprior specified for the shrinkage across interventions within the nest. This analysis will compare all interventions within a domain to all other interventions. This BHM analysis is used for the RAR assignments.

Whether nested analysis will be performed and, if so, the membership of category of more similar interventions will be specified in the DSA.

7.8.3.9. *Current strata and states*

The strata are defined, at the time of enrollment, by:

- Shock, defined in 2 categories, present or absent, with present defined as the patient is receiving continuous infusion of intravenous vasopressor or inotrope medications at the time of enrollment
- Influenza defined in two categories, present or absent, based on the results of microbiological tests for influenza. Any patient with suspected influenza who is not tested will be deemed positive. Any patient who is not suspected of having influenza and is not tested will be deemed negative. The availability and interpretation of microbiological tests are likely to change during the REMAP and an operational document will be used to specify how different tests are interpreted. Eligibility for a domain that tests antiviral medications active against influenza will be based on status with respect to influenza being proven or suspected at time of enrollment but it is noted that strata status is defined by the final results of influenza testing which may not be known at time of enrollment and may include analysis of samples collected after enrollment where it is reasonable to presume that the sample reflected influenza status at time of enrollment.
- Pandemic infection defined in two categories, proven or suspected pandemic infection or neither proven nor suspected pandemic infection. This is a ‘sleeping strata’ and will not be active before or after a pandemic but may be activated during a pandemic. The decision to activate a pandemic infection strata is specified in the Pandemic Appendix to the Core Protocol.

The default states are defined by the occurrence of:

- Hypoxemia, defined in 3 categories, comprising participants who are not receiving invasive mechanical ventilation; participants who are receiving invasive mechanical ventilation and

have a ratio of arterial partial pressure of oxygen to fractional inspired concentration of oxygen (P:F ratio) of ≥ 200 mmHg or are receiving invasive mechanical ventilation with the Positive End-Expiratory Pressure (PEEP) set to less than 5 cm of water (irrespective of the P:F ratio); and participants who are receiving invasive mechanical ventilation with a PEEP of 5 cm of water or more and have a P:F ratio of <200 mmHg.

The domains to which each strata or state applies, the unit-of-analysis (which determines which if any treatment-by-strata interactions are evaluated in the model), the relationship between the timing of domain eligibility and the revealing of allocation status, whether nested analysis will occur, and what treatment-by-treatment interactions will be evaluated are specified in each DSA.

7.8.3.10. *Pre-specified subgroup analysis after achievement of a Platform Conclusion*

Following the achievement of a Platform Conclusion it is permissible for additional sub-group analyses to be conducted. The variables that specify such sub-groups are outlined *a priori* in each DSA. These variables are different to those that define strata or states in the model and are not used in determination of a Statistical Trigger or RAR for that domain. In a domain in which the unit-of-analysis comprises two or more stratum, additional sub-group analyses can be conducted for variables that do specify stratum that have been combined to determine the unit-of-analysis.

All such analyses will only be conducted following the determination of a Platform Conclusion and, although reported, such analyses are always regarded as preliminary. Following a Platform Conclusion, the results of a pre-specified subgroup analysis may be used to make changes to the model and, where appropriate and to an appropriate degree, data derived from the REMAP can be used to set the prior distribution at the commencement of the new model.

7.8.4. Bayesian Statistical modeling

Inferences in this trial are based on a Bayesian statistical model, that will calculate the probability of superiority, inferiority, and equivalence of the interventions (known as a posterior probability distribution) within a unit-of-analysis that is defined by one or more stratum, taking into account the evidence accumulated during the trial (based on data on the outcomes of participants) and on assumed prior knowledge (known as a prior distribution). For the evaluation of the main effects of interventions within a domain (and evaluation of regimens) the default design assumes that parameters in the model have uninformative prior distributions at the first adaptive analysis. This means that any subsequent Platform Conclusion is not capable of being influenced by any discretionary choice regarding the pre-trial choice of prior distribution (i.e. it is the most

conservative approach, making no assumptions regarding the prior distribution). At each subsequent adaptive analysis, the prior distribution is determined by all accumulated data available at the time of the adaptive analysis. The Bayesian approach is seen as continually updating the distribution of the model parameters.

It is not precluded that, under certain circumstances, such as during a pandemic and where there was strong prior evidence along with an ethical imperative to evaluate a particular choice of therapy, that the design could allow an informative prior to be used for the analysis of results from the trial. It may also be permitted to use an informative prior when data that is incorporated in the informative prior is derived from patients already randomized within this REMAP. If informative priors are used this will be specified in the relevant DSA.

The study design can use informed priors to guide some elements of the design, such as for the evaluation of interaction terms, and will be described in the Statistical Analysis Appendix. As outlined above, gamma will be set to allow and influence the evaluation of treatment-by-strata interactions and lambda will be set to allow and influence the evaluation of treatment-by-treatment interactions.

This method of statistical analysis differs from conventional (frequentist) trials. Frequentist statistics calculate the probability of seeing patterns in the data from a trial if a hypothesis is true (including patterns not observed). This approach relies on assumptions about frequency distributions of trial results that would arise if the same trial were repeated *ad infinitum*. Thus, it requires specific sample sizes, which in turn requires pre-experiment assumptions regarding plausible effect sizes and outcome rates. Although many clinicians are comfortable with this approach, the pre-trial assumptions are frequently incorrect, and the design lacks the flexibility either to easily address the complex questions more reflective of clinical practice or to make mid-trial corrections when the pre-trial assumptions are wrong without concern that the integrity of the final analysis is violated. To allow increased flexibility and yet still generate robust statistical inferences, REMAP relies on an overarching Bayesian, rather than frequentist, framework for statistical inference.

A Bayesian approach calculates the probability a hypothesis is true, given the observed data and, optionally, prior information and beliefs. The advantage of this approach is that, as more data are accrued, the probability can be continually updated (the updated probability is called the posterior probability). In this trial, frequent adaptive analyses will be performed, creating a very complicated sample space, and hence the Bayesian approach is a very natural one for these adaptive designs. The characterization of the risk of false positive error, or power, are done through Monte Carlo trial

simulation. In contrast to frequentist confidence intervals which have awkward direct interpretation, Bayesian analyses return probability estimates that are directly interpretable as probabilities that statements are true (like the probability that one intervention is superior to another).

A number of variables are incorporated into the statistical model so as to provide 'adjustment'. The variables for which such adjustment will be made will be the country in which a participant is treated, changes in outcome that occur over time (era), stratum and state at enrollment (shock and hypoxemia as measures of severity of illness), and age.

The main effect in the model is the treatment effect of each intervention. Each stratum, combination of stratum, or state (where eligibility is defined by a state) is analyzed separately but the model captures the commonalities across such sub-groups. Additionally, and where specified, the statistical model allows evidence relating to the effectiveness of an intervention in one stratum to contribute (via 'borrowing') to the estimation of the posterior probability in other strata, but this only occurs to the extent that treatment effect is similar in different strata.

When a Platform Conclusion is achieved, the results derived from the model, including any contribution from borrowing, will be reported. It is acknowledged that the estimate of treatment effect for a stratum may be contributed to by borrowing from adjacent strata but the results from the strata that have contributed to borrowing will not be reported. The results of these analyses are used to achieve the primary objective of the trial which is to determine the effectiveness of interventions and, where specified, the extent to which that effectiveness varies between strata (intervention-stratum interaction). Additionally, but only where specified *a priori*, the model is able to estimate the effectiveness of an intervention in one domain contingent on the presence of an intervention in another domain (treatment-by-treatment interaction). Although the model can identify an optimal regimen this is not the primary objective of the trial.

Greater detail of the methods within the Bayesian model to be applied in this REMAP are provided in the Statistical Analysis Appendix. The adaptive analyses will use data submitted from participating sites to their regional database. Each provider of regional data management will provide regular updates of data to the SAC for utilization in the adaptive analyses. The frequency of adaptive analyses will occur approximately monthly, unless the amount of data in a month is deemed insufficient. The timely provision of outcome data from participating sites is critically important to the conduct of frequent adaptive analyses.

7.8.5. Statistical Handling of Ineligible Participants

The goal of this REMAP is to enroll as wide a participant population as possible. Because of this and the desire to explore multifactorial regimens it will not be uncommon that a participant will be ineligible for single interventions or entire domains, or interventions may be temporarily unavailable for use. In this section we present the details for how this REMAP deals with these possible circumstances.

If an intervention is unavailable at the time of randomization due to site restrictions (for example, exhausted supply or unavailable machinery) then the participant will be randomized to all remaining interventions and this participant will be included in the primary analysis set as though they were randomized unrestricted to their assigned intervention.

If a participant is ineligible for an entire domain then that participant will not be randomized to an intervention from that domain. The participant will be randomized to a regimen from all remaining domains. As long as the participant is randomized within at least one domain they will be included in the primary analysis. For the ineligible domain the participant will be assigned a covariate for that domain reflecting the ineligibility for the domain. This allows the model to learn about the relative efficacy of the remaining interventions in the domains in which the participant has been randomized. If there is a domain with only two interventions and participant is ineligible for one of the two then the participant will be treated as though they are ineligible for the domain. If there is a domain with more than two interventions but a participant is ineligible for all but one then the participant will be deemed ineligible for the domain. If a participant is only eligible for one intervention within a domain the allocation process may still provide a recommendation that the only available intervention should be provided to the participant (but this is so as to reinforce trial processes associated with successful embedding and such patients will not be included within any analysis of the relevant domain).

If there is a domain with more than two interventions and the participant is ineligible for at least one due to a patient-level factor (for example known intolerance to an intervention), but eligible for at least two, then the participant will be randomized among those interventions that the participant is eligible to receive. The participant will have their assignment included in the primary Bayesian model with an appropriate covariate identifying their ineligibility status that takes into account that a patient-level factor that determines partial eligibility could be associated independently with outcome. The impact of participants with partial eligibility will be taken into consideration by the

DSMB at the time of consideration of whether a Platform Decision is appropriate following a Statistical Trigger.

7.8.6. Intervention Superiority Statistical Trigger

At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population. This Statistical Trigger may also be applied for a state that defines the target population for a domain.

7.8.7. Intervention Inferiority Statistical Trigger

At any adaptive analysis, if a single intervention has less than a 0.01 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior for that target population. If superiority and inferiority were to be discovered simultaneously (for example when there are two interventions), the result will be interpreted as demonstrating superiority. This Statistical Trigger may also be applied for a state that defines the target population for a domain.

7.8.8. Intervention Equivalence Statistical Trigger

If two interventions within a domain, for a unit-of-analysis, have at least a 0.90 probability of being within a pre-specified delta for the primary endpoint then these interventions will be deemed as being equivalent. The size of the pre-specified odds ratio delta is 0.20, meaning equivalence is reached with at least a 90% probability of neither intervention increasing the odds ratio of mortality by more than 0.20. An odds ratio delta of 0.2 has been chosen on the basis that it is consistent with guidance from the Food and Drug Administration (FDA) (U.S. Department of Health and Human Services, 2016) and the European Medicines Agency (EMA) (European Medicines Agency, 2005), as well as discussed in academic literature, and the magnitude of treatment effect that has been specified in published superiority trials that enroll patients who are critically ill (Aberegg et al., 2010, Ware and Antman, 1997, European Medicines Agency, 2005, U.S. Department of Health and Human Services, 2016). A measure of relative treatment effect (odds ratio) is specified, rather than an absolute difference in treatment effect. This choice is made because it is reasonable to expect the mortality rates to vary between strata, and the relative effect is a more robust analysis method across these differences.

In a domain with two interventions equivalence is evaluated between the single pair of interventions. In a domain with more than two interventions, equivalence is evaluated for every possible pairwise comparison.

A DSA may define levels of delta for equivalence that are different from the default delta. This includes the possibilities of specifying a delta that may be asymmetrical for some or all pair-wise comparisons or both. The DSA will set out the rationale for any variation in delta and may include, but are not limited to, cost or burden.

This Statistical Trigger for equivalence may also be applied for a state that defines the target population for a domain.

7.8.9. Action when a Statistical Trigger is achieved

7.8.9.1. *Introduction*

If a Statistical Trigger is achieved this will be communicated by the SAC to the DSMB. Subject to the DSMB confirming that a Statistical Trigger has been reached validly, the DSMB will oversee a range of actions, as follows.

7.8.9.2. *Actions following Statistical Trigger for superiority*

If an intervention triggers a threshold for superiority and the DSMB declares this as a Platform Conclusion, the intervention is deemed as being superior. At that point randomization to all other remaining interventions in the domain in that unit-of-analysis will be halted at sites at which the superior intervention is available (randomization to the non-superior interventions may continue at sites at which the superior intervention is not available pending its availability). The result will be communicated to the ITSC who will take responsibility to undertake Public Disclosure as soon as practicable with the dissemination of the research result via presentation or publication or both.

Within the REMAP and at sites with access to the superior intervention, all participants will be allocated to the superior intervention (while still being randomized to interventions from the other domains). In this regard the domain remains active with what can be considered as 100% RAR to the superior intervention, pending the addition of any new interventions to be evaluated against the current superior intervention. It is also possible that a superior intervention will be retained but subject to further evaluation, by randomization, to refine the optimal characteristics of the superior intervention (for example duration of therapy or optimal dose).

7.8.9.3. *Actions following Statistical Trigger for inferiority*

If the trial triggers a threshold for inferiority and the DSMB declares this as a Platform Conclusion, the intervention is deemed as being inferior. At that point the intervention will not be randomized to any more participants in that unit-of-analysis. The result will be communicated to the ITSC who will take responsibility to undertake Public Disclosure as soon as practicable with the dissemination of the research result via presentation or publication or both.

Where a Platform Conclusion is reached for superiority or inferiority, the DSMB may recommend that Public Disclosure should be delayed until additional results are available, so as to allow further recruitment to evaluate interactions between interventions in different domains or for other clinically or statistically valid reasons. However, declaration of a Platform Conclusion will always result in the removal of inferior interventions from a domain and that all eligible participants within the REMAP receive a superior intervention.

7.8.9.4. *Actions following Statistical Trigger for equivalence*

If a Statistical Trigger arises because one or more pairs of interventions are deemed as being equivalent within a unit-of-analysis, this will be communicated to the ITSC by the DSMB. The ITSC in conjunction with the DSMB may undertake additional analyses, for example, of clinically relevant secondary endpoints.

The approach to a Statistical Trigger for equivalence is different depending on the number of interventions within a domain.

For domains with only two interventions a valid Statistical Trigger for equivalence will be reported as a Platform Conclusion. With respect to the adaptation of the domain, the following actions are possible:

- Removal of the domain from the Platform
- Switching the allocation status to deterministically assign one of the Interventions, for example the less burdensome or less expensive intervention
- No change to the interventions within the domain with continuation of RAR. This could be to further evaluate secondary endpoints, a smaller delta of equivalence, or interest in interactions with other Interventions. Such changes would require amendment to the DSA.

Factors that should be taken into account by the DSMB and the ITSC include the results of the primary analysis, analysis of clinically relevant secondary end-points, the possibility of treatment-by-treatment interactions, the relative burden and cost of the two interventions, the clinical interpretation of the adequacy of the delta, and the possibility that ongoing randomization with a smaller delta might also allow a Statistical Trigger for superiority (with a small effect size).

The options following a Statistical Trigger for a pair of Interventions in a Domain with three or more Interventions are more complex. Within a domain with three or more interventions the information provided by the DSMB to the ITSC may include specification of the ordinal rank of the equivalent interventions within the domain. With respect to reporting of Platform Conclusions and adaptations of the domain the following actions are possible:

- A pair of equivalent interventions may be compressed into a single group for the purposes of ongoing analysis. Both interventions continue to be interventions that are available within the domain for allocation, but the primary analysis considers the effect of the two interventions as a single group, where a balanced randomization will be assigned to each of the intervention pair within this compressed group. Secondary analyses can continue to be conducted to determine if equivalence is maintained with the possibility of the intervention being restored as individual interventions if results no longer support equivalence. It is acknowledged that re-analysis of the domain immediately following compression of one (or more) pairs of equivalent interventions may result in the occurrence of other Statistical Triggers (e.g. a compressed pair may be superior or inferior to all remaining interventions). Any statistical Trigger that results from compression of one or more pairs will be responded to as outlined in this section with reporting of the cascade of Statistical Triggers. Compression of a pair of interventions can occur with or without reporting of a Platform Conclusion.
- Removal of one of the pair of equivalent interventions from the domain, for example the more burdensome or more expensive intervention, which will result in a reporting of a Platform Conclusion.
- No change to the interventions within the domain with continuation of RAR. This could be to further evaluate secondary endpoints, a smaller delta of equivalence, or interest in interactions with other interventions. Such changes would require amendment to the DSA. This could occur with or without reporting a Platform Conclusion.

Factors that should be taken into account by the DSMB and the ITSC include the results of the primary analysis, analysis of clinically relevant secondary end-points, the possibility of treatment-by-treatment interactions, the relative burden and cost of the two interventions, the clinical interpretation of the adequacy of the delta, the possibility that ongoing randomization with a smaller delta might also allow a Statistical Trigger for superiority (with a small effect size) and the ordinal position of the equivalent pair within the domain.

In a domain that comprises three or more interventions, but in which two or more interventions are analyzed in a nested manner, the nested group may be combined for analyses of equivalence. Where compression converts a domain with three or more interventions into a domain with two interventions (and data continues to support equivalence of the compressed interventions) such a domain will be regarded as a two-intervention domain for the purposes of evaluation of Statistical Triggers for superiority, inferiority, and equivalence.

If a Platform Conclusion is reached, the ITSC will take responsibility to undertake Public Disclosure as soon as practicable with the dissemination of the research result via presentation or publication or both. There is no automated adaptation when equivalence is deemed to have occurred. Where appropriate each DSWG will produce an operational document, that is publicly accessible, that considers a range of plausible scenarios and provides guidance as to the actions that should occur in the event of a Statistical Trigger for equivalence for different pairs of interventions. If any of these documents are updated, previous versions will be archived but continue to be publicly accessible.

7.8.10. Analysis set for reporting

The primary analysis set that will be used for reporting a Public Disclosure will comprise all participants who are analyzed at the time the adaptive analysis results in the occurrence of a Statistical Trigger. As such, there will be some participants who have been randomized but are not included within this analysis, either because participants have not yet completed 90 days of follow up or because data for a participant who has completed 90 days of follow up has not yet been submitted. At the time of Public Disclosure, a secondary analysis will also be reported that comprises all participants who are evaluable through to the point at which there was cessation of randomization to the relevant comparator arms.

7.8.11. Simulations and statistical power

The design of the trial, at initiation, and in conjunction with the planning of the introduction of new interventions within a domain or of new domains, will be informed by the conduct of extensive

simulations using standard Monte Carlo methods. Simulations will be updated whenever a new intervention is added within a domain or whenever a new domain is added to the REMAP. However, simulations will not be updated when an intervention is removed from a domain because of the declaration of a Platform Conclusion that the intervention is inferior. These simulations will evaluate the impact of a range of plausible scenarios on the statistical properties of the trial.

Existing simulations indicate that when a single intervention in a domain with two interventions is beneficial, with a constant benefit for all participants, the power to be determined superior to the complement intervention as a function of its odds-ratio benefit is greater than 90% when there is at least a 25% odds-ratio decrease in the probability of mortality for the funded sample size of 6800 participants. The timing of these conclusions of superiority have a median time of less than 2000 participants. The probability that an intervention will be deemed superior to a complementary intervention when in truth the two are equal (a type I error) is typically less than 2.5%.

The results of detailed simulations of current domains is located in the Simulations Appendix which is maintained as an operational document that is publicly accessible and updated as required.

7.8.12. Updating model after monitoring

If any variable that contributes to the model is identified to be inaccurate at a monitoring visit, the data will be corrected and utilized for the next interim analysis. Any change to a previous statistical trigger will be reviewed by the DSMB to determine the implications. The DSMB will advise the ITSC if there is any material change in a Platform Conclusion which, if published, will be reported to the journal as an erratum.

7.9. Co-enrollment with other trials

Co-enrollment of participants in other research studies, including interventional trials, is strongly encouraged. The principle is that co-enrollment should always occur and is only not permitted when there is a clear threat to the validity of either study or it would materially influence the risk to participants. Decisions regarding co-enrollment with other trials will be made on a trial-by-trial basis. Where a potentially co-enrolling trial is being conducted in more than one region in which the REMAP is being conducted the decision regarding co-enrollment will lie with the ITSC. Where a potentially co-enrolling trial is being conducted only in one region in which the REMAP is being conducted the decision regarding co-enrollment will lie with the RMC. In all circumstances the ITSC and RMCs should liaise regarding decisions about co-enrollment. Decisions regarding co-enrollment

with other trials will be distributed to participating sites as an operational document and will not require or involve amendment of this protocol.

7.10. Cooperation between the REMAP and other trials with overlapping populations or interventions

During the life-time of the REMAP it is likely that there will be many other clinical trials that will have inclusion and exclusion criteria which would include participants who are eligible for this REMAP. This would include, obviously, trials with a primary interest in patients with CAP, but could also include patients with the Acute Respiratory Distress Syndrome (ARDS) and patients with severe sepsis or septic shock. Such trials will likely test a range of interventions, some of which may also be intervention options within this REMAP. This REMAP seeks to cooperate and coordinate maximally with other trials. Examples of such cooperation and coordination would include, but not be limited to, utilization of REMAP infrastructure for screening and recruitment to other trials, sharing of data collected by the REMAP, and sharing of allocation status so as to allow incorporation of allocation status within analysis models.

Where another trial is evaluating an intervention that is also included within this REMAP each site (or region) would need to establish rules that determine circumstances in which each trial has preference for recruitment. Where another trial and this REMAP are evaluating different interventions the extent to which cooperation is possible will also be determined by the extent to which the interventions are compatible, i.e. capable of having their effect evaluated independently within each trial.

7.11. Registry of non-randomized patients

In some locations, the REMAP may be nested within a registry. Where this occurs the operation of the registry, including eligibility criteria, ethical issues, and variables that will be collected, will be described in a separate Registry Appendix.

7.12. Criteria for termination of the trial

This trial is designed as a platform, allowing for continued research in patients with CAP admitted to an ICU. The platform allows for the study to be perpetual, with multiple different domains that can be evaluated at any one time, and over time. Frequent adaptive analyses are performed to determine whether the interventions under evaluation are still eligible for further testing or randomization should be stopped due to demonstrated inferiority, superiority or equivalence.

It is anticipated that after inclusion of the initially planned sample size, the study would continue to include additional participants and test additional domains and/or interventions until one of the following occurs:

- CAP is no longer deemed to be a public health problem
- The effectiveness and/or cost-effectiveness of all interventions are known and there are no new plausible interventions to test

Should the whole study be stopped, the end of trial is the date of the last scheduled follow up for any participant.

8. TRIAL CONDUCT

8.1. Site time-lines

8.1.1. Initiation of participation at a site

A range of options are available for the sequence of activities by which a site commences participation. The following outlines the default sequence of participation. The first level of participation is termed 'observational only'. During this stage eligible participants will be identified, preferably using a process of embedding with recognition by clinical staff and registration on the study website as soon as eligibility is recognized. Treatment decisions will be made by that site's clinical staff, and observational data using the study CRF or a sub-set of the CRF will be collected. The next level of participation is termed 'single domain'. During this time period, eligible participants are identified and randomized, but only within a single domain. The next level of participation is termed 'multiple domains' although this would typically include only the addition of a single domain at any one time-point with staggered introduction of additional domains. Decisions about transition through levels would be made by the site, in conjunction with the RCC, and would be influenced by factors including speed and accuracy of identification of eligible participants, accuracy of information provided at time of randomization, compliance with allocated treatment status, and timeliness of reporting of outcome variables that are used to determine RAR algorithms. It is also permissible to commence the trial with multiple domains being active at initiation.

8.1.1. Vanguard sites

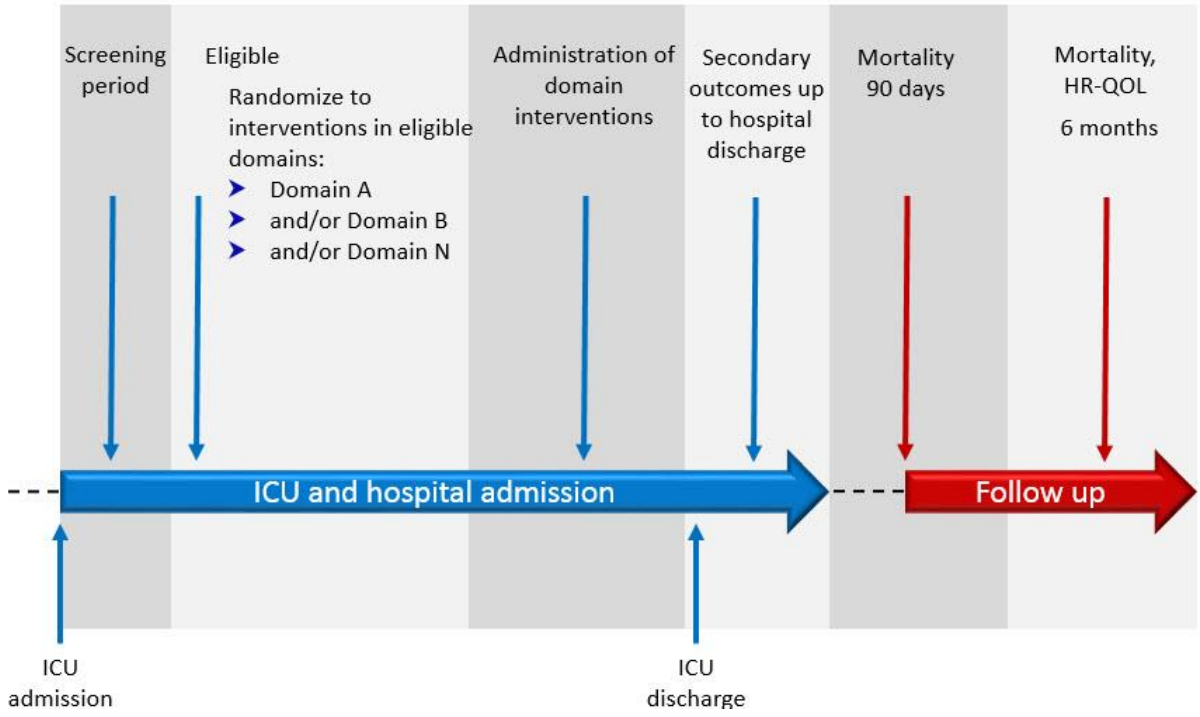
In each region or at the initiation of a new domain or both, the trial may consider commencing with only a small number of vanguard sites. The purpose of commencing the trial at vanguard sites is to learn about the effectiveness of different options for trial processes so that this information about

the most effective trial processes can be shared with subsequent non-vanguard sites. If a site is acting as a vanguard site this will be specified in any application for ethical approval at that site.

8.2. Summary of time-lines for recruited participants

A summary of the study and follow up schedule is outlined in Figure 6.

Figure 6: Study Procedures



8.3. Recruitment of participants including embedding

8.3.1. Embedding

The trial is designed to substitute allocation of treatment status by randomization where otherwise a treatment decision would have been made by clinical staff (where it is clinically and ethically appropriate to do so), and for this to occur at the time that the treatment decision would have otherwise been made. It is not essential that embedding is used to achieve recruitment and randomization but it is preferable and it is encouraged that participating sites work in conjunction with the trial team to achieve embedding wherever possible and as soon as possible.

The success of embedding can be evaluated by the proportion of eligible participants who are recruited and randomized, that recruitment and randomization occurs as soon as possible after

eligibility occurs, and that there is compliance with the allocated intervention. Successful embedding will enhance the internal and external validity of the results generated by the trial.

Each site, taking into account its own clinical work practices, will be asked to develop internal processes that will be used to achieve successful embedding. Wherever possible the RCC will advise and assist sites to achieve successful embedding. In brief, each participating site will identify their ICU admission procedures that occur with each new patient and then align these procedures to facilitate assessment of eligibility by clinical staff who provide routine care for each patient. This can be achieved through several methods including checklists on electronic Clinical Information Systems (eCIS).

8.3.2. Participant recruitment procedures at participating units

Once screened and identified as eligible the clinical staff (medical or nursing) or research staff will randomize the participant. Standard Operating Procedures (SOPs) will be developed to guide staff who undertake randomization. For example, in ICUs with an eCIS, an integrated website link may be used to allow direct access to the trial randomization webpage and, where possible, provide a summary (or direct population from the eCIS) of information that is required to be entered into the randomization web-site. To complement this system the research staff in each ICU will review patients admitted each day to assess the suitability of patients deemed not eligible out of hours, either because they were missed on screening or because the clinical situation has changed.

8.4. Treatment allocation

An eligible participant will receive a treatment allocation that is determined for all domains for which the participant is eligible to receive at least one of the available interventions. The management of the randomization process in each region is specified in each RSA. Information related to RAR is presented in the Interventions section of the Trial Design (Section 7.5.2) and in the Statistical Analysis Appendix. As noted elsewhere, all randomized allocation will be determined at the time of initial enrollment, but allocation status will not be made known for domains that operate using Randomization with Delayed Reveal (see Section 7.8.3.4). If the participants clinical condition changes and enters the state that confers eligibility this information will be provided to the randomization web-site and the allocation status will be revealed to the site.

8.5. Delivery of interventions

8.5.1. Treatment allocation and protocol adherence at participating units

In conjunction with participating sites, trial management staff will develop generic and site-specific documents that outline processes for implementation of and facilitate adherence with participant's allocated treatment status. Wherever possible these will seek to integrate trial processes with existing routine treatment processes to allow seamless adoption of the allocated treatments. For example, after randomization the clinical staff will be directed to use a pre-populated order sheet, necessary for the treating clinicians to authorize and for a bedside nursing staff to follow allocated treatment processes for that individual participant. It is intended that this process will not only reduce the complexity of ordering the study treatments but also reduce errors and increase adherence to the allocated protocol.

With respect to blinding, the default position within the REMAP is that treatments determined by randomization will be provided on an open-label basis. Where interventions are conducted on an open-label basis, all members of the ITSC and all other staff associated with a RCC of the trial will remain blinded until a Platform Conclusion is reported by the DSMB. Although the default is the provision of open-label treatments the blinding of treatment status is not precluded within the REMAP. Whether interventions are open-label or blinded will be specified in DSAs.

8.6. Unblinding of allocation status

Unblinding of any blinded treatment by site research staff or the treating clinician should only occur only in when it is deemed that knowledge of the actual treatment is essential for further management of the participant. A system for emergency unblinding will be provided in the DSA of any domain that includes interventions that are administered in a blinded fashion. Any unblinding process will ensure that the investigator can directly and rapidly unblind in an emergency situation. All unblindings and reasons as they occur will be documented in the CRF. Unblinding should not necessarily be a reason for study drug discontinuation.

8.7. Criteria for discontinuation of a participant in the trial

Trial participants may be discontinued from the trial entirely or from one or more domain-specific interventions according to predefined criteria for discontinuation. The criteria for discontinuation specific to each domain are specified in the relevant DSA.

Criteria for discontinuation from the REMAP interventions entirely include:

1. The treating clinician considers continued participation in the REMAP interventions are not deemed to be in the best interests of the patient
2. The participant or their Legal Representative requests withdrawal from ongoing participation in all REMAP interventions

In the case of discontinuation, the reasons for withdrawal will be documented. Consent to the use of study data, including data collected until the time of discontinuation and data to inform primary and secondary outcome data will be requested specifically from participants or their Legal Representative who request discontinuation. Following discontinuation of a REMAP intervention, participants will be treated according to standard ICU management. Participants who are withdrawn will not be replaced. All data will be analyzed using the ITT principle.

8.8. Concomitant care and co-interventions

All treatment decisions outside of those specified within the REMAP will be at the discretion of the treating clinician. Prespecified co-interventions related to specific domains will be recorded in the CRF and are outlined in the relevant DSAs.

8.9. Data collection

8.9.1. Principles of data collection

Streamlined data collection instruments and procedures will be used to minimize the workload in study sites. The CRF will be developed by the ITSC and made available to the participating sites as a paper and electronic CRF (eCRF) for ease of data collection. Data may be entered directly into the eCRF or first entered onto a paper copy of the CRF and entered subsequently into the eCRF. All data will be collected by trained staff who will have access to a comprehensive data dictionary. Information recorded in the CRF should accurately reflect the subject's medical/ hospital notes, must be completed as soon as it is made available, and must be collected from source data. The intent of this process is to improve the quality of the clinical study including being able to provide prompt feedback to the site staff on the progress, accuracy, and completeness of the data submitted. The eCRF will be web-based and accessible by a site or investigator specific password protected.

8.9.2. Variables to be collected

The generic variables to be collected for all domains in this REMAP are as detailed, indicatively, in the Core Protocol, below. Additional domain-specific variables are outlined in the relevant DSAs. Baseline variables are defined as at or before the time of randomization.

8.9.2.1. *Baseline and required for randomization*

- Overall REMAP Inclusion / exclusion check list
- Date and time of hospital admission
- Date and time of first ICU admission
- Domain-specific exclusion checklist
- Shock status
- Hypoxemia status
- Influenza status
- Pandemic status

8.9.2.2. *Baseline but not required for randomization*

- Demographic data (date of birth, age, sex, estimated body weight and height)
- Co-existing illnesses and risk factors for pneumonia
- Source of ICU admission
- Acute Physiology and Chronic Health Evaluation (APACHE) II variables
- Sequential Organ Failure Assessment (SOFA) variables
- Intervention allocation status within domains and randomization number
- Results of microbiological testing

8.9.2.3. *Daily from randomization until discharge from ICU or Day-28 whichever comes first*

- Hypotension and administration of vasopressors/inotropes
- Administration of dialysis
- Administration of invasive or non-invasive ventilation
- P:F ratio components

8.9.2.4. *ICU Outcome data*

- Date and time of ICU discharge
- Survival status at ICU discharge

- Dates of ICU readmission and discharge

8.9.2.5. *Hospital outcome data*

- Date and time of hospital discharge
- Survival status at hospital discharge
- Discharge destination
- Results of microbiological testing

8.9.2.6. *Antimicrobial Administration*

- Administration of antibiotic medications
- Administration of antiviral medications

8.9.2.7. *Outcome data*

At the discretion of the site, unless specified otherwise in a RSA or DSA, and collected by phone:

- Survival status at 90 days
- Survival status at 6 months
- HRQoL measured by EQ-5D at 6 months
- Disability status measured by WHODAS at 6 months and baseline information to interpret disability
- Opinions and beliefs regarding participation in research (reported at 6 months)

8.9.2.8. *Process-related outcomes*

- Time from index hospital admission to ICU admission
- Time from ICU admission to randomization
- Selected co-interventions
- Compliance with allocated intervention(s).

8.9.3. Data required to inform Response Adaptive Randomization

This REMAP will use frequent adaptive analyses and incorporate RAR. All variables used to inform RAR will be pre-specified. The key variables include:

1. Baseline and allocation status
    a. Unique trial-specific number
    b. Location (Country and Site code)

c. Date and time of randomization
d. Eligibility for each domain
e. Intervention allocation for each domain
f. Reveal status for each intervention allocation for each domain
g. Age category
h. Strata
    i. Shock or no shock
    ii. Influenza status
    iii. Pandemic strata
i. State
    i. Hypoxemia

2. Outcome
    a. All-cause mortality at 90 days
    b. Date of hospital discharge

Data fields required to inform the adaptive randomization process and Statistical Trigger will be pre-specified and will be required to be entered into the eCRF within 7 days of death and within 97 days of enrollment into the REMAP if the participant is alive at 90 days.

8.9.4. Blinding of outcome assessment

Wherever feasible outcome assessment will be undertaken by research staff who are blinded to allocation status. Such blinding will not be feasible for many outcomes, particularly those that occur while the participant is still admitted to an ICU or the hospital. However, the primary endpoint and key secondary endpoints are not variables that are open to interpretation and so accuracy will not be affected by outcome assessors not being blinded to allocation status.

8.10. Data management

8.10.1. Source Data

Source documents are where data are first recorded, and from which participants' eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarized into the eCRF), clinical and office charts, laboratory and pharmacy records, radiographs, and correspondence.

8.10.2. Confidentiality

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by a unique trial-specific number and/or code in any database, not by name. Information linking the participant's medical data to database materials will be maintained in a secure location at the participating site. This information will not be transmitted to the members of the ITSC, any DSWG, or RMC. The key to code and recode participant identifiers will only be accessible to local site investigators (research nurse and principal investigator) but not to members of the central study team. ICU and coded individual subject data and records will be held in strictest confidence by the site investigator and healthcare staff and by all central research staff, as permitted by law.

8.11. Quality assurance and monitoring

The trial will be conducted in accordance with the current approved protocol, Good Clinical Practice (GCP), relevant regulations and SOPs.

8.11.1. Plans for improving protocol adherence and complete data

Data entry and data management will be coordinated by the Regional Project Manager and the RCC, including programming and data management support.

Several procedures to ensure data quality and protocol standardization will help to minimize bias. These include:

- Start-up meeting for all research coordinators and investigators will be held prior to study commencement to ensure consistency in procedures;
- A detailed dictionary will define the data to be collected on the CRF;
- The data management center will perform timely validation of data, queries and corrections if errors are found during quality control checks;
- Data monitoring will occur as described below.

8.11.2. Data Monitoring

The study will be monitored by a representative of the RCC. A site initiation teleconference or visit will be conducted before site activation. Routine monitoring visits will be conducted the frequency of which will be determined by each site's rate of recruitment. Email and telephone communication will supplement site visits.

A monitoring report will be prepared following each visit and reviewed by the RMC if appropriate. A follow up letter will be sent to the principal investigator and research coordinator at the site and will be filed in the site investigator file.

Medical records, any other relevant source documents and the site investigator files must be made available to the representative of the RCC for these monitoring visits during the course of the study and at the completion of the study as needed.

Domain-specific monitoring and protocol adherence issues are addressed in each DSA.

8.12. Data safety and monitoring board

A single DSMB will take responsibility for the trial in all regions in which it is conducted. The DSMB compiled for this study will consist of 5-7 members; the chair has been selected to have expertise in clinical trial methodology, and to have experience with adaptive clinical trial design. Additional medical, statistical, and other experts will be selected to ensure all necessary expertise to oversee a trial of this complexity and scope. The DSMB will conduct its activities in accordance with a separate Charter; the Charter must be approved by the DSMB, and ITSC prior to the initiation of the trial. The DSMB will be unblinded to ensure the highest quality oversight of the trial, in accordance with current recommendations of regulatory authorities.

The DSMB will review received frequent updates of the trial's adaptive analyses from the SAC. The role of the DSMB will be to ensure that the pre-specified trial algorithm is being implemented as designed, that the design remains appropriate from a scientific and ethical point of view, to confirm when a Statistical Trigger has been reached, and to either reach or recommend that a Platform Conclusion has been reached, as outlined in Section 7.8.9. Trial enrollment and conduct will be continuous.

The DSMB will not make design decisions. If the DSMB believes the trial's algorithms are no longer acceptable from an ethical, safety, or scientific point of view it will make recommendations to the ITSC which has ultimate decision-making authority regarding the trial design. Where the DSMB and the SAC agree on a temporary deviation from the study protocol for safety reasons, they are not required to inform the ITSC of this decision. If the DSMB and SAC agree that a permanent change is necessary, the chairs of the DSMB, SAC and ITSC will meet to discuss the best way to proceed to ensure patient safety and the scientific integrity of the trial. Where the SAC and DSMB disagree on the need to deviate from the pre-specified trial design, the DSMB must inform the ITSC of their recommendations and the rationale for these.

8.13. Safety monitoring and reporting

8.13.1. Principles

The principles used in the conduct of safety monitoring and reporting in this trial are those outlined by Cook *et al.* in the manuscript "Serious adverse events in academic critical care research". (Cook et al., 2008) A high proportion of critically ill patients who will be enrolled in this trial will experience mortality or substantial morbidity. The case-fatality proportion for critically ill patients with CAP is likely to be in the order of 20 to 30% and high proportions of patients will have one or both of laboratory abnormalities or complications of critical illness and its treatment. Patients who are critically ill, irrespective of whether or not they are enrolled in a trial, will typically experience multiple events that would meet the conventional definition of a Serious Adverse Event (SAE).

Trials involving vulnerable populations must have research oversight that protects patient safety and patient rights and also ensures that there can be public trust that the trial is conducted in a manner that safeguards the welfare of participants. The strategy outlined for the definition, attribution, and reporting of SAEs in this trial is designed to achieve these goals but does so in a way that seeks to avoid the reporting of events that are likely to be part of the course of the illness or events that are recognized as important by their incorporation as trial endpoints.

8.13.2. Definition

In accordance with accepted standards a SAE is defined as an event that is fatal, life-threatening, results in (or may result) in disability that is long-lasting and significant, or results in a birth defect or congenital anomaly.

8.13.3. Reporting Procedures for Serious Adverse Events

The trial endpoints, as outlined in the Core Protocol and as specified in DSAs, are designed to measure the vast majority of events that might otherwise constitute an SAE. In particular, SAEs that might be attributable to specific interventions are included as secondary endpoints in each DSA but are recorded only for participants who are enrolled in that domain. If required, additional clarification of issues related to the identification of SAEs that are relevant to a specific domain will be described in the DSA. Generally, only SAEs that are not trial-end points require reporting. However, any SAE that is considered by the site-investigator to be attributable to a study intervention or study participation should be reported (Section 8.13.4). Where an SAE is not a trial end point it should be reported only where, in the opinion of the site-investigator, the event might

reasonably have occurred as consequence of a study intervention or study participation (Section 8.13.4).

Events that meet the definition of an SAE, require reporting in accordance with the criteria outlined above, and occur between trial enrollment but before hospital discharge will be reported to a RCC. These SAEs should be reported to a RCC within 72 hours of trial staff becoming aware of the event, unless otherwise specified in a RSA. The minimum information that will be reported will comprise:

- Unique trial-specific number
- Date(s) of the event
- Nature of the event, including its outcome, and the rationale for attribution to a trial intervention
- Whether treatment was required for the event and, if so, what treatment was administered

8.13.4. Attribution of serious events to study interventions

It is likely that many participants within the trial will experience events that could be attributed to one or more study interventions. However, it will often be difficult to distinguish, in real-time, between events that occur as a consequence of critical illness and treatments that are not specified by the trial, and interventions specified by the trial. Site investigators should exercise caution in attributing events to study interventions. However, the standard that should be applied to determine whether SAEs are attributable to study interventions in this trial is that it is possible, probable, or certain that there is a direct link between a trial intervention and the SAE or the SAE is not considered to be a normal feature of the evolution of critical illness and its treatment.

8.13.5. Attribution of a death to study interventions or study participation

Critically ill patients who will be enrolled in this trial are at high risk of death. The primary endpoint of the trial is mortality and the objective of the trial is to identify differences in the primary endpoint that can be attributed to treatment allocation which will often include treatments that are believed to be or known to be safe and effective but for which it is not known whether some treatments are more effective than others. Where the trial evaluates interactions that are novel and not part of usual standard care the threshold for considering attribution to the novel experimental intervention should be lower than if an intervention is already in widespread use and its safety profile has already been established.

9. GOVERNANCE AND ETHICAL CONSIDERATIONS

9.1. Management of participating sites and trial coordination

Each region will have a RCC. Each RCC will take primary responsibility for the management of participating sites, data management for those sites, and provide web-based randomization for sites in its region. The processes by which each RCC will provide trial management and coordination is set out in each RSA.

9.2. Ethics and regulatory issues

9.2.1. Guiding principles

The study will be conducted according to the principles of the latest version of the Declaration of Helsinki (version Fortaleza 2013) and in accordance with all relevant local ethical, regulatory, and legal requirements as specified in each RSA.

9.2.2. Ethical issues relevant to this study

Patients who will be eligible for this study are critically ill, and many eligible patients will be receiving sedative medications for comfort, safety and to facilitate standard life saving ICU procedures. In patients who are not necessarily receiving sedative medications, the presence of critical illness, itself, leads commonly to an altered mental state that will affect the patient's mental capacity. The presence of these factors will mean that most patients who are eligible for the study will not be able to provide prospective consent for participation. Additionally, many interventions within this trial must be initiated urgently, either because there is an immediate time critical imperative to initiate the intervention or because the most valid evaluation of the intervention occurs if the trial intervention is initiated at the same time-point as would occur in clinical practice.

The broad approach regarding consent that will be used in this study are as follows:

- Patients who, in the opinion of the treating clinician, are competent to consent will be provided with information about the trial and invited to participate
- The vast majority of patients who are eligible for the REMAP will not be competent to consent. For such patients, and as permitted by local laws and requirements for ethical approval:
    - For domains in which all interventions available at the participating site are regarded as being part of the spectrum of acceptable standard care by the

clinicians at that site, entry to the study is preferred to be via waiver-of-consent or some form of delayed consent. If required by local laws or ethical requirements and alternative to this pathway will be participation in conjunction with the agreement of an authorized representative of the participant.

- For domains in which at least one intervention available at the participating site is regarded as experimental or not part of the spectrum of acceptable standard care then prospective agreement by an authorized representative will be required. An exception to this principle is recognized when there is a time-imperative to commence the intervention which would routinely preclude obtaining the prospective agreement by an authorized representative.
- For domains in which eligibility may develop after initial enrollment in the trial it is permissible to obtain contingent consent from the participant or contingent agreement from an authorized representative, i.e. there is contingent approval to randomize the participant if the participant meets eligibility criteria for a domain subsequently.
- Where any participant is enrolled without having provided their own consent, the participant's authorized representative will be informed as soon as appropriate and informed of processes to cease trial participation. If required by local laws or processes for ethical approval, the authorized representative will be asked to provide agreement to on-going participation. In undertaking these trial processes research staff will be cognizant of the need to avoid unnecessary distress or create unnecessary confusion for authorized representatives and all other persons who have an interest in the participant's welfare.
- Where any participant is enrolled without having provided their own consent, the participant should be informed of their enrollment after regaining competency, in accordance with local practice and jurisdictional requirements. Where any participant is enrolled and does not regain competency (due to their death or neurological impairment) the default position, subject to local laws and ethical review processes, will be that the enrolled person will continue to be a participant in the trial.

It should be noted that once RAR is initiated, participants within the REMAP, on average, derive benefit from participation. As a consequence of RAR participants are more likely to be allocated to the interventions within each domain that are more likely to result in better outcomes.

9.2.3. Approvals

The protocol, consent form(s) and participant and/or authorized representative information sheet(s) will be submitted to an appropriate ethical review body at each participating institution and, as required, to any additional regulatory authorities. Written approval to commence the study is required for all relevant ethical and regulatory bodies.

9.3. Protocol modifications

9.3.1. Amendments

A "substantial amendment" is defined as an amendment to one or more of the Core Protocol, DSA, or RSA that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial;
- the quality or safety of any intervention used in the trial;
- cessation of any intervention or domain for any reason;
- the addition of any new intervention within a domain; or
- the addition of new interventions within a new domain

All substantial amendments to the original approved documents, including all modifications of interventions available within a domain and the addition of interventions within a new domain will be submitted for approval to all relevant ethical and regulatory review bodies that were required for original approvals. Non-substantial amendments will not be notified to such review bodies, but will be recorded and filed by the trial sponsors.

Where the cessation of any intervention or any domain occurs for any reason, this is an operational issue and randomization to that intervention or domain will no longer be available. Cessation of an intervention or domain, either entirely, or within a prespecified subgroup, will be reported to all relevant regulatory bodies.

9.4. Confidentiality

The principles of confidentiality that will apply to this trial, are that all trial staff will ensure that the confidentiality of all participants information will be maintained and preserved at all times. The participants will be identified only by a unique trial-specific number on all documents and electronic databases that contain any information specific to the participating individual. Each site will maintain a separate file that links each participant's unique trial-specific number to the participant's name and other identifying information such as date of birth, address, and other contact information. No other information will be maintained in the file that links the participant unique trial-specific number to participant identifying information.

9.5. Declarations of interest

All trial staff will be required to declare and update all interests that might or might be seen to influence one or both of the conduct of the trial or the interpretation of results. 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.

9.6. Post-trial care

The trial has no responsibility for the ongoing management or care of participants following the cessation of all trial specified interventions.

9.7. Communication

9.7.1. Reporting

Each participating site will comply with all local reporting requirements, as specified by that site's institution.

Should the entire trial be terminated, all relevant local ethical and regulatory bodies will be informed within 90 days after the end of the study. The end of the study is defined as the last participant's last follow-up.

9.7.2. Communication of trial results

Trial results will be communicated by presentation and publication.

9.8. Publication policy

Manuscript(s) and abstract(s) resulting from the data collected during this study will be prepared by the corresponding DSWG. Where results are influenced by interaction between domains, the DSWG for both domains will take responsibility for preparation of manuscripts and abstracts. All manuscripts and abstracts reporting trial results that are prepared by one or more DSWGs must be submitted to and approved by the ITSC before submission.

Site investigators will not publish or present interim or definite results, including but not restricted to oral presentations. The role of site investigators and research coordinators at participating sites will be acknowledged by their names being listed as collaborators. Where required publications will comply with the publication policies of clinical trials groups that have endorsed or supported the study.

9.9. Data access and ownership

9.9.1. Data ownership

All data are owned by the responsible sponsor under the custodianship of the ITSC. As the trial is intended to be perpetual, all data will be retained indefinitely.

9.9.2. Access to Data

Direct access will be granted to authorized representatives from ITSC, sponsors, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. The trial will comply with all relevant jurisdictional and academic requirements relating to access to data, as apply at the time that the data are generated. Ownership and access to data where a commercial organization is involved in the trial (for example by provision of goods or services that are tested within a domain) will be set out in a contract between trial sponsors and that commercial organization.

The trial will not enter into a contract with a commercial organization unless the contract specifies that:

- There is complete academic independence with regard to the design and conduct of all aspects of the trial including analysis and reporting of trial results

- May agree to provide a pre-publication version of presentations or manuscripts to a commercial organization but that the commercial organization has no authority to prevent or modify presentation or publication
- That all data are owned by the trial and the commercial organization has no authority to access data

9.10. Consent form

Template information and consent forms will be provided to participating sites as an operational document.

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

PANDEMIC APPENDIX TO THE CORE PROTOCOL (REMAP-COVID)

REMAP-CAP Pandemic Appendix to the Core Protocol Version 2.0 dated 18 May 2020

Summary

Background: REMAP-CAP is an adaptive platform trial that evaluates multiple aspects of care of patients who are admitted to an Intensive Care Unit (ICU) with severe Community Acquired Pneumonia. It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired Pneumonia with concomitant admission to an ICU. Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe Community Acquired Pneumonia (CAP) and admission to an Intensive Care Unit[1-3]. Admission to an ICU may occur at the time of first presentation to a hospital or may be preceded by admission to a non-ICU ward or floor. For patients admitted to a non-ICU ward there is an opportunity to intervene to prevent the development of severe CAP. A pandemic of respiratory infection is much more likely to be caused by a virus than a bacterium. Differences in trial design may be required for influenza, viruses which are known to result in periodic but unpredictable pandemics, in comparison with other viruses, such as Coronaviruses that may also have pandemic potential.

Previous pandemics and outbreaks of emerging infectious diseases have outlined the urgent need for evidence, preferably from Randomized Clinical Trials, to guide best treatment. However, there are substantial challenges associated with being able to organize such trials when the time of onset of a pandemic and its exact nature are unpredictable[4-6]. As an adaptive platform trial that enrolls patients during the interpandemic period, REMAP-CAP is ideally positioned to adapt, in the event of a respiratory pandemic, to evaluate existing potential as well as novel treatment approaches.

The precise nature of a respiratory pandemic cannot be known in advance. The Pandemic Appendix to the Core Protocol lists potential adaptations to trial design and management that are generic, in that they will occur irrespective of the nature of the pandemic, as well as adaptations that are possible, depending on the nature of the pandemic, and the process for determining which adaptations will be applied.

The Pandemic Appendix to the Core Protocol also achieves alignment with a separate document, REMAP-COVID Core Protocol, which comprises only those elements of the Core Protocol of REMAP-CAP and the Pandemic Appendix that applies to the COVID-19 pandemic. For the COVID-19 pandemic, a site can utilize either the REMAP-CAP Core Protocol combined with the Pandemic Appendix to the Core Protocol, or REMAP-COVID Core Protocol. Both sets of documents specify identical methods and data requirements. Data derived from sites using either set of documents is

analyzed in the same pandemic statistical model. A single site must use either REMAP-COVID Core Protocol or REMAP-CAP Core Protocol with this associated pandemic appendix.

The objective of the Pandemic Appendix to the Core Protocol (PAtC) is to describe the adaptations to the Core Protocol that would apply during a pandemic, including how analyses of domains already operative during the interpandemic period as well as domains that are pandemic-specific, will be integrated during a pandemic. This includes scientific, as well as governance and logistic aspects.

Aim: The primary objective of the REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for patients admitted to a hospital with acute illness due to suspected or proven pandemic infection, as defined by the pandemic primary end-point.

Methods: The methods that will be utilized during a pandemic are those in the Core Protocol but with potential for changes to the primary end-point, frequency and process for adaptive analyses, and determination of which domains will be analyzed using a statistical model that includes data from patients with proven or suspected pandemic infection. During a pandemic, patients who are neither suspected nor proven to have pandemic infection and for certain pre-existing domains, will continue to be analyzed using the statistical model that is outlined in the Core Protocol that was operating during the pre-pandemic period. Depending on the characteristics of a pandemic, one or more interpandemic domains may be analyzed within the pandemic statistical model and one or more pandemic-specific domains may be commenced for patients with suspected or proven pandemic infection.

Lay description

REMAP-CAP is a global trial examining the best treatments for community-acquired pneumonia. In the setting of a pandemic that causes life-threatening respiratory infection, some key aspects of the study will be changed to integrate new interventions into the trial, evaluate existing interventions within the trial specifically in patients with pandemic infection, alter trial governance, and provide time-critical data for public health. This will allow the platform to identify which treatments work best for patients during a pandemic.

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1. ABBREVIATIONS

CAP	Community-Acquired Pneumonia
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle-Eastern Respiratory Syndrome Coronavirus
NAI	Neuraminidase inhibitors
PAtC	Pandemic Appendix to the Core Protocol
PINSNP	Pandemic infection is neither suspected nor proven
PISOP	Pandemic infection is either suspected or proven
PWG	Pandemic Working Group
RAR	Response Adaptive Randomization
REMAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RCC	Regional Coordinating Center
RCT	Randomized Controlled Trial
RSA	Region Specific Appendix
SAC	Statistical Analysis Committee
SARS	Severe 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), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), a Registry Appendix, this Pandemic Appendix to the Core Protocol, and multiple Regions-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 of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis, because the analysis model will change over time in accordance with the domain and intervention trial adaptations, but this information is contained in the Statistical Analysis Appendix. 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 an 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.

3. PANDEMIC APPENDIX TO THE CORE PROTOCOL VERSION

The version of the Pandemic Appendix to the Core Protocol is in this document's header and on the cover page.

3.1. Version History

Version 1: Approved by the Pandemic Working Group on 31st January, 2020

Version 1.1: Approved by the Pandemic Working Group on 12th February, 2020

Version 2.0: Approved by the Pandemic Working Group on 18th May, 2020

4. PANDEMIC APPENDIX TO THE CORE PROTOCOL GOVERNANCE

The study administration structure is outlined in the Core Protocol. As outlined in the Core Protocol, a Pandemic Working Group (PWG) is established and works in conjunction with the International Trial Steering Committee (ITSC), to take responsibility for the Pandemic Appendix to the Core Protocol (PAtC) and to advise on operational aspects following emergence of a pandemic.

4.1. Pandemic Working Group

The responsibility of the PWG is to maintain and update this PAtC and to advise the ITSC regarding application of the PAtC during a pandemic. The PWG will liaise with individuals and organizations that are external to REMAP-CAP as required. Membership of the PWG is flexible. The core membership is listed but additional members can be added at any time and as required.

Chair: The Chair of the ITSC will Chair the Pandemic Working Group

Members: Prof. Derek Angus

Prof. Yaseen Arabi

Prof. Richard Beasley

A/Prof. Scott Berry

Prof. Frank Brunkhorst

Dr. Lennie Derde

Dr. Robert Fowler

Prof. Anthony Gordon

Mr. Cameron Green

Dr. Ed Litton

Prof. John Marshall

Dr. Colin McArthur

A/Prof Bryan McVerry

Dr. Srinivas Murthy

Prof. Alistair Nichol

Ms. Jane Parker

Prof. Kathy Rowan

Prof. Tim Uyeki

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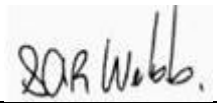
5. PANDEMIC WORKING GROUP AUTHORISATION

The Pandemic Working Group have read the appendix and authorize it as the official Pandemic Appendix to the Core Protocol for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair  Date 18th May, 2020

Steve Webb

6. BACKGROUND AND RATIONALE

6.1. Introduction

It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as life-threatening respiratory infection including Severe Acute Respiratory illness and severe Community Acquired Pneumonia (CAP) with concomitant admission to hospital, and for some patients, admission to an Intensive Care Unit (ICU). Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe CAP and ICU admission[1-3]. A pandemic of respiratory infection is much more likely to be caused by a virus than a bacterium and, among viruses a distinction should be drawn between influenza, which is known to result in periodic but unpredictable pandemics, and other viruses, such as Coronaviruses, that may have pandemic potential, as the features of trial design may be different.

Previous pandemics and outbreaks of emerging infectious diseases have outlined the urgent need for evidence, preferably from Randomized Controlled Trials (RCTs), to guide best treatment. However, there are substantial challenges associated with being able to organize such trials when the time of onset of a pandemic and its exact nature are unpredictable[4-6]. As an adaptive platform trial that enrolls patients during the interpandemic period, REMAP-CAP is ideally positioned to adapt, in the event of a respiratory pandemic, to evaluate existing treatments as well as novel approaches.

One of the challenges associated with planning clinical trials during a pandemic is that the precise nature of the infecting organism, clinical consequences, and suitable interventions (particularly those that are pathogen-specific) cannot be reliably known in advance. The speed of clinical progression, from initial infection to life-threatening severe respiratory infection is another feature

that cannot be reliably known in advance. It is likely that a proportion of patients will present with severe CAP but other patients may present to medical attention with illness that is less severe, but remain at risk of progression to severe illness. Patients who require hospital admission, but have less severe illness are a particularly important group, because early intervention at this stage of illness may prevent progression to life-threatening illness. It is also possible that proposed treatment interventions may have differential treatment effect depending on the level of illness severity at the time that treatment is commenced, including treatment effects that are divergent. Nevertheless, a range of scenarios can be anticipated and used to provide direction and guidance regarding the most appropriate research response.

The most likely organism responsible for a respiratory pandemic is a novel influenza virus that has undergone antigenic shift[7]; the most recent influenza pandemic occurred during 2009-2010. In recent years, there have been outbreaks of severe Community Acquired Pneumonia due to novel Coronaviruses which resulted in the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003 and the Middle-Eastern Respiratory Syndrome Coronavirus (MERS-CoV) outbreak that commenced in 2012. SARS-CoV-2 is the cause of a pandemic of severe respiratory disease (COVID-19), including pneumonia, that commenced in 2019. The pre-specified adaptations to REMAP-CAP will need to be different for influenza in comparison to a non-influenza pandemic pathogen.

6.2. Pandemic research preparedness

6.2.1. Introduction

The conceptual approach to pandemic preparedness has been influenced substantially by the occurrence of the 2009 Influenza A H1N1(2009)pdm pandemic, outbreaks of SARS and MERS-CoV, the Zika pandemic, and Ebola virus disease outbreaks in West Africa[8]. A broad conclusion from these outbreaks is that it is likely that high quality research can change the incidence and consequences of the epidemic but that such research is extremely difficult because planning of research only commences after the discovery of the epidemic. As a consequence, researchers and organizations interested in developing improved processes for research have identified three key elements to facilitate time-critical research about an epidemic. These elements are that the research must be pre-planned, pre-approved, and practiced[9,10]. REMAP-CAP and, in particular, the PAtC, is an attempt to establish these pre-requisites and to guide treatment for patients who may be critically ill with pneumonia as a consequence of infection with a pandemic organism.

The World Health Organization (WHO) has recommended establishing and strengthening outbreak-ready, multi-center clinical research networks in geographically diverse regions to facilitate research

during pandemics.[11] It has also recommended testing of protocols during interpandemic periods and stressed the value of such clinical research consortia in collecting and distributing information during a future pandemic.

6.2.2. Pre-planned

Pre-planned means that the trial protocol is written and that the trial processes related to project management, screening, recruitment, delivery of interventions, data collection, data management, analysis, and reporting are all in place. The PAtC, in conjunction with the existing REMAP-CAP protocol documents and trial processes, will mean that all aspects that can be pre-planned have been.

6.2.3. Pre-approved

The PAtC is a key component of the of the pre-approval strategy. The availability of this document allows ethics review boards, hospital research governance staff, existing and potential sites to understand and approve the study processes that would be implemented during a pandemic. Where different options need to exist, depending on the nature of the pandemic, these are pre-specified, as much as possible. Any unanticipated substantive deviation from this Appendix would be subject to an amendment, hopefully expedited, in the event of a pandemic. The PAtC, like the Core Protocol, does not specify any interventions that are evaluated within the REMAP. It is highly likely that one or more research questions (in domains already approved during the interpandemic period) will be relevant specifically in patients with severe respiratory disease including pneumonia caused by the pandemic infection. The PAtC allows these questions to continue to be answered specifically in patients with pandemic infection, where appropriate, using Bayesian prior probabilities derived from patients already enrolled during the interpandemic period. It is proposed to develop ‘sleeping domains’, which could be activated if appropriate during a pandemic, as well as retain the option of developing one or more completely new domains following the emergence of pandemic, which would require separate ethical approval and contracts with participating sites.

This strategy, as part of the study design, offers an ethically, clinically and legally acceptable mechanism for research in the context of a pandemic that can be initiated rapidly.

There are two further aspects relevant to ethical approval of the PAtC. The first is that existing or pandemic-specific domains of REMAP-CAP may include an intervention that specifies no treatment within that domain (noting that the Core Protocol specifies that all additional standard care is provided with treatment decisions being made by the treating clinician). This is clinically and

ethically appropriate as the response of critically ill patients to a range of different treatments has proven to be unpredictable. There are many examples of treatments that have resulted in harm[12] and situations in which surrogate outcome measures were not reliable indicators of improvement in patient-centered outcomes. As such, there should not be any presumption that it is better for patients to receive active interventions.

The second is the capacity to apply Response Adaptive Randomization (RAR) within the REMAP. As outlined in the Core Protocol, RAR results in an increasing proportion of patients being allocated to any intervention within a domain that has a higher probability of being superior with that proportion increasing as statistical confidence accrues. Participants within REMAP-CAP during a pandemic may be able to benefit from information about the relative effectiveness of interventions that is not in the public domain and not available to patients who are not participants in REMAP-CAP. As outlined in the Core Protocol, any intervention confirmed to be superior within the REMAP is then implemented by application of a RAR proportion that is equal to 100%. RAR will be implemented for pandemic patients as soon as sufficient data have accrued and operational implementation is feasible.

6.2.4. Practiced

REMAP-CAP will be recruiting during the interpandemic period in multiple countries in both Southern and Northern Hemispheres with the support of several Regional Coordinating Centers. This research activity, during the interpandemic period, ensures that sites, site training, project management, data management, analysis processes, and trial governance are functional and practiced. Furthermore, the eligibility process and delivery of trial interventions are optimized for embedding which allows study processes to occur within minimal disruption to the delivery of clinical care, which may well be under substantial strain during a pandemic. There is already extensive experience with the Case Report Form (CRF) that is used and will continue to be used during a pandemic.

6.2.5. Implications of REMAP design during a pandemic

6.2.5.1. Time-critical generation of evidence

A pandemic will likely result in a large number of affected persons with cases occurring over a short period of time, perhaps as short as a few months. Conventional clinical trials that utilize frequentist statistical techniques require a fixed sample size with limited capacity to analyze the results of the trial until recruitment is completed. The setting of the sample size requires an estimate of the size of the treatment effect and it is known that the assumptions that are made in setting the size of the

treatment effect are often incorrect[13,14]. A frequentist trial that over-estimates the size of the treatment effect may conclude without reaching a valid conclusion, whereas one that under-estimates the size of the treatment effect is delayed in providing time-critical information that the treatment is even more effective than estimated.

REMAP-CAP utilizes Bayesian statistical methods which allow frequent adaptive analyses to occur. This will ensure that time-critical information about the effectiveness of treatment interventions is not delayed unnecessarily. The REMAP design is particularly suited to pandemics because it requires no pre-trial assumptions about the size of the treatment effect and will allow dissemination of evidence as soon as possible. Furthermore, as the trial progresses during a pandemic the Data Safety Monitoring Board (DSMB) has access to information from adaptive analyses that may not achieve thresholds to allow reporting as a Platform Conclusion but may be relevant to public health which, under appropriate circumstances, can be shared with public health authorities and the DSMBs of other trials evaluating the same or similar interventions without threatening the scientific validity of the ongoing trial.

6.2.5.2. Multifactorial design and evaluation of interactions

If there are multiple interventions, each of which may have independent effects on outcome, the multi-factorial nature of a REMAP allows these to be evaluated simultaneously, rather than in series or in separate parallel trials (see *Figure 1*). This design feature contributes to efficiency and is also anticipated to result in more clinical evidence being generated more rapidly during a time-critical pandemic.

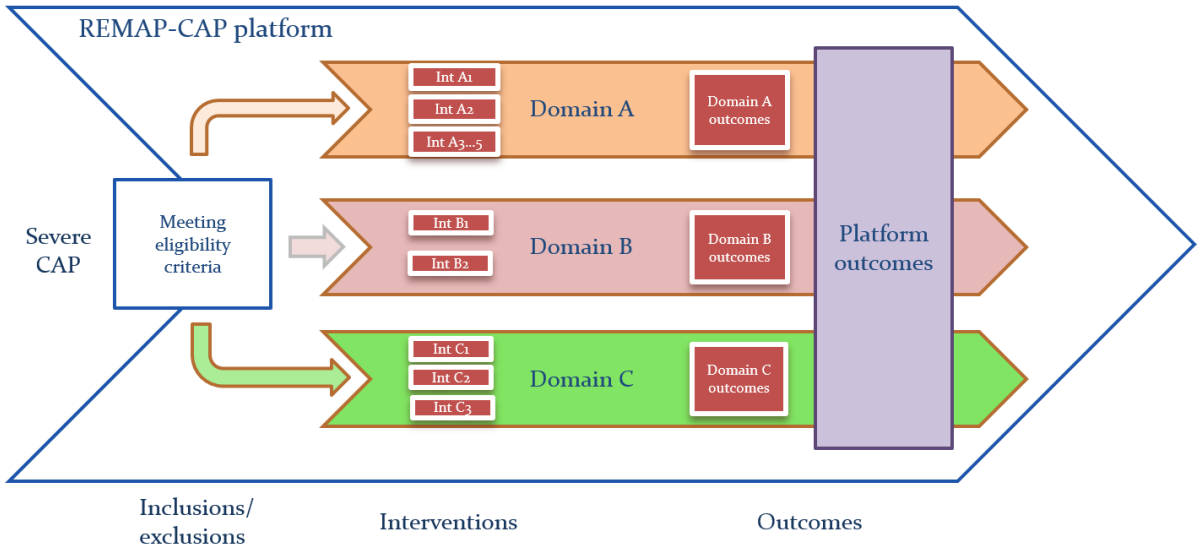


Figure 1. The multifactorial structure of REMAP-CAP

Furthermore, where pre-specified, the statistical model utilized in REMAP-CAP will allow estimation of treatment effect of interventions that may be contingent on other treatment assignments within the pandemic component of the REMAP. For example, it is plausible that the effectiveness of an intervention for immune modulation is dependent on co-delivery of an agent that is effective at inhibiting growth or replication of the pathogen. Conventional trials, in which only a single domain of treatment is evaluated, are not capable of detecting this type of treatment-by-treatment interaction, and thereby unable to identify the best overall treatment strategy for these patients.

6.2.6. Setting of research priorities

In 2017, the WHO outlined the research priorities for a pandemic that was caused by a novel strain of influenza. These priorities were:

- Research on the effectiveness of empirical treatment with oseltamivir and other neuraminidase inhibitors (NAI) in critically ill patients, including placebo-controlled trials during seasonal as well as pandemic influenza.
- Investigating alternative strategies to NAI monotherapy to increase antiviral potency and improve clinical outcomes.
- Research on immune-modulatory strategies in severe influenza, including corticosteroids and macrolides.
- A need for high quality data on the effectiveness of most aspects of supportive care related to influenza.
- A need to assess the roles of virologic factors (e.g. replication sites, duration and viral load levels) in larger numbers of patients (including critically ill patients) in causing severe disease and associated complications, linking them to clinical outcomes.

REMAP-CAP is not able to meet all of these requirements but is well suited to evaluate the effectiveness of antiviral therapies active against influenza, immune modulatory strategies and different aspects of supportive care[15]. Identical or similar research questions would exist for any pandemic caused by an organism that was not influenza and REMAP-CAP has also similar capabilities in this scenario.

6.3. WHO endorsement

REMAP-CAP has been designated by the WHO as a Pandemic Special Study. Under this designation, it has been tasked with helping answer crucial questions during a declared pandemic, as listed above. This designation ensures that knowledge translation of clinical trial results can occur directly

with policymakers and public health officials for rapid implementation around the globe. It ensures that results generated from REMAP-CAP during a declared pandemic can be translated in an efficient and transparent manner to benefit affected patients.

7. ADAPTATION OF REMAP-CAP DURING A PANDEMIC

This PAtC supplements the Core Protocol during a pandemic including deactivation at the conclusion of a pandemic. Decisions regarding the operationalization of the Pandemic Appendix to the Core Protocol are made by the ITSC with advice from the PWG (see Section 8.1). The Appendix sets out all potential adaptations of the Core Protocol and unless otherwise specified, all other aspects of the Core Protocol remain active. Activation of the PAtC will be advised to the DSMB with specification of the selected operational characteristics.

7.1. Objectives

The primary objective of this REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for adult patients admitted to hospital with acute illness due to suspected or proven pandemic infection, as defined by the pandemic primary end-point.

The secondary objective is to determine the effect of a range of interventions on additional endpoints, including endpoints developed by the World Health Organization and adopted core outcome sets.

7.2. Study setting: definition of an ICU and relationship of setting to severity of illness

During the interpandemic period, the REMAP recruits only participants who are admitted to an ICU, and a combination of admission to ICU as well as provision of treatments to support failed organs is used to define severity and eligibility. During a pandemic, there are several factors that may influence the relationship between admission to an ICU and severity of illness. Firstly, there may be insufficient ICU beds available to care for all critically ill patients. This may result in provision of advanced organ support occurring in locations that do not usually provide ICU-level care. During a pandemic, such a location is referred to as a re-purposed ICU. However, a re-purposed ICU needs to be distinguished from a usual hospital ward that is capable of providing some forms of organ support, such as non-invasive ventilation. During a pandemic, there may be substantial delays in transferring a patient from an emergency department to either a ward or an ICU (or a re-purposed ICU). Patients in an emergency department who have been accepted for admission to an ICU are regarded as being admitted to an ICU. Patients in an emergency department who have been

accepted for admission to a ward are regarded as being admitted to a ward. Secondly, patients who are not critically ill may be treated on an ICU for reasons that are not related to severity of illness, such as access to single rooms to achieve objectives related to infection control and prevention. This can influence both admission as well as discharge practices. Thirdly, the threshold at which support for failed organs is provided may be influenced by infection control practices. For example, some forms of respiratory support may be withheld because of concerns related to the risk that staff who are caring for patients may acquire the infection.

To minimize these issues, during a pandemic, the primary determinant of severity is the provision of ICU-level care, which can be interpreted in conjunction with the physical location in which care is being provided. Determination of severity may also take into account a decision to withhold some form of organ failure support that would otherwise have be provided. Where a definition of an ICU is needed, at sites at which the pandemic stratum (see below) has been activated, an area within the hospital that is repurposed so as to be able to deliver one or more of the qualifying organ failure supports specified in the Core Protocol (non-invasive ventilation, invasive ventilation, and vasopressor therapy) will meet the definition of an Intensive Care Unit. It is preferred in such circumstances that the patient is under the care of a specialist who is trained in the provision of critical care, but this is not an essential requirement. A respiratory or other ward that provides non-invasive ventilation (including oxygen therapy delivered by high flow nasal cannula) and continues to do so during a pandemic, will not, generally, meet the definition of an ICU, particularly if the patient is not under the care of a specialist who is trained in the provision of critical care.

In some DSAs, an exclusion criteria is applied to only permit enrollment during a time-window that commences with ICU admission. For the reasons noted above, this may be operationalized using a time-window, of the same duration, that commences with the provision of sustained organ failure support.

7.3. Eligibility criteria

Platform-level eligibility criteria may be modified if necessary to accommodate a published case definition, to align with criteria specified in guidelines, such as the ATS/IDSA guidelines on CAP[16], or to accommodate necessary modifications to the online eligibility system used for enrollment. In previous epidemics of community-based infection, nosocomial acquisition has been well described. Relaxation of the requirement for community acquisition or organ failure criteria or both may be appropriate. In this regard, Version 2.0 of this Appendix modifies the organ failure support criteria so that these no longer apply as a platform-level inclusion criteria, permitting the enrollment of

patients into the platform who are admitted to hospital or an ICU, either with or without organ failure support criteria. In association with the removal of the organ failure requirement, the requirement for a patient to meet criteria for pneumonia may be replaced with a requirement for acute illness due to suspected or proven pandemic infection. All changes to eligibility criteria would apply only to patients in the pandemic stratum (see section 7.4).

As such, the modified platform-level inclusion and exclusion criteria are:

In order to be eligible to participate in the pandemic aspects of REMAP-CAP, a patient must meet the following criteria:

1. Adult patient admitted to hospital with acute illness due to suspected or proven pandemic infection

A potentially eligible patient who meets any of the following criteria will be excluded from participation in this trial:

1. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
2. Patient is expected to be discharged from hospital today or tomorrow
3. More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection
4. Previous participation in this REMAP within the last 90 days

This extension of the platform-level inclusion criteria can apply to patients admitted to an ICU or a ward. In association with the involvement of different clinical teams, the domains and interventions that are available for patients admitted to a ward compared with those admitted to an ICU are permitted to be, but do not have to be, different.

7.4. Pandemic stratum

7.4.1. Introduction

As outlined in the Core Protocol, a pre-specified stratum of the REMAP is the presence or absence of suspected or proven pandemic infection. This is maintained as a ‘passive stratum’ during the interpandemic period that can become active during a pandemic. It consists of two exclusive strata categories: pandemic infection is neither suspected nor proven (PINSNP) and pandemic infection is

either suspected or proven (PISOP) at baseline. At times when the PAtC is not activated, i.e. during the interpandemic period, all participants are categorized as PINSNP.

7.4.2. Activation and deactivation of the PAtC and PISOP stratum

In response to a pandemic (see section 8.1), the PISOP stratum is activated using a two-step process. First there is a decision of the ITSC to open the PISOP stratum for the platform. The second step is site-by-site activation of the PISOP stratum, requiring agreement of both the site and the Regional Coordinating Centre (RCC). This allows variation in activity of the pandemic infection to be accommodated with sites only open for PISOP recruitment when there is active pandemic infection locally. Switching-on of the stratum can occur at any time and expected to always be available with less than 24 hours lead time. The capacity to enroll patients into the PISOP stratum can be switched-off on a site-by-site basis, but the ITSC can switch off the PISOP stratum for all sites if it is believed that a pandemic is no longer ongoing. The REMAP applies a new and separate statistical model for participants in the PISOP stratum which can utilize, where appropriate, informative priors derived from pre-pandemic PINSNP participants.

It should be noted that for sites in which the pandemic stratum is open, that the REMAP allows for continued recruitment of patients into the REMAP who are in the PINSNP stratum. For example, during an influenza pandemic, PINSNP would include patients with infection that has been proven to be a non-pandemic strain of influenza. During a pandemic, patients who are in the PINSNP stratum continue to be analyzed using the interpandemic statistical model (see below). As such, there are two categories of PINSNP participants- those included during the interpandemic phase and those included during a pandemic. Both categories of patients contribute to the interpandemic model for all active domains.

The PAtC is activated and deactivated for a site at the same time as the PISOP stratum is opened and closed. If a pandemic commences prior to ethical and governance approval of the PAtC, the PISOP stratum can be activated using approvals for the Core Protocol, and the PAtC would be activated as soon as ethical approval is obtained.

7.5. The pandemic statistical model

7.5.1. Introduction

The model that is active during the pandemic and includes only PISOP patients (for some or all domains) is referred to as the ***pandemic model***. The model that is active before (and after) the

pandemic, which includes PINSNP patients during the pandemic and may include some PISOP patients for some domains, is referred to as the ***interpandemic model*** (see *Figure 2*).

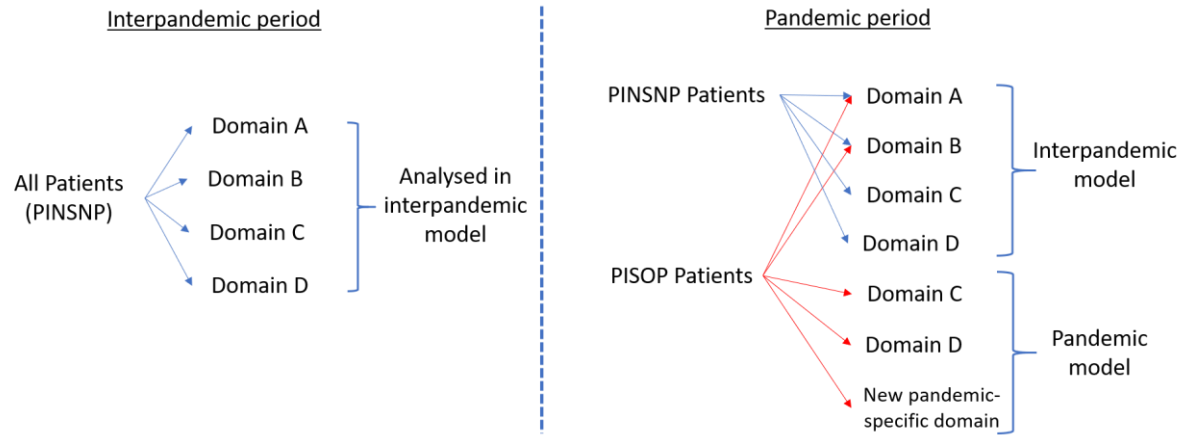


Figure 2. Diagram of the interpandemic and pandemic models

The pandemic model is only used for PISOP participants and only for those domains selected by the ITSC. A PISOP patient can contribute to both the pandemic and interpandemic model in different domains but each patient's contribution to a model is mutually exclusive with respect to each domain. The ITSC will select the domains to be included in the pandemic model where a differential treatment effect is postulated in the presence of pandemic infection or the need exists to learn about the outcome quickly, or both. The extension of this platform-level entry criteria does not apply to domains that are analyzed exclusively within the interpandemic statistical model.

A consequence of the application of two separate statistical models is that treatment-by-treatment interactions can only be evaluated for those domains that are in the same model. The principal advantages of the use of two models are:

- that this is necessary where the pandemic model requires a different primary end-point
- the platform is able to continue recruitment of patients with CAP who are neither suspected nor proven to have pandemic infection
- where appropriate informative priors can be included at commencement of the pandemic model
- where appropriate thresholds for a Statistical Trigger can be modified
- only those domains that are relevant to the pandemic are included within the pandemic model.

During the interpandemic period, it is intended that there may be some domains, for example the Ventilation Domain, that will utilize a separate domain-specific statistical model. It should be noted

that during the interpandemic period, such a domain is not part of the interpandemic statistical model. During a pandemic any such domain would continue to be evaluated with its own domain-specific statistical model. During a pandemic, the operating characteristics of the domain-specific statistical model may be modified in the same way that the pandemic model is modified from the interpandemic model. For example, PISOP patients may be analyzed within a pandemic version of the domain specific statistical model utilizing a modified primary end-point, with application of informative priors derived from the interpandemic time period.

7.5.2. Pre-specification of trial parameter options

There are many clinical features of a respiratory pandemic that cannot be predicted in advance. For several parameters related to trial design and statistical analysis, this Appendix pre-specifies a range of options from which the actual modifications will be chosen at the commencement of a pandemic. The appendix provides guidance regarding the principles that would guide selection from within the available options and often provides the planned default option. The provision of flexibility regarding limited aspects of trial design provides the capacity to tailor aspects of the trial to the characteristics of the pandemic. For these decisions, the ITSC has decision-making responsibility, with advice from the PWG. These decisions would be regarded as operational and, unless otherwise specified (5.3.4), will be made prior to the conduct of the first adaptive analysis using the pandemic model and would be made only from within the range of options pre-specified in this Appendix. It is not intended that the selected parameters would be modified in any way during the pandemic unless advised to do so by the DSMB. The selected trial parameters would be placed in the public domain, on the study website, and provided as an update to participating sites and relevant ethical review bodies prior to the first adaptive analysis of the PISOP stratum. These parameters are set out in a document termed Operating Characteristics and this document applies to both REMAP-CAP core protocol documents as well as the REMAP-COVID Core Protocol, to the extent that is necessary. It is also acknowledged that specification in a new domain, may influence a pre-existing domain, such as specification of evaluation of an interaction between domains. In this situation, the DSA for the pre-existing domain will not necessarily be amended immediately with the most recently approved or amended DSA serving to specify the inter-relationship between the two domains.

7.5.3. Application of other strata specified in the Core Protocol in the pandemic model

The shock strata may be applied to the PISOP stratum. The default position is that the shock strata will not be applied to the PISOP stratum.

If the pandemic is caused by a novel strain of influenza the pre-existing influenza strata is not applied in the pandemic model. For PINSNP patients, the "influenza present" stratum would continue to apply and would be used to differentiate patients infected with a non-pandemic strain of influenza from patients in the "influenza not present" stratum. Membership of PISOP and influenza present stratum are mutually exclusive. It is anticipated that the influenza present stratum would apply only to patients with infection due to a proven non-pandemic strain of influenza at baseline. Patients in whom influenza was suspected, but the results of strain-specific diagnostic tests were not available at the time of assessment of eligibility, will be allocated to the PISOP stratum at sites where the stratum is active.

7.5.4. Strata within the PISOP stratum

A strata applied within the PISOP stratum is the confirmation status of pandemic infection, defined in two categories, present or absent, based on the results of microbiological tests for the pandemic organism. Any patient with clinically suspected pandemic infection who is not tested or the result is not yet known will be deemed positive.

The availability and interpretation of microbiological tests are likely to change during the pandemic and an operational document will be used to specify how different tests are interpreted. It is noted that pandemic infection confirmed status is defined by the final results of testing for the pandemic organism which may include analysis of samples collected after enrollment where it is reasonable to presume that the sample reflected pandemic infection status at time of enrollment.

The sensitivity of microbiological testing for the pandemic organism may not be known at the beginning or even during the pandemic[17]. It is anticipated that initial analysis of the pandemic model will occur without application of this pandemic confirmation status strata but this would be applied when there was sufficient confidence about the operating characteristics of diagnostic tests in patients who are critically ill. If the pandemic confirmation status is applied, the probabilities derived from patients who have confirmed pandemic infection will be used to determine the RAR proportions for patients receiving treatment assignments in the pandemic specific domains within the PISOP stratum. Borrowing is permitted between the pandemic infection confirmed stratum and the pandemic infection not present stratum, using the methods outlined in the Core Protocol (with gamma = 0.15).

If eligibility criteria were modified to allow inclusion of a wider spectrum of illness severity, two or more states, related to severity of illness, may be applied within the PISOP stratum to distinguish current versus extended severity of illness.

7.5.5. States within the PISOP stratum

The Core Protocol defines 'state' as a set of mutually exclusive and exhaustive categories, defined by characteristics of a patient within the REMAP, that are capable of changing over time for a single patient at different time-points during the patient's participation in the REMAP (i.e. they can be dynamic). During the pandemic, and only for patients in the PISOP stratum, two or more states may be defined, depending on illness severity. The default categorization of severity will be into two categories:

- Severe State, defined by receiving organ failure support in an ICU
- Moderate State, defined by
    - Not being admitted to an ICU, or
    - Admitted to an ICU but not receiving organ failure support

Organ failure supports that qualify a patient as severe are aligned to those that previously determined eligibility to the platform (i.e. the Severe State corresponds to the previous platform eligibility criteria). These criteria are:

- Provision of invasive mechanical ventilation
- Provision of non-invasive mechanical ventilation (including high flow nasal cannula with a flow rate of at least 30 litres per minutes and a fractional inspired oxygen concentration of 40% or higher)
- Receiving infusion of vasopressor or inotropes or both

Where states are defined, eligibility for domains or selected interventions within a domain, may be specified according to state. As such, a domain may be available in one or more states. Where a domain is available in two or more states, the interventions available in that domain in each state are permitted to vary. States can also be utilized within the statistical model to define the unit-of-analysis, with declaration of Platform Conclusions, independently in one or more states, with borrowing permitted between states.

A single patient can move between states, one or more times, during a period of time which the patient is potentially eligible within the REMAP. For the purposes of assessment of eligibility for one or more domains, state is 'instantaneous' as at the time of that assessment. A patient who has previously received non-invasive ventilation or an infusion of vasopressor or inotrope or both, but is not receiving either of those therapies at time of assessment is deemed to be in the Moderate State. A patient who has been in the Severe State, as a consequence of receiving invasive mechanical

ventilation in an ICU, cannot re-enter the Moderate State for the purposes of assessment of eligibility. A patient who receives an assignment in the REMAP while in the Severe State cannot receive any subsequent assignments in the Moderate State. Where trial related processes, such as reveal of assignment or obtaining consent, create a time gap between initial assessment of eligibility and awareness of the patient's assignment, the state in which the patient is analyzed is that which occurred at the time of assessment, not the time of reveal of the assignment.

A patient enrolled while in the Moderate State, if reassessed for eligibility for additional domains having progressed to the Severe State, may have new microbiological information that has accumulated during this interval of time. This could result in a patient with suspected pandemic infection having information that results in pandemic infection being excluded, at the time of reassessment. In this situation, the patient is analyzed in the pandemic model, as enrolled, in the Moderate State and is not eligible for enrollment in new domains in the Severe State (including domains evaluated in the interpandemic model). It is also noted that, for a patient who is enrolled in both states, that other time-varying basline variables may have changed between each enrolment. For such aptients, potentially time-varying baseline variables will be collected in reference to enrolment in the Moderate State and again in reference to enrolment in the Severe State.

7.5.6. Domains incorporated in the pandemic model and use of informative priors derived from the interpandemic model

The domains that will be included within the pandemic model will be determined at the onset of a pandemic by the ITSC with advice from the PWG. Where appropriate and prior to the first adaptive analysis that is undertaken after activation of the PAtC, informative priors, derived from the interpandemic model (comprising patients enrolled in the REMAP prior to the pandemic), may be applied. If informative priors are applied, this is done by the Statistical Analysis Committee (SAC) who review the frequent adaptive analyses (and communicate these results to the DSMB on a regular basis). This will occur without knowledge of the values of the priors by the ITSC or any other investigator. The amount of influence that priors apply and how quickly priors are applied in combination with accruing new data will be specified by the ITSC. Coding that specifies the weighting of priors will be done by statisticians who are separate to the SAC and blind to results from adaptive analyses. With regard to selection of domains and the use of informative priors, the following principles will be applied.

7.5.6.1. Non-influenza pandemic organism

If the pandemic organism is not influenza, the following domains are intended to be included within the pandemic model:

- Corticosteroid Domain, without application of informative priors.
- Macrolide Duration Domain, without application of informative priors.
- New domains, as appropriate for the pandemic organism, without application of informative priors.

The Influenza Antiviral Domain (which includes only antiviral agents active against influenza) would not be applied in the pandemic model. It is noted that a patient at baseline could have suspected influenza and suspected pandemic infection which could lead to enrollment in the influenza domain (evaluated in the interpandemic model) and enrollment in other domains (evaluated in the pandemic model). It is not anticipated that the Antibiotic Domain is evaluated in the pandemic model, though this may be revised if the pandemic was caused by a bacterial pathogen. In this situation only those antibiotics that are known to be active against the pandemic organism would be available within the Antibiotic Domain for patients in the PISOP stratum.

7.5.6.2. Influenza pandemic

If the pandemic organism is influenza, the following domains are intended to be included within the pandemic model:

- Corticosteroid Domain, using informative priors derived from the influenza present stratum.
- Antiviral domain, using informative priors derived from the influenza positive stratum but with exclusion of any antiviral interventions that are clinically inappropriate because of the resistance profile of the pandemic strain of influenza. If there were no antiviral agents to which the pandemic strain of influenza was susceptible the Antiviral domain would not be applied in the PISOP stratum. During the pandemic if the pandemic strain of influenza acquired resistance to antiviral agents in the Antiviral Domain, these agents would be withdrawn from the domain at affected sites.
- Macrolide Duration Domain using informative priors derived from the unit-of-analysis of the Macrolide Duration Domain in the interpandemic model.
- New domains, as appropriate, without application of informative priors.

A number of other domains, related to organ failure support may be operative at the time of a pandemic. Domains such as oxygen saturation and hemodynamic targets would be expected to remain active during a pandemic. The default plan is that during a pandemic, patients in the PISOP and PINSNP strata will be eligible to receive an assignment in these domains and will be analyzed in the interpandemic model which will continue to be analyzed for statistical triggers and platform conclusions. Patients with pandemic infection will have their treatment assignments in such domains

weighted according to RAR as specified by the interpandemic model which will continue to be updated during a pandemic.

The ventilation domain, which utilizes a statistical model that applies only to that domain, is expected to continue during a pandemic. If appropriate, the pandemic strata may be applied to this domain. If so, the PISOP stratum would apply informative priors.

Any new domain that is initiated during a pandemic will be submitted for ethical review and require ethical approval prior to commencement.

7.5.7. Use of informative priors derived from information available from outside the REMAP

The default position is that informative priors derived from information that is external to the REMAP will not be utilized. However, if appropriate, based on high quality evidence, informative priors may be applied. The decision to apply informative priors lies with the ITSC and must involve consultation with relevant external stakeholders, the DSMB, and appropriate statistical advice regarding the potential implications for the use of informative priors.

7.6. Endpoints

7.6.1. Pandemic primary endpoint

Specified domains, for patients in the PISOP stratum, will be analyzed using a separate statistical model, for which the primary endpoint is called the “pandemic primary endpoint”. The default pandemic primary endpoint will be an ordinal scale that is a composite end-point that comprises mortality during the acute hospital admission and the number of whole and part study days for which the patient is alive and not requiring organ failure support while admitted to an ICU up until the end of study day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after D21, will be coded as –1 day. All patients who never receive organ failure support while admitted to an ICU will be coded as 22. Patients who die between D21 and discharge from an acute hospital will be updated at the time of the next adaptive analysis. All whole and part days after discharge from an acute hospital and before D21 will be counted as being not admitted to an ICU. Hospital readmission that included a new admission to ICU between first discharge from an acute hospital and D21 will not contribute to the primary end-point.

If appropriate, based on an understanding of clinical and biological factors, as well as operational factors, an alternative pandemic primary end-point may be specified at the time of activation of the PAtC or at any time prior to the first interim analysis using the pandemic statistical model. Other

possible primary end-points include days alive and outside the ICU with alternative durations of follow up or the use of an alternative composite based on admission to ICU. The pandemic primary endpoint will be used for the adaptive analyses that inform the RAR and for Statistical Triggers.

If the primary end-point includes a time-based outcome measure, assignment to one or more domains will occur at different time-points if the patient receives assignments in one or more domains while in the Moderate State and one or more domains in the Severe State. The commencement of the period of observation commences at the time of assignment, which can lead to the same patient having different values for different domains, as determined by the state in which enrollment occurred. This can be accommodated because there are separate statistical models for each state. Where a patient is eligible for two or more domains in a state, assignment can only occur at a single time-point, i.e. it is not possible to have more than one time of assignment for different domains in the same state.

7.6.2. Secondary endpoints

All secondary endpoints that are specified in the Core Protocol and active DSAs will continue to be active. The primary end-point specified in the Core Protocol (all-cause mortality at day 90) is a secondary end-point in the PISOP stratum.

7.7. Principles of the statistical analysis

7.7.1. Adaptive analyses

Adaptive analyses may be conducted more frequently and with varying cadence during a pandemic. For analyses conducted in the pandemic model and the PISOP stratum of the ventilation model, data from all available patients will be utilized using, where appropriate, modelling to impute missing data. Adaptive analyses may be conducted at different frequency for the PISOP and PINSNP stratum.

7.7.2. Response adaptive randomization

For PISOP patients, RAR proportions for domains that are analyzed using the pandemic model will be derived from the pandemic model and the RAR proportions for domains that are analyzed using the interpandemic model will be derived from the interpandemic model. For PINSNP patients, the RAR proportions for all qualifying domains will be derived from the interpandemic model.

If feasible, the option of allowing sites to start with imbalanced RAR proportions may be utilized. During a pandemic, issues related to equipoise for sites to participate may be facilitated by allowing sites to select from a range of starting RAR proportions that are imbalanced. Being able to

implement this would be dependent on logistic feasibility as well as evaluation to exclude any adverse impact on inference.

Within the PISOP stratum, and only for domains with five or more interventions, the minimum RAR proportion may be decreased to less than 10% but will not be decreased to less than 5%.

7.7.3. Unit-of-analysis

7.7.3.1. Application of additional strata

Patients within the PISOP stratum may be further stratified dependent on whether pandemic infection is confirmed or not confirmed by microbiological testing. Additional strata may be applied and this can be specified in a DSA. Any or all of these strata can be utilized to determine eligibility for a domain or an intervention within a domain. These strata can also be used to define a unit-of-analysis in the pandemic statistical model.

7.7.3.2. Application of state

The state, at time of first enrollment, can also be used to determine eligibility or be used to define a unit-of-analysis or both. Where specified in the statistical model, the treatment effect of an intervention is allowed to vary between different states. A Bayesian Hierarchical Model (BHM) is used for all treatment-by-state interactions. In the BHM a hyperprior is used for the differing treatment effects across states. The standard deviation of the hyperprior, gamma, is a modelling starting estimate for the variation in the magnitude of the difference in treatment effects between states. By default, the starting estimate of the difference is zero. The gamma parameter influences the extent to which the treatment effect of interventions is permitted to vary between states. At the commencement of a model, the gamma parameter must be set, for each domain-state pair.

In this REMAP, only three options are permitted with respect to specifying the gamma parameter for each domain-state pair. Firstly, gamma may be set to zero. The effect of this is that treatment effect of an intervention is assumed proportional between specified states. The unit-of-analysis is not sub-divided according to state. If gamma is set to zero for all states for a domain, the unit of analysis is all patients randomized in that domain. Secondly, and at the opposite extreme, gamma can be set to infinity. In this situation treatment effect is evaluated separately and independently in each state (with no borrowing between states). Thirdly, gamma may be set to a defined number between zero and infinity. This parameter value cannot be varied for different domain-state pairs, a global REMAP value has been selected. This specified value for gamma places a constraint on the variance of the difference in treatment effect in different states but permits the model to estimate treatment effect for patients enrolled in one state by borrowing from patients enrolled in one or more adjacent

states. Borrowing occurs to the extent that it is supported by the accumulated data, but the setting of gamma influences the amount of borrowing and how quickly borrowing is able to occur. The value of gamma that has been chosen has been determined by simulations to achieve a compromise between type I and type II error in baseline scenarios that assume either equivalence or superiority. Where a value for gamma is specified in the pandemic statistical model, in this REMAP the value of gamma will be 0.15.

A patient who is enrolled in a defined state, may have a clinical course that evolves with the patient entering a new state. Progression from one state, to another, may trigger eligibility for one or more domains. Where this occurs and the change in state defines a new unit-of-analysis, the RAR proportions may be different in each state. In this situation the RAR proportions that are relevant to that patient's state will be applied. In this regard, randomization to one or more domains in an initial state will occur, using RAR proportions that apply to that state with a separate subsequent randomization to one or more domains occurring if the patient enters a new state, with RAR proportions that apply to that state. When a new state commences there may be insufficient patients to determine valid RAR proportions for that domain in the new state. In this situation either RAR proportions are balanced or RAR proportions from an adjacent state are applied (unless otherwise specified in a DSA).

The RAR proportions that apply when state is used to define a unit-of-analysis are derived from all patients who receive an assignment in a domain in that state, irrespective of whether the patient was assigned an intervention in a different domain in a different state.

7.7.3.3. Analyses for combinations of therapies

Unless otherwise specified in a DSA, a Platform Conclusion can be reached for combinations of treatments that are being evaluated within the platform. This applies to interventions within a domain as well as interventions in different domains. As such, all of the following can be reported as Platform Conclusions: an interaction between interventions in different domains and that the treatment effect of more than one active intervention is different to a no treatment (standard of care) intervention. A domain that contains two or more treatments, each of which is assigned against a no treatment control in a factorial manner (i.e. the N x N table of yes / no for n treatments) will be analyzed as an N x N factorial. Structuring the analysis in this way allows the model to learn more quickly about the effectiveness of each treatment, recognizing common treatment exposure across intervention assignments.

7.7.4. Thresholds for statistical triggers

7.7.4.1. Introduction

The Core Protocol specifies thresholds for Statistical Triggers that apply to superiority, inferiority, and equivalence. For PISOP patients, different thresholds for Statistical Triggers may apply during a pandemic. The decision to modify a statistical threshold will be made by the ITSC prior to the first adaptive analysis of the pandemic model. Different thresholds may be applied to different domains. Thresholds can also be specified that are asymmetric for example less stringent for inferiority than superiority. Factors that the ITSC will take into account in considering whether to modify a threshold include whether the interventions being evaluated are comparative effectiveness options (i.e. interventions that are available as part of standard care and available outside the platform) or experimental interventions with uncertain safety and risk profile that may be available only within the platform.

All decisions regarding thresholds for Statistical Triggers will be communicated to participating sites and placed in the public domain on the study website. Once specified, thresholds cannot be modified unless recommended by the DSMB.

The default thresholds are outlined in the following sections.

7.7.4.2. Intervention Superiority Statistical Trigger

At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population.

The declaration of a Platform Conclusion by the DSMB for superiority will result in application of 100% RAR (see section 7.6.4). Following implementation of 100% RAR, the posterior probability will continue to be updated and evaluated by the DSMB who are empowered to act if they have concerns regarding the validity of a Platform Conclusion.

7.7.4.3. Intervention Efficacy Statistical Trigger

For any domain that has (or had) a non-active control intervention, statistical triggers for efficacy of other interventions can be determined. At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being superior to the inactive control intervention, for that unit-of-analysis, then that intervention will be deemed as being effective in that domain in that target population. At any adaptive analysis, if a single intervention has a greater than 90% probability of

being harmful, compared to an inactive control intervention, for that unit-of-analysis, then the intervention will be deemed as being harmful in that domain in that target population.

The declaration of a Platform Conclusion by the DSMB for efficacy may not result in any actions and may occur after the non-active intervention has been removed. This Platform Conclusion mathematically would occur simultaneously to Superiority in a 2-intervention domain. If a determination of efficacy for an intervention with a currently randomized non-active control then the non-active control should be dropped and the RAR set to 0. In contrast, declaration of a Platform Conclusion for harm will result in removal of that intervention from the platform for that unit-of-analysis, together with Public Disclosure.

7.7.4.4. Intervention Inferiority Statistical Trigger

At any adaptive analysis, if a single intervention has less than a 0.01 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior to other interventions in the domain for that target population. The 0.01 threshold is reduced as a function of how many units-of-analysis are available for the inferiority calculation (divided by the number of units minus 1). An asymmetrical inferiority statistical trigger may be set, particularly if an active intervention was being evaluated against an intervention that specifies no active treatment in that domain.

7.7.4.5. Equivalence and futility

The equivalence boundary (delta) for different endpoints selected for the PISOP stratum may be changed depending on the clinical impact of the delta for the chosen endpoint. The default delta for the Core Protocol will be used to select clinically similar effects on the chosen primary endpoint. If a mortality or 21-day ICU- or organ support-free day endpoint is selected the 20% proportional odds equivalency delta will be the default.

Alternatively, a DSA may specify a futility boundary (delta) with respect to the primary end-point. For the pandemic primary end-point, the default futility boundary for an intervention will be set as a posterior probability of less than 0.05 for at least a 20% odds-ratio improvement. This rule corresponds to the one-sided equivalency region.

7.7.4.6. Statistical thresholds for early phase interventions

During the pandemic there may be need to test multiple candidate interventions that are at an early phase of development, identifying those interventions that are most promising to be retained within the platform. Such interventions may be evaluated after a fixed recruitment against a ‘stop-go’

criteria for retention, and expansion, within the platform. The default threshold for retention and expansion of an intervention will be a posterior probability of 0.5 or more that there is at least a 30% benefit in odds ratio.

7.7.5. Actions when a Statistical Trigger is achieved

The actions that occur when a statistical trigger is achieved are those which are specified in the Core Protocol. At the time of a Platform Conclusion that is relevant to public health or clinical management of patients with suspected or proven pandemic infection, the DSMB and ITSC are empowered to liaise directly with relevant public health authorities prior to public presentation or publication of results.

7.7.6. Pre-specified subgroup analyses after achievement of a platform conclusion

Pre-specified subgroup analyses that will be conducted after a Platform Conclusion are outlined in each DSA. If a DSA does not specify a sub-group analysis related to the pandemic strata such analysis is permitted if the PISOP stratum has been open.

7.7.7. Closure of the PISOP stratum and incorporation of data from pandemic statistical model into the interpandemic statistical model

The ITSC is permitted to close or suspend the PISOP stratum. At this time, evaluation of new patients within the pandemic model will cease. After the permanent closure of the PISOP stratum, the information related to domains that have been analyzed for PISOP patients within the pandemic model will be added to the interpandemic model retaining, if appropriate, a co-variate or stratum status, to reflect that the patient was enrolled in the PISOP stratum.

7.7.8. Domains with their own statistical model

It is intended that domains with their own statistical model (e.g. as anticipated for the ventilation domain) will continue to be analyzed using the separate statistical model. If the PISOP stratum was applied to such a domain it is intended that a pandemic version of the separate model would be commenced and enroll only patients in the PISOP stratum. This model would utilize the pandemic primary end-point and would use informative priors derived from the preceding model. An operational decision may be made to apply an end-point that is different to the pandemic primary end-point in a domain with its own model.

8. GOVERNANCE, ETHICAL, AND OPERATIONAL CONSIDERATIONS IN A PANDEMIC

8.1. Decision to activate pandemic stratum

The decision to open the pandemic stratum lies with the ITSC. In deciding to activate the pandemic stratum the ITSC should take into account, but is not dependent on, declaration of a pandemic by the WHO and decisions about pandemic activation by regional pandemic preparedness consortia.

The decision to open will be communicated to RCCs and participating sites as an operational document. Each RCC will maintain a log of the dates for which sites were activated for the PISOP stratum.

8.2. Safety Monitoring and Reporting

During the interpandemic period, the platform evaluates solely or predominantly interventions that are in widespread clinical use for severe CAP and for which the safety profile of the intervention is well described. During a pandemic, the platform may evaluate therapeutic agents that have been repurposed or are an Investigational Medical Product. Such therapeutic agents may not have an established safety profile or an established safety profile when used in critically ill patients. Where an intervention is not regarded as having an established safety profile, this will be specified in the DSA. For this type of interventions more specific or more detailed SAE reporting will be required that is specified in the Core Protocol, as follows.

This may include Adverse Events of Special Interest (AESI). SAEs that might be attributable to specific interventions are included as secondary endpoints in each DSA but are recorded only for participants who are enrolled in that domain. If more detailed SAE or AE/AESI reporting is required for an intervention, then this additional safety reporting requirement will be specified in the relevant DSA and recorded only for participants who are enrolled in that domain. The following arrangements apply to such

When submitting the SAE form the local site PI should determine if the SAE is attributable to one or more study interventions in this trial. The local PI will assess if it is possible, probable, or certain that there is a direct link between a trial intervention and the SAE (a Serious Adverse Drug Reaction, SADR).

The regional / country project manager should review the SAE form for completeness and query any missing data with the site. Preliminary SAE report forms should be submitted as soon as the site becomes aware. It is recognised that follow-up information may be available later.

The regional lead investigator, or medically qualified designee, should review the SAE to assess expectedness and causality. The regional lead investigator or delegate cannot downgrade the site's assessment of expectedness and causality. The following requirements are specified:

- The regional Sponsor should be made aware of the SAE within 24 hours of the SAE being reported.
- All SAEs must be followed-up until resolution, or end of trial if this is sooner.
- SAEs will be reported to the relevant ethics committee and competent authority according to local regulations and requirements.

All SAEs, pooled from all regions, will be reported to the DSMB at intervals agreed by the REMAP-CAP investigators and the DSMB. This may vary depending on the specific intervention being evaluated. The DSMB may request additional specialist review of safety data for certain interventions.

If drugs have been supplied by a pharmaceutical company, then reporting of safety data to the company may be required. The details of this reporting will be included in individual Safety Data Exchange Agreements (SDEA).

On an annual basis a Developmental Safety Update Report (DSUR) will be produced including all SAE data from all regions in REMAP-CAP and will be submitted to the relevant competent authorities as required. This may be shared with pharmaceutical companies as part of the SDEA.

If an SAE is determined to be unexpected (not previously described in the Summary of Product Characteristics / Investigator Brochure / Protocol) and related to the study medication then it is considered a SUSAR. In these cases, the following steps should also be undertaken, in addition the performing the steps described above for handling SAEs:

- The relevant competent authorities and ethics committees should be notified of the SUSAR by the Sponsor or designee in each region.
- A SUSAR that results in death or is life-threatening, should be reported to the aforementioned bodies within 7 days of the Sponsor (or designee) becoming aware of the

event. Further relevant information should be sought and a follow-up report completed as soon as possible and submitted within 8 additional days.

A SUSAR which does not result in death or is not life-threatening should be reported within 15 days of the Sponsor (or designee) becoming aware of the event or in accordance with the local regulatory requirements. Further relevant information should be given as soon as possible. The regional / country project managers should notify all investigators at all sites that a SUSAR has occurred. The REMAP-CAP DSMB should be notified that a SUSAR has occurred.

It may be necessary to take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body. If this occurs the regulatory bodies should be notified as soon as possible and in any event within three days, in the form of a substantial amendment, that such measures have been taken and the reasons why.

SAEs reported will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA). Coding will be to lowest level terms. The preferred term, and the primary system organ class will be listed. Summaries of all SAEs by treatment group will include:

- The number and percentage of patients with at least 1 SAE by system organ class and preferred term
- The number of SAEs by relationship to treatment (related, not related), presented by system organ class and preferred term

8.3. Data collection and management

A pandemic is likely to result in a substantial increase in clinical workload for sites participating in REMAP-CAP. This is acknowledged by the REMAP-CAP management, as is the primacy of patient care. The importance of contemporaneous data collection, particularly with respect to variables that are needed for adaptive analyses will be emphasized to sites. RCCs will seek to support sites as much as possible, including with requests to healthcare systems, public health authorities, and funding agencies to provide resources that allow sites to maintain data collection that is timely and complete.

8.4. Role of the DSMB

In a pandemic the role of the DSMB is modified, taking into account the public health importance of clinical evidence during a pandemic. In meeting the requirements of their Charter during a pandemic

the DSMB should consider issues of public health in addition to the well-being of participants and the scientific integrity of the platform. The in-principle views of the DSMB may be obtained by the ITSC with regard to the setting of modified thresholds for statistical triggers.

While the PISOP stratum is open the DSMB is also permitted to liaise with public health authorities, regulatory authorities, or the DSMBs of trials evaluating the same or similar interventions regarding the results and appropriate interpretation of adaptive analyses in keeping with prevailing international standards. If the DSMB communicates with external groups the ITSC may be informed that such communication has occurred but the content of that communication may remain confidential between the DSMB and the relevant group. The DSMB may recommend to the ITSC that public reporting of posterior probabilities that have not attained a threshold for a Statistical Trigger should occur.

The workload of the DSMB may be substantial during a pandemic and, if requested by the DSMB, the ITSC will appoint additional members.

8.5. Communication of trial results

Any Platform Conclusion that is relevant to public health that occurs during a pandemic will be presented or published as soon as possible, noting that additional work to report baseline status and secondary end-points will need to occur prior to presentation and publication of results.

8.6. Funding of the trial

The trial is currently funded as described in the Core Protocol.

During the interpandemic period and during a pandemic, additional funding will be sought to provide resources for activities that exceed those that will be occurring during the interpandemic period. Possible sources of additional resources include, but are not limited to, healthcare systems, pharmaceutical companies, public health authorities, and local and international research funding bodies.

A section of the Core Protocol indicates that “the trial will not enter into a contract with a commercial organization unless the contract specifies that, among other clauses, “that all data are owned by the trial and the commercial organization has no authority to access data”. This clause should not be interpreted as indicating that access to data by a commercial organization is not permitted. Such as access can be agreed, for example, by licensing access to data, if agreed by both a commercial partner and trial sponsors.

8.7. Monitoring

It is acknowledged that during a pandemic site monitoring may be delayed for logistical reasons. The operational monitoring plan may be updated to reflect issues that are specific to a pandemic. As outlined in Core Protocol, the DSMB will take into account intensity of monitoring and time of consideration of a Platform Conclusion. If appropriate, the contribution of data that has not been monitored as per the non-pandemic monitoring plan will be acknowledged in the public reporting of Platform Conclusions.

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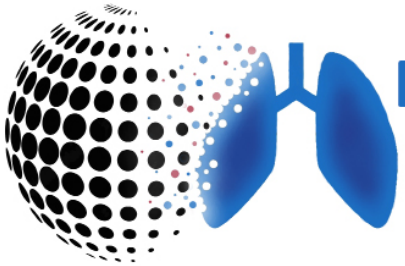

Domain-Specific Appendix: COVID-19 Antiviral Therapy

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

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 (PAtC).

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

REMAP-CAP: COVID-19 Antiviral Therapy Domain Summary	
Interventions	• No antiviral for COVID-19 (no placebo) • Lopinavir/ritonavir • Hydroxychloroquine • Hydroxychloroquine and lopinavir/ritonavir
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 SARC-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	Patients will be eligible for this domain if: • COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing • Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur
Domain-Specific Exclusions	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 • The treating clinician believes that participation in the domain would not be in the best interests of the patient
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 HIV infection will exclude a patient from receiving lopinavir/ritonavir • Known or suspected pregnancy will result in exclusion from any intervention that includes 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
Outcome measures	Primary REMAP endpoint: as defined in an operational document specified from the Pandemic Appendix to the Core Protocol Section 7.5.1 Secondary REMAP endpoints: refer to Core Protocol Section 7.5.2

	Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment): • Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinically indicated testing) • Serious Adverse Events (SAE) as defined in Core Protocol

CONTENTS

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
PAtC	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).

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):

Professor Yaseen Arabi

Members:

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

Dr Steve Tong

Dr Tim Uyeki

Dr Frank van de Veerdonk

Professor Steve Webb

4.2. *Contact Details*

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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 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. 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-β1b, 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 24th 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-α or interferon-β, 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-β1b (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®, Abbott Laboratories, Chicago, IL, USA, 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-β1b 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-β1b 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-β1b (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)-α, 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-β1b, 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-β1b) is being conducted in Saudi Arabia to assess the efficacy of administering a combination of lopinavir/ritonavir and recombinant IFN-β1b 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-β1a which, results in an evaluation of the treatment effect of lopinavir/ritonavir in combination with interferon-β1a.

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-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 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 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 arrythmia 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

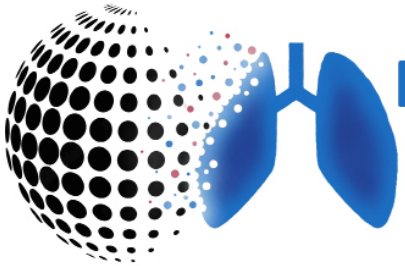
Drug	Possible interaction	Management	Action from enrollment until cessation of study drug
Amiodarone	Increased risk of amiodarone toxicity (hypotension, bradycardia, sinus arrest). Increased QT-interval prolongation.	Concurrent use is contraindicated	Consider alternatives to amiodarone. If no alternative 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 β-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.wolterskluwercdi.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.
The following drugs are listed as potential interactions in the Liverpool COVID-19 list but there is no data in other interaction references to provide details. Caution is required.			
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 mexilitine concentrations		
DAbigatran	Potential increased dabigatran concentrations		
Rivaroxaban	Potential increased rivaroxaban concentrations		
Rifampicin	Potential decreased HCQ concentrations		



Domain-Specific Appendix: COVID-19 Antiviral Therapy

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

COVID-19 Antiviral Therapy Domain-Specific Appendix Version 2.1 dated 09 June 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 (PAtC).

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

REMAP-CAP: COVID-19 Antiviral Therapy Domain Summary	
Interventions	• No antiviral for COVID-19 (no placebo) • Lopinavir/ritonavir • Hydroxychloroquine • Hydroxychloroquine and lopinavir/ritonavir
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 SARC-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	Patients will be eligible for this domain if: • COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing • Microbiological testing for SARS-CoV-2 infection of upper or lower respiratory tract secretions or both has occurred or is intended to occur
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 48 hours has elapsed since ICU admission • Patient has already received more than 36 hours of treatment with any non-trial prescribed systemic antiviral medication, other than remdesivir, 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 • The treating clinician believes that participation in the domain would not be in the best interests of the patient
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 HIV infection will exclude a patient from receiving lopinavir/ritonavir • Known or suspected pregnancy will result in exclusion from any intervention that includes 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
Outcome measures	Primary REMAP endpoint: as defined in an operational document specified from the Pandemic Appendix to the Core Protocol Section 7.5.1 Secondary REMAP endpoints: refer to Core Protocol Section 7.5.2

	Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment): • Serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinically indicated testing) • Serious Adverse Events (SAE) as defined in Core Protocol

CONTENTS

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
PAtC	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).

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

Version 2.1: Approved by the COVID-19 DSWG on 9 June, 2020

4. COVID-19 ANTIVIRAL DOMAIN GOVERNANCE

4.1. *Domain members*

Chair (Antiviral Domain):

Professor Yaseen Arabi

Members:

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

Dr Steve Tong

Dr Tim Uyeki

Dr Frank van de Veerdonk

Professor Steve Webb

4.2. *Contact Details*

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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 Date 9 June 2020
Yaseen Arabi

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 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. 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-β1b, 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 24th 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-α or interferon-β, 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-β1b (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®, Abbott Laboratories, Chicago, IL, USA, 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-β1b 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-β1b 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-β1b (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)-α, 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-β1b, 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-β1b) is being conducted in Saudi Arabia to assess the efficacy of administering a combination of lopinavir/ritonavir and recombinant IFN-β1b 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-β1a which, results in an evaluation of the treatment effect of lopinavir/ritonavir in combination with interferon-β1a.

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-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 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 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 48 hours has elapsed since ICU admission

- Patient has already received more than 36 hours of treatment with any non-trial prescribed systemic antiviral medication, other than remdesivir, 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, other than administration of off-trial remdesivir, 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 arrythmia 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 β-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.wolterskluwercdi.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.
The following drugs are listed as potential interactions in the Liverpool COVID-19 list but there is no data in other interaction references to provide details. Caution is required.			
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 mexilitine concentrations		
DAbigatran	Potential increased dabigatran concentrations		
Rivaroxaban	Potential increased rivaroxaban concentrations		
Rifampicin	Potential decreased HCQ concentrations		

Appendix to Core Protocol:

STATISTICAL ANALYSIS APPENDIX

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

REMAP-CAP Statistical Analysis Appendix Version 3 dated 24 August 2019

TABLE OF CONTENTS

1. ABBREVIATIONS

CAP	Community-Acquired Pneumonia
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
ITT	Intention To Treat
MCMC	Markov Chain Monte Carlo
mITT	Modified Intention To Treat
NDLM	Normal Dynamic Linear Model
P:F ratio	Ratio of Partial Pressure of Oxygen in Arterial Blood and Fraction of Inspired Oxygen Concentration
PP	Per Protocol
RAR	Response Adaptive Randomization
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia
SAC	Statistical Analysis Committee

2. STATISTICAL ANALYSIS APPENDIX PROTOCOL VERSION

The version of the Statistical Analysis Appendix is indicated in this document's header and on the cover page.

2.1. *Version History*

Version 1: Approved by the International Trial Steering Committee (ITSC) on 7 November 2016

Version 1.1: Approved by the ITSC on 12 April 2017

Version 2: Approved by the ITSC on 12 December 2017

Version 3: Approved by the ITSC on 24 August 2019

3. INTRODUCTION

This trial design is built as a process – with the possibility of multiple interventions within multiple domains and multiple patient groups being investigated. The trial design is built prospectively to be flexible. These flexible aspects are designed and planned and are part of the protocol. In this report, we describe the details of the prospective statistical design. In contrast to many clinical trial designs, where there is a single intervention or a small number of interventions, this REMAP is designed generically so that it may incorporate a flexible number of interventions, with the possibility of these numbers evolving as the science evolves. This statistical analysis plan describes the statistical design in the most general way possible, and thus applies for all imaginable trial design states. The current trial design state is described a separate document, Current Statistical Modeling.

Similar interventions are grouped within *domains*. Each patient is randomized to a single intervention from each domain. This set of randomized interventions across the domains is the patient's *regimen*. Patients are also grouped into *strata* and into disease *states*. The efficacy of the interventions may vary by strata. Optimal interventions will be identified by strata. Some interventions may only be administered to patients in certain disease states. The specific domains, interventions, strata, and states being investigated in REMAP are allowed to evolve throughout the perpetual nature of this trial. These evolutionary aspects are described. The adaptations in the design are controlled by a statistical model. This statistical model is described in the section entitled "Statistical Modeling" (Section 5). The modeling can expand and contract to accommodate the

number of domains, interventions, strata, and states being evaluated at any time. The section entitled "Trial adaptation and stopping criteria and guidelines for interventions" (Section 9) describes the adaptations in this REMAP. These include the timing of adaptive analyses, the Response Adaptive Randomization (RAR), and the requirements for declaration of superiority, inferiority, or equivalence of interventions. A separate document, The Current Statistical Modeling document, describes the current domains, interventions, strata, states and specifies the current statistical modeling. Another separate document, the Simulations Appendix, presents a range of simulation-based operating characteristics based on the current state of the trial. This includes simulating from various assumptions of treatment effects and observing the behavior of the trial design: for example, the number of patients assigned to each intervention and the probability of declaring interventions superior, inferior, or equivalent by strata.

4. STRUCTURE OF TRIAL

4.1. *Primary Endpoint*

The primary endpoint for the trial is all-cause mortality at 90 days. This is considered as a dichotomous endpoint where outcomes will be failure (mortality within 90 days of enrollment) or success (not a failure). We label the outcome for a patient as Y, where Y=1 is defined as a failure (death within 90 days) and Y=0 is a patient success.

4.2. *Domains*

For the purposes of REMAP, a domain defines a specific set of competing treatments within a common clinical mode. Each domain has a set of mutually exclusive and exhaustive interventions. Every eligible patient will be randomized to one and only one of the available interventions from each domain.

We label the domains as d = 1, 2,…, D. A specific domain may also be referred to by a letter: A, B, C, …. Interventions within a domain are labeled with a subscript index, j. Therefore, d_j refers to intervention j within domain d. There are j = 1, …, J_d interventions in each domain d. It is expected that the number of domains, and the number of interventions within each domain will expand or contract as the trial progresses.

4.3. *Regimens*

Every patient will be randomized to a set of interventions, exactly one from each domain. The set of interventions are referred to as a regimen. All possible combinations define the set of available arms in the trial. We label a regimen as *r*. As an example, assuming 4 domains denoted as domain A, B, C, and D, a regimen would be:

$$r = (A_a, B_b, C_c, D_d).$$

4.4. *Strata*

There are multiple covariates within this REMAP to describe patients' baseline characteristics, but some of these covariates are treated as possibly prognostic in that the treatment effect may vary across these covariates. We label these select covariates as prospectively defined strata and the treatment effect of an intervention is modeled as possibly varying across the strata.

Within each stratum, patients will be grouped in a dichotomous manner. If a strata is defined as an ordinal-type variable, then dichotomous indicator variables according to the desired contrasts will be defined. Therefore, let $x_1, \ldots, x_K$ be the set of K dichotomous indicator variables that define the different strata. The number of unique strata (or sub-groups) is 2^K. We label the dichotomous groups in each stratum as g=1,2. For example, the trial will begin with a single stratum – shock. Therefore, shock is strata x_1. Within this stratum, patients will either not be in shock (g = 1) or will be in shock (g = 2).

The number of strata may be expanded, or the existing strata may be modified as the trial progresses. The description here is expandable when strata are defined by a dichotomous structure.

4.5. *State*

A state is a clinical condition of a patient that may change during the course of their treatment. The different states within the REMAP are used to define possible eligibility of the patient for different domains at different times in the trial and as a covariate of analysis within the statistical model to adjust for disease severity. A state is a set of mutually exclusive categories, defined by characteristics of a patient, and states are dynamic in that they can change for a single patient, at different time-points, during the patient's participation in the REMAP.

The number of state variables and the number of states within the REMAP may be varied, depending on the impact of the number of states on statistical power, as determined by simulations. The *a priori* defined states that are used may be changed during the life of the REMAP as knowledge is accumulated.

The states are modeled as additive covariates within the statistical model. We label the different states as s=1,…,S.

4.6. *Randomization*

Randomization assignments are performed for patients at baseline. Randomization is performed separately by strata in that the randomization probabilities to the interventions may vary depending on the group membership of the patient within the strata. Patients are randomized to a full regimen, and not to individual interventions within the domains. Section 9.6 describes the response adaptive randomization allocation procedure.

However, there may be domains where the therapy is specific to a certain disease state. Some patients will not be in disease states that require the interventions from a particular domain. For example, a domain may be specific to a more severe disease state. Initially the patient may not be in that severe disease state but could transition to that disease state. Randomization at baseline will assign an intervention in each domain regardless of disease state. However, the domains may differ in the timing of when the randomization assignment is revealed. Some domains will employ an *immediate* reveal at baseline. For these immediate reveal domains the randomization will be treated in an intent-to-treat fashion for the primary analysis in that all patients will be included in the analysis of that domain. Some domains may employ *deferred reveal*, in which the randomization assignment is revealed based on an initial eligibility criterion at the time of randomization but the information to assess that eligibility criterion only becomes known after some time. These domains will be treated analogously to the immediate reveal domains for analysis. Finally, some domains will employ *delayed reveal*, in which the randomization is revealed only for patients in the disease states, or who progress to the disease states, that require that domain. The revealing of the domain will be tracked and the analysis of delayed reveal domains will censor from the analysis the patients that did have that randomization assignment revealed. In the case of interventions within a delayed reveal domain, the specific modeling of the intervention effects and modeling the time varying aspects of

states will be custom to that domain and will be prespecified in a separate document, Current Statistical Modeling.

5. STATISTICAL MODELING

Inferences in this trial are based on a Bayesian statistical model, which estimates the posterior probability of all-cause mortality at 90 days (primary endpoint) for each regimen based on the evidence that has accumulated during the trial in terms of the observed 90-day mortality outcomes and assumed prior knowledge in the form of a prior distribution. This differs from conventional (frequentist) analysis methods where inferences are based on a likelihood of observed outcomes against a null hypothesis.

The statistical model takes into account the variation in outcomes by region, strata, disease states, age group, and time since the start of the trial. The model estimates treatment effects for each intervention as well as determines if these treatment effects vary by strata and if treatment effects of individual interventions in one domain vary when paired with interventions from other domains.

Let

- R = region
- s = disease state
- k = strata and g_k = the yes/no dichotomous status within strata k where g_k = 1 means the strata condition is “no” and g_k = 2 means the strata condition is “yes”
- age = age group
- T = era measured in 13-week increments since the start of the trial
- d = domain and d_j is intervention j within domain d

We model the log odds of the probability of 90-day all-cause mortality, π, as

$$\log\left(\frac{\pi}{1-\pi}\right) = \sum_{R=1}^{R} \nu_R + \sum_{k=1}^{K}\sum_{s=1}^{S} \alpha_{s,g_k} + \sum_{age=1}^{AGE} \lambda_{age} + \sum_{T=1}^{T} \theta_T + \sum_{d=1}^{D}\sum_{j=1}^{J_d} \beta_{d_j} + \sum_{k=1}^{K}\sum_{d=1}^{D}\sum_{j=1}^{J_d} I(g_k = 2)\gamma_{kd_j} + \sum_{d=1}^{D}\sum_{j=1}^{J_d}\sum_{d'=d+1}^{D}\sum_{j'=1}^{J'_{d'}} \delta_{d_j d'_{j'}}$$

The interpretation of each term in the model is:

ν_R is the covariate that adjusts for region. There is one ν_R term estimated for each R = 1,…,R where R = 1 is the referent group and the remaining terms estimate the increase or decrease in mortality associated with region

α_{s,g_k} is the covariate that adjusts for both strata and disease state. For each strata *k* where k = 1,…K, there is one term for every pairwise combination of *s* = 1,…,*S* and g_k = 1,2. The referent by strata *k* is when both s = 1 and g_k = 1. The remaining terms then estimate the increase or decrease in mortality associated with the strata and disease state combinations. When s = 1 (the referent disease state) this term estimates the increase or decrease in mortality associated with the strata condition (g_k = 2 versus g_k = 1). For g_k = 1 (the referent strata group) this term estimates the increase or decrease in mortality associated with disease state (s = 2,…,S versus s = 1). When both s > 1 and g_k = 2 this term estimates the additional effect of the strata condition (g_k = 2) in each of the disease states.

λ_{age} is the covariate that adjusts for age group. Age will be modeled as categorical age groups. There is one λ_{age} term for each age group being modeled. The referent will be a middle age group and the remaining terms estimate the increase or decrease in mortality associated with the other age group categories.

θ_T is the covariate that adjusts for time since the start of the trial. There is one term for each T = 1,…,T where each represents an era, or a 13-week period of calendar time. The trial era in which the analysis is being conducted (the most current era) will be the referent and every other θ_T then represents the increase or decrease in mortality associated with calendar time since the start of the trial.

β_{d_j} are the terms that estimate the main effects of each intervention. There is one β_{d_j}term for each intervention in each domain. Intervention j = 1 in domain d = 1 is the referent and every other β_{d_j} estimates the relative increase or decrease in mortality associated with each other intervention in the trial.

$\gamma_{kd_j}$are the terms that estimate intervention by strata interactions. There is one term for every pairwise combination between the k = 1,…, K strata in the trial and the j = 1,…,J_d interventions across all d = 1,…D domains in the trial. We define $I(g_k = 2)$ as an indicator variable for g_k = 2 in strata *k*. Therefore, this term estimates the increase or decrease in morality associated with an intervention when g_k = 2 (strata condition is “yes”) versus when g_k = 1 (strata condition is “no”).

$\delta_{d_j d'_{j'}}$ are the terms that estimate the intervention by intervention interactions. There is one term for every pairwise combination between all the interventions j = 1,…, J_d in one domain all interventions $j' = 1,\ldots, J'_{d'}$ in every other domain. These terms estimate the increase or decrease in the effectiveness of each intervention when it is paired with another intervention from another domain.

As described above, there may be two types of domains. There will be immediate reveal domains that investigate interventions that do not depend on disease state and the randomization assignments in these domains can be made known immediately. There may be delayed reveal domains that investigate interventions that are appropriate only for patients in certain disease states that evolve within patients during the trial. The randomization assignment can be made known only to patients in these disease states. Therefore, there will be three groups of patients relative to a delayed reveal domain:

1. The randomization is never revealed because the patient is never in an eligible disease state
2. The patient enters the trial in the eligible disease state and the randomization assignment is effectively immediately revealed
3. The patient transitions to the eligible disease state after the initial randomization and the randomization status is a delayed reveal

We define a model that includes terms for the treatments in both immediate and delayed reveal domains. However, there will be no interaction terms estimated with the interventions in the delayed reveal domains and any other domains. This model will be fit based on all randomized patients where patients are included in the model based on the initial disease state they are in at the time they are randomized. The efficacy of delayed reveal domains among patients who transition to the eligible disease state (group 3 above) will be modeled through a "sub-model" that only informs the relative efficacy of the interventions within the delayed reveal domain. The sub-model will include adjustment for the covariates of region, age and era, and will include the main effect terms for the interventions in the delayed reveal domain. The sub-model will be dependent on the primary model in that the estimation of the sub-model will be conditional upon the estimates of region, age, and era from the primary model.

5.1. *Modeling Covariates for ineligibilities for interventions and / or domains*

The modeling of the primary endpoint is a logistic regression form:

$$\log\left(\frac{\pi}{1-\pi}\right) = f(R, k, s, age, T, d, j).$$

In order to add covariates in the model, for sensitivity or exploration they will be added as (possibly multiple covariates):

$$\log\left(\frac{\pi}{1-\pi}\right) = f(R, k, s, age, T, d, j) + \zeta Z$$

where *Z* is a normalized covariate and ζ is the model coefficient. Individual patients may enter the trial ineligible to one or more individual interventions within a domain or one or more domains. If a patient is ineligible for one or more interventions within a domain but there are at least two interventions for which the patient is eligible to be randomized among then the patient is allocated an intervention from among the eligible interventions and the data for such a patient is included in the full analysis set and a covariate indicating ineligibility to the interventions will be fit.

If a patient is ineligible for an entire domain then an indicator for the domain ineligibility is created and a covariate, *Z*, for this ineligibility is created. No treatment allocation variable nor interactions for this patient are included in the model.

The coefficients for all covariates for these ineligibility interventions/domains will have the following priors:

$$[\zeta] \sim N(0, 10^2).$$

A list of all models, model terms, and their prior distributions specific to the current state of the trial are provided in a separate document.

All models will be fit using Markov Chain Monte Carlo (MCMC) methods.

6. MISSING DATA

There will be no imputation of missing primary endpoint values. Patients with missing values for the primary endpoint will be excluded from the modeling. If randomization assignment or reveal of randomization assignment is missing, the patient will be assumed to be ineligible for that domain. Patients with unknown region, age, or era may have these covariates imputed. Where possible, missing values will be calculated based on other available data. Otherwise, the mean value will be imputed for missing values.

If strata or state is missing for a subject, it will be multiply imputed in the Bayesian algorithm. This multiple imputation will be based on the primary outcome variable and each of the variables in the model through the Bayesian posterior distribution. An important aspect of this model is a prior distribution of the missing strata or state. In some cases, this may be a specified prior (such as having a sleeping strata become active in which the status of the previous patients' strata status was never collected. The prior probability may be quite small in the case of a new pandemic). If there is no scientifically informed prior distribution then the relative frequency of the strata or state in the region and era will be used as the prior distribution for each state.

7. MODEL PRIORS

In this section, we present the prior distributions used for each of the parameters.

7.1. *Region Effects*

For identifiability, the region parameter for region 1 is considered the baseline and is set to 0. For every other region, the prior distributions for the parameter are modelled in a tiered (hierarchical) fashion. We refer to a *region* as the smallest classification of the geographical location. Typically, a region will be a site, but not always (a region may be a collection of sites). Regions are grouped hierarchically within country. We model the effects individually at the smallest unit – the regions. The model explicitly models the regions as being grouped, hierarchically, within country. For a region, label the parent country as c_R, where c_R=1,…, C. The parameter for each region is labeled ν_R and is modeled hierarchically as:

$$[\nu_R] \sim N\left(\mu_{C_R}, \tau^2_{C_R}\right) R = 2, \ldots, N_R,$$

with hierarchical priors

$$[\mu_C] \sim N(0,1);\ [\tau_C^2] \sim IG(0.25,0.1), \text{ where c=1,...,C.}$$

The hierarchical distribution for the region effects creates a meta-analytic type model for the estimation of individual effects. The hyper-prior distributions have a mean estimate of 0, which is the same as the baseline, Region 1, and a prior centered at 0.20^2 for the standard deviation across countries, but with a relative weight of only 0.5 observations. This prior allows the observations across regions/countries to empirically shape the hyper-distribution.

7.2. *Strata and State Effects*

For every strata and state combination a single parameter captures the relative severity of the population. For identifiability we restrict the parameter for g_k=1 and s=1 to be set at 0. Thus, for the shock stratum, $g_1 = 1$ and s = 1 corresponds to non-shock, not ventilated. The prior distributions for the parameters are set as fixed priors with weak prior distributions

These prior distributions are modelled separately as they are expected to be quite different, but will be shaped very quickly by the large amount of data within each group by state pair.

7.3. *Time (Era) Effects*

The time eras will be sequential "buckets" of 13-week time periods measured from the start of the trial. For identifiability, the era parameter for the most recent time period, θ_T, is considered the baseline and is set to 0. For every previous era, the prior distributions for the parameters are modelled with a first-order normal dynamic linear model (NDLM). The first-order NDLM is defined by "walking backwards" in time,

$$[\theta_{T-1}] \sim N(\theta_T, \tau_T^2); T = 1, \dots, N_T - 1,$$

with hyper prior on the "drift" parameter

$$[\tau_T^2] \sim IG(0.25,0.1).$$

The NDLM model for the eras allows borrowing (smoothing) the estimate of each era over the course of the trial. The drift parameter τ_T^2 is the variance component that creates the amount of borrowing from one era to the next. This is shaped by the data, using a hyper-prior distribution. The

prior distribution is equivalent to 1 observation worth of data that the era effects have small changes, 0.10^2, from one era to the next. The individual era effects will be heavily shaped by the data from patients within the eras.

7.4. *Age Effects*

For identifiability, the age parameter for the middle age group, 41 to 65 will be set to 0. We model the three remaining age effects with independent normal priors:

$$[\lambda_{age}] \sim N(0, 10^2); age = 1,3,4.$$

7.5. *Intervention Common Effects*

Each intervention parameter β_{d_j} for d=1,…,D; j=1,…,J_d is considered the relative effect of each intervention. For identifiability, the effect for the first intervention within each domain is set to 0.

For some domains, there may be sets of interventions that are considered "nested". For these nested interventions, the intervention effects are modeled hierarchically, which allows borrowing among the intervention effect estimates for the interventions within the nest. Each domain-specific appendix will specify which interventions, if any, will be considered nested for the model.

For all non-nested interventions, the intervention effects are given weak independent priors:

$$\left[\beta_{d_j}\right] \sim N(0, 10^2).$$

For the set of nested interventions within a domain, the prior for interventions within the nest is

$$\left[\beta_{d_j}\right] \sim N\left(\mu_\beta, \tau_\beta^2\right),$$

With hierarchical priors

$$[\mu_\beta] \sim N(0, 10^2); [\tau_\beta^2] \sim IG(0.125, 0.00281).$$

For the set of nested interventions within a domain, the hyperparameters are selected such that the prior for τ_β is centered at 0.15 with weight 0.25. For non-nested interventions, the intervention effects are modeled separately, corresponding to large τ_β^2.

For the purpose of assessing statistical triggers that lead to platform decisions, the analysis will be repeated, with nested interventions pooled together ($\tau_{\beta}^{2} = 0$). However, the model with hierarchically modeled nested interventions will be the primary model that drives the adaptive randomization.

7.6. *Intervention by Strata Effects*

It is anticipated that there may be interactions between stratum membership and some interventions, but in general expected to be small. The protocol enumerates three choices for modelling the intervention by strata interaction terms. These choices are described in the protocol as the "gamma parameter" though they actually refer to choices for the standard deviation of the prior distribution for the interaction parameter. Each domain-specific appendix will pre-specify which of the following options is selected for each intervention-strata pair within that domain:

- On one extreme, the interaction parameter may be set to zero, $\gamma_{kd_j} = 0$, forcing the model to estimate no interaction; thus, the treatment effect of the intervention is not permitted to differ between strata.
- On the opposite extreme, the interaction parameter may be given a weak prior,

$$\left[\gamma_{kd_j}\right] \sim N(0, 10^2)$$

which is described in the protocol as gamma = infinity. This prior spreads its mass over the real line.

- Finally, the prior for the interaction parameter may be selected as

$$\left[\gamma_{kd_j}\right] \sim N(0, 0.15^2)$$

which has a standard deviation of 0.15 (referred to as gamma = 0.15 in the protocol). This prior places most of its mass on small values, effectively shrinking the estimate of the interaction towards zero. For reference, on the log-odds scale (in which the parameter $\gamma$are) an effect of 0.15 is an odds-ratio of 1.16, which would make a probability of 0.20 increase to 0.225. This prior standard deviation value was selected by the ITSC in evaluating the model behavior versus possible scenarios.

7.7. *Intervention by intervention interactions*

It is anticipated that there may be interactions between some interventions, but that these would likely be relatively small.

For all two-way interaction parameters, three choices are available for modeling purposes. These choices are described in the protocol as the "lambda parameter" though they actually refer to choices for the standard deviation of the prior distribution for the interaction parameter. One of the following options will be pre-specified for each intervention-intervention pair:

- The model may force no interaction between a pair of interventions by setting the interaction parameter equal to zero. That is, $\delta_{d_j,d'_{j'}} = 0$ for the interaction between intervention j in domain d and intervention j' in domain d' (where $d \neq d'$). In the protocol, this option is written as lambda = 0.
- On the opposite extreme, the interaction term may be given a weak prior:

$$\left[\delta_{d_j,d'_{j'}}\right] \sim N(0, 10^2)$$

which is described in the protocol as lambda = infinity.

- Finally, the prior for the interaction parameter may be selected as

$$\left[\delta_{d_j,d'_{j'}}\right] \sim N(0, 0.05^2)$$

For reference, on the log-odds scale (in which the parameter δ are) an effect of 0.05 is an odds-ratio of 1.05, which would make a probability of 0.20 increase to 0.208. These prior values were selected by the ITSC in evaluating the model behavior versus possible scenarios.

8. STATISTICAL QUANTITIES

The following statistical quantities are used in the design of the trial. The posterior distribution of the model parameters is calculated using MCMC. The algorithm allows the generating of at least M (100,000) draws from the joint posterior distribution. The following posterior quantities are calculated during the MCMC algorithm. For each regimen, r, we define π_{r,g_k} as the relative

effectiveness of the regimen, for group *g* within strata *k*. Similarly, $\pi_{r,g_k}^{(m)}$ as the relative effectiveness of regimen *r* for group *g* within strata *k*, for the *m*th draw from the MCMC algorithm.

8.1. *Probability of Optimal Regimen*

Let $O_{g_k}(r)$ be the posterior probability that a regimen, *r*, is the optimal regimen for group *g* within strata *k*. For the *m*=1,…,*M* draws from the posterior, the frequency of draws in which each unique regimen, *r*, is optimal in group g_k, is tracked. The frequency each regimen is optimal is the posterior probability that the regimen is the optimal regimen:

$$O_{g_k}(r) = \frac{1}{M}\sum_{m=1}^{M} I\left[\pi_{r,g_k} < \pi_{q,g_k} \text{ for all } q \neq r\right]$$

8.2. *Probability of Optimal Intervention*

While $O_{g_k}(r)$ tracks the posterior probability that a regimen is optimal, we also track the probability that an individual intervention is in the optimal regimen. We refer to the posterior probability an intervention *j*, from domain *d*, is in the optimal regimen for group g_k, as $\Lambda_{g_k}(d_j)$:

$$\Lambda_{g_k}(d_j) = \frac{1}{M}\sum_{m=1}^{M} I\left[d_j \in r | \pi_{r,g_k} < \pi_{q,g_k} \text{ for all } q \neq r\right].$$

9. TRIAL ADAPTATION AND STOPPING CRITERIA AND GUIDELINES FOR INTERVENTIONS

The trial design is an adaptive perpetual platform trial design. The platform aspect of the trial refers to the fact that there will be multiple investigational interventions being simultaneously studied. The trial is designed to be perpetual and continue studying severe community-acquired pneumonia (severe CAP), with no designated end. The goals of the trial are to both treat patients effectively while also investigating the relative benefit of different interventions, within different groups of patients. The design is adaptive in that the key aspects of the trial will evolve in a pre-planned way based on accruing data.

First, there will be a starting status with regard to strata, domains, and the interventions within a domain. These aspects are expected to change during the course of the REMAP trial. Strata can be

added or removed. Similarly, domains can be added or removed, and interventions within the domains can be added or removed based on internal or external information. The trial design is generic in terms of the number of strata, domains, and interventions within a domain, so that the trial functions seamlessly, based on predefined rules, as the questions being evaluated within the trial evolve. Each section below describes aspects of the trial design that will evolve in a predetermined fashion based on accruing empirical information.

9.1. *Data Sources*

All patients in the perpetual trial will become a part of the accruing data in the trial. There will be a set of patients in the primary analysis population. All patients in the primary analysis population will remain in that population for as long as the trial is running.

9.2. *Primary Analysis Population*

The primary analysis population will consist of all patients that are randomized to at least one of the interventions and at least one intervention is revealed. The primary analysis population will be used for all efficacy endpoints and will be determined in accord with the intention to treat (ITT) principle and will comprise all randomized patients, analyzed by the regimen to which they were randomized and their stratum membership as determined at the time of randomization.

Other analysis populations may be used in supportive analyses of efficacy endpoints (when a Public Disclosure has been triggered) and in the analyses of domain-specific safety endpoints.

- A modified intention to treat (mITT) population, which will include only participants who received at least 1 dose of the allocated treatment (or similarly defined in the DSA for non-pharmacological interventions)
- A per protocol (PP) population, which will include only eligible patients who received the allocated intervention with no major protocol violations and where all outcomes were observed.

9.3. *Adaptive Analyses*

Adaptive analyses will be conducted frequently throughout the trial process. The first adaptive analysis will occur when there are a significant number of patients with 90-day outcome data. After that first adaptive analysis, they will be planned to be repeated monthly, perpetually, for the

remainder of the trial. Interim analyses may be skipped if, due to seasonal variations, enrollment is slow and little new information has accrued during the month. A regular time period (e.g. first of the month) will be selected and this will trigger the running of an adaptive analysis. These adaptive analyses will consist of all currently available data being analyzed according to the current trial model. Only data for patients reaching a 90-day window from time of randomization will be used in the analysis to avoid biases that may arise from differential timing of known failure compared with known success. The model run will be used to trigger allocation updates and possible Statistical Triggers (determining superiority, inferiority, and equivalence). These rules are presented in the following sections.

9.4. *Allocation (Response Adaptive Randomization)*

The allocation during the platform trial is adaptively set based on the accruing efficacy data. The data on the primary endpoint (mortality) will shape the randomization proportions for each regimen, within each stratum.

9.5. *Initial randomization ratio*

During the start to this trial there will be a period of time, the burn-in period, in which a response adaptive randomization scheme will be used with no new data. This response adaptive randomization will be based on initial prior parameters. Unless priors are selected favoring certain treatments within stratum these probabilities will be equal for each intervention.

9.6. *Response Adaptive Randomization*

After the burn-in period, RAR will be used for the allocation for each regimen. Allocation to the regimens will be allowed to vary across the patient groups defined by the strata. Patients will be enrolled in the trial and randomized to a regimen according the group they belong to within each strata. The randomization for each patient is based on the probability that each regimen is the optimal regimen for a patient within that patient strata, but balanced by the sample size already allocated to that regimen. This balancing creates better learning about the optimal regimen by allowing a less aggressive randomization to regimens that already have a larger number of patients allocated. We refer to this scheme as maximizing the information about the optimal regimen within a stratum.

The randomization for a patient in group *g* within strata *k* is proportional to

$$\rho_{r,g_k} \propto \sqrt{\frac{O_{g_k}(r)}{n_{r,g_k}+1}}.$$

Where $O_{g_k}(r)$ is the probability that regimen *r* is optimal for patients in group *g* of strata k and n_{r,g_k} is the total number of patients in group *g* of strata *k* who have already been allocated to regimen *r*. Multiple normalizations are done to create the final randomization probabilities. The following steps are carried out.

1. Each randomization probability is normalized to sum to 1 by dividing by the sum of quantities over all regimens.
2. Any single intervention with a sum of probabilities across all regimens within a stratum less than 10% will be increased to sum to the floor randomization per intervention of 0.10. Note that a minimum randomization of 10% implies a maximum randomization probability of 90%
    a. A nuisance parameter (φ) will be added to the odds ratio for each intervention that does not achieve at least a 10% randomization probability. The value of φ will be selected to create a minimum randomization probability of 10% for each intervention.

The result is a set of randomization probabilities for each regimen, for each group as defined by the strata.

9.7. *Introduction of new interventions*

While this REMAP is running, if a new intervention is started then the randomization will be "blocked" for the new intervention in order to guarantee an initial sample size. If there are J_d interventions in a domain after the new intervention is started, then a fixed allocation of $1/J_d$ will be used to allocate patients to the new intervention. The remaining $1-\frac{1}{J_d}$ probability will be allocated to the other interventions using the RAR. This burn-in for each intervention will last until 25 patients have been allocated to the new intervention. At that point this restriction will be removed and adaptive randomization to all regimens will be carried out.

9.8. *Intervention Efficacy Announcement / Conclusion*

At each adaptive analysis the results of the relative efficacy of different interventions can trigger adaptive decision rules. These include Public Disclosure of the results, removal of interventions within strata, and deterministic allocation to interventions within strata. The following sections present the prospective rules for these adaptive decisions. The adaptive analyses will be carried out by the Statistical Analysis Committee (SAC).

9.9. *Intervention Superiority*

At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being the optimal intervention for a strata group, $\Lambda_{g_k}(d_j) > 0.99$, and there are at least 250 patients randomized to that intervention in that strata group, then that intervention, within that domain, will be deemed as being superior within that strata group, triggering a Public Disclosure. At that point, the remaining interventions in the domain will be halted for inferiority for that strata group. All future patients in that strata group will then be allocated to that superior intervention and randomized to interventions in the other domains. This will continue until new interventions are added to the domain that contains the superior intervention.

9.10. *Intervention Inferiority*

At any adaptive analysis, if a single intervention has less than a $0.01/(J_d-1)$ posterior probability of being the optimal intervention for a strata group $\Lambda_{g_k}(d_j) < 0.01$, then that intervention will be deemed as being inferior within that domain, for that strata group, triggering a report to the Data Safety and Monitoring Board (DSMB). The DSMB then makes a judgment on whether a Platform Conclusion has been reached and whether to trigger a Public Disclosure. If so, no additional patients in that strata group will be randomized to that intervention. When simultaneous superiority/inferiority occurs (for example when there are 2 interventions they are always simultaneous), then the result will be released as an intervention demonstrating superiority.

9.11. *Intervention Equivalence*

If the two interventions within the domain have at least a 90% posterior probability that the odds ratio comparing the two within any stratum is between 1/1.2, and 1.2, the two interventions will be considered equivalent for that stratum. This result will be communicated to the ITSC and they will

take the appropriate action (Public Disclosure, removal of one intervention, no action). There is no automatic adaptation when this occurs.

9.12. *Deviation from pre-specified analyses (contingency plans, non-convergence, testing model fit etc.)*

The SAC will monitor the model behavior, including numerical stability and scientific appropriateness. Simpler models will be constructed and evaluated determining any root cause issues, data issues, or inappropriate model fit. If any numeric instabilities can be fit in statistical numeric methods, these will be done by the SAC and the adjustments recorded and noted. If the model is deemed to provide an inappropriate fit then the SAC will inform the DSMB of appropriate adjustments which will be reported to the ITSC in a way that does not risk unblinding trial results. Possible adjustments could include:

1. If there are issues within an intervention for limited data the parameter for that intervention can be fixed for model stability.
2. If there is missing data on whether there were revelations of delayed reveals and/or state values then an ITT Model ignoring the changing states will be fit to explore the effects
3. A reasonable solution should technology fail or data issues arise would be to keep the randomization unchanged, fix the randomization for an intervention, or create equal randomization for all interventions/regimens.

Statistical Analysis Plan for the COVID-19 Antiviral Therapy Domain for Patients with COVID-19 Pandemic Infection Suspected Or Proven (PISOP)

COVID-19 Antiviral Domain SAP Version 1.0 dated 14 January 2021

CONTENTS

1. COVID-19 ANTIVIRAL DOMAIN SAP VERSION

The version is in this document's header and on the cover page.

1.1 VERSION HISTORY

Version 1: Draft dated January 5, 2021.

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3. INTRODUCTION

This statistical plan for the analysis of the COVID-19 Antiviral Therapy Domain in the pandemic stratum of REMAP-CAP is an appendix to the Pandemic Appendix to Core (PAtC) Statistical Analysis Plan (SAP). This plan details the statistical analyses in the original REMAP-CAP core SAP and the pandemic stratum SAP applied to the analysis of the COVID-19 Antiviral Therapy Domain interventions in the Severe State. This plan is prespecified for the imminent unblinding of the data for the COVID-19 Antiviral Therapy Domain interventions within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

Enrollment in the COVID-19 Antiviral Therapy Domain started on April 8th, 2020. The hydroxychloroquine arms (including hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir arms) in the COVID-19 Antiviral Therapy Domain were halted in the PISOP stratum on May 23rd, 2020, based on concerns regarding the safety and efficacy of hydroxychloroquine which was later substantiated by the press release of the results of the RECOVERY trial (https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf). The lopinavir/ritonavir arm in the COVID-19 Antiviral Therapy Domain was halted in the PISOP stratum on Nov 19th, 2020 after reaching a prespecified futility threshold.

The authors of this document are blinded to the data and results in REMAP-CAP other than those already publicly disclosed results.

4. DESIGN CONSIDERATIONS

REMAP-CAP is designed with Bayesian analyses as the primary analysis method for the trial. There is one overarching Bayesian model, prespecified in the SAP, driving all adaptations, platform conclusions, and result summaries. Similar to the SAP used for the Corticosteroids and the Immune Modulation Therapy Domains, the primary statistical analysis model will be used to report the results for the severe state in the COVID-19 Antiviral Therapy Domain within the PISOP stratum. At the time of concluding enrollment in the lopinavir/ritonavir, hydroxychloroquine and lopinavir/ritonavir plus hydroxychloroquine arms, there were <100 patients enrolled in the moderate state, therefore it was decided to only report descriptive data by assignment for this state to facilitate future systematic reviews by others.

The decision to use a Bayesian analysis in REMAP-CAP was driven in part by the uncertainty of the extent of the pandemic. The sample size could be small, or large, and there may be unexpected external events, that alter the design of REMAP-CAP. Given the expected

evolution of the design, and uncertain sample size, a Bayesian approach was deemed more appropriate.

REMAP-CAP defines several statistical triggers within the trial that, at any analysis of the trial, would result in public disclosure and a declaration of a platform conclusion.

The following internal statistical triggers were pre-defined for the interventions in the COVID-19 Antiviral Therapy Domain:

1. **Domain Superiority**. If an intervention in the COVID-19 Antiviral Therapy Domain has at least a 99% posterior probability of being in the best regimen for patients in state s of the PISOP stratum (i.e. superior to all other interventions in the domain), this would trigger domain superiority of that intervention within that state.
2. **Intervention Efficacy**. If an intervention in the COVID-19 Antiviral Therapy Domain is deemed to have at least a 99% posterior probability of being superior to the control in state s, then a declaration of efficacy of that intervention would be declared for state s. This statistical trigger is active for each of the non-control arms in the COVID-19 Antiviral Therapy Domain.
3. **Intervention Equivalence**. If two non-control interventions have a 90% probability of equivalence, this would trigger a public disclosure of intervention equivalence.
4. **Intervention Futility**. Because the hydroxychloroquine arms have been stopped for external reasons, no futility analyses will be reported for this arm. For lopinavir/ritonavir, if an intervention is deemed to have a less than 5% probability of at least a 20% odds ratio improvement compared to the control, then a declaration of futility would be declared.

The 99% threshold for efficacy was selected to have good properties for potential outbreak sample sizes. For example, the type I error rate of any conclusion of efficacy for a single intervention 'A' vs. control is less than 2.5% for approximately less than 1000 patients on intervention 'A' with multiple interim analyses (see main and pandemic SAP).

Importantly, the ITSC halted the hydroxychloroquine and the combination of hydroxychloroquine and lopinavir/ritonavir arms of REMAP-CAP before the first interim analysis. At the time of analysis, being halted early does not change the Bayesian statistical triggers of the domain; the same thresholds apply. However, since there will be no further

enrollment into the hydroxychloroquine and the combination of hydroxychloroquine and lopinavir/ritonavir arms of the COVID-19 Antiviral Therapy Domain for patients within the pandemic stratum, the results are still of value regardless of whether they support any particular internal trigger. Thus, we emphasize the posterior probabilities (and 95% credible intervals) are more informative in contributing to overall knowledge about hydroxychloroquine in COVID-19 than whether a particular posterior probability exceeded a pre-defined threshold in REMAP-CAP.

5. UNBLINDING

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. At the unblinding of the COVID-19 Antiviral Therapy Domain, there are other interventions to which patients have been randomized that will not be unblinded at this analysis unless a statistical trigger is hit at the time of the primary analysis. In the analysis plan, there will be analyses conducted by the Statistical Analysis Committee (SAC) using additional randomizations and also unblinding of other randomizations. The SAC is unblinded to all arms/domains in their function for REMAP-CAP. There will also be analyses that are conducted with only knowledge of unblinded interventions and domains. At this time, that includes the COVID-19 Antiviral Therapy Domain allocation, the Corticosteroid Domain allocation, and the reported arms of the Immune Modulation Therapy Domain. These may be conducted by investigators who are blinded to other information about other domains. These analyses are identified below.

6. INTERVENTIONS

There are 4 interventions within the COVID-19 Antiviral Therapy Domain. These are

1. No antiviral for COVID-19
2. Lopinavir/ritonavir
3. Hydroxychloroquine
4. Hydroxychloroquine and lopinavir/ritonavir

For the primary analysis completed by the SAC and all secondary analyses completed by blinded investigators, all four arms will be modeled, and analysis results for all arms will be reported.

In addition, the models in this SAP will estimate and report the interaction effects of the interventions in the COVID-19 Antiviral Therapy Domain with the Corticosteroid Domain and reported arms of the Immune Modulation Therapy Domain.

7. DISEASE STATES

There are 2 disease states in the PAtC, which are **moderate** and **severe**. In most participating sites, the COVID-19 Antiviral Therapy Domain randomized to patients in the severe state, and as indicated earlier, this SAP describes the analysis of patients in the severe state. In one site, patients were randomized to the hydroxychloroquine and no antiviral therapy arms in the moderate state. Descriptive data on these patients will be reported separately.

8. ANALYSIS POPULATIONS

1. REMAP-COVID intent-to-treat (ITT). All patients within the PISOP stratum initially randomized in the severe state randomized within at least one domain.
2. Unblinded ITT. All patients within the PISOP stratum initially randomized in the severe state randomized to an intervention in the COVID-19 Antiviral Therapy Domain, the Corticosteroid Domain, or reported arms of the Immune Modulation Therapy Domain. Note the assignment to the interventions mentioned above will be unblinded, the other intervention assignments will not be unblinded to the analysis team.
3. Unblinded ITT Non-negative. All patients within the Unblinded ITT population after removing those with $\geq$1 negative test for COVID **and** no positive tests.
4. Antiviral specific ITT. All patients within the PISOP stratum initially randomized in the severe state randomized to an intervention or no antiviral for COVID-19 Antiviral Therapy Domain.
5. Antiviral specific ITT Moderate State. All patients within the PISOP stratum in the moderate state randomized to an intervention or no antiviral for COVID-19 Antiviral Therapy Domain.

9. ENDPOINTS

The following endpoints will be analyzed, graphically displayed, and/or summarized through descriptive statistics.

1. **Organ-Support Free-Days** (OSFD)
    a. An ordinal endpoint with mortality as the worst outcome. The primary endpoint for the REMAP-CAP PISOP stratum. The types of organ support considered are cardiovascular (vasopressor/inotrope support) and respiratory support. See Appendix A for a detailed description.

2. **In-Hospital Mortality**
    a. A dichotomous endpoint of survival/in-hospital death where the death component corresponds to a –1 on the OSFD endpoint.

3. **Mortality**
    a. This is a time-to-event endpoint through 90-days.
    b. Any patient currently in the hospital or transferred on organ support to an alternative care facility will be censored at their last known status alive.
    c. Any patient successfully discharged from hospital, alive, without organ support, will be censored at the date of discharge, if 90-day mortality data are not yet recorded.

4. **Progression to intubation and mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death**
    a. A dichotomous endpoint of whether a patient progresses to intubation and mechanical ventilation, ECMO or death in hospital.
    b. This endpoint will only be analyzed for subjects that are not on intubation, mechanical ventilation, or ECMO at baseline.

5. **Cardiovascular (Vasopressor/Inotrope) Free-Days**
    a. An ordinal outcome of number of days free of Vasopressor/Inotropes. This is the exact calculation of OSFD, with Vasopressor/Inotropes as the only organ support category. In-hospital death is considered a –1.

6. **Respiratory support Free-Days**
    a. An ordinal outcome of number of days free of respiratory support. This is the exact calculation of OSFD, with respiratory support as the only organ support category. In-hospital death is considered a –1.

7. **Duration of ICU stay**
    a. A time-to-event endpoint of leaving the ICU alive. If a patient is known to leave the ICU and return to the ICU within 14-days that intervening time will be ignored.

b. This variable will be truncated at 90-days: all deaths in ICU will be considered 90-days with no liberation of ICU.
c. Patients still in the ICU at data snapshot will be considered censored.

8. **Duration of hospital stay**
   a. A time-to-event endpoint of leaving the hospital alive. If a patient is known to leave and return to the hospital within 14-days that intervening time will be ignored.
   b. This variable will be truncated at 90-days and all deaths in-hospital will be considered 90-days with no events.
   c. Patients still in the hospital at data snapshot will be considered censored.

9. **At least one serious adverse event (SAE)**
   a. A dichotomous endpoint of SAE.
   b. This endpoint will be summarized descriptively. Counts and proportions of SAEs will be provided by intervention.

10. **Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital.**
    a. A dichotomous endpoint
    b. This endpoint will be summarized descriptively. Counts and proportions will be provided by intervention.

11. **The World Health Organization (WHO) 8-point ordinal scale, measured at day 14.**

    A modified WHO ordinal scale will be used:

    0 + 1 + 2 = No longer hospitalized

    3 = Hospitalized, no oxygen therapy

    4 = Oxygen by mask or nasal prongs

    5 = Non-invasive ventilation or high-flow oxygen

    6 = Intubation and mechanical ventilation

    7 = Ventilation + additional organ support: vasopressors, renal replacement therapy (RRT), ECMO

    8 = Death

12. **Time to SARS-CoV-2 RNA clearance**
    a. A time-to-event endpoint of time to SARS-CoV-2 RNA clearance

b. This variable is calculated for COVID-19 positive patients as the time from enrollment to the first negative test not followed by a positive test (Appendix B).

10. GRAPHICAL DATA SUMMARIES

1. Ordinal endpoints will be graphed using stacked cumulative bar plots.
2. Time-to-event endpoints will be plotted using Kaplan-Meier plots. Positive clinical event outcomes will be plotted as the cumulative rate of event, and negative events will be plotted as the cumulative rate of event-free.

11. DESCRIPTIVE STATISTICS

1. Ordinal endpoints will be summarized by the cumulative frequency of each outcome for each state. The 25th, 50th, and 75th percentiles will be summarized.
2. Dichotomous endpoints will be summarized by the proportion in each category for each state.
3. Time-to-event outcomes will summarize the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates by state.

12. BASELINE CHARACTERISTICS

The following demographics will be summarized across arms. More may be added as baseline summaries.

Age, sex, BMI, ethnicity, APACHE II score (measured from hospital admission to randomization), confirmed SARS CoV-2 infection, preexisting conditions, baseline use of high-flow nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, randomization to corticosteroids, tocilizumab or sarilumab within REMAP-CAP and miscellaneous physiological values.

13. COMPLIANCE

The compliance to lopinavir/ritonavir and hydroxychloroquine use will be summarized descriptively as the fraction of use, the amount, and duration for each randomized arm.

14. ANALYTIC APPROACH

Each inferential analysis will be done using a Bayesian model. Some default frequentist methods are used for exploration and description. A summary of the analysis methods is provided below.

14.1 PRIMARY ANALYSIS OF PRIMARY ENDPOINT

The **primary analysis model** is a Bayesian cumulative logistic model for the ordinal primary endpoint. The model is described below. The primary endpoint for the severe state has 24 possible, ordered outcomes. Let the outcome for a patient by labeled as $Y_{i,s}$, with possible values, –1 (death), 0, 1, …, 21, 22. The outcome of 22 (never received organ support) for the severe state is not possible. Hence there are 23 possible outcomes in the severe state. A cumulative logistic model is specified. The model is structured so that an odds-ratio >1 implies patient benefit. The full details of the model are specified in the Current State Version 2.3 AV. The model has factors for:

- Each level of the ordinal endpoint
- Each Global site, nested within country
- Age; ≤39, 40-49, 50-59, 60-69, 70-79, 80+
- Sex
- Time; 2-week buckets of time working backwards from the last enrolled patient, with the most recent bucket being 4 weeks. Time buckets are defined to be the same time periods for both moderate and severe patients.
- For each domain an effect for being randomized to the domain
- An effect for each intervention within each domain
- Specified interactions in the model between domains

The primary analysis for the lopinavir/ritonavir and hydroxychloroquine uses the following rules:

- All sites within a country that have <5 patients randomized in a state will have their results combined into a single site within that country.
- If there is an outcome in the ordinal scale that did not occur in the data, then that outcome will be combined to a single outcome with a neighboring outcome (the worse outcome). This is done by state for model stability. For example, if the outcome 11 never

occurred in moderate a combined outcome of 10 & 11 will be modeled for the moderate analysis.

- If a time bucket has <5 patients in a state, the bucket will be collapsed with the adjacent earlier bucket in that state.
- The high-dose 7-day hydrocortisone arm will be combined with the 7-day hydrocortisone arm (fixed-duration). They were originally nested, which allows their pooling, and there were very few patients randomized to the high-dose 7-day hydrocortisone arm.
- All interactions between the shock-based steroid arm and other domains will be dropped (assumed to be zero)
- The two IL-6 receptor agonists, Tocilizumab and Sarilumab, will be combined in to a single IL-6ra arm
- For patients who were randomized as part of REMAP-CAP COVID-19 severe state ITT after the closure of Corticosteroid Domain (June 17, 2020), the subjects are coded as receiving fixed-dose hydrocortisone.

The primary analysis model will be referenced with certain model assumptions for sensitivity analyses. For example, the “time effects” in the model could be assumed to be 0.

14.2 PROPORTIONAL ODDS ASSUMPTION

The primary analysis model is based on an assumption of a proportional effect of treatment across the scale of the ordinal outcome. In order to assess the robustness of the results to this assumption, a dichotomous model is fit to every level of the ordinal outcome across the scale and the odds-ratio for each dichotomous break is presented. For tail events, if the cumulative probabilities are less than 5% or greater than 95% these dichotomous may be ignored. No statistical test of proportional odds is conducted.

14.3 ANALYTIC APPROACH FOR SECONDARY DICHOTOMOUS ENDPOINTS

A Bayesian logistic regression model will be used for each dichotomous outcome. The model will always specify the “event” as the negative outcome, so that an odds-ratio >1 implies benefit to patients within each model. The model is the standard logistic link function model with state-specific intercept, α_s and state-specific coefficients for all factors in the model:

$$\log\left(\frac{\pi_s}{1-\pi_s}\right) = \alpha_s - [\text{factors}_s]$$

References will be made to the factors in the model and their prior distribution. Many of these factors will be the same as the primary analysis model, with the same priors, as the parameters have similar interpretation. If not otherwise specified, the prior distribution for the main effect is $\beta \sim N(0, 1.82^2)$ (similar to a uniform prior on the probability scale).

14.4 ANALYTIC APPROACH FOR SECONDARY TIME-TO-EVENT ENDPOINTS

All inferential time-to-event analyses will be done using a Bayesian piecewise exponential model. The Bayesian time-to-event model is intended to mirror a Cox proportional hazards model, with the underlying state-specific hazard rate modeled with a piecewise exponential model. The underlying hazard will be modeled with a hazard rate for 10-day period each day in the model. The prior distribution for each day hazard rate is a gamma distribution with 1 day of exposure and a mean equal to the total exposure divided by the total number of events for each state. This prior will have very little weight but will provide numerical stability to the model. Each factor is incorporated as a proportional hazard rate through an additive linear model of the log-hazard. The default prior for each factor is the same as for the log-odds in the ordinal model. If other non-specified variables are added to the model, then a normal distribution with mean 0 and standard deviation 10 will be utilized.

14.5 MARKOV CHAIN MONTE CARLO (MCMC) MODEL STABILITY

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence of the MCMC and the mixing behavior. These instabilities may be based on sparse data on the outcome or covariates. The statisticians running the model may make changes that do not affect the overall outcome but provide reliable model diagnostics and scientific rigor. Any alterations will be noted.

14.6 MODEL OUTPUTS

The standard model outputs for each treatment effect will be the mean, standard deviation, median, and 95% credible intervals (all credible intervals will range from equal-tailed percentiles, so 95% credible intervals will range from the 2.5^{th} percentile to the 97.5^{th} percentile). For the ordinal model the odds-ratio will be summarized for each state. For the dichotomous endpoints, the odds-ratio will be summarized for each state. For the time-to-event model the hazard ratio will be summarized for each state. For consistency, all models

will be parameterized so that an odds-ratio or hazard-ratio greater than 1 indicates clinical benefit.

For each inferential model, a posterior probability that one arm is superior will be provided for each comparison between arms and for each state. This posterior probability has been identified as the primary analysis metric between arms. A posterior probability greater than 99% of superiority has been identified as statistically significant in REMAP-CAP.

14.7 EXPLORATORY ANALYSES

Exploratory analyses after unblinding will not be considered inferential and no p-values will be presented. Any post-hoc exploratory analyses will use the following methods:

1. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the odds-ratio, with 95% confidence intervals and Wilcoxon test for robustness against a lack of proportional odds.
2. Time-to-Event analyses will utilize a Cox proportional hazards model, summarizing the hazard ratios and 95% confidence intervals.
3. Continuous endpoints will compare means with 95% confidence intervals based on two-sample t-test procedures.
4. Dichotomous proportions will be compared using logistic regressions summarizing the odds-ratio and 95% confidence intervals. Differences between proportions will be summarized using observed differences and normal approximations for the 95% credible intervals.

15. SPECIFIC PROSPECTIVE ANALYSES

There are 32 specific prospective analyses, summarized in the table and described in detail below.

#	Status	Population	Endpoint	Other
15.1	Primary	REMAP-CAP COVID-19 severe state ITT	OSFD	Includes all interventions and interactions.
15.2	Primary	REMAP-CAP COVID-19 severe state ITT	In-Hospital Mortality	Includes all interventions and interactions.
15.3	Sensitivity	REMAP-CAP COVID-19 severe state ITT	OSFD	Includes all interventions and interactions. Includes less informative standard normal priors on pre-specified combinations of antivirals, steroids, tocilizumab and sarilumab.

#	Status	Population	Endpoint	Other
15.4	Sensitivity	REMAP-CAP COVID-19 severe state ITT	Dichotomized OSFD	A logistic regression will be run for each dichotomization of OSFDs as a robustness check.
15.5	Secondary	Unblinded ITT	OSFD	
15.6	Secondary	Unblinded ITT	In-Hospital Mortality	
15.7	Subgroup*	Unblinded ITT	OSFD	Including differential treatment effects by the presence or absence of shock at enrollment
15.8	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by the presence or absence of shock at enrollment
15.9	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by invasive mechanical ventilation at enrollment
15.10	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by invasive mechanical ventilation at enrollment
15.11	Sensitivity	Unblinded ITT	OSFD	Remove site and time effects
15.12	Sensitivity	Unblinded ITT	In-Hospital Mortality	Remove site and time effects
15.13	Sensitivity	Unblinded ITT	OSFD	Alternative coding of steroid interventions after closure of steroid domain.
15.14	Sensitivity	Unblinded ITT	In-Hospital Mortality	Alternative coding of steroid interventions after closure of steroid domain.
15.15	Secondary	Unblinded ITT Non-negative	OSFD	
15.16	Secondary	Unblinded ITT Non-negative COVID-19	In-Hospital Mortality	
15.17	Secondary	Antiviral therapy specific ITT	OSFD	
15.18	Secondary	Antiviral therapy specific ITT	In-Hospital Mortality	
15.19	Sensitivity	Antiviral therapy specific per protocol	OSFD	
15.20	Sensitivity	Antiviral therapy specific per protocol	In-Hospital Mortality	
15.21	Secondary	Unblinded ITT	Mortality	
15.22	Secondary	Unblinded ITT not on MV, ECMO at baseline	Progression to intubation, ECMO, death	
15.23	Secondary	Unblinded ITT	Days-Free of vasopressor/inotropes	
15.24	Secondary	Unblinded ITT	Respiratory support free days	
15.25	Secondary	Unblinded ITT	Length of ICU Stay	
15.26	Secondary	Unblinded ITT	Length of Hospital Stay	
15.27	Secondary	Unblinded ITT	WHO Scale at 14 days	

#	Status	Population	Endpoint	Other
15.28	Secondary	Unblinded ITT	Time to SARS-CoV-2 RNA clearance	
15.29	Primary Safety Analysis	Antiviral therapy specific ITT	Serious adverse events per patient	Time effects removed from model.
15.30	Primary Safety Analysis	Antiviral therapy specific ITT	Serious ventricular arrhythmia	Time effects removed from model.
15.31	Graphical Summaries	Antiviral therapy specific ITT	All endpoints	Including combinations across unblinded domains.
15.32	Descriptive summaries	Antiviral therapy specific ITT, moderate state	All endpoints	

* There are 2 additional subgroups defined in the DSA based on the co-infection with influenza and bacterial pathogens that will not be perused, due to the small numbers.

15.1 THE PRIMARY ANALYSIS FOR THE COVID-19 ANTIVIRAL THERAPY DOMAIN

- Population: REMAP-COVID severe state ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids, and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the unblinded SAC

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility
d. Only information on the Corticosteroid Domain, the COVID-19 Antiviral Therapy Domain and the reported arms of the Immune Modulation Therapy Domain will be disclosed.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ * IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.2 THE PRIMARY MORTALITY ANALYSIS FOR THE COVID-19 ANTIVIRAL THERAPY

- Population: REMAP-COVID severe state ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-

based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.

- Analysis: Conducted by the unblinded SAC

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility
d. Only information on the Corticosteroid Domain, the COVID-19 Antiviral Therapy Domain and the reported arms of the Immune Modulation Therapy Domain will be disclosed.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.3 A SENSITIVITY ANALYSIS OF THE PRIMARY ANALYSIS OF THE COVID-19 ANTIVIRAL THERAPY WITH LESS INFORMATIVE PRIORS ON INTERACTION EFFECTS

- Population: REMAP-CAP COVID-19 severe state ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model with weaker priors for the interaction effects
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the unblinded SAC

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between each antiviral and corticosteroid intervention and tocilizumab and sarilumab will be reported relative to control.
d. The prior distributions will be set to N(0,1) for the following interactions: each antiviral intervention with fixed-dose corticosteroid intervention, each antiviral intervention with IL-6.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.4 A SENSITIVITY ANALYSIS OF THE PRIMARY ANALYSIS OF THE COVID-19 ANTIVIRAL THERAPY FOR THE PROPORTIONAL ODDS ASSUMPTIONS

- Population: REMAP-CAP COVID-19 severe state ITT

- Endpoint: Dichotomized Organ Support-Free Days
- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the unblinded SAC

Notes

a. For this analysis, the primary dichotomous model will be fit to each dichotomization of OSFDs and the summaries of the odds-ratio of lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be reported.

   The following summaries will be reported for the lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir odds-ratios:

OSFD Dichotomization	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir				
-1 vs ≥0				
≤0 vs ≥1				
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				
Hydroxychloroquine				
-1 vs ≥0				
≤0 vs ≥1				

OSFD Dichotomization	Mean	SD	Median	95% Credible Interval
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				
Hydroxychloroquine combined with lopinavir/ritonavir				
-1 vs ≥0				
≤0 vs ≥1				
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				

15.5 A SECONDARY ANALYSIS RESTRICTED TO THE UNBLINDED ITT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.6 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO UNBLINDED ITT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain or the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.7 A SUBGROUP ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY SHOCK AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by shock status, a fixed effect for shock status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across shock status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by shock status. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with shock	
Lopinavir/ritonavir is futile in patients with shock	
HCQ is in superior to control in patients with shock	
HCQ is futile in patients with shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with shock	
Lopinavir/ritonavir and HCQ combination is futile in patients with shock	
Lopinavir/ritonavir is superior to control in patients with no shock	
Lopinavir/ritonavir is futile in patients with no shock	
HCQ is superior to control in patients with no shock	
HCQ is futile in patients with no shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no shock	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir in shock				
Lopinavir/ritonavir in no shock				
Hydroxychloroquine in shock				
Hydroxychloroquine in no shock				
Lopinavir/ritonavir and HCQ combination in shock				
Lopinavir/ritonavir and HCQ combination in no shock				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.8 A SUBGROUP ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY THE PRESENCE OF SHOCK AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: in-hospital mortality
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by shock status, a fixed effect for shock status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across shock status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by the presence of shock. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control within each shock status.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with shock	
Lopinavir/ritonavir is futile in patients with shock	
HCQ is in superior to control in patients with shock	
HCQ is futile in patients with shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with shock	
Lopinavir/ritonavir and HCQ combination is futile in patients with shock	
Lopinavir/ritonavir is superior to control in patients with no shock	
Lopinavir/ritonavir is futile in patients with no shock	
HCQ is superior to control in patients with no shock	
HCQ is futile in patients with no shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no shock	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir in shock				
Lopinavir/ritonavir in no shock				
Hydroxychloroquine in shock				
Hydroxychloroquine in no shock				
Lopinavir/ritonavir and HCQ combination in shock				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination in no shock				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.9 A SUBGROUP ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY INVASIVE MECHANICAL VENTILATION AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by IMV status, a fixed effect for IMV status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across IMV status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by invasive mechanical ventilation. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with invasive mechanical ventilation	
HCQ is superior to control in patients with invasive mechanical ventilation	
HCQ is futile in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with no invasive mechanical ventilation	
HCQ is superior to control in patients with no invasive mechanical ventilation	
HCQ is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir with IMV				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir with no IMV				
Hydroxychloroquine with IMV				
Hydroxychloroquine with no IMV				
Lopinavir/ritonavir and HCQ combination with IMV				
Lopinavir/ritonavir and HCQ combination with no IMV				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.10 A SUBGROUP ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY INVASIVE MECHANICAL VENTILATION AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: in-hospital mortality
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by shock status, a fixed effect for shock status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across shock status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by invasive mechanical ventilation. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with invasive mechanical ventilation	
HCQ is superior to control in patients with invasive mechanical ventilation	
HCQ is futile in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with no invasive mechanical ventilation	
HCQ is superior to control in patients with no invasive mechanical ventilation	
HCQ is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir with IMV				
Lopinavir/ritonavir with no IMV				
Hydroxychloroquine with IMV				
Hydroxychloroquine with no IMV				
Lopinavir/ritonavir and HCQ combination with IMV				
Lopinavir/ritonavir and HCQ combination with no IMV				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.11 A SENSITIVITY ANALYSIS RESTRICTED TO THE UNBLINDED ITT POPULATION WITH SITE AND TIME FACTORS REMOVED

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.

- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Lopinavir/ritonavir				
Hydroxychloroquine				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.12 A SENSITIVITY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO UNBLINDED ITT POPULATION WITH FACTORS FOR SITE AND TIME REMOVED

- Population: Unblinded ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: Age, sex, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (as a combined IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and tocilizumab and sarilumab will be reported relative to control.

The following posterior probabilities will be reported:

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	

Quantity of Interest	Posterior Probability
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.13 A SENSITIVITY ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT POPULATION WITH DIFFERENT STEROID CODING

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, antiviral domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids and shock-based steroids combined as a corticosteroid arm and

reported interventions of the Immune Modulation Therapy Domain: tocilizumab and no immune modulation combined as an IL-6 arm.

- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and each corticosteroid intervention and IL-6 will be reported relative to control.
d. Fixed-dose and shock-based steroids are pooled for this analysis.
e. Patients randomized after the closure of the Corticosteroid Domain (June 17, 2020) will be coded as receiving steroids if they received steroids within the first two study days.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * corticosteroids				
HCQ * corticosteroids				
Lopinavir/ritonavir and HCQ combination* corticosteroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.14 A SENSITIVITY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENT STEROIDS CODING

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids and shock-based steroids (combined as a corticosteroid arm) and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and corticosteroid intervention, IL-6 will be reported relative to control.
d. Fixed-dose and shock-based steroids are pooled for this analysis.
e. Patients randomized after the closure of the Corticosteroid Domain (June 17, 2020) will be coded as receiving steroids if they received steroids within the first two study days.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir *corticosteroids				
HCQ * corticosteroids				
Lopinavir/ritonavir and HCQ combination* corticosteroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.15 A SECONDARY ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT POPULATION NON-NEGATIVE COVID POPULATION

- Population: Unblinded ITT, Non-negative COVID
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention, IL-6will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.16 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT POPULATION NON-NEGATIVE COVID POPULATION

- Population: Unblinded ITT, Non-negative COVID
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir,

hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention, IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.17 A SECONDARY ANALYSIS OF OSFD FOR ANTIVIRAL THERAPY SPECIFIC ITT

- Population: Antiviral Therapy specific ITT
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.18 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY FOR ANTIVIRAL THERAPY SPECIFIC ITT

- Population: Antiviral specific ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.19A SECONDARY ANALYSIS OF OSFD IN ANTIVIRAL THERAPY SPECIFIC PER PROTOCOL

- Population: Antiviral therapy specific Per Protocol
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.20 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY IN ANTIVIRAL SPECIFIC PER PROTOCOL

- Population: Antiviral specific Per Protocol
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	

Quantity of Interest	Posterior Probability
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.21 A SECONDARY ANALYSIS OF MORTALITY

- Population: Unblinded ITT
- Endpoint: Time-to-death
- Model: Primary TTE model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.22 A SECONDARY ANALYSIS OF PROGRESSION TO INTUBATION, ECMO, OR DEATH, RESTRICTED TO PATIENTS NOT ON MV OR ECMO AT BASELINE

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain or the reported arms of the Immune Modulation Therapy Domain) not on MV or ECMO at baseline.
- Endpoint: Progression to MV, ECMO, or death
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the

same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.23 A SECONDARY ANALYSIS OF DAYS-FREE OF VASOPRESSOR/INOTROPES USE

- Population: Unblinded ITT
- Endpoint: Vasopressor/Inotropes free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
a. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * Tocilizumab				
HCQ* Tocilizumab				
Lopinavir/ritonavir and HCQ combination* Tocilizumab				

15.24 A SECONDARY ANALYSIS OF DAYS FREE OF RESPIRATORY SUPPORT

- Population: Unblinded ITT
- Endpoint: Respiratory support free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune

Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.

- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
a. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.25 A SECONDARY ANALYSIS OF LENGTH OF ICU STAY

- Population: Unblinded ITT
- Endpoint: Length of ICU stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.26 A SECONDARY ANALYSIS OF LENGTH OF HOSPITAL STAY

- Population: Unblinded ITT
- Endpoint: Length of Hospital stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
a. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.27 A SECONDARY ANALYSIS OF THE MODIFIED WHO SCALE AT DAY 14

- Population: Unblinded ITT
- Endpoint: Modified WHO scale at 14-days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir,

hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.28 A SECONDARY ANALYSIS OF TIME-TO-SARS-COV-2 RNA CLEARANCE

- Population: Unblinded ITT
- Endpoint: time-to-SARS-CoV-2 RNA clearance
- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control
d. Because repeated rRT-PCR was not done routinely, this analysis will be carried out only if there is sufficient number of patients with follow-up tests.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.29 THE PRIMARY SAFETY ANALYSIS

- Population: Antiviral specific ITT
- Endpoint: Serious Adverse Events (SAE)
- Model: Primary dichotomous model

- Factors: Age, sex, site, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superior safety or inferior safety.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is inferior to control	
Hydroxychloroquine is superior to control	
Hydroxychloroquine is inferior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is superior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is inferior to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Hydroxychloroquine combined with lopinavir/ritonavir				

15.30 THE PRIMARY SAFETY ANALYSIS-SERIOUS VENTRICULAR ARRHYTHMIA

- Population: Antiviral specific ITT
- Endpoint: Serious ventricular arrhythmia
- Model: Primary dichotomous model
- Factors: Age, sex, site, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir Analysis: Conducted by the ITSC Analysis Center

Notes

b. Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superior safety or inferior safety.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is inferior to control	
Hydroxychloroquine is superior to control	
Hydroxychloroquine is inferior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is superior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is inferior to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Hydroxychloroquine combined with lopinavir/ritonavir				

15.31 GRAPHICAL SUMMARIES

The following graphical summaries will be provided for all endpoints:

- Population: Antiviral specific ITT
- Endpoint: all endpoints
- Factors: lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions

The following additional graphical summaries will be provided for OSFD and in-hospital mortality:

- Population: Antiviral specific ITT
- Endpoint: OSFD, in-hospital mortality

- Factors:
    - Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions interacted with fixed-dose steroids
    - Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions interacted with IL-6
- Analysis: Conducted by the ITSC Analysis Center

15.32 DESCRIPTIVE ANALYSIS OF THE MODERATE STATE

- Population: Antiviral specific ITT-Moderate State
- Endpoint: all baseline characteristics, interventions and endpoints
- Factors: lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions

Appendix A: Definition of organ support-free days

This outcome is an ordinal scale of integers from –1 to 22 for each state (Moderate or Severe) derived from a composite of the patient's vital status at the end of acute hospital admission and days spent receiving organ failure support while admitted to an ICU (including a repurposed ICU) during the 21 days (504 hours) after randomisation.

A patient enrolled in the Severe State while still in an Emergency Department is regarded as 'admitted to an ICU' and the time of commencement of organ failure support is the time of randomisation, as it is for all other patients in the Severe State.

Patents who survive to hospital discharge and are enrolled in one or more domains in the Moderate State and are enrolled in one or more domains in the Severe State have a primary end point value for each state, which may be different.

If deceased between first enrolment and ultimate hospital discharge, code OutcomeDay21 as -1

If not deceased, ModerateOutcomeDay21 = 21 – (the sum of the length of time in days and part-days between time of first commencement of organ failure support while admitted to an ICU and the time of last cessation of organ failure support during that ICU admission plus time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at the 504 hours after enrolment in the Moderate State)

- A patient who is enrolled in the Moderate State who never receives organ failure support while admitted to an ICU has an ModerateOutcomeDay21 = 22.

- A patient who is enrolled in the Moderate State in a ward location who commences organ failure support on the ward and is transferred to an ICU while receiving organ failure support has a commencement time of organ failure support corresponding to the time of ICU admission.

If not deceased, SevereOutcomeDay21 = 21 – (the sum of the length of time in days and part- days between time of enrolment and the time of last cessation of organ failure support during that ICU admission plus the lengths of time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at 504 hours after the time of enrolment

Decimals are rounded up or down to nearest whole day.

If transferred between hospitals before the last study day 21 and known to be alive at ultimate hospital discharge use all available information to calculate Outcome Day21 with an assumption that no subsequent organ failure support in an ICU was provided.

If transferred between hospitals before the last study day 21 and vital status at ultimate hospital discharge is not known, code as follows:

- If last known to be on a ward use all available information to calculate Outcome Day 21 with an assumption that the patient has not died prior to ultimate hospital discharge and that there were no subsequent ICU admissions.

- If last known to be in an ICU, code OutcomeDay21 as missing (999)

If a patient is discharged alive from the ultimate hospital before 504 hours from each enrolment, assume all subsequent time is alive and without provision of organ failure support in an ICU.

If the patient is alive at the end of one or both censoring time points, the hours will be calculated as above. If the patient dies after the end of one or both of the censoring time points and before hospital discharge, the value will be updated to -1

A patient who remains admitted to an acute hospital and is still alive at the end of study day 90 no further changes to coding will be made.

Appendix B: Definition of time-to-SARS-CoV-2 RNA clearance.

a) Time-to-SARS-CoV-2 RNA clearance in respiratory samples is assessed in patients who had at least 1 follow-up rRT-PCR performed after the first confirmatory test of SARS-CoV-2.
b) Time-to-SARS-CoV-2 RNA clearance is calculated from the time of enrollment until the final rRT-PCR test, if negative.
c) If the final rRT-PCR test is positive, the follow-up time is censored by the date of that test (survival analysis).

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

Statistical Analysis Plan for the COVID-19 Antiviral Therapy Domain for Patients with COVID-19 Pandemic Infection Suspected Or Proven (PISOP)

COVID-19 Antiviral Domain SAP Version 1.0 dated 14 January 2021

COVID-19 Antiviral Domain SAP Version 1.1, with Amendment dated 29 January 2021

CONTENTS

1. COVID-19 ANTIVIRAL DOMAIN SAP VERSION

The version is in this document's header and on the cover page.

1.1 VERSION HISTORY

Version 1: Draft dated January 5, 2021.

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3. INTRODUCTION

This statistical plan for the analysis of the COVID-19 Antiviral Therapy Domain in the pandemic stratum of REMAP-CAP is an appendix to the Pandemic Appendix to Core (PAtC) Statistical Analysis Plan (SAP). This plan details the statistical analyses in the original REMAP-CAP core SAP and the pandemic stratum SAP applied to the analysis of the COVID-19 Antiviral Therapy Domain interventions in the Severe State. This plan is prespecified for the imminent unblinding of the data for the COVID-19 Antiviral Therapy Domain interventions within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

Enrollment in the COVID-19 Antiviral Therapy Domain started on April 8th, 2020. The hydroxychloroquine arms (including hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir arms) in the COVID-19 Antiviral Therapy Domain were halted in the PISOP stratum on May 23rd, 2020, based on concerns regarding the safety and efficacy of hydroxychloroquine which was later substantiated by the press release of the results of the RECOVERY trial (https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf). The lopinavir/ritonavir arm in the COVID-19 Antiviral Therapy Domain was halted in the PISOP stratum on Nov 19th, 2020 after reaching a prespecified futility threshold.

The authors of this document are blinded to the data and results in REMAP-CAP other than those already publicly disclosed results.

4. DESIGN CONSIDERATIONS

REMAP-CAP is designed with Bayesian analyses as the primary analysis method for the trial. There is one overarching Bayesian model, prespecified in the SAP, driving all adaptations, platform conclusions, and result summaries. Similar to the SAP used for the Corticosteroids and the Immune Modulation Therapy Domains, the primary statistical analysis model will be used to report the results for the severe state in the COVID-19 Antiviral Therapy Domain within the PISOP stratum. At the time of concluding enrollment in the lopinavir/ritonavir, hydroxychloroquine and lopinavir/ritonavir plus hydroxychloroquine arms, there were <100 patients enrolled in the moderate state, therefore it was decided to only report descriptive data by assignment for this state to facilitate future systematic reviews by others.

The decision to use a Bayesian analysis in REMAP-CAP was driven in part by the uncertainty of the extent of the pandemic. The sample size could be small, or large, and there may be unexpected external events, that alter the design of REMAP-CAP. Given the expected

evolution of the design, and uncertain sample size, a Bayesian approach was deemed more appropriate.

REMAP-CAP defines several statistical triggers within the trial that, at any analysis of the trial, would result in public disclosure and a declaration of a platform conclusion.

The following internal statistical triggers were pre-defined for the interventions in the COVID-19 Antiviral Therapy Domain:

1. **Domain Superiority**. If an intervention in the COVID-19 Antiviral Therapy Domain has at least a 99% posterior probability of being in the best regimen for patients in state s of the PISOP stratum (i.e. superior to all other interventions in the domain), this would trigger domain superiority of that intervention within that state.
2. **Intervention Efficacy**. If an intervention in the COVID-19 Antiviral Therapy Domain is deemed to have at least a 99% posterior probability of being superior to the control in state s, then a declaration of efficacy of that intervention would be declared for state s. This statistical trigger is active for each of the non-control arms in the COVID-19 Antiviral Therapy Domain.
3. **Intervention Equivalence**. If two non-control interventions have a 90% probability of equivalence, this would trigger a public disclosure of intervention equivalence.
4. **Intervention Futility**. Because the hydroxychloroquine arms have been stopped for external reasons, no futility analyses will be reported for this arm. For lopinavir/ritonavir, if an intervention is deemed to have a less than 5% probability of at least a 20% odds ratio improvement compared to the control, then a declaration of futility would be declared.

The 99% threshold for efficacy was selected to have good properties for potential outbreak sample sizes. For example, the type I error rate of any conclusion of efficacy for a single intervention 'A' vs. control is less than 2.5% for approximately less than 1000 patients on intervention 'A' with multiple interim analyses (see main and pandemic SAP).

Importantly, the ITSC halted the hydroxychloroquine and the combination of hydroxychloroquine and lopinavir/ritonavir arms of REMAP-CAP before the first interim analysis. At the time of analysis, being halted early does not change the Bayesian statistical triggers of the domain; the same thresholds apply. However, since there will be no further

enrollment into the hydroxychloroquine and the combination of hydroxychloroquine and lopinavir/ritonavir arms of the COVID-19 Antiviral Therapy Domain for patients within the pandemic stratum, the results are still of value regardless of whether they support any particular internal trigger. Thus, we emphasize the posterior probabilities (and 95% credible intervals) are more informative in contributing to overall knowledge about hydroxychloroquine in COVID-19 than whether a particular posterior probability exceeded a pre-defined threshold in REMAP-CAP.

5. UNBLINDING

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. At the unblinding of the COVID-19 Antiviral Therapy Domain, there are other interventions to which patients have been randomized that will not be unblinded at this analysis unless a statistical trigger is hit at the time of the primary analysis. In the analysis plan, there will be analyses conducted by the Statistical Analysis Committee (SAC) using additional randomizations and also unblinding of other randomizations. The SAC is unblinded to all arms/domains in their function for REMAP-CAP. There will also be analyses that are conducted with only knowledge of unblinded interventions and domains. At this time, that includes the COVID-19 Antiviral Therapy Domain allocation, the Corticosteroid Domain allocation, and the reported arms of the Immune Modulation Therapy Domain. These may be conducted by investigators who are blinded to other information about other domains. These analyses are identified below.

6. INTERVENTIONS

There are 4 interventions within the COVID-19 Antiviral Therapy Domain. These are

1. No antiviral for COVID-19
2. Lopinavir/ritonavir
3. Hydroxychloroquine
4. Hydroxychloroquine and lopinavir/ritonavir

For the primary analysis completed by the SAC and all secondary analyses completed by blinded investigators, all four arms will be modeled, and analysis results for all arms will be reported.

In addition, the models in this SAP will estimate and report the interaction effects of the interventions in the COVID-19 Antiviral Therapy Domain with the Corticosteroid Domain and reported arms of the Immune Modulation Therapy Domain.

7. DISEASE STATES

There are 2 disease states in the PAtC, which are **moderate** and **severe**. In most participating sites, the COVID-19 Antiviral Therapy Domain randomized to patients in the severe state, and as indicated earlier, this SAP describes the analysis of patients in the severe state. In one site, patients were randomized to the hydroxychloroquine and no antiviral therapy arms in the moderate state. Descriptive data on these patients will be reported separately.

8. ANALYSIS POPULATIONS

1. REMAP-COVID intent-to-treat (ITT). All patients within the PISOP stratum initially randomized in the severe state randomized within at least one domain.
2. Unblinded ITT. All patients within the PISOP stratum initially randomized in the severe state randomized to an intervention in the COVID-19 Antiviral Therapy Domain, the Corticosteroid Domain, or reported arms of the Immune Modulation Therapy Domain. Note the assignment to the interventions mentioned above will be unblinded, the other intervention assignments will not be unblinded to the analysis team.
3. Unblinded ITT Non-negative. All patients within the Unblinded ITT population after removing those with $\geq$1 negative test for COVID **and** no positive tests.
4. Antiviral specific ITT. All patients within the PISOP stratum initially randomized in the severe state randomized to an intervention or no antiviral for COVID-19 Antiviral Therapy Domain.
5. Antiviral specific ITT Moderate State. All patients within the PISOP stratum in the moderate state randomized to an intervention or no antiviral for COVID-19 Antiviral Therapy Domain.

9. ENDPOINTS

The following endpoints will be analyzed, graphically displayed, and/or summarized through descriptive statistics.

A. **Organ-Support Free-Days** (OSFD)
   a. An ordinal endpoint with mortality as the worst outcome. The primary endpoint for the REMAP-CAP PISOP stratum. The types of organ support considered are cardiovascular (vasopressor/inotrope support) and respiratory support. See Appendix A for a detailed description.

B. **In-Hospital Mortality**
   a. A dichotomous endpoint of survival/in-hospital death where the death component corresponds to a –1 on the OSFD endpoint.

C. **Mortality**
   a. This is a time-to-event endpoint through 90-days.
   b. Any patient currently in the hospital or transferred on organ support to an alternative care facility will be censored at their last known status alive.
   c. Any patient successfully discharged from hospital, alive, without organ support, will be censored at the date of discharge, if 90-day mortality data are not yet recorded.

D. **Progression to intubation and mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death**
   a. A dichotomous endpoint of whether a patient progresses to intubation and mechanical ventilation, ECMO or death in hospital.
   b. This endpoint will only be analyzed for subjects that are not on intubation, mechanical ventilation, or ECMO at baseline.

E. **Cardiovascular (Vasopressor/Inotrope) Free-Days**
   a. An ordinal outcome of number of days free of Vasopressor/Inotropes. This is the exact calculation of OSFD, with Vasopressor/Inotropes as the only organ support category. In-hospital death is considered a –1.

F. **Respiratory support Free-Days**
   a. An ordinal outcome of number of days free of respiratory support. This is the exact calculation of OSFD, with respiratory support as the only organ support category. In-hospital death is considered a –1.

G. **Duration of ICU stay**
   a. A time-to-event endpoint of leaving the ICU alive. If a patient is known to leave the ICU and return to the ICU within 14-days that intervening time will be ignored.

b. This variable will be truncated at 90-days: all deaths in ICU will be considered 90-days with no liberation of ICU.
c. Patients still in the ICU at data snapshot will be considered censored.

H. **Duration of hospital stay**

a. A time-to-event endpoint of leaving the hospital alive. If a patient is known to leave and return to the hospital within 14-days that intervening time will be ignored.
b. This variable will be truncated at 90-days and all deaths in-hospital will be considered 90-days with no events.
c. Patients still in the hospital at data snapshot will be considered censored.

I. **At least one serious adverse event (SAE)**

a. A dichotomous endpoint of SAE.
b. This endpoint will be summarized descriptively. Counts and proportions of SAEs will be provided by intervention.

J. Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital.

a. A dichotomous endpoint
b. This endpoint will be summarized descriptively. Counts and proportions will be provided by intervention.

K. **The World Health Organization (WHO) 8-point ordinal scale, measured at day 14.**

A modified WHO ordinal scale will be used:

0 + 1 + 2 = No longer hospitalized

3 = Hospitalized, no oxygen therapy

4 = Oxygen by mask or nasal prongs

5 = Non-invasive ventilation or high-flow oxygen

6 = Intubation and mechanical ventilation

7 = Ventilation + additional organ support: vasopressors, renal replacement therapy (RRT), ECMO

8 = Death

L. Time to SARS-CoV-2 RNA clearance

a. A time-to-event endpoint of time to SARS-CoV-2 RNA clearance

b. This variable is calculated for COVID-19 positive patients as the time from enrollment to the first negative test not followed by a positive test (Appendix B).

10. GRAPHICAL DATA SUMMARIES

1. Ordinal endpoints will be graphed using stacked cumulative bar plots.
2. Time-to-event endpoints will be plotted using Kaplan-Meier plots. Positive clinical event outcomes will be plotted as the cumulative rate of event, and negative events will be plotted as the cumulative rate of event-free.

11. DESCRIPTIVE STATISTICS

1. Ordinal endpoints will be summarized by the cumulative frequency of each outcome for each state. The 25th, 50th, and 75th percentiles will be summarized.
2. Dichotomous endpoints will be summarized by the proportion in each category for each state.
3. Time-to-event outcomes will summarize the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates by state.

12. BASELINE CHARACTERISTICS

The following demographics will be summarized across arms. More may be added as baseline summaries.

Age, sex, BMI, ethnicity, APACHE II score (measured from hospital admission to randomization), confirmed SARS CoV-2 infection, preexisting conditions, baseline use of high-flow nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, randomization to corticosteroids, tocilizumab or sarilumab within REMAP-CAP and miscellaneous physiological values.

13. COMPLIANCE

The compliance to lopinavir/ritonavir and hydroxychloroquine use will be summarized descriptively as the fraction of use, the amount, and duration for each randomized arm.

14. ANALYTIC APPROACH

Each inferential analysis will be done using a Bayesian model. Some default frequentist methods are used for exploration and description. A summary of the analysis methods is provided below.

14.1 PRIMARY ANALYSIS OF PRIMARY ENDPOINT

The **primary analysis model** is a Bayesian cumulative logistic model for the ordinal primary endpoint. The model is described below. The primary endpoint for the severe state has 24 possible, ordered outcomes. Let the outcome for a patient by labeled as $Y_{i,s}$, with possible values, –1 (death), 0, 1, …, 21, 22. The outcome of 22 (never received organ support) for the severe state is not possible. Hence there are 23 possible outcomes in the severe state. A cumulative logistic model is specified. The model is structured so that an odds-ratio >1 implies patient benefit. The full details of the model are specified in the Current State Version 2.3 AV. The model has factors for:

- Each level of the ordinal endpoint
- Each Global site, nested within country
- Age; ≤39, 40-49, 50-59, 60-69, 70-79, 80+
- Sex
- Time; 2-week buckets of time working backwards from the last enrolled patient, with the most recent bucket being 4 weeks. Time buckets are defined to be the same time periods for both moderate and severe patients.
- For each domain an effect for being randomized to the domain
- An effect for each intervention within each domain
- Specified interactions in the model between domains

The primary analysis for the lopinavir/ritonavir and hydroxychloroquine uses the following rules:

- All sites within a country that have <5 patients randomized in a state will have their results combined into a single site within that country.
- If there is an outcome in the ordinal scale that did not occur in the data, then that outcome will be combined to a single outcome with a neighboring outcome (the worse outcome). This is done by state for model stability. For example, if the outcome 11 never

occurred in moderate a combined outcome of 10 & 11 will be modeled for the moderate analysis.

- If a time bucket has <5 patients in a state, the bucket will be collapsed with the adjacent earlier bucket in that state.
- The high-dose 7-day hydrocortisone arm will be combined with the 7-day hydrocortisone arm (fixed-duration). They were originally nested, which allows their pooling, and there were very few patients randomized to the high-dose 7-day hydrocortisone arm.
- All interactions between the shock-based steroid arm and other domains will be dropped (assumed to be zero)
- The two IL-6 receptor agonists, Tocilizumab and Sarilumab, will be combined in to a single IL-6ra arm
- For patients who were randomized as part of REMAP-CAP COVID-19 severe state ITT after the closure of Corticosteroid Domain (June 17, 2020), the subjects are coded as receiving fixed-dose hydrocortisone.

The primary analysis model will be referenced with certain model assumptions for sensitivity analyses. For example, the “time effects” in the model could be assumed to be 0.

14.2 PROPORTIONAL ODDS ASSUMPTION

The primary analysis model is based on an assumption of a proportional effect of treatment across the scale of the ordinal outcome. In order to assess the robustness of the results to this assumption, a dichotomous model is fit to every level of the ordinal outcome across the scale and the odds-ratio for each dichotomous break is presented. For tail events, if the cumulative probabilities are less than 5% or greater than 95% these dichotomous may be ignored. No statistical test of proportional odds is conducted.

14.3 ANALYTIC APPROACH FOR SECONDARY DICHOTOMOUS ENDPOINTS

A Bayesian logistic regression model will be used for each dichotomous outcome. The model will always specify the “event” as the negative outcome, so that an odds-ratio >1 implies benefit to patients within each model. The model is the standard logistic link function model with state-specific intercept, α_s and state-specific coefficients for all factors in the model:

$$\log\left(\frac{\pi_s}{1-\pi_s}\right) = \alpha_s - [\text{factors}_s]$$

References will be made to the factors in the model and their prior distribution. Many of these factors will be the same as the primary analysis model, with the same priors, as the parameters have similar interpretation. If not otherwise specified, the prior distribution for the main effect is $\beta \sim N(0, 1.82^2)$ (similar to a uniform prior on the probability scale).

14.4 ANALYTIC APPROACH FOR SECONDARY TIME-TO-EVENT ENDPOINTS

All inferential time-to-event analyses will be done using a Bayesian piecewise exponential model. The Bayesian time-to-event model is intended to mirror a Cox proportional hazards model, with the underlying state-specific hazard rate modeled with a piecewise exponential model. The underlying hazard will be modeled with a hazard rate for 10-day period each day in the model. The prior distribution for each day hazard rate is a gamma distribution with 1 day of exposure and a mean equal to the total exposure divided by the total number of events for each state. This prior will have very little weight but will provide numerical stability to the model. Each factor is incorporated as a proportional hazard rate through an additive linear model of the log-hazard. The default prior for each factor is the same as for the log-odds in the ordinal model. If other non-specified variables are added to the model, then a normal distribution with mean 0 and standard deviation 10 will be utilized.

14.5 MARKOV CHAIN MONTE CARLO (MCMC) MODEL STABILITY

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence of the MCMC and the mixing behavior. These instabilities may be based on sparse data on the outcome or covariates. The statisticians running the model may make changes that do not affect the overall outcome but provide reliable model diagnostics and scientific rigor. Any alterations will be noted.

14.6 MODEL OUTPUTS

The standard model outputs for each treatment effect will be the mean, standard deviation, median, and 95% credible intervals (all credible intervals will range from equal-tailed percentiles, so 95% credible intervals will range from the 2.5th percentile to the 97.5th percentile). For the ordinal model the odds-ratio will be summarized for each state. For the dichotomous endpoints, the odds-ratio will be summarized for each state. For the time-to-event model the hazard ratio will be summarized for each state. For consistency, all models

will be parameterized so that an odds-ratio or hazard-ratio greater than 1 indicates clinical benefit.

For each inferential model, a posterior probability that one arm is superior will be provided for each comparison between arms and for each state. This posterior probability has been identified as the primary analysis metric between arms. A posterior probability greater than 99% of superiority has been identified as statistically significant in REMAP-CAP.

14.7 EXPLORATORY ANALYSES

Exploratory analyses after unblinding will not be considered inferential and no p-values will be presented. Any post-hoc exploratory analyses will use the following methods:

1. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the odds-ratio, with 95% confidence intervals and Wilcoxon test for robustness against a lack of proportional odds.
2. Time-to-Event analyses will utilize a Cox proportional hazards model, summarizing the hazard ratios and 95% confidence intervals.
3. Continuous endpoints will compare means with 95% confidence intervals based on two-sample t-test procedures.
4. Dichotomous proportions will be compared using logistic regressions summarizing the odds-ratio and 95% confidence intervals. Differences between proportions will be summarized using observed differences and normal approximations for the 95% credible intervals.

15. SPECIFIC PROSPECTIVE ANALYSES

There are 32 specific prospective analyses, summarized in the table and described in detail below.

#	Status	Population	Endpoint	Other
15.1	Primary	REMAP-CAP COVID-19 severe state ITT	OSFD	Includes all interventions and interactions.
15.2	Primary	REMAP-CAP COVID-19 severe state ITT	In-Hospital Mortality	Includes all interventions and interactions.
15.3	Sensitivity	REMAP-CAP COVID-19 severe state ITT	OSFD	Includes all interventions and interactions. Includes less informative standard normal priors on pre-specified combinations of antivirals, steroids, tocilizumab and sarilumab.

#	Status	Population	Endpoint	Other
15.4	Sensitivity	REMAP-CAP COVID-19 severe state ITT	Dichotomized OSFD	A logistic regression will be run for each dichotomization of OSFDs as a robustness check.
15.5	Secondary	Unblinded ITT	OSFD	
15.6	Secondary	Unblinded ITT	In-Hospital Mortality	
15.7	Subgroup*	Unblinded ITT	OSFD	Including differential treatment effects by the presence or absence of shock at enrollment
15.8	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by the presence or absence of shock at enrollment
15.9	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by invasive mechanical ventilation at enrollment
15.10	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by invasive mechanical ventilation at enrollment
15.11	Sensitivity	Unblinded ITT	OSFD	Remove site and time effects
15.12	Sensitivity	Unblinded ITT	In-Hospital Mortality	Remove site and time effects
15.13	Sensitivity	Unblinded ITT	OSFD	Alternative coding of steroid interventions after closure of steroid domain.
15.14	Sensitivity	Unblinded ITT	In-Hospital Mortality	Alternative coding of steroid interventions after closure of steroid domain.
15.15	Secondary	Unblinded ITT Non-negative	OSFD	
15.16	Secondary	Unblinded ITT Non-negative COVID-19	In-Hospital Mortality	
15.17	Secondary	Antiviral therapy specific ITT	OSFD	
15.18	Secondary	Antiviral therapy specific ITT	In-Hospital Mortality	
15.19	Sensitivity	Antiviral therapy specific per protocol	OSFD	
15.20	Sensitivity	Antiviral therapy specific per protocol	In-Hospital Mortality	
15.21	Secondary	Unblinded ITT	Mortality	
15.22	Secondary	Unblinded ITT not on MV, ECMO at baseline	Progression to intubation, ECMO, death	
15.23	Secondary	Unblinded ITT	Days-Free of vasopressor/inotropes	
15.24	Secondary	Unblinded ITT	Respiratory support free days	
15.25	Secondary	Unblinded ITT	Length of ICU Stay	
15.26	Secondary	Unblinded ITT	Length of Hospital Stay	
15.27	Secondary	Unblinded ITT	WHO Scale at 14 days	

#	Status	Population	Endpoint	Other
15.28	Secondary	Unblinded ITT	Time to SARS-CoV-2 RNA clearance	
15.29	Primary Safety Analysis	Antiviral therapy specific ITT	Serious adverse events per patient	Time effects removed from model.
15.30	Primary Safety Analysis	Antiviral therapy specific ITT	Serious ventricular arrhythmia	Time effects removed from model.
15.31	Graphical Summaries	Antiviral therapy specific ITT	All endpoints	Including combinations across unblinded domains.
15.32	Descriptive summaries	Antiviral therapy specific ITT, moderate state	All endpoints	

* There are 2 additional subgroups defined in the DSA based on the co-infection with influenza and bacterial pathogens that will not be perused, due to the small numbers.

15.1 THE PRIMARY ANALYSIS FOR THE COVID-19 ANTIVIRAL THERAPY DOMAIN

- Population: REMAP-COVID severe state ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids, and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the unblinded SAC

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility
d. Only information on the Corticosteroid Domain, the COVID-19 Antiviral Therapy Domain and the reported arms of the Immune Modulation Therapy Domain will be disclosed.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ * IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.2 THE PRIMARY MORTALITY ANALYSIS FOR THE COVID-19 ANTIVIRAL THERAPY

- Population: REMAP-COVID severe state ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-

based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.

- Analysis: Conducted by the unblinded SAC

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility
d. Only information on the Corticosteroid Domain, the COVID-19 Antiviral Therapy Domain and the reported arms of the Immune Modulation Therapy Domain will be disclosed.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.3 A SENSITIVITY ANALYSIS OF THE PRIMARY ANALYSIS OF THE COVID-19 ANTIVIRAL THERAPY WITH LESS INFORMATIVE PRIORS ON INTERACTION EFFECTS

- Population: REMAP-CAP COVID-19 severe state ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model with weaker priors for the interaction effects
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the unblinded SAC

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between each antiviral and corticosteroid intervention and tocilizumab and sarilumab will be reported relative to control.
d. The prior distributions will be set to N(0,1) for the following interactions: each antiviral intervention with fixed-dose corticosteroid intervention, each antiviral intervention with IL-6.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.4 A SENSITIVITY ANALYSIS OF THE PRIMARY ANALYSIS OF THE COVID-19 ANTIVIRAL THERAPY FOR THE PROPORTIONAL ODDS ASSUMPTIONS

- Population: REMAP-CAP COVID-19 severe state ITT

- Endpoint: Dichotomized Organ Support-Free Days
- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the unblinded SAC

Notes

a. For this analysis, the primary dichotomous model will be fit to each dichotomization of OSFDs and the summaries of the odds-ratio of lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be reported.

The following summaries will be reported for the lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir odds-ratios:

OSFD Dichotomization	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir				
-1 vs ≥0				
≤0 vs ≥1				
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				
Hydroxychloroquine				
-1 vs ≥0				
≤0 vs ≥1				

OSFD Dichotomization	Mean	SD	Median	95% Credible Interval
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				
Hydroxychloroquine combined with lopinavir/ritonavir				
-1 vs ≥0				
≤0 vs ≥1				
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				

15.5 A SECONDARY ANALYSIS RESTRICTED TO THE UNBLINDED ITT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.6 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO UNBLINDED ITT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain or the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.7 A SUBGROUP ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY SHOCK AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by shock status, a fixed effect for shock status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across shock status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by shock status. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with shock	
Lopinavir/ritonavir is futile in patients with shock	
HCQ is in superior to control in patients with shock	
HCQ is futile in patients with shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with shock	
Lopinavir/ritonavir and HCQ combination is futile in patients with shock	
Lopinavir/ritonavir is superior to control in patients with no shock	
Lopinavir/ritonavir is futile in patients with no shock	
HCQ is superior to control in patients with no shock	
HCQ is futile in patients with no shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no shock	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir in shock				
Lopinavir/ritonavir in no shock				
Hydroxychloroquine in shock				
Hydroxychloroquine in no shock				
Lopinavir/ritonavir and HCQ combination in shock				
Lopinavir/ritonavir and HCQ combination in no shock				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.8 A SUBGROUP ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY THE PRESENCE OF SHOCK AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: in-hospital mortality
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by shock status, a fixed effect for shock status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across shock status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by the presence of shock. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control within each shock status.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with shock	
Lopinavir/ritonavir is futile in patients with shock	
HCQ is in superior to control in patients with shock	
HCQ is futile in patients with shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with shock	
Lopinavir/ritonavir and HCQ combination is futile in patients with shock	
Lopinavir/ritonavir is superior to control in patients with no shock	
Lopinavir/ritonavir is futile in patients with no shock	
HCQ is superior to control in patients with no shock	
HCQ is futile in patients with no shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no shock	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir in shock				
Lopinavir/ritonavir in no shock				
Hydroxychloroquine in shock				
Hydroxychloroquine in no shock				
Lopinavir/ritonavir and HCQ combination in shock				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination in no shock				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.9 A SUBGROUP ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY INVASIVE MECHANICAL VENTILATION AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by IMV status, a fixed effect for IMV status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across IMV status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by invasive mechanical ventilation. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with invasive mechanical ventilation	
HCQ is superior to control in patients with invasive mechanical ventilation	
HCQ is futile in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with no invasive mechanical ventilation	
HCQ is superior to control in patients with no invasive mechanical ventilation	
HCQ is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir with IMV				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir with no IMV				
Hydroxychloroquine with IMV				
Hydroxychloroquine with no IMV				
Lopinavir/ritonavir and HCQ combination with IMV				
Lopinavir/ritonavir and HCQ combination with no IMV				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.10 A SUBGROUP ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY INVASIVE MECHANICAL VENTILATION AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: in-hospital mortality
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by shock status, a fixed effect for shock status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across shock status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by invasive mechanical ventilation. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with invasive mechanical ventilation	
HCQ is superior to control in patients with invasive mechanical ventilation	
HCQ is futile in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with no invasive mechanical ventilation	
HCQ is superior to control in patients with no invasive mechanical ventilation	
HCQ is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir with IMV				
Lopinavir/ritonavir with no IMV				
Hydroxychloroquine with IMV				
Hydroxychloroquine with no IMV				
Lopinavir/ritonavir and HCQ combination with IMV				
Lopinavir/ritonavir and HCQ combination with no IMV				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.11 A SENSITIVITY ANALYSIS RESTRICTED TO THE UNBLINDED ITT POPULATION WITH SITE AND TIME FACTORS REMOVED

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.

- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Lopinavir/ritonavir				
Hydroxychloroquine				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.12 A SENSITIVITY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO UNBLINDED ITT POPULATION WITH FACTORS FOR SITE AND TIME REMOVED

- Population: Unblinded ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: Age, sex, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (as a combined IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and tocilizumab and sarilumab will be reported relative to control.

The following posterior probabilities will be reported:

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	

Quantity of Interest	Posterior Probability
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.13 A SENSITIVITY ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT POPULATION WITH DIFFERENT STEROID CODING

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, antiviral domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids and shock-based steroids combined as a corticosteroid arm and

reported interventions of the Immune Modulation Therapy Domain: tocilizumab and no immune modulation combined as an IL-6 arm.

- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and each corticosteroid intervention and IL-6 will be reported relative to control.
d. Fixed-dose and shock-based steroids are pooled for this analysis.
e. Patients randomized after the closure of the Corticosteroid Domain (June 17, 2020) will be coded as receiving steroids if they received steroids within the first two study days.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * corticosteroids				
HCQ * corticosteroids				
Lopinavir/ritonavir and HCQ combination* corticosteroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.14 A SENSITIVITY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENT STEROIDS CODING

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids and shock-based steroids (combined as a corticosteroid arm) and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and corticosteroid intervention, IL-6 will be reported relative to control.
d. Fixed-dose and shock-based steroids are pooled for this analysis.
e. Patients randomized after the closure of the Corticosteroid Domain (June 17, 2020) will be coded as receiving steroids if they received steroids within the first two study days.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir *corticosteroids				
HCQ * corticosteroids				
Lopinavir/ritonavir and HCQ combination* corticosteroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.15 A SECONDARY ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT POPULATION NON-NEGATIVE COVID POPULATION

- Population: Unblinded ITT, Non-negative COVID
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention, IL-6will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.16 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT POPULATION NON-NEGATIVE COVID POPULATION

- Population: Unblinded ITT, Non-negative COVID
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir,

hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention, IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.17 A SECONDARY ANALYSIS OF OSFD FOR ANTIVIRAL THERAPY SPECIFIC ITT

- Population: Antiviral Therapy specific ITT
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.18 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY FOR ANTIVIRAL THERAPY SPECIFIC ITT

- Population: Antiviral specific ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.19A SECONDARY ANALYSIS OF OSFD IN ANTIVIRAL THERAPY SPECIFIC PER PROTOCOL

- Population: Antiviral therapy specific Per Protocol
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.20 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY IN ANTIVIRAL SPECIFIC PER PROTOCOL

- Population: Antiviral specific Per Protocol
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	

Quantity of Interest	Posterior Probability
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.21 A SECONDARY ANALYSIS OF MORTALITY

- Population: Unblinded ITT
- Endpoint: Time-to-death
- Model: Primary TTE model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.22 A SECONDARY ANALYSIS OF PROGRESSION TO INTUBATION, ECMO, OR DEATH, RESTRICTED TO PATIENTS NOT ON MV OR ECMO AT BASELINE

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain or the reported arms of the Immune Modulation Therapy Domain) not on MV or ECMO at baseline.
- Endpoint: Progression to MV, ECMO, or death
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the

same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.23 A SECONDARY ANALYSIS OF DAYS-FREE OF VASOPRESSOR/INOTROPES USE

- Population: Unblinded ITT
- Endpoint: Vasopressor/Inotropes free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
a. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * Tocilizumab				
HCQ* Tocilizumab				
Lopinavir/ritonavir and HCQ combination* Tocilizumab				

15.24 A SECONDARY ANALYSIS OF DAYS FREE OF RESPIRATORY SUPPORT

- Population: Unblinded ITT
- Endpoint: Respiratory support free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune

Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.

- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

a. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.25 A SECONDARY ANALYSIS OF LENGTH OF ICU STAY

- Population: Unblinded ITT
- Endpoint: Length of ICU stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.26 A SECONDARY ANALYSIS OF LENGTH OF HOSPITAL STAY

- Population: Unblinded ITT
- Endpoint: Length of Hospital stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
a. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.27 A SECONDARY ANALYSIS OF THE MODIFIED WHO SCALE AT DAY 14

- Population: Unblinded ITT
- Endpoint: Modified WHO scale at 14-days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir,

hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.28 A SECONDARY ANALYSIS OF TIME-TO-SARS-COV-2 RNA CLEARANCE

- Population: Unblinded ITT
- Endpoint: time-to-SARS-CoV-2 RNA clearance
- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control
d. Because repeated rRT-PCR was not done routinely, this analysis will be carried out only if there is sufficient number of patients with follow-up tests.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.29 THE PRIMARY SAFETY ANALYSIS

- Population: Antiviral specific ITT
- Endpoint: Serious Adverse Events (SAE)
- Model: Primary dichotomous model

- Factors: Age, sex, site, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superior safety or inferior safety.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is inferior to control	
Hydroxychloroquine is superior to control	
Hydroxychloroquine is inferior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is superior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is inferior to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Hydroxychloroquine combined with lopinavir/ritonavir				

15.30 THE PRIMARY SAFETY ANALYSIS-SERIOUS VENTRICULAR ARRHYTHMIA

- Population: Antiviral specific ITT
- Endpoint: Serious ventricular arrhythmia
- Model: Primary dichotomous model
- Factors: Age, sex, site, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir Analysis: Conducted by the ITSC Analysis Center

Notes

b. Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superior safety or inferior safety.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is inferior to control	
Hydroxychloroquine is superior to control	
Hydroxychloroquine is inferior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is superior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is inferior to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Hydroxychloroquine combined with lopinavir/ritonavir				

15.31 GRAPHICAL SUMMARIES

The following graphical summaries will be provided for all endpoints:

- Population: Antiviral specific ITT
- Endpoint: all endpoints
- Factors: lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions

The following additional graphical summaries will be provided for OSFD and in-hospital mortality:

- Population: Antiviral specific ITT
- Endpoint: OSFD, in-hospital mortality

- Factors:
    - Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions interacted with fixed-dose steroids
    - Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions interacted with IL-6
- Analysis: Conducted by the ITSC Analysis Center

15.32 DESCRIPTIVE ANALYSIS OF THE MODERATE STATE

- Population: Antiviral specific ITT-Moderate State
- Endpoint: all baseline characteristics, interventions and endpoints
- Factors: lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions

Appendix A: Definition of organ support-free days

This outcome is an ordinal scale of integers from –1 to 22 for each state (Moderate or Severe) derived from a composite of the patient's vital status at the end of acute hospital admission and days spent receiving organ failure support while admitted to an ICU (including a repurposed ICU) during the 21 days (504 hours) after randomisation.

A patient enrolled in the Severe State while still in an Emergency Department is regarded as 'admitted to an ICU' and the time of commencement of organ failure support is the time of randomisation, as it is for all other patients in the Severe State.

Patents who survive to hospital discharge and are enrolled in one or more domains in the Moderate State and are enrolled in one or more domains in the Severe State have a primary end point value for each state, which may be different.

If deceased between first enrolment and ultimate hospital discharge, code OutcomeDay21 as -1

If not deceased, ModerateOutcomeDay21 = 21 – (the sum of the length of time in days and part-days between time of first commencement of organ failure support while admitted to an ICU and the time of last cessation of organ failure support during that ICU admission plus time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at the 504 hours after enrolment in the Moderate State)

- A patient who is enrolled in the Moderate State who never receives organ failure support while admitted to an ICU has an ModerateOutcomeDay21 = 22.

- A patient who is enrolled in the Moderate State in a ward location who commences organ failure support on the ward and is transferred to an ICU while receiving organ failure support has a commencement time of organ failure support corresponding to the time of ICU admission.

If not deceased, SevereOutcomeDay21 = 21 – (the sum of the length of time in days and part- days between time of enrolment and the time of last cessation of organ failure support during that ICU admission plus the lengths of time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at 504 hours after the time of enrolment

Decimals are rounded up or down to nearest whole day.

If transferred between hospitals before the last study day 21 and known to be alive at ultimate hospital discharge use all available information to calculate Outcome Day21 with an assumption that no subsequent organ failure support in an ICU was provided.

If transferred between hospitals before the last study day 21 and vital status at ultimate hospital discharge is not known, code as follows:

- If last known to be on a ward use all available information to calculate Outcome Day 21 with an assumption that the patient has not died prior to ultimate hospital discharge and that there were no subsequent ICU admissions.

- If last known to be in an ICU, code OutcomeDay21 as missing (999)

If a patient is discharged alive from the ultimate hospital before 504 hours from each enrolment, assume all subsequent time is alive and without provision of organ failure support in an ICU.

If the patient is alive at the end of one or both censoring time points, the hours will be calculated as above. If the patient dies after the end of one or both of the censoring time points and before hospital discharge, the value will be updated to -1

A patient who remains admitted to an acute hospital and is still alive at the end of study day 90 no further changes to coding will be made.

Appendix B: Definition of time-to-SARS-CoV-2 RNA clearance.

a) Time-to-SARS-CoV-2 RNA clearance in respiratory samples is assessed in patients who had at least 1 follow-up rRT-PCR performed after the first confirmatory test of SARS-CoV-2.
b) Time-to-SARS-CoV-2 RNA clearance is calculated from the time of enrollment until the final rRT-PCR test, if negative.
c) If the final rRT-PCR test is positive, the follow-up time is censored by the date of that test (survival analysis).

Amendment Dated January 29-2021

A. Definition of the per-protocol cohort:

1. No antiviral for COVID-19 group: Patients who received no dose of lopinavir/ritonavir and no dose of hydroxychloroquine.
2. Lopinavir/ritonavir: Patients who received one dose or more of lopinavir/ritonavir but no dose of hydroxychloroquine.
3. Hydroxychloroquine: Patients who received one dose or more of hydroxychloroquine but no dose of lopinavir/ritonavir.
4. Hydroxychloroquine and lopinavir/ritonavir: Patients who received one dose or more of hydroxychloroquine and one dose or more of lopinavir/ritonavir.

B. The per-protocol cohort and compliance data will be calculated for all patients except those with missing medication data, defined as no information on any medication documented.