



# Multiplatform Randomized Controlled Trial Statistical Analysis Plan: REMAP-CAP Vitamin C domain for Patients with COVID-19 Pandemic Infection Suspected Or Proven (PISOP) and LOVIT trials

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## **1. COVID-19 VITAMIN C DOMAIN SAP VERSION**

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

### **1.1. Version history**

Version 1: Finalized on 2 October 2022

Version 1.1: Updated on 5 December 2022

Clarification has been added that the analysis populations are restricted to randomizations that occurred on or before July 15, 2022 coinciding with the halting of randomization in the LOVIT-COVID trial.

## **2. SAP AUTHORS**

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### 3. INTRODUCTION

This multiplatform randomized controlled trial (mpRCT) statistical analysis plan (SAP) describes the joint analysis of Vitamin C for the treatment of COVID-19 in hospitalized patients in the REMAP-CAP platform trial and Lessening Organ Dysfunction with Vitamin C (LOVIT) trials. The term ‘LOVIT trials’ refers to the LOVIT-COVID trial and to patients with confirmed COVID-19 randomized in the LOVIT trial. This plan synthesizes the statistical analyses outlined in the previous documents from each trial: the REMAP-CAP core SAP, the REMAP-CAP pandemic stratum SAP, and the LOVIT protocol and SAP (Trials 2020;21(1):42 and JMIR Res Protoc 2022;11(5):e36261). The analysis plan that follows describes the combined and separate analyses of data from the REMAP-CAP platform and the LOVIT-COVID trial. Of note, data from patients with confirmed COVID-19 randomized in the published LOVIT trial (N Engl J Med 2022;386:2387-2398) will be included only in sensitivity analysis, together with data from LOVIT-COVID and REMAP-CAP.

This analysis plan includes participants in the Pandemic Infection Suspected or Proven (PISOP) stratum of the REMAP-CAP Vitamin C domain. The PISOP stratum includes patients with suspected or confirmed COVID-19 who are admitted to hospital (ward or intensive care unit [ICU]). The LOVIT umbrella includes the LOVIT and LOVIT-COVID trials. The LOVIT trial includes patients with sepsis (including confirmed COVID-19) who are admitted to the ICU and are receiving vasopressors. The LOVIT-COVID trial includes patients who are admitted to hospital (ward or ICU) with a confirmed diagnosis of COVID-19 but who have not received vasopressors in the current hospitalization and are not receiving them at randomization. This analysis plan includes all participants in LOVIT-COVID and, in a sensitivity analysis, the participants in LOVIT with a confirmed COVID-19 diagnosis. A detailed comparison of the REMAP-CAP, LOVIT, and LOVIT-COVID trials including the eligibility/inclusion criteria/endpoints is provided in Appendix A.

The authors of this document are blinded to all individual participant data and randomization assignments other than publicly disclosed results, including the fact that statistical triggers for futility and harm have been reached in the vitamin C domain of the REMAP-CAP platform trial. The full analysis model will be run once all randomized patients have completed the primary outcome follow-up period (21 days for organ support-free days [OFSDs] for REAMP-CAP and 28 days for persistent organ dysfunction for the LOVIT trials). The primary publication may not include all outcomes specified in this SAP.

## 4. DESIGN CONSIDERATIONS

REMAP-CAP explores the effects of treatments in multiple treatment domains on the primary outcome of OSFDs by randomizing patients within multiple domains simultaneously. The adaptive platform trial was designed to produce modular results for individual interventions or full domains. REMAP-CAP is designed with a hierarchical Bayesian analysis as the primary analysis method. There is one overarching Bayesian model for the PISOP population, prespecified in the SAP, driving result summaries. That primary statistical analysis model will be fit for the analysis of the Vitamin C domain, incorporating vitamin C and placebo data from the LOVIT-COVID trial. This primary analysis model is used to report the results for the Vitamin C interventions (vitamin C and control) in the moderate and severe states (separately). Additional statistical models will be analyzed using data from the LOVIT-COVID trial and REMAP-CAP separately to report the results for the vitamin C interventions (vitamin C versus control/placebo) by platform.

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. These platform conclusions also apply to the joint analysis of REMAP-CAP and LOVIT. The following statistical triggers are defined for this joint analysis:

1. **Vitamin C efficacy.** If vitamin C therapy is deemed to have at least a 99% posterior probability of being superior to the control, then efficacy of vitamin C would be declared.
2. **Vitamin C inferiority.** If vitamin C therapy is deemed to have less than a 1% posterior probability of being in the optimal regimen, then inferiority of vitamin C would be declared.
3. **Vitamin C equivalence.** If vitamin C therapy is deemed to have at least 90% posterior probability of an odds ratio (OR) comparing vitamin C to control between 1/1.2 and 1.2, then equivalence would be declared.
4. **Vitamin C futility.** If vitamin C therapy is deemed to have less than 5% posterior probability of OR comparing vitamin C to control greater than 1.2, then futility would be declared.
5. **Vitamin C harm.** If vitamin C therapy is deemed to have at least 90% posterior probability of OR comparing vitamin C to control less than 1.0, then harm 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).

The triggers for efficacy, inferiority, and equivalence were contained in the initial draft version of this SAP. After the publication of LOVIT (N Engl J Med 2022;386:2387-2398), while the REMAP-CAP Vitamin C domain in PISOP patients was still recruiting and data were blinded, triggers for futility and harm were added. On 14 July 2022, the REMAP-CAP DSMB advised closure of the enrollment to the Vitamin C domain in REMAP-CAP on the basis of statistical triggers for futility and harm being met in the model of 22 April 2022, for both moderate and severe states. On 15 July 2022, the LOVIT-COVID DSMB recommended pausing enrolment in LOVIT-COVID, based on the findings in the vitamin C domain of REMAP-CAP.

## **5. UNBLINDING**

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. At the time of unblinding of the Vitamin C domain in the moderate and severe states of REMAP-CAP, there are other interventions within other domains to which patients may have been randomized that remain blinded. These interventions will not be unblinded at this analysis unless a statistical trigger is hit at the time of the primary analysis. At the time of this analysis, the LOVIT trial for sepsis has been published, and enrollment to the LOVIT-COVID trial has been paused. The Statistical Analysis Committee is unblinded to all interventions and domains as part of their role for REMAP-CAP. There will be other analyses conducted with only knowledge of the unblinded vitamin C/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 is one active intervention and one control within this analysis plan:

1. Vitamin C
2. Control (No vitamin C or placebo)

REMAP-CAP is an open-label trial and the control arm is “no Vitamin C”. The LOVIT trials are blinded and placebo controlled. The control groups from each platform will be combined into a single control group in this joint analysis. In REMAP-CAP, interaction effects of the Vitamin C domain with other domains are not considered possible and are not incorporated into the statistical models.

## 7. DISEASE STATES

Two disease states will be analyzed, which are **moderate** and **severe**. Moderate is defined as not admitted to an ICU, or admitted to an ICU and not receiving organ support. Severe is defined as receiving organ support (defined below) in an ICU. Qualifying organ failure supports are invasive mechanical ventilation, non-invasive mechanical ventilation via sealed mask, continuous infusion of vasopressor or inotrope medication, or high-flow nasal oxygen with a flow rate of  $\geq 30$  L/min and  $FiO_2$  of 0.4 or greater.

The REMAP-CAP Vitamin C domain was available for randomization in patients in the moderate and severe states. The LOVIT-COVID trial was open in both moderate and severe states.

The primary analysis model will estimate distinct effects of each intervention in the moderate and severe states; only the intervention effects for the unblinded intervention(s) and state(s) will be reported. The secondary analysis models run by blinded investigators will be run on only the unblinded intervention(s) and state(s).

## 8. ANALYSIS POPULATIONS

1. **REMAP-CAP/LOVIT-COVID Intention to Treat (ITT)**. This population consists of
  - a) all PISOP participants in REMAP-CAP randomized to any domain
  - b) all participants randomized in LOVIT-COVID
2. **REMAP-CAP/LOVIT-COVID Unblinded ITT**. This population consists of
  - a) all PISOP participants in REMAP-CAP randomized in an unblinded state to the Vitamin C domain or to any other unblinded intervention/domains
  - c) all participants randomized in LOVIT-COVID
3. **REMAP-CAP/LOVIT-COVID Vitamin C specific Unblinded ITT**. This population consists of
  - a) all PISOP participants in REMAP-CAP randomized in an unblinded state to the Vitamin C domain
  - b) all participants randomized in LOVIT-COVID
4. **LOVIT-COVID Unblinded ITT**. This population consists of
  - a) all participants randomized in LOVIT-COVID
5. **REMAP-CAP Unblinded ITT**. This population consists of
  - a) all PISOP participants in REMAP-CAP randomized in an unblinded state to the Vitamin C domain or to any other unblinded intervention/domains

6. **REMAP-CAP/LOVIT-COVID and LOVIT Unblinded ITT.** This population consists of
  - a) all PISOP participants in REMAP-CAP randomized in an unblinded state to the Vitamin C domain or to any other unblinded intervention/domains
  - b) all participants randomized in LOVIT-COVID
  - c) all participants randomized in LOVIT with a confirmed COVID-19 diagnosis

All analysis populations are restricted to randomizations that occurred on or before July 15, 2022 coinciding with the halting of randomization in LOVIT-COVID. All analysis populations will consider the primary endpoints and the secondary endpoint of Composite of Death or Persistent Organ Dysfunction (as defined in Section 9). Analysis population 2 will consider most of the secondary endpoints specified in Section 9.

## 9. ENDPOINTS

The following endpoints will be analyzed, displayed graphically, and summarized through descriptive statistics. Endpoints will be reported separately in each state (moderate and severe).

Primary endpoints:

### 1. Organ Support-Free Days (OSFD) to Day 21

- a. An ordinal endpoint with in-hospital mortality as the worst outcome. This is the primary endpoint for the REMAP-CAP PISOP stratum. The organ support considered is cardiovascular (vasopressor/inotrope support) and respiratory support, as defined in Section 7. Day 21 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. -1 indicates a patient death in hospital prior to the end of 90 days after their last randomization. For patients randomized to more than one domain, Outcome values are updated to -1 if the patient dies during the acute hospital stay and before day 90 after their last randomization.

### 2. Survival to Hospital Discharge (a component of the primary endpoint)



- a. A dichotomous endpoint of in-hospital death where the death component corresponds to a -1 on the OSFD endpoint. Follow-up for this outcome is censored at 90 days.
- b. This endpoint will be reported as “survival to hospital discharge” where OR >1 denotes benefit and OR <1 denotes harm (directionally consistent with OSFD).

Secondary endpoints:

**3. Composite of Death or Persistent Organ Dysfunction**

- a. A dichotomous endpoint of death or dependency on invasive mechanical ventilation, new renal replacement therapy, or a vasopressor/inotrope infusion measured at 28 days (where day 1 is the day of randomization).

**4. 90-Day 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 assumed to be alive at 90 days, if 90-day mortality data are not yet recorded.

**5. Vasopressor/Inotrope-Free Days**

- a. An ordinal outcome of the number of days free of vasopressor/inotropes through 28 days. This is the exact calculation of OSFD, with vasopressor/inotropes as the only organ support category. In-hospital death up to 90 days is considered a -1.

**6. Respiratory Support-Free Days**

- a. An ordinal outcome of the number of days free of respiratory support through 28 days. This is the exact calculation of OSFD, with mechanical respiratory support as the only organ support category (includes high flow nasal oxygen and non-invasive and invasive mechanical ventilation as previously defined). In-hospital death up to 90 days is considered a -1.

**7. Endotracheal Intubation**

- a. A binary outcome in patients not intubated at baseline, recorded up to 28 days after randomization. For the LOVIT trials, intubation status is based on day 1 data, which

could (in principle) reflect patient status after randomization but on the same calendar day.

#### **8. Extracorporeal Membrane Oxygenation (ECMO)**

- a. A binary outcome in patients not on ECMO at baseline, recorded up to 28 days after randomization. For the LOVIT trials, ECMO status is based on day 1 data, which could (in principle) reflect patient status after randomization but on the same calendar day.

#### **9. 28-day Mortality**

- a. This is a binary endpoint at 28 days.
- b. Any patient successfully discharged from hospital, alive, without organ support, will be assumed to be alive at 28 days, if 28-day mortality data are not recorded.

#### **10. 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 to have a duration of 90 days, with no liberation of ICU.
- c. Patients still in the ICU at data snapshot will be considered censored.

#### **11. 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 to have a duration of 90 days with no discharge event.
- c. Patients still in the hospital at data snapshot will be considered censored.

#### **12. The World Health Organization (WHO) 8-Point Ordinal Scale, Measured at Day 14.**

- a. A modified WHO ordinal scale will be used:
  - i. 0 + 1 + 2 = No longer hospitalized
  - ii. 3 = Hospitalized, no oxygen therapy
  - iii. 4 = Oxygen by mask or nasal prongs
  - iv. 5 = Non-invasive ventilation or high-flow oxygen

- v. 6 = Intubation and mechanical ventilation
- vi. 7 = Ventilation + additional organ support: vasopressors, renal replacement therapy, ECMO
- vii. 8 = Death

Note that states 3 and 4 cannot be distinguished in LOVIT and will be collapsed into a single category for the analysis of this endpoint.

### **13. At Least One Serious Adverse Event (SAE)**

A dichotomous endpoint of at least one SAE, as reported by site investigators.

### **14. Hemolysis**

- a. A dichotomous endpoint of at least one hemolysis event during the hospital stay and up to day 28. This is recorded specifically in LOVIT-COVID and as a freetext SAE in REMAP-CAP.

### **15. Hypoglycemia**

- a. A dichotomous endpoint of at least one hypoglycemia event during the hospital stay and up to day 28. This is recorded specifically in LOVIT-COVID and as a freetext SAE in REMAP-CAP.

### **16. European Quality of Life–5 Dimension 5-Level (EQ5D-5L), measured at 180 days**

- a. A continuous endpoint measuring health-related quality of life, measured at 180 days in survivors. (This outcome will not be reported in the primary manuscript.)

Note that endpoints 13-16 will be described rather than modeled. Outcomes 13-15 will be reported separately by trial rather than combined.

Some patients may be randomized both to LOVIT-COVID and to treatment domains other than Vitamin C in REMAP-CAP. In these circumstances, there may be minor differences in the time of randomization across the two trials and different baseline times. In these circumstances, all patient outcomes will be calculated from the REMAP-CAP source data except for two secondary endpoints (hemolysis and hypoglycemia), which will use LOVIT-COVID source data.

## **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.
3. All continuous endpoints will be plotted using histograms and boxplots.

## **11. DESCRIPTIVE STATISTICS**

Endpoints will be modeled with the following conventions. For interventions with <10 participants, outcomes may be summarized numerically without the use of modeling due to model estimate instability in view of small sample size. Similarly, endpoints with <5 occurrences will be reported numerically without the use of modeling.

1. Ordinal endpoints will be summarized by the cumulative frequency of each outcome. The 25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> 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 2.5<sup>th</sup>, 10<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, 90<sup>th</sup>, and 97.5<sup>th</sup> percentiles from the Kaplan-Meier estimates, as available.
4. Continuous endpoints will be summarized by the mean, standard deviation, median and IQR.
5. Composite endpoints will be summarized overall and for each component individually.

## **12. BASELINE CHARACTERISTICS AND CO-INTERVENTIONS**

The following demographics and baseline variables will be summarized across arms, stratified by state. If some variables are not available in all trials, then data will be taken from the trial(s) reporting the variables. More may be added as baseline summaries: age, sex, body mass index (BMI), race/ethnicity (REMAP-CAP only), country of enrollment, confirmed SARS-CoV-2 infection, illness severity at admission (APACHE II score), Clinical Frailty Score, pre-existing conditions as defined by APACHE II (including immunosuppression), time from hospital admission to enrollment, baseline receipt of organ support (high-flow nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy), and receipt of corticosteroids at baseline.

Baseline variables will be reported in Table 1 of the manuscript for the combined REMAP-CAP/LOVIT-COVID analysis population, in the entire population and by randomized group.

Supplementary tables will report baseline characteristics (1) separately for moderate and severe disease states, and (2) for the REMAP-CAP/LOVIT-COVID/LOVIT sensitivity population, together and separately for moderate and severe disease states.

For patients randomized to both REMAP-CAP (in other domains) and LOVIT-COVID (in Vitamin C domain), baseline characteristics will be derived from REMAP-CAP source data. The only exception to this is for Vitamin C specific fields that would only be collected in LOVIT-COVID.

### **13. TREATMENT DELIVERY**

Adherence is documented differently in REMAP-CAP and LOVIT-COVID, and reporting of treatment deliver may change from the plan outlined here when data from the 2 trials are merged. Receipt and number of doses of vitamin C (REMAP-CAP and LOVIT-COVID) or placebo (LOVIT-COVID) will be reported for patients in intervention and control groups. For patients in the Vitamin C intervention groups (REMAP-CAP and LOVIT-COVID) adherence will be measured as a 3-category variable: 0 or 1 missed doses, 2 to 4 missed doses, and greater than 4 missed doses. If data are available on the reason for missed doses (e.g. adverse event or discharge from ICU), this may be incorporated into the adherence summaries. For patients in the control groups, adherence will be measured by administration of  $\geq 90\%$  of scheduled doses of placebo (LOVIT-COVID) and non-administration of vitamin C (LOVIT-COVID and REMAP-CAP). For a dose to be counted as scheduled in LOVIT-COVID, the patient must have been alive randomized on the medical ward (LOVIT-COVID) or randomized in the ICU and still in the ICU (LOVIT-COVID).

For patients randomized to both REMAP-CAP (in other domains) and LOVIT-COVID in (Vitamin C domain), treatment delivery data will be derived from LOVIT-COVID.

### **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. This primary analysis model is used for the populations described above. Small adjustments are made to the model for the LOVIT-COVID ITT population, as noted in the listed factors 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, ..., 21, 22. The outcome of 22 for the severe state (never received organ support) is not possible since participants are on organ support at baseline. A cumulative logistic model is specified. The model is structured so that an OR >1 implies clinical benefit. The full details of the model will be specified in the Current State of The Statistical Model at the time of a Platform Conclusion or final analysis. Currently 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 (reference), 70-79, 80+
- Sex; Male (reference) or female
- 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 (not included for LOVIT-COVID ITT population)
- For each domain, an effect for being ineligible for the domain (not included for LOVIT-COVID ITT population)
- An effect for each intervention within each domain (only includes Vitamin C domain for LOVIT-COVID ITT population)
- Specified interactions in the model between interventions across domains (not included for LOVIT-COVID ITT population).
- A platform effect for LOVIT COVID versus REMAP-CAP (reference). For the sensitivity analysis including both LOVIT and LOVIT COVID, two effects will be estimated, comparing each LOVIT trial to REMAP-CAP. If any identifiability issues arise due to collinearity with sites, this term will be removed.

The primary analysis 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 OR for each dichotomous break is presented. No statistical test of proportional odds is conducted. This sensitivity analysis will be run in models including both the severe and moderate states.

### **14.2. Analytic Approach for Secondary Dichotomous Endpoints**

A Bayesian logistic regression model will be used for each dichotomous outcome. 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. Analytic Approach for Secondary Continuous Endpoints

A Bayesian linear regression model will be used for each continuous outcome. The model is a standard linear model:

$$Y = \alpha + Y_{baseline} + [factors] + \epsilon$$

$$\epsilon \sim Normal(0, \sigma^2)$$

Priors:

$$\alpha \sim N(0,1)$$

$$\left(\frac{1}{\sigma^2}\right) \sim Gamma(0.5, 0.5)$$

Each continuous outcome  $Y$  will be centered and scaled, and other transformations of the outcome may be considered if the normality assumption is violated. The term  $Y_{baseline}$  refers to the baseline measurement of the (standardized) outcome. The prior on the coefficient for  $Y_{baseline}$  will be a normal distribution with mean 0 and standard deviation 1. The formulation of this continuous model will be the same as the primary analysis model. Unless a hierarchical distribution is specified, all coefficients in the model will have a prior that is normally distributed with mean 0 and standard deviation 1. All hierarchical distribution hyperpriors for precision parameters will have a Gamma prior with shape 0.5 and rate 0.5. If other non-specified variables are added to the model, then a normal distribution with mean 0 and standard deviation 1 will be utilized. Model parameters may be summarized on the scale of the standardized outcome and/or on the scale of the original outcome measure.

#### 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 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.

#### 14.6. 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 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 ORs will be summarized. For the dichotomous endpoints, the ORs will



be summarized. For the time-to-event endpoints, the hazard ratios will be summarized. For continuous endpoints, the estimated change in mean will be summarized.

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% has been identified as statistically significant in REMAP-CAP. In addition, a posterior probability comparing whether the estimated OR of vitamin C to placebo from the LOVIT-COVID ITT population is greater than the estimated OR of vitamin C to control from the REMAP-CAP ITT population will be reported. This will provide a summary of the similarity of effect across the platforms. In addition, a forest plot comparing the OR estimates from the LOVIT-COVID ITT, REMAP-CAP ITT, and combined ITT will be shown.

### **14.7. Subgroup Analyses**

For the primary outcome of OFSD only, the following subgroups will be evaluated:

- Age (<65 vs.  $\geq$  65 years; hypothesis: more effective in  $\geq$  65 years);
- Sex (hypothesis: no difference);
- Frailty (Clinical Frailty scale 1-4 vs.  $\geq$  5; hypothesis: more effective in  $\geq$  5);
- Baseline vasopressors/inotropes (hypothesis: more effective in patients on vasopressors/inotropes);
- Baseline endotracheal intubation (hypothesis: more effective in intubated patients);
- For patients enrolled in an ICU, severity of illness based on baseline APACHE II score (subgroups defined by quartiles; hypothesis: more effective as severity of illness increases);
- World Bank Income Classification (high, upper middle, lower middle, low) of country of enrollment (for a complete list of countries, see Data Dictionary for REMAP-CAP Analytic Dataset: Statistical Analysis Committee; hypothesis: more effective in low-middle and low-income countries);
- 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);
- BMI (lower than versus at or above the median; hypothesis: more effective at lower BMI).

## 14.8. Exploratory Analyses

Exploratory analyses after unblinding will not be considered inferential and no p-values will be presented. Any *post hoc* exploratory analyses will be clearly labeled as exploratory and may use the conventions below.

1. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the OR, 95% credible 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 OR and 95% confidence intervals. Differences between proportions will be summarized using observed differences and normal approximations for the 95% credible intervals.
5. For REMAP-CAP only, an exploratory analysis will be reported calculating the effect of vitamin C on the primary outcome of OSFD by time period, where time periods are defined by the time points corresponding to when response adaptive randomization proportions were updated.
6. The primary outcome of OSFD will be compared
  - a. In moderate and severe states with borrowing
  - b. In moderate and severe states separately, without borrowing.

## 15. SPECIFIC PROSPECTIVE ANALYSES

**Table 1.** Prospective analysis.

#	Status	Population	Endpoint	State(s)	Intervention	Other
15.1	Primary	REMAP-CAP/LOVIT-COVID ITT	OSFD	Moderate and Severe	Vitamin C and control/placebo	Includes all interventions and pre-specified interactions
15.2	Primary	REMAP-CAP/LOVIT-COVID ITT	Survival to hospital discharge	Moderate and Severe	Vitamin C and control/placebo	Includes all interventions and pre-specified interactions

<b>15.3</b>	Secondary	REMAP-CAP/LOVIT-COVID ITT	Composite of Death or Persistent Organ Dysfunction	Moderate and Severe	Vitamin C and control/placebo	Includes all interventions and pre-specified interactions
<b>15.4</b>	Sensitivity	REMAP-CAP/LOVIT-COVID ITT	Dichotomized OSFD	Moderate and Severe	Vitamin C and control/placebo	A logistic regression will be run for each dichotomization of OSFDs as a robustness check
<b>15.5</b>	Sensitivity	REMAP-CAP/LOVIT-COVID Unblinded ITT	OSFD	Moderate and Severe	Vitamin C and control/placebo	Includes all unblinded interventions and pre-specified interactions
<b>15.6</b>	Sensitivity	REMAP-CAP/LOVIT-COVID Unblinded ITT	Survival to hospital discharge	Moderate and Severe	Vitamin C and control/placebo	Includes all unblinded interventions and pre-specified interactions
<b>15.7</b>	Sensitivity	LOVIT-COVID ITT	OSFD	Moderate and Severe	Vitamin C and placebo	Only Vitamin C interventions are modeled
<b>15.8</b>	Sensitivity	LOVIT-COVID ITT	Survival to hospital discharge	Moderate and Severe	Vitamin C and placebo	Only Vitamin C interventions are modeled
<b>15.9</b>	Sensitivity	REMAP-CAP Unblinded ITT	OSFD	Moderate and Severe	Vitamin C and control	Includes all unblinded interventions and pre-specified interactions
<b>15.10</b>	Sensitivity	REMAP-CAP Unblinded ITT	Survival to hospital discharge	Moderate and Severe	Vitamin C and control	Includes all unblinded interventions and pre-specified interactions
<b>15.11</b>	Sensitivity	REMAP-CAP/LOVIT-COVID and LOVIT Unblinded ITT	OSFD	Moderate and Severe	Vitamin C and control/placebo	Includes all unblinded interventions and pre-specified interactions
<b>15.12</b>	Sensitivity	REMAP-CAP/LOVIT-COVID and LOVIT Unblinded ITT	Survival to hospital discharge	Moderate and Severe	Vitamin C and control/placebo	Includes all unblinded interventions and pre-specified interactions

<b>15.13</b>	Secondary	REMAP-CAP/LOVIT-COVID Unblinded ITT	Composite of Death or Persistent Organ Dysfunction	Moderate and Severe	Vitamin C and control/placebo	Includes all unblinded interventions and pre-specified interactions
<b>15.14</b>	Sensitivity	REMAP-CAP/LOVIT-COVID Vitamin C specific Unblinded ITT	Composite of Death or Persistent Organ Dysfunction	Moderate and Severe	Vitamin C and control/placebo	Only Vitamin C interventions are modeled
<b>15.15</b>	Sensitivity	LOVIT-COVID ITT	Composite of Death or Persistent Organ Dysfunction	Moderate and Severe	Vitamin C and placebo	Only Vitamin C interventions are modeled
<b>15.16</b>	Sensitivity	REMAP-CAP Unblinded ITT	Composite of Death or Persistent Organ Dysfunction	Moderate and Severe	Vitamin C and control/placebo	Includes all unblinded interventions and pre-specified interactions
<b>15.17</b>	Sensitivity	REMAP-CAP/LOVIT-COVID and LOVIT Unblinded ITT	Composite of Death or Persistent Organ Dysfunction	Moderate and Severe	Vitamin C and control/placebo	Includes all unblinded interventions and pre-specified interactions
<b>15.18</b>	Secondary	REMAP-CAP/LOVIT-COVID Unblinded ITT	90-day mortality	Moderate and Severe	Vitamin C and control/placebo	Includes all unblinded interventions and pre-specified interactions. Time to event analysis.
<b>15.19</b>	Secondary	REMAP-CAP/LOVIT-COVID Unblinded ITT	Vasopressor/Inotrope-free days	Moderate and Severe	Vitamin C and control/placebo	Includes all unblinded interventions and pre-specified interactions
<b>15.20</b>	Secondary	REMAP-CAP/LOVIT-COVID Unblinded ITT	Respiratory support-free days	Moderate and Severe	Vitamin C and control/placebo	Includes all unblinded interventions and pre-specified interactions

<b>15.21</b>	Secondary	REMAP-CAP/LOVIT-COVID Unblinded ITT	Endotracheal intubation	Moderate and Severe	Vitamin C and control/place bo	Includes all unblinded interventions and pre-specified interactions
<b>15.22</b>	Secondary	REMAP-CAP/LOVIT-COVID Unblinded ITT	ECMO	Moderate and Severe	Vitamin C and control/place bo	Includes all unblinded interventions and pre-specified interactions
<b>15.23</b>	Secondary	REMAP-CAP/LOVIT-COVID Unblinded ITT	28-day mortality	Moderate and Severe	Vitamin C and control/place bo	Includes all unblinded interventions and pre-specified interactions
<b>15.24</b>	Secondary	REMAP-CAP/LOVIT-COVID Unblinded ITT	Duration of ICU Stay	Moderate and Severe	Vitamin C and control/place bo	Includes all unblinded interventions and pre-specified interactions. Time to event analysis.
<b>15.25</b>	Secondary	REMAP-CAP/LOVIT-COVID Unblinded ITT	Duration of Hospital Stay	Moderate and Severe	Vitamin C and control/place bo	Includes all unblinded interventions and pre-specified interactions. Time to event analysis.
<b>15.26</b>	Secondary	REMAP-CAP/LOVIT-COVID Unblinded ITT	WHO Scale	Moderate and Severe	Vitamin C and control/place bo	Includes all unblinded interventions and pre-specified interactions
<b>15.27</b>	Secondary	REMAP-CAP/LOVIT-COVID Unblinded ITT	EQ-5D-5L	Moderate and Severe	Vitamin C and control/place bo	Includes all unblinded interventions and pre-specified interactions
<b>15.28</b>	Primary Safety	REMAP-CAP/LOVIT-COVID Vitamin C specific ITT	SAE	Moderate and Severe	Vitamin C and control/place bo	Includes only Vitamin C interventions
<b>15.29</b>	Primary Safety	REMAP-CAP/LOVIT-COVID Vitamin C specific ITT	Hemolysis	Moderate and Severe	Vitamin C and control/place bo	Includes only Vitamin C interventions
<b>15.30</b>	Primary Safety	REMAP-CAP/LOVIT-COVID Vitamin C specific ITT	Hypoglycemia	Moderate and Severe	Vitamin C and control/place bo	Includes only Vitamin C interventions

For subgroup analyses, a separate model for each subgroup listed will be estimated in the REMAP-CAP/LOVIT-COVID Unblinded ITT population for OSFD. These models will be estimated separately for moderate and severe.

Note that the primary safety outcomes will be described only (not modelled).

### 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				
Vitamin C				
Main effect of subgroup				
Vitamin C by subgroup				

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

- Vitamin C intervention will be compared to control (no vitamin C/placebo) 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.
- For the sensitivity analysis assessing the proportional odds assumption, the vitamin C intervention 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: Combined Unblinded ITT, LOVIT ITT, REMAP-CAP Unblinded ITT
- Endpoint: all endpoints
- Factors: Vitamin C and control

The following additional graphical summaries will be provided for OSFD and in-hospital mortality:

- Population: Combined Unblinded ITT, LOVIT ITT, REMAP-CAP Unblinded ITT

- Endpoint: OSFD, in-hospital mortality
- Factors:
  - Vitamin C and control
- Analysis: Conducted by the International Trial Steering Committee Statistical Team.

## Appendix A. Protocol Comparison tables

### a. Eligibility criteria

The inclusion criteria are similar across the three trials and key differences are summarized in Table A1. All three trials include adult patients with diagnoses that include COVID-19. LOVIT includes only patients admitted to the ICU, whereas LOVIT-COVID and REMAP-CAP includes patients admitted to the hospital (ward or ICU).

Table A1: Comparison of Inclusion Criteria

	<b>LOVIT</b>	<b>LOVIT-COVID</b>	<b>REMAP-CAP</b>
Age	Patients ≥ 18 years old	≥ 18 years old	Adult patients
Diagnosis	Admitted to the ICU with proven or suspected infection as the main diagnosis	Confirmed diagnosis of COVID-19	Adult patient admitted to hospital with acute illness due to suspected or proven pandemic infection
Diagnosis	Currently treated with a continuous intravenous infusion of vasopressors (norepinephrine, epinephrine, vasopressin, dopamine, phenylephrine).	Admitted to hospital (ward or ICU)	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

The exclusion criteria are also similar across the three trials, with differences and similarities listed in Table A2.

Table A2: Comparison of Exclusion Criteria

	<b>LOVIT</b>	<b>LOVIT-COVID</b>	<b>REMAP-CAP*</b>
Timing	> 24 hours of ICU admission	> 24 hours has elapsed since receipt of non-invasive ventilatory support (high-flow nasal cannula or continuous positive airway pressure or non-invasive ventilation) or invasive mechanical ventilation	> 24 hours has elapsed since ICU admission (noting that this may be operationalized as more than 24 hours has elapsed since commencement of sustained organ failure support)
Timing		> 14 days have elapsed since the commencement of hospital admission with respiratory illness	
Vasopressors		Receiving or have received vasopressors during the current hospitalization	
Hospital discharge		Patient is expected to be discharged from the hospital in the next 24 hours	
Glucose-6-phosphate dehydrogenase (G6PD) deficiency	Known G6PD deficiency		
Sickle cell anemia		Known sickle cell anemia	
Pregnancy	Pregnancy	Pregnancy or breastfeeding	Known or suspected pregnancy is not an exclusion criterion unless required by the competent national authority in that jurisdiction
Vitamin C allergy	Known allergy to vitamin C		
Kidney stones	Known kidney stones within the past 1 year		
Received vitamin C	Received any intravenous vitamin C during this hospitalization unless incorporated in parenteral nutrition		
Expected death	Expected death or withdrawal of life-sustaining treatments within 48 hours	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	



	<b>LOVIT</b>	<b>LOVIT-COVID</b>	<b>REMAP-CAP*</b>
Previous enrollment	Previously enrolled in this study		Previous participation in this REMAP within the last 90 days
Co-enrollment	Previously enrolled in a trial for which co-enrollment is not allowed (co-enrollment to be determined case by case)		Patient has been randomized in a trial evaluating vitamin C, where the protocol of that trial requires ongoing administration of study drug
Patient's best interest			The treating clinician believes that participation in the domain would not be in the best interests of the patient

\*as per the REMAP-CAP Core Protocol and Pandemic Appendix, available at remapcap.org. The criteria listed apply to the PISOP stratum.

### **b. COVID-19 status**

Each trial includes patients with COVID-19. LOVIT (COVID-19 subgroup) and LOVIT-COVID require a confirmed diagnosis of COVID-19. Of note, participants enrolled in the LOVIT trial may have been enrolled with a diagnosis other than COVID-19, but baseline COVID-19 testing may have subsequently been reported as positive. As noted, these participants will be included in the mpRCT in a sensitivity analysis.

REMAP-CAP includes patients with suspected or proven COVID-19. Of note, there are few suspected cases of COVID-19 enrolled in REMAP-CAP and review of CT scans suggests that the suspected participants have COVID-19 even if their PCR test was negative. These participants were likely enrolled early in the pandemic when testing was not available.

Table A3: Comparison of COVID-19 Status

	<b>LOVIT</b>	<b>LOVIT-COVID</b>	<b>REMAP-CAP</b>
COVID-19 Diagnosis	Confirmed diagnosis of COVID-19		Suspected or proven pandemic infection
Includes patients without COVID-19	Yes	No	Yes

### c. Interventions

The interventions are the same for all three trials. LOVIT and LOVID-COVID include a placebo control, whereas REMAP-CAP does not include a placebo.

Table A4: Comparison of Interventions

	<b>LOVID</b>	<b>LOVIT-COVID</b>	<b>REMAP-CAP</b>
Treatment	Vitamin C 50 mg/kg every 6 hours for 96 hours		
Control	Placebo		No vitamin C

### d. Endpoints

The REMAP-CAP primary and secondary endpoints will be used for this statistical plan. The primary and secondary endpoints are the same for LOVIT and LOVIT-COVID, with the exception of the number of whole and part study days for which the patient is alive and not admitted to an ICU up until the end of study day 21, which is collected in LOVIT-COVID and not applicable to LOVIT, as the participants are already admitted to the ICU. There are differences in outcomes between REMAP-CAP and the LOVIT and LOVIT-COVID trials, which are summarized in Table A5 and Table A6. While the endpoints differ, LOVIT and LOVIT-COVID capture the data required for the REMAP-CAP endpoints.

Table A5: Comparison of Primary Endpoint

<b>LOVIT</b>	<b>LOVIT-COVID</b>	<b>REMAP-CAP</b>
Composite of death or persistent organ dysfunction (defined as dependency on mechanical ventilation, new renal replacement therapy, or vasopressors) at 28 days		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

Table A6: Comparison of Secondary Endpoints

<b>LOVIT</b>	<b>LOVIT-COVID</b>	<b>REMAP-CAP</b>
Not applicable	Number of whole and part study days for which the patient is alive and not	Collected

<b>LOVIT</b>	<b>LOVIT-COVID</b>	<b>REMAP-CAP</b>
	admitted to an ICU up until the end of study day 21	
Persistent organ dysfunction-free days in ICU, up to day 28		Organ failure free days censored at day 28
Mortality at 6 months		6-month survival
Health-related quality of life in 6-month survivors assessed by the EuroQol-5D (EQ-5D)		
Global tissue dysoxia		
Organ function (including renal function) assessed by the SOFA score (days 1, 2, 3, 4, 7, 10, 14, and 28)		
Inflammation assessed by interleukin-1 beta (IL-1 $\beta$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), C-reactive protein (CRP)		
Infection assessed by procalcitonin (PCT)		
Endothelial injury assessed by thrombomodulin (TM) and angiopoietin-2 (ANG-2)		
Occurrence of stage 3 acute kidney injury as defined by KDIGO criteria daily		
Acute hemolysis as diagnosed by the clinical site team (daily)		
Hypoglycemia (glucose value(s) < 3.8 mmol/L validated by core lab)		
Collected		All-cause mortality at 90 days
Collected		ICU mortality
Collected		Duration of ICU stay
Collected		Duration of hospital stay
Collected		Ventilator free days censored at day 28
Collected		Serious adverse events