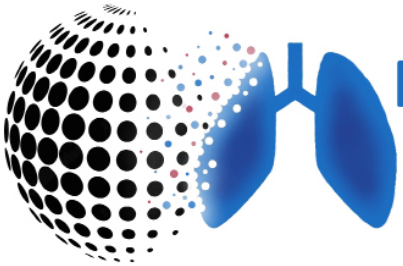

REMAP-CAP

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

Statistical Analysis Plan for the Corticosteroid Domain for Patients with COVID-19 Pandemic Infection Suspected Or Proven (PISOP)

COVID-19 Corticosteroid Domain SAP Version 1.0 dated 20 July 2020

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1. COVID-19 CORTICOSTEROID DOMAIN SAP VERSION

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

1.1. Version history

Version 1: Finalized on July 21st, 2020.

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3. INTRODUCTION

This statistical plan for the corticosteroid domain in the pandemic stratum of REMAP-CAP is an appendix to the Pandemic Appendix to Core (PAtC) Statistical Analysis Plan (SAP). This document synthesizes that information and describes the details of the statistical analysis of the corticosteroid domain within the pandemic stratum of REMAP-CAP. This plan details the statistical analyses in the REMAP-CAP core SAP and the pandemic stratum SAP applied to the corticosteroid domain. The plan here is completely prespecified for the imminent unblinding of the results for the corticosteroid domain within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

The corticosteroid domain was halted in the PISOP stratum following the release of the results of the RECOVERY trial on June 16th showing strong positive effects of dexamethasone in moderate and severe patients (The RECOVERY Collaborative Group. *NEJM* July 17th 2020). The REMAP-CAP International Trial Steering Committee (ITSC) decided on June 17th 2020 to stop the corticosteroid domain of REMAP-CAP within the PISOP stratum and report the results. REMAP-CAP explores multiple treatment domains by randomizing patients within multiple domains and was designed to have modular results for individual interventions or full domains announced upon reaching a platform conclusion. For this domain, there have not been any interim analyses conducted and it was closed based on external results, and hence the results for the corticosteroid domain will be unblinded and made public. This document prespecifies the analysis plan for this unblinding.

The authors of this document are completely blinded to the data and results in REMAP-CAP.

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. That primary statistical analysis model will be used to report the results for the corticosteroid domain within the PISOP stratum.

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 the RECOVERY trial report, 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 corticosteroid domain:

1. **Domain Superiority**. If a single intervention within the corticosteroid 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 domain 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 corticosteroid 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 domain has been stopped no analyses for futility will be conducted.

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 this portion of REMAP-CAP before the first interim analysis, which by coincidence is now due. At analysis, therefore, being halted early does not change the Bayesian statistical triggers of the domain: the same thresholds apply. That said, because there will be no further enrollment into this domain for patients within the pandemic stratum (and possibly no further randomization to corticosteroids or not in any RCT of COVID19), the results are 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 corticosteroid therapy in COVID-19 than whether a particular posterior probability exceeded a pre-defined threshold or not. For example, a posterior probability of benefit of 80% or higher would be quite promising, especially in light of the findings of RECOVERY.

5. UNBLINDING

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. At the unblinding of the corticosteroid domain there are other domains to which the patients have been randomized that will not be unblinded at this 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 other analyses that are conducted with only knowledge of the corticosteroid allocation status for patients. 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 corticosteroid domain. These are

1. No corticosteroid/hydrocortisone (control)
2. Fixed duration hydrocortisone for 7 days (fixed-duration)
3. Shock-Dependent hydrocortisone (shock-dependent)
4. High-Dose hydrocortisone for 7 days

For all analyses and data summaries the high-dose 7-day hydrocortisone arm will be combined with the fixed-duration arm. These interventions were originally nested, which allows their pooling, and very few patients were randomized to Intervention #4. The results for Intervention #4 will be reported in a stacked bar plot.

7. DISEASE STATES

There are 2 disease states in the PAtC, which are **moderate** and **severe**. The corticosteroid domain was only randomized to patients in the severe state, so only patients in the severe state will be analyzed.

8. ANALYSIS POPULATIONS

1. REMAP-COVID severe state intent-to-treat (ITT). This population consists of all PISOP patients in the severe state randomized within at least one domain.
2. Corticosteroid Domain ITT. All patients randomized to an intervention in the corticosteroid domain within the PISOP stratum.
3. Corticosteroid domain Non-negative COVID. All patients randomized in the corticosteroid domain after removing those with $\geq$1 negative test for COVID **and** no positive tests.

9. ENDPOINTS

The following end points will be analyzed, graphically displayed, 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 organs considered are cardiovascular (vasopressor/inotrope support) and respiratory (ventilation support). See the PAtC SAP for a detailed description.

2. **In-Hospital Mortality**
    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 imputed as a 90-day "no mortality" event if 90-day mortality data is 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. **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. **Ventilator Free-Days**
    a. An ordinal outcome of number of days free of ventilation. This is the exact calculation of OSFD, with ventilation 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.

10. **The World Health Organization (WHO) 8-point ordinal scale, measured at day 14.**
    a. The WHO 8-point ordinal scale:
        1 = No limitations
        2 = Limitation of activities
        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 graphed using stacked cumulative bar plots
2. All time-to-event endpoints will be plotted using Kaplan-Meier plots

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 summarize the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates.

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 etomidate, and miscellaneous physiological values.

13. COMPLIANCE

The compliance to corticosteroid 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 23 possible, ordered outcomes. Let the outcome for a patient by 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. Hence there are 23 possible outcomes. 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 of The Statistical Model, dated July 21, 2020. 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 a month.
- 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 Corticosteroid domain uses the following rules:

- For the primary analysis, 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 sites within a country that have <5 patients randomized 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 for model stability. For example, if the outcome 11 never occurred a combined outcome of 10 & 11 will be modeled for the analysis.

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. 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:

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

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. 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 24-hour 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. 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 a 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 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.

14.5. 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 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 the dichotomous endpoints, the odds-ratio will be summarized. For the time-to-event model the hazard ratio 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% 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 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 20 specific prospective analyses, summarized in the table and described in detail below.

#	Status	Population	Endpoint	Other
15.1	Primary	REMAP-COVID severe state ITT	OSFD	Includes all interventions and interactions
15.2	Primary	REMAP-COVID severe state ITT	In-Hospital Mortality	Includes all interventions and interactions
15.3	Secondary	REMAP-COVID severe state ITT	OSFD	Includes all interventions and interactions, combined corticosteroid arms
15.4	Secondary	REMAP-COVID severe state ITT	In-Hospital Mortality	Includes all interventions and interactions, combined corticosteroid arms
15.5	Secondary	Corticosteroid Domain ITT	OSFD	
15.6	Secondary	Corticosteroid Domain Non-negative COVID	OSFD	
15.7	Secondary	Corticosteroid Domain ITT	OSFD	Combined corticosteroid arms
15.8	Sensitivity	Corticosteroid Domain ITT	OSFD	Remove site and time effects
15.9	Secondary	Corticosteroid Domain ITT	In-Hospital Mortality	
15.10	Secondary	Corticosteroid Domain Non-negative COVID	In-Hospital Mortality	
15.11	Secondary	Corticosteroid Domain ITT	In-Hospital Mortality	Combined corticosteroid arms
15.12	Sensitivity	Corticosteroid Domain ITT	In-Hospital Mortality	Remove site and time effects
15.13	Secondary	Corticosteroid Domain ITT	Mortality	Time-to-events modeling
15.14	Secondary	Corticosteroid Domain ITT not on MV, ECMO at baseline	Progression to intubation, ECMO, death	
15.15	Secondary	Corticosteroid Domain ITT	Days-Free of vasopressor/inotropes	
15.16	Secondary	Corticosteroid Domain ITT	Days-Free of ventilation	
15.17	Secondary	Corticosteroid Domain ITT	Length of ICU Stay	
15.18	Secondary	Corticosteroid Domain ITT	Length of Hospital Stay	
15.19	Secondary	Corticosteroid Domain ITT	WHO Scale at 14 days	
15.20	Primary Safety Analysis	Corticosteroid Domain ITT	Serious adverse events per patient	The time components are removed from the model

15.1. The primary analysis for the Corticosteroid 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, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the unblinded SAC

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration and the shock-based intervention would hit the statistical trigger for equivalence.
d. No information on the effects of the other domains or their interactions will be reported. This information will remain blinded until each domain/intervention reaches a conclusion.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.2. The primary mortality analysis for the Corticosteroid Domain

- Population: REMAP-COVID severe state ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the unblinded SAC

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.
d. No information on the effects of the other domains or their interactions will be reported. This information will remain blinded until each domain/intervention reaches a conclusion.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.3. The secondary analysis combining corticosteroid arms for the Corticosteroid Domain

- Population: REMAP-COVID severe state ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, corticosteroid interventions: control, corticosteroids: combined fixed-duration and shock-based
- Analysis: Conducted by the unblinded SAC

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Corticosteroids will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. No information on the effects of the other domains or their interactions will be reported. This information will remain blinded until each domain/intervention reaches a conclusion.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Corticosteroid use is in the optimal regimen	

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				
Corticosteroids				

15.4. The secondary mortality analysis combining corticosteroid arms for the Corticosteroid Domain

- Population: REMAP-COVID severe state ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, corticosteroid interventions: control, corticosteroids: combined fixed-duration and shock-based
- Analysis: Conducted by the unblinded SAC

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Corticosteroids will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. No information on the effects of the other domains or their interactions will be reported. This information will remain blinded until each domain/intervention reaches a conclusion.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Corticosteroid use is in the optimal regimen	

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				
Corticosteroids				

15.5. A secondary analysis restricted to the Corticosteroid Domain ITT

- Population: Corticosteroid Domain ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.6. A secondary analysis restricted to the Corticosteroid Domain Non-negative COVID

- Population: Corticosteroid Domain Non-negative COVID
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.7. A secondary analysis for the Corticosteroid Domain ITT combining corticosteroid intervention arms.

- Population: Corticosteroid Domain ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, corticosteroid interventions: control, corticosteroids: combined fixed-duration and shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Corticosteroids will be compared to the control arm. A posterior probability of superiority of 99% will be used to as a statistical trigger for efficacy.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Corticosteroids use is in the optimal regimen	

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				
Corticosteroids				

15.8. A sensitivity analysis restricted to the Corticosteroid Domain ITT with site and time factors removed

- Population: Corticosteroid Domain ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.9. A secondary analysis of in-hospital mortality restricted to the Corticosteroid Domain ITT

- Population: Corticosteroid Domain ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.10. A secondary analysis of in-hospital mortality for Corticosteroid Domain Non-negative patients

- Population: Corticosteroid Domain Non-Negative
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-Duration Corticosteroids				
Shock-based Corticoteroids				
Shock-based Corticoteroids vs. Fixed-Duration Corticosteroids				

15.11. A sensitivity analysis of in-hospital mortality restricted to the Corticosteroid Domain ITT with factors for site and time removed

- Population: Corticosteroid Domain ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: Age, sex, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration corticosteroids				

15.12. A secondary analysis of in-hospital mortality restricted to the Corticosteroid Domain ITT with the steroid interventions combined

- Population: Corticosteroid Domain ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: Age, sex, corticosteroid interventions: control, corticosteroids: combined fixed-duration and shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Corticosteroids will be compared to the control arm. A posterior probability of superiority of 99% will be used to as a statistical trigger for efficacy.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Corticosteroid use is in the optimal regimen	

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				
Corticosteroids				

15.13. A sensitivity analysis of in-hospital mortality restricted to the Corticosteroid Domain ITT with factors for site and time removed

- Population: Corticosteroid Domain ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: Age, sex, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.14. A secondary analysis of progression to intubation, ECMO, or death, restricted to patients not on MV or ECMO at baseline

- Population: Corticosteroid Domain ITT not on MV or ECMO at baseline.
- Endpoint: Progression to MV, ECMO, or death
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.15. A secondary analysis of days-free of vasopressor/inotropes use

- Population: Corticosteroid Domain ITT.
- Endpoint: Vasopressor/Inotropes free-days
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.16. A secondary analysis of days-free of ventilation

- Population: Corticosteroid Domain ITT.
- Endpoint: Ventilation free-days
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

d. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
e. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
f. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 odds-ratio difference between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.17. A secondary analysis of length of ICU stay

- Population: Corticosteroid Domain ITT
- Endpoint: Length of ICU stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 hazard-ratio between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

The following will be reported:

Hazard-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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.18. A secondary analysis of length of hospital stay

- Population: Corticosteroid Domain ITT
- Endpoint: Length of Hospital stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 hazard-ratio between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

The following will be reported:

Hazard-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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.19. A secondary analysis of the WHO Ordinal Scale

- Population: Corticosteroid Domain ITT
- Endpoint: WHO scale at 14-days
- Model: Primary Ordinal model
- Factors: Age, sex, site, time, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that each intervention is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. The two corticosteroid interventions will be compared for equivalence. A 90% probability of a smaller than 1.2 hazard-ratio between the fixed-duration intervention and the shock-based intervention would hit the statistical trigger for equivalence.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	
Fixed-duration is in the optimal regimen	
Shock-based is in the optimal regimen	
Fixed-duration is superior to control	
Shock-based is superior to control	
Fixed-duration is equivalent to shock-based	

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				
Fixed-duration Corticosteroids				
Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				

15.20. The primary safety analysis for the Corticosteroid Domain

- Population: Corticosteroid Domain ITT
- Endpoint: Serious Adverse Events (SAE)
- Model: Primary dichotomous model
- Factors: age, sex, site, corticosteroid interventions: control, fixed-duration, shock-based
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Each intervention will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. A posterior probability of 99% superiority of the control will be used for inferiority of the corticosteroids interventions

b. No information on the effects of the other domains or their interactions will be reported. This information will remain blinded until each domain/intervention reaches a conclusion.

The following posterior probabilities will be reported

Quantity of Interest	**Posterior Probability**
Fixed-duration is superior to control	
Shock-based is superior 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				
Fixed-duration Corticosteroids				

Shock-based Corticosteroids				
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids				