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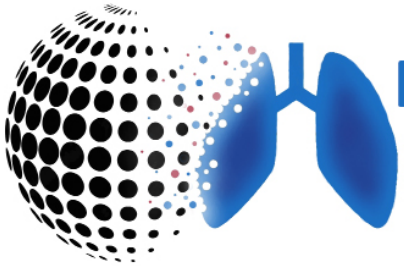

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

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

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1. COVID-19 ANTIVIRAL (IVERMECTIN) THERAPY DOMAIN SAP VERSION

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

1.1. Version history

Version 1: Finalized on 19 February 2023.

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3. INTRODUCTION

This statistical plan for the analysis of the Anti-viral (Ivermectin) Therapy Domain in the pandemic stratum of the REMAP-CAP trial is an appendix to the Pandemic Appendix to Core (PAtC) Statistical Analysis Plan (SAP). This plan details the statistical analyses in the original REMAP-CAP core SAP and the pandemic stratum SAP applied to the analysis of the ivermectin therapy in the Anti-viral Therapy Domain. This plan is prespecified for the unblinding of the data for the ivermectin and control interventions in the Anti-viral Therapy Domain within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

REMAP-CAP explores multiple treatment domains by randomizing patients within multiple domains simultaneously. The adaptive platform trial was designed to produce modular results for individual interventions or full domains upon reaching platform conclusions. This document prespecifies the analysis plan for this unblinding.

The authors of this document are blinded to all individual data other than publicly disclosed results.

This domain was halted due to operational futility secondary to low recruitment following the publication of external trial results in community patients suggesting no benefit with ivermectin therapy in COVID-19.

4. DESIGN CONSIDERATIONS

REMAP-CAP is designed with a Bayesian analysis as the primary analysis method for the trial. There is one overarching Bayesian model, prespecified in the SAP, driving all adaptations, statistical triggers, and result summaries. That primary statistical analysis model will be used to report the results for the interventions in the Antiviral (Ivermectin) Therapy Domain within the moderate and severe state of 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 other trial results, that alter the design of REMAP-CAP. Given the expected evolution of the design and uncertain sample size, the Bayesian approach was decided to be 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 Ivermectin Domain within each state:

1. Ivermectin Efficacy. If Ivermectin Therapy is deemed to have at least a 99% posterior probability of being superior to the control, then a declaration of efficacy of Ivermectin would be made.
2. Ivermectin futility. If Ivermectin therapy is deemed to have a less than 5% probability of at least a 20% odds ratio improvement compared to the control, then a declaration of futility of Ivermectin would be made.

Ivermectin harm. If Ivermectin therapy is deemed to have at least a >90% probability that the odds ratio is <1 vs control, then a declaration of harm of Ivermectin would be made. The statistical trigger for harm was predefined in the Pandemic Appendix to Core (PAtC), but was not implemented at adaptive analyses because the futility trigger necessarily precedes the harm trigger.

The 99% threshold for efficacy was selected to have good properties for potential outbreak sample sizes. For example, the type I error rate of any conclusion of efficacy for a single intervention 'A' vs. control is less than 2.5% for approximately less than 1000 patients on intervention 'A' with multiple interim analyses (see main and pandemic SAP).

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

5. UNBLINDING

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. At the unblinding of the Ivermectin/control interventions, there are other interventions to which patients have been randomized in other domains that will not be unblinded at this analysis unless a statistical trigger is hit at the time of the primary analysis. In the analysis plan, there will be analyses conducted by the Statistical Analysis Committee (SAC) using additional randomizations and unblinding of other randomizations. The SAC is unblinded to all interventions and domains as part of their role for REMAP-CAP. There will be other analyses that are conducted with only knowledge of the Ivermectin/control allocation status for patients or the allocation status to other unblinded interventions. These may be conducted by investigators who are blinded to information about other interventions and domains. These analyses are identified below.

6. INTERVENTIONS

There are two interventions within the Ivermectin Therapy Domain:

1. No Ivermectin (control)
2. Ivermectin

7. DISEASE STATES

There are two disease states in the PAtC, which are moderate and severe. The Anti-viral (Ivermectin) Therapy Domain has been open for randomization in patients in the 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 state(s) will be reported. The secondary analysis models run by blinded investigators will be run on only the unblinded state(s).

8. ANALYSIS POPULATIONS

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

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

9. ENDPOINTS

The following end points will be analyzed, displayed graphically, and summarized through descriptive statistics.

1. **Organ Support-Free Days** (OSFD)
    a. An ordinal endpoint with in-hospital mortality as the worst outcome. The primary endpoint for the REMAP-CAP PISOP stratum. The organ support considered is cardiovascular (vasopressor/inotrope support) and respiratory support. See Appendix A for a detailed description.
2. **Survival to Hospital Discharge** (a component of the primary outcome)
    a. A dichotomous endpoint of in-hospital death where the death component corresponds to a –1 on the OSFD endpoint.
    b. Follow-up for this outcome is censored at 90 days. This endpoint will be reported as "survival to hospital discharge" where OR>1 suggests benefit and OR<1 suggests harm (directionally consistent with OSFD).
3. **90-day Survival**
    a. Landmark survival at day 90.
    b. This is analyzed as a dichotomous endpoint of whether a patient is alive at 90 days
4. **180-day Mortality**
    a. This is a time-to-event endpoint through 180-days. This will maximize use of available data due to some sites and regions not collecting data on patient status following 90 days post randomization.

b. Any patient without 180-day mortality data recorded will be censored at their last known status alive.

5. **Progression to intubation and mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death**

    a. A dichotomous endpoint of whether a patient progresses to intubation and mechanical ventilation, ECMO or death in hospital.

    b. The analysis of this endpoint will be restricted to patients not on mechanical ventilation/ECMO at baseline.

6. Cardiovascular support-free days

    a. An ordinal outcome of the number of days free of Vasopressor/Inotropes. This is the exact calculation of OSFD, with Vasopressor/Inotropes as the only organ support category. In-hospital death is considered a –1.

7. Respiratory support-free days

    a. An ordinal outcome of the number of days free of respiratory support. This is the exact calculation of OSFD, with respiratory support as the only qualifying organ support category. In-hospital death is considered a –1.

8. 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.

9. 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.

10. At least one serious adverse event (SAE)

a. A dichotomous endpoint of SAE.

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

a. A modified WHO ordinal scale will be used:

0 + 1 + 2 = No longer hospitalized

3 = Hospitalized, no oxygen therapy

4 = Oxygen by mask or nasal prongs

5 = Non-invasive ventilation or high-flow oxygen

6 = Intubation and mechanical ventilation

7 = Ventilation + additional organ support: vasopressors, renal replacement therapy (RRT), ECMO

8 = Death

10. SUMMARIES

1. All ordinal endpoints will be plotted using stacked cumulative bar plots and cumulative probability plots.
2. All time-to-event endpoints will be plotted using Kaplan-Meier plots. Positive clinical event outcomes will be plotted as the cumulative rate of event, and negative events will be plotted as the cumulative rate of event-free.

11. DESCRIPTIVE STATISTICS

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 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.
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

The following demographics and baseline variables will be summarized across arms, stratified by state. 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, medications (i.e. remdesivir, corticosteroids, tocilizumab / sarilumab) and miscellaneous physiological values, inflammatory biomarker laboratory values and geographical distribution of recruitment.

13. COMPLIANCE

The compliance to Ivermectin use will be summarized descriptively as the fraction of use, for each randomized arm.

14. ANALYTIC APPROACH

Each inferential analysis will be done using a Bayesian model. Some default frequentist methods are used for exploration and description. A summary of the analyses methods is provided below.

14.1. Primary Analysis of Primary Endpoint

The **primary analysis model** is a Bayesian cumulative logistic model for the ordinal primary endpoint. The model is described below.

The primary endpoint for the severe state has 23 and the moderate state has 24 possible ordered outcomes respectively. Let the outcome for a patient 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. A cumulative logistic model is specified. The model is structured so that an odds-ratio >1 implies clinical benefit. The full details of the model are specified in the Current State of The Statistical Model document. The model has factors for:

- Each level of the ordinal endpoint
- State at randomization
- Each global site, nested within country
- Age; ≤39, 40-49, 50-59, 60-69, 70-79, 80+
- Sex
- Time; 2-week buckets of time working backwards from the last enrolled patient, with the most recent bucket being 4 weeks.
- For each domain, an effect for being randomized to the domain
- For each domain, an effect for being ineligible for the domain
- An effect for each intervention within each domain
- Specified interactions in the model between interventions across domains

The primary analysis for Ivermectin uses the following rules:

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

The primary analysis model will be referenced with certain model assumptions for sensitivity analyses. For example, the “time effects” in the model could be assumed to be 0.

14.1.1. Proportional Odds Assumption

The primary analysis model is based on an assumption of a proportional effect of treatment across the scale of the ordinal outcome. In order to assess the robustness of the results to this assumption, a

dichotomous model is fit to every level of the ordinal outcome across the scale and the odds-ratio for each dichotomous break is presented. No statistical test of proportional odds is conducted.

14.2. Analytic Approach for Secondary Dichotomous Endpoints

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

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

References will be made to the factors in the model and their prior distribution. Many of these factors will be the same as the primary analysis model, with the same priors, as the parameters have similar interpretation. For example, all in-hospital mortality models should use the Beta prior distribution implied by the Dirichlet prior in the OSFD model. If not otherwise specified, the prior distribution for the main effect is $\alpha \sim N(0, 1.82^2)$ (similar to a uniform prior on the probability scale).

14.3. Analytic Approach for Secondary Time-To-Event Endpoints

All inferential time-to-event analyses will be done using a Bayesian piecewise exponential model. The Bayesian time-to-event model is intended to mirror a Cox proportional hazards model, with the underlying hazard rate modeled with a piecewise exponential model. The underlying hazard will be modeled with a hazard rate for each 10-day period in the model. The prior distribution for the hazard rate for each day is a gamma distribution with 1 day of exposure and a mean equal to the total exposure divided by the total number of events. This prior will have very little weight but will provide numerical stability to the model. Each factor is incorporated as a proportional hazard rate through an additive linear model of the log-hazard. The default prior for each factor is the same as for the log-odds in the ordinal model. If other non-specified variables are added to the model, then a normal distribution with mean 0 and standard deviation 10 will be utilized.

14.4. Markov Chain Monte Carlo (MCMC) Model Stability

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence and mixing behavior of the MCMC sampler. These instabilities may be based on sparse data on the outcome or covariates. The statisticians running the model may make changes that do not affect the overall interpretation but provide reliable model diagnostics and scientific rigor. Any alterations will be noted.

14.5. Model Outputs

The standard model outputs for each treatment effect will be the mean, standard deviation, median, and 95% credible intervals (all credible intervals will be equal-tailed intervals, so 95% credible intervals will range from the 2.5th percentile to the 97.5th percentile of the posterior distribution). For the ordinal/dichotomous endpoints, the odds-ratios will be summarized. For the time-to-event endpoints, the hazard ratios 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. Subgroup Analyses

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

- Baseline administration of any antiviral licensed for the treatment of COVID-19 (i.e. remdesivir)
- Receiving invasive mechanical ventilation at baseline

14.7. Exploratory Analyses

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

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

5. An exploratory analysis will be reported calculating the effect of Ivermectin on the primary outcome of OFSD by time period. Time periods may be defined by approximate timing of when response adaptive randomization proportions were updated, coarsened versions of the time epochs defined in the primary model (e.g. instead of 2-week time buckets, 4 week time buckets may be used), and/or other disease altering timelines (timing of variants and/or changes in vaccination).

15. SPECIFIC PROSPECTIVE ANALYSES

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

#	Status	Population	Endpoint	Other
1	Primary	REMAP-CAP COVID-19 moderate/severe state ITT	OSFD	Includes all interventions
2	Primary	REMAP-CAP COVID-19 moderate/severe state ITT	In-Hospital Mortality	Includes all interventions
3	Sensitivity	REMAP-CAP COVID-19 moderate/severe state ITT	Dichotomized OSFD	A logistic regression will be run for each dichotomization of OSFDs as a robustness check.
4	Secondary	Unblinded population ITT	OSFD	
5	Secondary	Unblinded population ITT	Survival to Hospital Discharge	
6	Sensitivity	Unblinded population ITT	OSFD	Independent estimates of Ivermectin effect across severe/moderate states
7	Sensitivity	Unblinded population ITT	Survival to Hospital Discharge	Independent estimates of Ivermectin effect across severe/moderate states
8	Sensitivity	Unblinded population ITT	OSFD	Remove site and time effects
9	Sensitivity	Unblinded population ITT	Survival to Hospital Discharge	Remove site and time effects
10	Sensitivity	Ivermectin specific ITT	OSFD	Only Antiviral (Ivermectin) Therapy Domain Interventions modeled.
11	Sensitivity	Ivermectin specific ITT	Survival to Hospital Discharge	Only Antiviral (Ivermectin) Therapy Domain Interventions modeled.
12	Secondary	Unblinded population ITT	90-Day Survival	
13	Secondary	Unblinded population ITT	180-Day Mortality	
14	Secondary	Unblinded population ITT Non-negative COVID-19	OSFD	
15	Secondary	Unblinded population ITT Non-negative COVID-19	Survival to Hospital Discharge	
16	Secondary	Ivermectin specific per protocol	OSFD	Only Antiviral (Ivermectin) Therapy Domain Interventions modeled.

17	Secondary	Ivermectin specific per protocol	Survival to Hospital Discharge	Only Antiviral (Ivermectin) Therapy Domain Interventions modeled.
18	Secondary	Unblinded population ITT not on MV, ECMO at baseline	Progression to intubation, ECMO, death	
19	Secondary	Unblinded population ITT	Days-Free of vasopressor/inotropes	
20	Secondary	Unblinded population ITT	Respiratory support-free days	
21	Secondary	Unblinded population ITT	Length of ICU Stay	
22	Secondary	Unblinded population ITT	Length of Hospital Stay	
23	Secondary	Unblinded population ITT	WHO Scale at 14 days	
24	Subgroup	Unblinded population ITT	OSFD	Baseline use of Remdesivir
25	Subgroup	Unblinded population ITT	Survival to Hospital Discharge	Baseline use of Remdesivir
26	Subgroup	Unblinded population ITT	OSFD	Baseline use of mechanical ventilation (Non-MV vs MV)
27	Subgroup	Unblinded population ITT	Survival to Hospital Discharge	Baseline use of mechanical ventilation (Non-MV vs MV)
30	Primary Safety	Ivermectin specific ITT	Serious adverse events per patient	Time effects removed from model. Only Antiviral (Ivermectin) Therapy Domain Interventions modeled.
31	Graphical Summaries	Unblinded population ITT	All endpoints	Including combinations across unblinded domains.

15.1. Reporting of Analysis Results

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

Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40-49				
Age 50-59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Moderate to severe transition				
Ivermectin (vs no ivermectin)				
Main effect of subgroup				
Ivermectin by subgroup				

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

- Ivermectin will be compared to the control (no Ivermectin) 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.
- Ivermectin will be compared to no Ivermectin for futility. A 95% probability of a smaller than 1.2 odds ratio for Ivermectin relative to no will be used as a statistical trigger for futility. In subgroup models, this probability will be provided by subgroup.
- For the sensitivity analysis assessing the proportional odds assumption, the Ivermectin 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: Ivermectin specific ITT
- Endpoint: all endpoints
- Factors: Ivermectin and no Ivermectin interventions

Appendix A. Definition of organ support-free days

This outcome is an ordinal scale of integers from –1 to 22 for each state (Moderate or Severe) derived from a composite of the patient's vital status at the end of acute hospital admission and days spent receiving organ failure support while admitted to an ICU (including a repurposed ICU) during the 21 days (504 hours) after randomization.

A patient enrolled in the Severe State while still in an Emergency Department is regarded as 'admitted to an ICU' and the time of commencement of organ failure support is the time of randomization, as it is for all other patients in the Severe State.

Patents who survive to hospital discharge and are enrolled in one or more domains in the Moderate State and are enrolled in one or more domains in the Severe State have a primary end point value for each state, which may be different.

If deceased between first enrolment and ultimate hospital discharge, code OutcomeDay21 as -1
If not deceased, ModerateOutcomeDay21 = 21 – (the sum of the length of time in days and part- days between time of first commencement of organ failure support while admitted to an ICU and the time of last cessation of organ failure support during that ICU admission plus time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at the 504 hours after enrolment in the Moderate State)

- A patient who is enrolled in the Moderate State who never receives organ failure support while admitted to an ICU has a ModerateOutcomeDay21 = 22.

- A patient who is enrolled in the Moderate State in a ward location who commences organ failure support on the ward and is transferred to an ICU while receiving organ failure support has a commencement time of organ failure support corresponding to the time of ICU admission.

  If not deceased, SevereOutcomeDay21 = 21 – (the sum of the length of time in days and part- days between time of enrolment and the time of last cessation of organ failure support during that ICU admission plus the lengths of time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at 504 hours after the time of enrolment

  Decimals are rounded up or down to nearest whole day.

  If transferred between hospitals before the last study day 21 and known to be alive at ultimate hospital discharge use all available information to calculate Outcome Day21 with an assumption that no subsequent organ failure support in an ICU was provided.

  If transferred between hospitals before the last study day 21 and vital status at ultimate hospital discharge is not known, code as follows:

- If last known to be on a ward use all available information to calculate OutcomeDay21 with an assumption that the patient has not died prior to ultimate hospital discharge and that there were no subsequent ICU admissions.

- If last known to be in an ICU, code OutcomeDay21 as missing (999)

If a patient is discharged alive from the ultimate hospital before 504 hours from each enrolment, assume all subsequent time is alive and without provision of organ failure support in an ICU.

If the patient is alive at the end of one or both censoring time points, the hours will be calculated as above. If the patient dies after the end of one or both of the censoring time points and before hospital discharge, the value will be updated to -1

A patient who remains admitted to an acute hospital and is still alive at the end of study day 90 no further changes to coding will be made.