



# Statistical Analysis Plan of the Simvastatin Therapy Domain for Patients with COVID-19 Pandemic Infection Suspected Or Proven (PISOP)

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COVID-19 Simvastatin Therapy Domain SAP Version 1.0 dated 18 November 2022



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## **1. COVID-19 SIMVASTATIN THERAPY DOMAIN SAP VERSION**

The version is in this document's header and on the cover page.

### **1.1. Version history**

Version 1: Finalized on 18 November 2022.

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### **3. INTRODUCTION**

This statistical plan for the analysis of the Simvastatin Therapy Domain in the pandemic stratum of the REMAP-CAP trial is an appendix to the Pandemic Appendix to Core (PA<sub>t</sub>C) 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 simvastatin therapy in the Simvastatin Therapy Domain. This plan is prespecified for the unblinding of the data for the simvastatin and control interventions in the Simvastatin Therapy Domain within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

REMAP-CAP explores multiple treatment domains by randomizing patients within multiple domains simultaneously. The adaptive platform trial was designed to produce modular results for individual interventions or full domains upon reaching platform conclusions. When a predefined statistical trigger for efficacy or futility for simvastatin is met, the results for the simvastatin and control interventions will be unblinded and made public. This document prespecifies the analysis plan for this unblinding.

The authors of this document are blinded to all individual data other than publicly disclosed results and that the statistical trigger for efficacy, futility or harm has been reached for simvastatin or control. The primary analysis for this SAP will be conducted when the patient last randomized, before closing of the simvastatin/control arm, reaches 21 days of follow-up (completion of the primary end-point). The full analysis model will be run once all the randomized patients have completed the follow-up period and the results of the full analysis will be added to the reporting.

In the setting of a large number of participants already recruited and ongoing slow recruitment in the absence of meeting a statistical trigger, consideration was given to operational futility. A series of simulations were undertaken (Appendix C). Based on these simulations, the likelihood of meeting either a futility or efficacy trigger with substantially more recruited patients was low.

### **4. DESIGN CONSIDERATIONS**

REMAP-CAP is designed with a Bayesian analysis as the primary analysis method for the trial. There is one overarching Bayesian model, prespecified in the SAP, driving all adaptations, statistical triggers, and result summaries. That primary statistical analysis model will be used to report the results for the intervention in the Simvastatin Therapy Domain within the moderate and severe state of the PISOP stratum.

Domain-specific post-trial sub-groups will be used in analysis. The a priori patient sub-groups of interest are:

- Baseline C-Reactive Protein (by terciles of CRP)
- Baseline ferritin (by terciles of ferritin)
- Ventilatory status at baseline – MV vs non-MV
- Inflammatory phenotype (Appendix B). This was specified as a domain-specific strata for the analysis of this domain. However, the strata was not applied in the primary efficacy model so this variable will be evaluated as a post-trial sub-group. This sub-group will be applied if the frequency distribution of the inflammatory phenotypes allows.
- Immunosuppression (as defined by APACHE II: malignancy requiring chemotherapy in the last 3 months, neutropenia [ANC < 500/mL], receiving chronic immunosuppressive medications [azathioprine, cyclosporine, cyclophosphamide, tacrolimus, methotrexate, mycophenolate, anti-TNF agents, interleukin-2 agents], or transplantation [including stem cell] at any time, or HIV positive; hypothesis: more effective in immunosuppressed patients);

The decision to use a Bayesian analysis 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, such as other trial results, that alter the design of REMAP-CAP. Given the expected evolution of the design and uncertain sample size, the Bayesian approach is 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 defined for the Simvastatin Domain within each state:

1. Simvastatin Efficacy. If simvastatin therapy is deemed to have at least a 99% posterior probability of being superior to the control, then a declaration of efficacy of simvastatin would be declared.
2. Simvastatin futility. If simvastatin therapy 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 of simvastatin would be declared.
3. Simvastatin harm. If simvastatin therapy is deemed to have at least a >90% probability that the odds ratio is <1 for a general “active” intervention vs control, then a declaration of harm of simvastatin would be declared. The statistical trigger for harm was predefined in the Pandemic

Appendix to Core (PATC), but was not implemented at adaptive analyses because the futility trigger necessarily precedes the harm trigger.

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).

The pre-specified design adaptations outlined in this section of the SAP will be incorporated into an amendment of the Simvastatin DSA as soon as possible. The updated DSA may not be submitted for regulatory approval but will be dated and placed in the public domain at REMAP-CAP.org.

## **5. UNBLINDING**

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. The simvastatin domain has only one active intervention. At the unblinding of the Simvastatin/control interventions, there are other interventions to which patients have been randomized in other domains 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 unblinding of other randomizations. The SAC is unblinded to all interventions and domains as part of their role for REMAP-CAP. There will be other analyses that are conducted with only knowledge of the Simvastatin/control allocation status for patients or the allocation status to other unblinded interventions. These may be conducted by investigators who are blinded to information about other interventions and domains. These analyses are identified below.

## **6. INTERVENTIONS**

There are two arms (interventions) within the Simvastatin Therapy Domain. These are

1. No Simvastatin (control)
2. Simvastatin (active comparator)

For the primary analysis completed by the SAC, the results for simvastatin relative to control will be reported. For all secondary analyses completed by blinded investigators, simvastatin will be compared to the control.

Interaction effects of the Simvastatin Therapy Domain with other domains is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

## 7. DISEASE STATES

There are two disease states in the PAAtC, which are **moderate** and **severe**. Simvastatin has been open for randomization in patients in both the disease states and patients randomized into both the disease states will be analysed. The DSMB recommendation could suggest continuation or termination of recruitment for the disease states individually based on the criteria stated in section 4.

Only the intervention effects for the unblinded state(s) will be reported. The secondary analysis models run by blinded investigators will be run on only the unblinded state(s).

## 8. ANALYSIS POPULATIONS

1. REMAP-CAP COVID-19 moderate/severe state intent-to-treat (ITT). This population consists of all PISOP patients in the moderate/severe state.
2. Unblinded ITT. All patients randomized to Simvastatin or no Simvastatin interventions in the Simvastatin Therapy Domain and all other domains / interventions that have stopped randomization and have been unblinded within the PISOP stratum.
3. Unblinded non-negative COVID-19. All patients in the Unblinded ITT population after removing those with  $\geq 1$  negative test for COVID-19 **and** no positive tests. This population comprises of patients who were randomized as “suspected” COVID-19 but never proven to either have the disease or not, due to any reason.
4. Simvastatin specific ITT population. All patients randomized to Simvastatin or no Simvastatin interventions in the Simvastatin Therapy Domain within the PISOP stratum only.
5. Simvastatin specific per protocol. This consists of the patients in the Simvastatin specific ITT population who have been treated as per protocol. In this analysis that is defined as patients randomized to Simvastatin, **and** received at least one dose, or randomized to no Simvastatin **and** did not receive any interventions in the Simvastatin Therapy Domain.

There may be ongoing enrolment of patients to some of the states being analyzed in this SAP. Each of these analysis populations will include only the patients randomized on or before the decision to stop enrolment to the simvastatin therapy domain is made. If a statistical trigger is met within a disease state and enrolment continues in the remaining state, the unblinded analysis populations (#2-5 above) will include only the unblinded state.

## 9. ENDPOINTS

The following end points will be analyzed, displayed graphically, and 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 organ support considered is cardiovascular (vasopressor/inotrope support) and respiratory support. See Appendix A for a detailed description.

### 2. In-Hospital Survival

- a. A dichotomous endpoint of 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.

5. **Cardiovascular support-free days** An ordinal outcome of the 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 the number of days free of respiratory support. This is the exact calculation of OSFD, with respiratory support as the only qualifying 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.

**10. The World Health Organization (WHO) 8-point ordinal scale, measured at day 14.**

- a. 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

**10. GRAPHICAL DATA SUMMARIES**

1. All ordinal endpoints will be plotted using stacked cumulative bar plots and cumulative probability plots.
2. All 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. The 25th, 50th, and 75th percentiles will be summarized.
2. Dichotomous endpoints will be summarized by the proportion in each category.
3. Time-to-event outcomes will be summarized by the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates, as available.

## 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-frequency nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, and miscellaneous physiological values and inflammatory biomarker laboratory values.

## 13. COMPLIANCE

The compliance to Simvastatin use will be summarized descriptively as the fraction of use, 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 analyses 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 23 and the moderate state has 24 possible ordered outcomes respectively. Let the outcome for a patient be labeled as  $Y_i$ , with possible values,  $-1$  (death),  $0, 1, \dots, 21, 22$ . The outcome of 22 for the severe state (never received organ support) is not possible. A cumulative logistic model is specified. The model is structured so that an odds-ratio  $>1$  implies clinical benefit. The full details of the model are specified in the Current State of The Statistical Model document. The model has factors for:

- Each level of the ordinal endpoint
- State at randomization
- 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.
- For each domain, an effect for being randomized to the domain
- For each domain, an effect for being eligible for the domain
- An effect for each intervention within each domain
- Specified interactions in the model between interventions across domains

The primary analysis for Simvastatin uses the following rules:

- All sites within a country that have <5 patients randomized will be combined into a single site within that country.
- If there is an outcome in the ordinal scale that did not occur in the data in a given state, then that outcome will be combined with a neighboring outcome (the worse outcome). This is done for model stability. For example, if the outcome 11 never occurred in the severe state, then a combined outcome of 10 & 11 will be modeled for the severe state in that analysis.
- Time buckets with <5 randomized subjects in a state may be combined with the more recent neighboring bucket for that state.

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.

#### **14.1.1. 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. No statistical test of proportional odds is conducted.

#### **14.2. 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 and be parameterized so that an odds-ratio >1 implies benefit to patients. The model is the standard logistic link function model:

$$\log \left( \frac{\pi}{1 - \pi} \right) = \alpha - [factors]$$

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. For example, all in-hospital mortality models should use the Beta prior distribution implied by the Dirichlet prior in the OSFD model. If not otherwise specified, the prior distribution for the main effect is  $\alpha \sim N(0, 1.82^2)$  (similar to a uniform prior on the probability scale).

### **14.3. 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 hazard rate modeled with a piecewise exponential model. The underlying hazard will be modeled with a hazard rate for each 10-day period in the model. The prior distribution for the hazard rate for each day is a gamma distribution with 1 day of exposure and a mean equal to the total exposure divided by the total number of events. 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.

### **14.4. Markov Chain Monte Carlo (MCMC) Model Stability**

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence and mixing behavior of the MCMC sampler. 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 interpretation but provide reliable model diagnostics and scientific rigor. Any alterations will be noted.

### **14.5. 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 be equal-tailed intervals, so 95% credible intervals will range from the 2.5<sup>th</sup> percentile to the 97.5<sup>th</sup> percentile of the posterior distribution). For the ordinal endpoints, the odds-ratios will be summarized. For the dichotomous endpoints, the odds-ratio will be summarized. For the time-to-event endpoints, the hazard ratios will be summarized. 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. 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.

#### 14.6. Exploratory Analyses

Exploratory analyses after unblinding will not be considered inferential and no p-values will be presented. Any post-hoc exploratory analyses may use the following methods:

1. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the odds-ratio, 95% confidence intervals, and Wilcoxon tests 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 regression 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.
5. An exploratory analysis will be reported calculating the effect of simvastatin on the primary outcome of OFSD by time period. Time periods may be defined by approximate timing of when response adaptive randomization proportions were updated, coarsened versions of the time epochs defined in the primary model (e.g. instead of 2-week time buckets, 4 week time buckets may be used), and/or other disease altering timelines (timing of variants and/or changes in vaccination).

#### 15. SPECIFIC PROSPECTIVE ANALYSES

The specific prospective analyses are summarized in the table and described in detail below.

#	Status	Population	Endpoint	Other
	Primary	REMAP-CAP COVID-19 moderate/severe state ITT	OSFD	Includes all interventions and pre-specified interactions.
	Primary	REMAP-CAP COVID-19 moderate/severe state ITT	In-Hospital Mortality	Includes all interventions and pre-specified interactions.

	Sensitivity	REMAP-CAP COVID-19 moderate/severe state ITT	Dichotomized OSFD	A logistic regression will be run for each dichotomization of OSFDs as a robustness check.
	Secondary	Unblinded population ITT	OSFD	
	Secondary	Unblinded population ITT	In-Hospital Mortality	
	Sensitivity	Unblinded population ITT	OSFD	Remove site and time effects
	Sensitivity	Unblinded population ITT	In-Hospital Mortality	Remove site and time effects
	Sensitivity	Unblinded population ITT	OSFD	Sensitivity analysis with independent Statin effects across severe and moderate states
	Sensitivity	Unblinded population ITT	In-Hospital Mortality	Sensitivity analysis with independent Statin effects across severe and moderate states
	Secondary	Unblinded population ITT Non-negative COVID-19	OSFD	
	Secondary	Unblinded population ITT Non-negative COVID-19	In-Hospital Mortality	
	Secondary	Simvastatin specific per protocol	OSFD	
	Secondary	Simvastatin specific per protocol	In-Hospital Mortality	
	Secondary	Unblinded population ITT	Mortality	
	Secondary	Unblinded population ITT not on MV, ECMO at baseline	Progression to intubation, ECMO, death	
	Secondary	Unblinded population ITT	Days-Free of vasopressor/inotropes	
	Secondary	Unblinded population ITT	Respiratory support-free days	
	Secondary	Unblinded population ITT	Length of ICU Stay	
	Secondary	Unblinded population ITT	Length of Hospital Stay	
	Secondary	Unblinded population ITT	WHO Scale at 14 days	
	Subgroup	Unblinded population ITT	In-Hospital Mortality	Inflammatory phenotype
	Subgroup	Unblinded population ITT	OSFD	Inflammatory phenotype

	Subgroup	Unblinded population ITT	In-Hospital Mortality	Including differential treatment effects by terciles of CRP.
	Subgroup	Unblinded population ITT	OSFD	Including differential treatment effects by terciles of CRP.
	Subgroup	Unblinded population ITT	In-Hospital Mortality	Including differential treatment effects by terciles of ferritin.
	Subgroup	Unblinded population ITT	OSFD	Including differential treatment effects by terciles of ferritin.
	Subgroup	Unblinded population ITT	In-Hospital Mortality	Baseline use of mechanical ventilation (Non-MV vs MV)
	Subgroup	Unblinded population ITT	OSFD	Baseline use of mechanical ventilation (Non-MV vs MV)
	Subgroup	Unblinded population ITT	In-Hospital Mortality	Immunosuppression
	Subgroup	Unblinded population ITT	OSFD	Immunosuppression
	Primary Safety Analysis	Statin specific ITT	Serious adverse events per patient	Time effects removed from model.
	Graphical Summaries	Unblinded population ITT	All endpoints	Including combinations across unblinded domains.

### 15.1. Reporting of Analysis Results

For each analysis model, the following summaries will be reported when applicable:

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				
Moderate to severe transition				
Simvastatin (vs no simvastatin)				
Main effect of subgroup				
Simvastatin by subgroup				

For each analysis model, the following comparisons will be made by state, when applicable:

- Simvastatin will be compared to the control (no simvastatin) arm. The posterior probability that  $OR > 1$  will be used to define efficacy, whereas this probability may also be reported as the probability of harm if  $OR < 1$ . In subgroup models, this probability will be provided by subgroup.
- Simvastatin will be compared to no simvastatin for futility. A 95% probability of a smaller than 1.2 odds ratio for simvastatin relative to no simvastatin will be used as a statistical trigger for futility. In subgroup models, this probability will be provided by subgroup.
- For the sensitivity analysis assessing the proportional odds assumption, the simvastatin OR will be reported for each dichotomization of OSFD and each unblinded state.

## **15.2. Graphical summaries**

The following graphical summaries will be provided for all endpoints:

- Population: Simvastatin specific ITT
- Endpoint: all endpoints
- Factors: Simvastatin and no Simvastatin interventions



## **Appendix A. Definition of organ support-free days**

This outcome is an ordinal scale of integers from -1 to 22 for the Moderate state, or -1 to 21 for the Severe state. It is derived from a composite of the patient's vital status at the end of acute hospital admission (censored at day 90 after each randomization) and duration of organ failure support while admitted to an ICU (including a re-purposed ICU) during the 21 days (504 hours) after randomization in that state. The outcome of -1 indicates a patient death in hospital prior to the end of 90 days after their last randomization.

Patients 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.

Final OSFD decimals are rounded up or down to nearest whole day

If the patient has received allocations in both the Moderate and Severe states, and is alive at the end of both the Moderate and Severe censoring time points (i.e. day 90 after each randomization), the outcomes will be calculated as above. If the patient dies after the end of the Moderate censoring day 90 time point but before the Severe censoring day 90 time point, and before hospital discharge, the endpoint values will be updated to "-1" for BOTH ModerateOutcomeDay21 and SevereOutcomeDay21 endpoints. For patients who receive an allocation in both the Moderate and Severe states, if SevereOutcomeDay21 = -1, then ModerateOutcomeDay21 must therefore also be -1.

Outcome values are updated to -1 if the patient dies during the acute hospital stay and before day 90 after their last randomization. For a patient who remains admitted to an acute hospital and is still alive at the end of day 90 after their last randomization, no further changes to coding will be made.

## Appendix B. Phenotype allocation.

### Pre-processing:

- Establish data structure, variable distribution (Temperature, Heart rate, Systolic blood pressure, Respiratory rate, White cell count, Bicarbonate and Albumin), and missingness of the predictor variables in the model.
- Data cleaning followed by data selection. A priori we will exclude a variable if missingness is > 35%.

### Model Building:

- Model performance will be tested in REMAP-CAP (Sinha et al 2020 AJRCCM).
- A grid matrix to ascertain the most accurate probability cut-off will be developed. We will use 0.5 as the primary cut-off to assign class.
- In the eventuality that these models suggest the prevalence of inflammatory phenotypes are low in this population, we will use two further strategies to identify phenotypes in the population:
  1. We will use baseline characteristics including demographics (age, BMI, gender), vital signs (respiratory rate, PaO<sub>2</sub>/FiO<sub>2</sub>, temperature, heart rate), laboratory values (creatinine, platelets, bilirubin, lactate, Ferritin, D-Dimer, C-reactive Protein, neutrophil count, lymphocyte count, bicarbonate, albumin, ALT) to perform a de novo LCA. These analyses will be performed blinded to outcome data and treatment allocation. The cohort will be randomly split into half with one cohort serving as the discovery cohort and the second cohort as the validation. For seeking heterogeneity of treatment effect, should the same classes emerge in both cohorts, we will combine the cohorts to test for the interaction term of treatment group and latent classes with the primary outcome as the dependent variable. We will also seek differences in outcome with the identified classes.
  2. A second approach would be to use a classifier model built to identify previously described latent classes in hospitalized COVID-19 patients where heterogeneity of treatment effect was observed with corticosteroid therapy (Lyons et al AJRCCM 2022 A5626). We will use a classifier model that comprised of lactate, bicarbonate, neutrophil count, and albumin to assign class. Heterogeneity of treatment effect will be sought in the identified classes and simvastatin therapy.

### Model application in REMAP-CAP

#### 1. Primary Analysis

- Apply the clinical classifier model and generate probabilities for belonging to the inflammatory class
- Plot a histogram the probabilities to examine its distribution
- Assign class based on a cut-off of 0.5 ( $\geq$  hyperinflammatory and  $<$  hypoinflammatory).

#### 2. Secondary Analysis

- Determine inflammatory class for analysis based on the 2 alternative approaches below :
- Five latent class models will be fit to the randomly split cohorts independently. Class-defining variables will be tested for collinearity after transformation and

standardisation, only one of a pair of variables with a Pearson's correlation coefficient of  $> 0.5$  will be used in the modelling. Only variables with  $< 30\%$  missingness will be considered for the modelling. Optimal model fit will be determined using Bayesian information criteria, entropy, Vuong-Lo-Mendall-Rubin test, and the size of the smallest class. Once optimal model has been selected, class-membership will be determined based on the highest probability.

- COVID-19 classes will determined using the 4-variable classifier model and classes assigned using a cut-off of 0.5.

- (1) Sinha P, Churpek MM, Calfee CS. Machine Learning Classifier Models Can Identify Acute Respiratory Distress Syndrome Phenotypes Using Readily Available Clinical Data. *Am J Respir Crit Care Med.* 2020;202(7):996-1004.
- (2) Lyons PG, Bewley AF, Calfee CS, Sinha P. Novel EHR-Derived SARS-CoV-2 Pneumonia Subphenotypes Show Divergent Clinical Outcomes with Differential Responses to Corticosteroids. *Am J Respir Crit Care Med.* 2022; 205: A5626.

## Appendix C. Simulation appendix.

This appendix describes simulations performed during enrolment of the Simvastatin domain to inform the operational decision of whether to continue enrolment. As of November 4, 2022, 2901 PISOP patients were randomized to the Simvastatin domain (~200 moderate and ~2700 severe) with no statistical trigger met at the most recent adaptive analysis. Given the lack of a conclusion and the slow enrolment of PISOP patients, this simulation study was conducted to evaluate the possible treatment effect sizes that would not satisfy futility/superiority triggers at the current sample size and the likelihood of making a conclusion at future analyses if enrolment continues.

This simulation study of the Simvastatin domain in the severe state makes the following assumptions:

- We assume that the distribution of OSFD is similar to the proportions observed in the unblinded no antiplatelet intervention in the Antiplatelet domain. The 23-level OSFD outcome is collapsed into 5 categories with the following proportions:

OSFD level	-1 (death)	0-5	6-10	11-15	16-21
Probability	0.318	0.170	0.066	0.148	0.297

- We simulate a range of Simvastatin treatment effects relative to control: odds ratios (ORs) of 1, 1.05, 1.1, 1.15, and 1.2. We focus on this range of moderate effect sizes since larger/smaller effect sizes are highly likely to have stopped by the current sample size.
- We assume that adaptive analyses occur every 500 patients with complete OSFD up to a maximum of 5000 total patients.
- 1000 simulations are run for each of the treatment effect scenarios for a total of 5000 simulations across the treatment effect scenarios.

At each adaptive analysis, the Bayesian model is estimated and posterior summaries are calculated to assess futility and superiority of simvastatin to control. In addition, RAR probabilities are updated with a 10% minimum applied. When presenting results, we first focus on the results of interims with 2500 complete subjects to provide context similar to the current status of the Simvastatin domain in REMAP-CAP.

### Adaptive analysis 2500

We begin by summarizing the results of the 2500 patient interim to reflect the possible results if an adaptive analysis was performed on the current enrolment of the severe state in the simvastatin domain. For each of the true OR scenarios, we summarize in Table A1 the proportion of trials that reach the 2500 patient interim, the proportion that hit futility prior to 2500 patients, and the

proportion that hit superiority prior to the 2500 interim. If the true simvastatin OR is 1 (null scenario), there is a 76.2% chance that the trial would have hit futility prior to enrolling 2500 patients, a 2.1% chance the trial would have hit superiority prior to enrolling 2500 patients (type I error rate), and a 21.7% chance the trial would reach no conclusion prior to the 2500 patient analysis.

Summary of result prior to 2500 patient analysis					
Proportion of trials:	OR = 1	OR = 1.05	OR = 1.1	OR = 1.15	OR = 1.2
Enroll to 2500 with no prior conclusion	0.217	0.384	0.482	0.477	0.409
Futility prior to 2500 patient interim	0.762	0.557	0.335	0.194	0.089
Superiority prior to 2500 patient interim	0.021	0.057	0.183	0.328	0.502

Table A1: Summary of simulated trials prior to the 2500 patient adaptive analysis. Table shows the proportion of trials that reach the 2500 patient interim, the proportion of trials that have been previously stopped for futility, and the proportion of trials that have been previously stopped for superiority.

Of the trials that reach the 2500 patient interim with no prior conclusion, we summarize the decision made at the 2500 patient adaptive analysis in Figures A1 and Table A2. Of the 5000 total simulated trials (1000 for each of the 5 treatment scenarios), 39.5% of trials reach the 2500 patient interim with no prior conclusion and are summarized here. Figure A1 displays the model-estimated OR and posterior probability of superiority ( $\Pr(\text{OR} > 1)$ ) for each remaining simulated trial where color indicates the conclusion made at the 2500 patient analysis (red – futility, green – superiority, yellow – inconclusive/continue to next interim). In general, ORs less than 1.05 meet the futility trigger and ORs above 1.25 are likely to meet the superiority trigger. At the 2500 patient analysis, the ORs that are likely to continue to the next adaptive analysis are between 1.05 and 1.25.

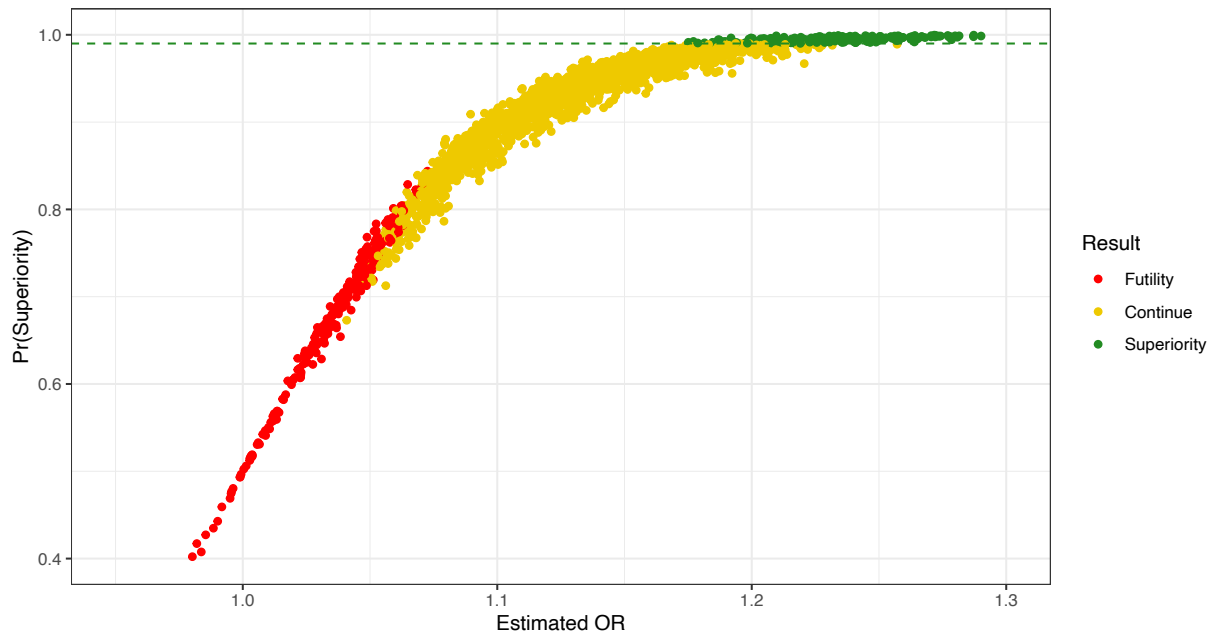


Figure A1: Summary of simulated trials that reach the 2500 patient adaptive analysis where x-axis represents the estimated OR of simvastatin to no simvastatin and the y-axis is the posterior probability of superiority of simvastatin ( $Pr(OR>1)$ ). Each point represents a single simulated trial that is still active at 2500 patients and the color indicates conclusion made at the 2500 patient adaptive analysis.

Table A2 provides an additional summary of the conclusion of trials at the 2500 patient analysis broken down by the true OR. For each of the true ORs, we summarize the total number of trials that enrol to the 2500 adaptive analysis, the proportion of those trials that stop for futility at 2500, and the proportion of trials that meet superiority at 2500. With a true OR of 1.1, 503 simulated trials enrolled to the 2500 patient analysis, 12.7% of those 503 trials stop for futility at 2500 and 8.8% of those 503 trials will stop for superiority. Therefore, if the true OR is 1.1 and the trial reaches 2500 with no prior conclusion, there is a high probability (78.5%) of not meeting a trigger at 2500 and continuing to the next interim.

Summary of result conditional on reaching the 2500 interim					
	OR = 1	OR = 1.05	OR = 1.1	OR = 1.15	OR = 1.2
Number of trials enrolling to 2500	223	406	503	496	428
Proportion of trials that hit futility at 2500	0.278	0.200	0.127	0.059	0.033

Proportion of trials that hit superiority at 2500	0.036	0.049	0.088	0.105	0.187
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Table A2: Summary of simulated trials that reach the 2500 patient adaptive analysis broken down by true underlying OR. For each OR scenario, we display the number of trials that reach 2500, the proportion that will stop for futility given they've reached 2500, and the proportion that will stop for superiority given they've reached 2500.

### **Adaptive analysis 3000**

Next, we summarize the results at the adaptive analysis when 3000 subjects have complete OSFD outcomes. For each of the true OR scenarios, Table A3 summarizes the proportion of trials that reach this 3000 subject interim, the proportion of trials that hit futility before 3000, and the proportion of trials that have hit superiority before 3000.

Summary of result prior to 3000 patient analysis					
Proportion of trials	OR = 1	OR = 1.05	OR = 1.1	OR = 1.15	OR = 1.2
Enroll to 3000 with no prior conclusion	0.146	0.295	0.378	0.400	0.321
Futility prior to 3000 patient interim	0.824	0.626	0.393	0.219	0.100
Superiority prior to 3000 patient interim	0.030	0.079	0.229	0.382	0.579

Table A3: Summary of simulated trials prior to the 3000 patient adaptive analysis. Table shows the proportion of trials that reach the 3000 patient interim, the proportion of trials that have been previously stopped for futility, and the proportion of trials that have been previously stopped for superiority.

Like the 2500 interim, we summarize the decision made at the 3000 patient adaptive analysis in Figures A3 and Table A4. Figure A2 shows that the range of ORs that continue beyond the 3000 interim has narrowed to the range of approximately 1.08 to 1.2.

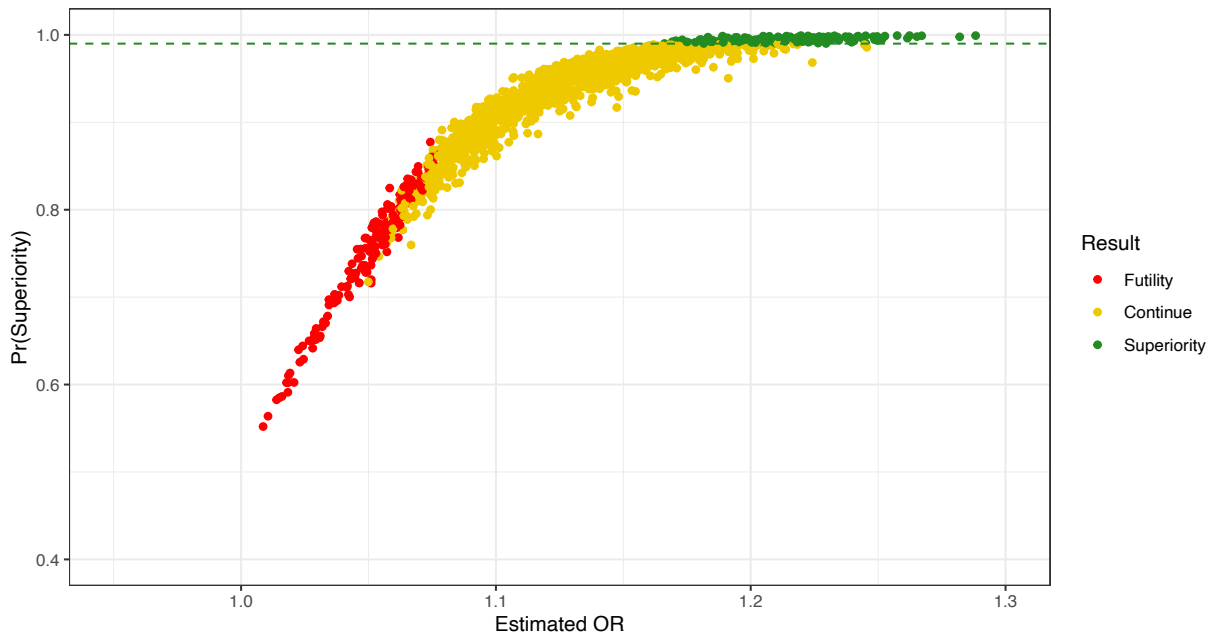


Figure A2: Summary of simulated trials that reach the 3000 patient adaptive analysis where x-axis represents the estimated OR of simvastatin to no simvastatin and the y-axis is the posterior probability of superiority of simvastatin ( $Pr(OR>1)$ ). Each point represents a single simulated trial that is still active at 3000 patients and the color indicates conclusion made at the 3000 patient adaptive analysis.

Table A2 summarizes that, averaging across ORs, 21% of trials that enrol to 3000 will reach a conclusion at 3000. These results suggest that, if the Simvastatin domain continues enrolling up to 3000 patients, there is an approximately 80% chance that no trigger will be met.

Summary of result conditional on reaching the 3000 interim					
	OR = 1	OR = 1.05	OR = 1.1	OR = 1.15	OR = 1.2
Number of trials enrolling to 3000	152	305	392	411	333
Proportion of trials that hit futility at 3000	0.270	0.164	0.107	0.058	0.015
Proportion of trials that hit superiority at 3000	0.033	0.056	0.089	0.134	0.183

Table A4: Summary of simulated trials that reach the 3000 patient adaptive analysis broken down by true underlying OR. For each OR scenario, we display the number of trials that reach 3000, the proportion that will stop for futility given they’ve reached 3000, and the proportion that will stop for superiority given they’ve reached 3000.