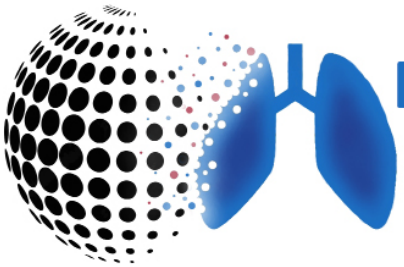

Statistical Analysis Plan for fixed dose hydrocortisone for patients in whom pandemic infection is neither suspected nor proven (PINSNP)

Fixed dose hydrocortisone for non-pandemic pneumonia SAP Version 1.0 dated 5 February 2024

TABLE OF CONTENTS

1. FIXED DOSE HYDROCORTISONE FOR NON-PANDEMIC PNEUMONIA SAP VERSION

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

1.1. Version history

Version 1: Finalized on 5 February 2024.

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3. INTRODUCTION

This statistical plan for the analysis of fixed dose hydrocortisone in the non-pandemic stratum of the REMAP-CAP trial is an appendix to the Core protocol Statistical Analysis Plan (SAP). The general statistical approach is outlined in detail in the Core protocol SAP. This appendix provides specific details regarding the application of the general approach to the specific case in which we proposed to analyze the effect of fixed dose hydrocortisone in severe non-pandemic pneumonia. This analysis is being conducted because this intervention triggered the pre-set futility trigger (<5% probability of ≥20% improvement in the odds of death at 90 days compared to control) within all unit of analyses made up of the shock and influenza strata, leading to cessation of enrolment as recommended by the Data Safety and Monitoring Board (DSMB).

REMAP-CAP explores multiple treatment domains by randomizing patients within multiple domains simultaneously. The adaptive platform trial was designed to produce modular results for individual interventions (compared to relevant control groups) or full domains upon reaching platform conclusions. When a predefined statistical trigger is met, the results are unblinded, analyzed based on a pre-specified plan, and made public. This document prespecifies the analyses to be conducted and reported on the unblinded data. The unblinded data will be for all patients eligible for fixed dose hydrocortisone who were randomized to fixed dose hydrocortisone or control interventions in the Corticosteroid Domain within the severe state non-pandemic stratum (pandemic infection neither suspected nor proven - PINSNP).

The authors of this document are blinded to all individual data other than: a.) prior publicly disclosed results for other domains and interventions, and; b.) correspondence from the DSMB attesting to the fact that the statistical trigger for futility has been reached for fixed dose hydrocortisone in all four units of analyses made up of shock and influenza strata. The primary analysis for this SAP will be conducted when the patient last randomized before closing of the fixed dose hydrocortisone arm reaches 90 days of follow-up (completion of the primary endpoint).

4. DESIGN CONSIDERATIONS

REMAP-CAP is designed with a Bayesian analysis as the primary analysis method for the trial. There is one overarching Bayesian hierarchical model, prespecified in the Core protocol SAP, driving all adaptations, statistical triggers, and result summaries. That primary statistical analysis model will be used to report the primary results for the effect of fixed dose hydrocortisone in the PINSNP stratum.

The Domain Specific Appendix specified the primary analysis populations based on three analytic patient strata (with "strata" defined at time of randomization into the domain and considered to be non-dynamic). The three domain-specific strata included: (1) age (children vs. adults); (2) source of infection (influenza vs. non-influenza pneumonia); and (3) shock (present or absent at enrollment). At the time of closure of randomization to the fix dose hydrocortisone intervention, no children had yet been enrolled and therefore this analytic stratum is not considered (all patients are in the adult stratum). However, the other two analytic strata are included (as per, and as defined in, the Core Protocol and Corticosteroid Domain-specific Appendix). Although the domain also specified units of analysis based on illness severity (moderate/noncritically ill vs. severe/critically ill), moderately ill patients were not eligible for the fixed dose hydrocortisone intervention and therefore this stratum is not considered herein (all patients are severe). The analyses herein pertain only to the fixed dose hydrocortisone group (the only closed intervention in this domain), and the analysis of all ongoing interventions in this domain will be considered in a future SAP. The primary analysis will report the effect of hydrocortisone compared to no hydrocortisone in each unit of analysis defined by influenza and shock strata.

5. UNBLINDING

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. During the time that severe state PINSNP patients have been eligible for fixed dose hydrocortisone, 2 other active interventions have been available within the Corticosteroid domain: fixed dose dexamethasone and shock-dependent hydrocortisone. Only data for patients who were randomized to control or fixed dose hydrocortisone will be unblinded. No data on patients randomized to the other interventions in the Corticosteroid domain or on the effect of other interventions that are still being evaluated in other domains will be unblinded. However, the primary analysis will be conducted by the independent and unblinded Statistical Analysis Committee (SAC), using all available information required for the primary model (including information to which only the SAC and DSMB are unblinded). Secondary analyses will be conducted on the unblinded data set (fixed dose hydrocortisone vs. control) by investigators who are blinded to information about other interventions and domains. These analyses are identified below.

6. INTERVENTIONS

There are two arms (interventions) analyzed herein:

1. No corticosteroids assigned (control)

2. Fixed dose hydrocortisone (active comparator)

No interaction effects with other interventions within other domains will be evaluated.

7. DISEASE STATES

There are two disease states (**moderate** and **severe**) in REMAP-CAP. However, as noted above only severe state patients were eligible for the fixed dose hydrocortisone intervention, and therefore this analysis is restricted to patients in the severe state.

8. ANALYSIS POPULATION

1. REMAP-CAP severe state non-pandemic (PINSNP) pneumonia intent-to-treat (ITT) population. This population includes all patients randomized to at least one domain in the PINSNP stratum. This analysis population is used for the primary analysis.
2. Hydrocortisone specific ITT. This population consists of non-pandemic (PINSNP) pneumonia patients randomized to either fixed dose hydrocortisone or control. This analysis population is used for secondary analyses.
3. Hydrocortisone eligible ITT. This population consists of non-pandemic (PINSNP) pneumonia patients eligible for both control and fixed dose hydrocortisone and randomized to either fixed dose hydrocortisone or control. This analysis population is used for sensitivity analyses and descriptive summaries of endpoints that are not analyzed.

Each of these analysis populations will include only the patients randomized on or before 6 December 2023 (date that enrollment into the fixed dose hydrocortisone intervention was closed).

9. ENDPOINTS

The following endpoints will be analyzed, displayed graphically, and summarized through descriptive statistics. Section 15 below itemizes which specific endpoints will be analyzed in which specific populations.

1. **Primary endpoint: 90-day mortality**
   - A dichotomous endpoint of all-cause mortality at 90-days.
   - The primary analysis will analyze landmark mortality. In addition, Kaplan Meier curves will be generated to illustrate when deaths occurred with the accompanying hazard ratio estimated from a secondary analysis of mortality up to day 90 as a time-to-event endpoint.
2. **ICU mortality, censored at 90 days**

- A dichotomous endpoint of death in ICU up to 90 days. ICU mortality is defined as any death in the ICU within the same hospital admission.

3. **ICU length of stay, censored at 90 days**
   - A time-to event endpoint of leaving the ICU alive. If a patient is known to leave and then return to the ICU within 14 days of discharge, the intervening days while on the ward will be counted as ICU days.
   - Patients that die in the ICU will be considered to have 90-days of follow-up with no discharge event (i.e., the worst possible outcome).
   - Patients still in the ICU at data snapshot will be censored.
4. **Ventilator-free days (VFD), censored at 28 days**
   - VFD will be calculated by counting the number of days that the participant is not ventilated.. If the participant is discharged alive from hospital, the remainder of days censored at 28 days are counted as ventilator-free days. In hospital mortality through day 90 is considered a -1 (worst outcome).
5. **Organ-support free days (OSFD), censored at 28 days**
   - OSFD is an ordinal endpoint with in-hospital mortality through day 90 as the worst outcome. The organ support considered is cardiovascular (vasopressor/inotrope support) and respiratory support, calculated through 28 days.

6. **Progression to intubation and mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death**
   - A dichotomous endpoint of whether a patient progresses to intubation and mechanical ventilation, ECMO or death in hospital. This endpoint is defined for patients that are not on mechanical ventilation or ECMO at baseline.
7. **Proportion of intubated patients who receive a tracheostomy, censored at 28 days**
   - This endpoint will be summarized descriptively only.
8. **Hospital length of stay, censored at 90 days**
   - A time-to event endpoint of leaving the hospital alive.
   - Patients that die in-hospital will be considered to have 90-days of follow-up with no discharge event (i.e., the worst possible outcome).
   - Patients still in the hospital at data snapshot will be considered censored.
9. **Destination at time of hospital discharge (home, rehabilitation hospital, nursing home or long-term care facility, or another acute hospitalization)**
   - This endpoint will be summarized descriptively only.

10. **Readmission to the index ICU during the index hospitalization in the 90 days following enrollment**
    - This endpoint will be summarized descriptively only.
11. **At least one serious adverse event (SAE)**
    - The proportion of patients with at least one SAE will be reported and analyzed.

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 event-free rate.

11. DESCRIPTIVE STATISTICS

1. Ordinal endpoints will be summarized by the cumulative frequency of each outcome. The 25th, 50th, and 75th percentiles will be summarized.
2. Dichotomous endpoints will be summarized by the proportion in each category.
3. Time-to-event outcomes will be summarized by the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates, as available.

12. BASELINE CHARACTERISTICS

The following demographics will be summarized across arms: age, sex, BMI, ethnicity, APACHE II score (measured from hospital admission to randomization), suspected and confirmed influenza infection, preexisting conditions, baseline use of high-frequency nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, and miscellaneous physiological values and inflammatory biomarker laboratory values.

13. COMPLIANCE

The compliance to steroid use over the first seven days will be summarized descriptively as follows:

- Proportion for whom we have dosing information for study day 1 thru 8
- Proportion who received at least one dose
- Additional proportion who received an alternative systemic steroid
- Proportion who received no steroid

- Proportion who received first dose HC before midnight on first day
- Median duration and IQR of HC therapy and of any systemic steroid therapy

Use of corticosteroids in the control arm over the first seven days will be summarized descriptively as follows:

- Proportion for whom we have medication inventory for study day 1 thru 8
- Proportion who received any hydrocortisone
- Proportion who received any systemic steroid
- Median duration and IQR of systemic steroids

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.

The protocol permitted fixed borrowing (shrinkage) between the analytic populations. Accordingly, treatment effects were estimated for the treatment in each stratum by combining all analytic groups into a single Bayesian hierarchical model, but allowing sharing of information between analysis groups through the use of a shrinkage parameter in the model. This effect averages treatment effects across groups and may increase power within a single group depending on the findings from other groups.

14.1. Analytic Approach for Primary Endpoint and Secondary Dichotomous Endpoints

A Bayesian cumulative logistic regression model will be used for the primary endpoint and for each dichotomous secondary outcome. The model will specify the "event" as the negative outcome and be parameterized so that an odds-ratio <1 implies benefit to patients. The model is the standard logistic link function model:

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

References will be made to the factors in the model and their prior distribution. Full details of the model are specified in the Current State of the Statistical Model: Non-Pandemic Model Version 3.1. The model has factors for:

- Strata and state effects
- Each global site, nested within country
- Age; ≤40, 41-65, 66-75, 76+
- Sex

- Time; 13-week buckets of time working backwards from the last enrolled patient
- For each domain, an effect for being randomized to the domain
- For each domain, an effect for being ineligible for the domain
- An effect for each intervention within each domain
- Specified interactions in the model between interventions and strata
- Specified interactions in the model between interventions across domains

The 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.
- Time buckets with <5 randomized subjects in a state may be combined with the more recent neighboring bucket for that state.

The 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. **Analytic Approach for Sensitivity Analyses of the Primary Outcome**

Several sensitivity analyses will be included. First, the primary outcome will be analyzed within each analysis population without the use of statistical borrowing – estimating independent treatment effects for each analytic stratum. Second, the primary outcome will be analyzed within each analysis population estimating a single effect of hydrocortisone compared to no hydrocortisone. Finally, the effect of fixed dose hydrocortisone will be examined using only patients eligible for both fixed dose hydrocortisone and control (not just those eligible for this domain), as specified as the third analysis population (Hydrocortisone eligible ITT). Given that there were no intervention-specific exclusion criteria in this domain, this analysis population is likely to resemble the original analysis population, primarily differing based on sites participating in the domain but not participating in the fixed dose hydrocortisone or control interventions. The specified analysis models adjust for site as a factor. Nevertheless, this sensitivity analysis is included.

14.2. Analytic Approach for Secondary Ordinal Endpoints

Ordinal outcomes will be analyzed using Bayesian cumulative logistic models. The model is structured so that an odds-ratio <1 implies clinical benefit to be consistent with the primary endpoint. The model assumes a proportional effect of treatment across the scale of the ordinal outcome. The model includes all factors specified for the primary analysis model and the same prior distributions, if applicable. The reference probabilities of observing each ordinal outcome will be modeled with a non-

informative Dirichlet prior with total weight of 1 with equal weight across all modeled ordinal categories.

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 is intended to have little weight but to 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 applicable. If other non-specified variables are added to the model, then a normal distribution with mean 0 and standard deviation 10 will be utilized.

14.4. Markov Chain Monte Carlo (MCMC) Model Stability

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence and mixing behavior of the MCMC sampler. These instabilities may be based on sparse data on the outcome or covariates. The statisticians running the model may make changes that do not affect the overall interpretation but provide reliable model diagnostics and scientific rigor. Any alterations will be noted. For treatment effects estimated in groups with small sample sizes or low event rates, we will report the effect, if possible, from the analysis model and care will be taken as to not overinterpret the effect.

14.5. Model Outputs

The standard model outputs for each treatment effect will be the mean, standard deviation, median, and 95% credible intervals (all credible intervals will be equal-tailed intervals, so 95% credible intervals will range from the 2.5th percentile to the 97.5th percentile of the posterior distribution). For the dichotomous endpoints, the odds-ratio will be summarized. For the ordinal endpoints, the odds-ratios will be summarized. For the time-to-event endpoints, the hazard ratios will be summarized. For consistency, all models will be parameterized so that an odds-ratio or hazard-ratio less than 1 indicates clinical benefit (and a posterior probability of $\geq$99% that the odds ratio <1 is assumed to be statistically significant). Futility is defined as <5% posterior probability of a $\geq$20% reduction in the odds of death at 90 days.

14.6. Exploratory Analyses

Exploratory analyses after unblinding will not be considered inferential and no p-values or posterior probabilities will be presented. Any post-hoc exploratory analyses may use the following methods (with a frequentist or Bayesian inference):

1. Dichotomous proportions will be compared using logistic regression summarizing the odds-ratio and 95% confidence intervals. Differences between proportions will be summarized using observed differences and normal approximations for the 95% credible intervals.
2. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the odds-ratio, 95% confidence intervals, and Wilcoxon tests for robustness against a lack of proportional odds.
3. Time-to-Event analyses will utilize a Cox proportional hazards model or piecewise exponential model, summarizing the hazard ratios and 95% confidence intervals.
4. Continuous endpoints will compare means with 95% confidence intervals based on two-sample t-test procedures.

15. SPECIFIC PROSPECTIVE ANALYSES

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

#	Status	Population	Endpoint	Other
1	Primary	REMAP-CAP PINSNP severe state ITT	90-day mortality	Includes all interventions and pre-specified interactions.
2	Sensitivity	REMAP-CAP PINSNP severe state ITT	90-day mortality	Estimates an overall/pooled treatment effect for hydrocortisone (i.e., no interaction modeled between steroid domain interventions and strata)
3	Sensitivity	REMAP-CAP PINSNP severe state ITT	90-day mortality	Prior on interaction between intervention and strata is weakened to $N(0, 1^2)$
4	Sensitivity	Hydrocortisone eligible ITT	90-day mortality	Restricted to hydrocortisone eligible controls
5	Sensitivity	Hydrocortisone specific ITT	90-day mortality	Pre-specified prior on intervention by strata effects
6	Sensitivity	Hydrocortisone specific ITT	90-day mortality	Estimates an overall treatment effect for hydrocortisone (i.e., no interaction modeled between steroid domain interventions and strata)

7	Sensitivity	Hydrocortisone specific ITT	90-day mortality	Prior on interaction between intervention and strata is weakened to N(0, 1^2)
8	Sensitivity	Hydrocortisone eligible ITT	90-day mortality	Estimates an overall treatment effect for hydrocortisone (i.e., no interaction modeled between steroid domain interventions and strata)
9	Sensitivity	Hydrocortisone eligible ITT	90-day mortality	Prior on interaction between intervention and strata is weakened to N(0, 1^2)
10	Secondary	Hydrocortisone specific ITT	ICU mortality	Dichotomous analysis
11	Secondary	Hydrocortisone specific ITT	ICU length of stay	Time-to-event analysis
12	Secondary	Hydrocortisone specific ITT	Ventilator-free days	Ordinal analysis
13	Secondary	Hydrocortisone specific ITT	Organ support-free days	Ordinal analysis
14	Secondary	Hydrocortisone specific ITT	Hospital length of stay	Time-to-event analysis
15	Secondary	Hydrocortisone specific ITT	90-day mortality	Time-to-event analysis.
16	Subgroup	Hydrocortisone specific ITT	90-day mortality	Source of infection (influenza or not)
17	Subgroup	Hydrocortisone specific ITT	90-day mortality	Source of infection confirmed (influenza confirmed or not)
18	Subgroup	Hydrocortisone specific ITT	90-day mortality	Baseline shock (present or not)
19	Subgroup	Hydrocortisone specific ITT	90-day mortality	Baseline ventilation (ventilated vs not)
20	Primary Safety Analysis	Hydrocortisone specific ITT	Serious adverse events per patient	Time effects removed from model.

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 41-65				
Age 66-75				
Age 76+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Hydrocortisone (vs control)				
Main effect of subgroup				
Fixed dose hydrocortisone by subgroup				

15.2. Graphical summaries

The following graphical summaries will be provided for all endpoints:

- Population: Hydrocortisone specific ITT
- Endpoint: all endpoints
- Factors: Fixed dose hydrocortisone and no corticosteroid interventions