Supplementary Online Content

The REMAP-CAP Writing Committee for the REMAP-CAP Investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. doi:10.1001/jama.2020.17022

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Severe COVID-19 Eligibility

Platform Inclusion criteria

1. Adult patient admitted to hospital with acute illness due to suspected or proven pandemic (COVID-19) infection

Platform Exclusion criteria

1. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment

2. Patient is expected to be discharged from hospital today or tomorrow

3. More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection

4. Previous participation in this REMAP within the last 90 days

Corticosteroid Domain Specific Inclusion criteria

1. Severe disease state, defined by receiving respiratory or cardiovascular organ failure support in an intensive care unit (ICU).

    a. Respiratory organ support is defined as invasive or non-invasive mechanical ventilation including via high flow nasal cannula if flow rate >30 L/min and FIO_2 >0.4. If non-invasive ventilation would normally be provided but is being withheld, due to infection control concerns associated with aerosol generating procedures, then the patient still meets the severe disease state criteria.

    b. Cardiovascular organ support was defined as the intravenous infusion of any vasopressor or inotrope.

    c. Pandemic surge capacity means that provision of advanced organ support may need to occur in locations that do not usually provide ICU-level care. Therefore, an ICU is defined as an area within the hospital that is repurposed so as to be able to deliver one or more of the qualifying organ failure supports (non-invasive ventilation, invasive ventilation, and vasopressor therapy)

Corticosteroid Domain Specific Exclusion criteria

1. Known hypersensitivity to hydrocortisone

2. Intention to prescribe systemic corticosteroids for a reason that is unrelated to the current episode of CAP / COVID-19 (or direct complications of CAP / COVID-19), such as chronic corticosteroid use before admission, acute severe asthma, or suspected or proven Pneumocystis jiroveci pneumonia

3. More than 36 hours have elapsed since ICU admission (noting that this may be operationalized as more than 24 hours has elapsed since commencement of sustained organ failure support)

4. Patient has been randomized in a trial evaluating corticosteroids, where the protocol of that trial requires ongoing administration of study drug

5. The treating clinician believes that participation in the domain would not be in the best interests of the patient

eAppendix 2. Site Participation in the Corticosteroid Domain

During the study period, 113 sites were open for enrollment in the Corticosteroid Domain. Of these, 24 (21%) only offered active hydrocortisone assignments (fixed dose and shock-dependent). These sites included 18 (22%) of the 82 UK and Irish sites, 2 (33%) of the 6 continental European sites, and 4 (25%) of the 16 Australasian sites. Among the 384 patients enrolled in the Corticosteroid Domain cohort, 70 (18%) were enrolled at the 24 sites that only offered the 2 active hydrocortisone groups. The baseline characteristics were similar for those enrolled at sites that did (n=314) and did not (n=70) offer a 'no hydrocortisone' assignment (mean APACHE II score: 17 vs. 18; mean time from ICU admission to enrollment: 13.5 vs. 12.2 hours; baseline invasive mechanical ventilation rate: 55% vs. 56%; baseline vasopressor use: 35% versus 34%).

eTable 1. Secondary Analyses of Primary Outcome (Organ Support-free Days), restricted to participants enrolled in Corticosteroid Domain

Analysis	Fixed Dose Hydrocortisone (N=137)	Shock-dependent Hydrocortisone (N=141)	No Hydrocortisone (N=101)
Excluding those ruled out (n=89) for COVID-19 (n=290)			
Adjusted OR - mean (SD)	1.36 (0.36)	1.06 (0.29)	1
- median (95% CrI)	1.32 (0.79 - 2.16)	1.02 (0.60 - 1.73)	1
Probability of superiority to no hydrocortisone, %	85	53	-
With removal of site and time from model (n=379)			
Adjusted OR - mean (SD)	1.50 (0.34)	1.42 (0.31)	1
- median (95% CrI)	1.46 (0.94 - 2.26)	1.38 (0.90 - 2.12)	1
Probability of superiority to no hydrocortisone, %	95	93	-

Analyses were restricted to participants enrolled in the Corticosteroid Domain (n=379) and did not include information on assignment to interventions other than hydrocortisone. Models are structured such that a higher OR is favorable.

SD - standard deviation; CrI - credible interval; OR - odds ratio.

eTable 2. Secondary Analyses of Primary Outcome and of Mortality with Fixed Dose and Shock-dependent Hydrocortisone Groups Combined

Outcome and Analysis	Combined Hydrocortisone Groups (N=278)	No Hydrocortisone (N=101)
Organ Support Free-Days		
Model using data from all COVID-19 severe state participants (n=576)		
Adjusted OR - mean (SD)	1.37 (0.29)	1
- median (95% CrI)	1.34 (0.88 - 2.02)	1
Probability of superiority to no hydrocortisone, %	91	-
Model restricted to participants enrolled in Corticosteroid Domain (n=379)		
Adjusted OR - mean (SD)	1.40 (0.30)	1
- median (95% CrI)	1.36 (0.91 - 2.07)	1
Probability of superiority to no hydrocortisone, %	93	-
In-hospital Mortality		
Model using data from all COVID-19 severe state participants (n=576)		
Adjusted OR - mean (SD)	1.12 (0.30)	1
- median (95% CrI)	1.08 (0.64 - 1.78)	1
Probability of superiority to no hydrocortisone, %	61	-
Model restricted to participants enrolled in Corticosteroid Domain (n=379)		
Adjusted OR - mean (SD)	1.21 (0.34)	1
- median (95% CrI)	1.17 (0.67 - 2.00)	1
Probability of superiority to no hydrocortisone, %	71	-

The analyses of both organ support-free days (OSFDs) and in-hospital mortality using data from all participants enrolled in the trial who met COVID-19 severe state criteria and were randomized within at least one domain (n=576) adjusted for age, sex, time period, site, region, domain and intervention eligibility and intervention assignment (see COVID-19 Corticosteroid Domain SAP in Supplement 1 and full report from Statistical Analysis Committee in eAppendix 3 of Supplement 2).

The analyses of both OSFDs and in-hospital mortality restricted to participants enrolled in the Corticosteroid Domain (n=379) did not include information on assignment to interventions other than hydrocortisone. Definitions of OSFDs and other outcomes are provided in Methods and the study protocol (see Supplement 1). Models are structured such that a higher OR is favorable.

SD - standard deviation; CrI - credible interval; OR - odds ratio.

eTable 3. Secondary Analyses of In-hospital Mortality

Analysis	Fixed Dose Hydrocortisone (N=137)	Shock-dependent Hydrocortisone (N=141)	No Hydrocortisone (N=101)
Model restricted to participants enrolled in Corticosteroid Domain (n=379)			
Adjusted OR - mean (SD)	1.17 (0.37)	1.26 (0.41)	1
- median (95% CrI)	1.11 (0.60 - 2.05)	1.19 (0.65 - 2.21)	1
Probability of superiority to no hydrocortisone, %	64	71	-
Model restricted to participants enrolled in Corticosteroid Domain, excluding those ruled out (n=89) for COVID-19 (n=290)			
Adjusted OR - mean (SD)	1.05 (0.36)	1.21 (0.44)	1
- median (95% CrI)	0.99 (0.50 - 1.90)	1.13 (0.56 - 2.29)	1
Probability of superiority to no hydrocortisone, %	49	64	-
Model restricted to participants enrolled in Corticosteroid Domain, with removal of site and time period from model (n=379)			
Adjusted OR - mean (SD)	1.22 (0.35)	1.45 (0.42)	1
- median (95% CrI)	1.17 (0.67 - 2.03)	1.39 (0.80 - 2.43)	1
Probability of superiority to no hydrocortisone, %	71	88	-

The analyses of in-hospital mortality restricted to participants enrolled in the Corticosteroid Domain (n=379) did not include information on assignment to interventions other than hydrocortisone. Models are structured such that a higher OR is favorable.

SD - standard deviation; CrI - credible interval; OR - odds ratio.

eAppendix 3. Technical Report from the Statistical Analysis Committee for SAP Outcome Analyses 15.1-4

REMAP-CAP (REMAP-COVID)

Analysis of the Corticosteroid Domain

August 14, 2020

Contents

1 Introduction

1.1 Overview of the Adaptive Design

This trial is a Randomized, Embedded, Multifactorial Adaptive Platform (REMAP) trial that was originally designed to investigate treatments for Community-Acquired Pneumonia (CAP). The platform trial has the ability to investigate multiple interventions within multiple domains, across different patient strata. The number of interventions, domains, and strata may increase or decrease as the trial progresses. The platform trial includes a pandemic stratum that was activated when COVID-19 emerged. The pandemic stratum-specific protocol details are provided in a Pandemic Appendix to the Core (PAtC) protocol. The PAtC investigates therapies for patients with pandemic infection that are classified as suspected or proven (PISOP). This report focuses on the COVID-19 PISOP stratum

For the PISOP stratum, patients may be randomized to interventions while they are in a Severe disease state or a Moderate disease state. State definitions are in the PAtC. Patients initially randomized in a Moderate state may progress in their disease severity, and subsequently meet the criteria for Severe state, and have additional randomization and reveal of interventions for Severe state domains.

1.2 Purpose of this Report

The international trial steering committee (ITSC) closed randomization to the corticosteroid domain within the PISOP stratum on June 17, 2020 and started a process for reporting results. This decision was made following the release of the RECOVERY trial results on June 16, 2020 which reported strong positive effects of dexamethasone in moderate and severe patients. The ITSC prepared a statistical analysis plan (SAP) for the corticosteroid domain (Version 1.0) and provided this to the Statistical Analysis Committee (SAC) on July 21, 2020. Although the ITSC will be unblinded to the corticosteroid domain, they will not be unblinded to the other domains to which the patients have been randomized. The fully unblinded SAC will conduct the set of the analyses that use the full statistical model including data from all domains in the PISOP stratum. This report summarizes the data and the results for the corticosteroid domain resulting from the analyses using the full statistical model. This report is restricted to only summarize the results pertaining to the corticosteroid domain. Summaries for other domains are contained in a separate unblinded report only viewed by the SAC and DSMB.

1.3 Endpoints

1.3.1 Primary Endpoint: Organ-Support Free-Days (OSFD)

The primary endpoint for the analysis is a composite endpoint that comprises the number of whole study days for which the patient is alive and not receiving organ support in an ICU up until the end of study day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after day 21, will be coded as -1. All patients who receive no organ support in an ICU will be coded as 22 days. An outcome of 22 days is not possible for patients in Severe state.

1.3.2 Secondary Endpoint: In-Hospital Mortality

The secondary endpoint is a dichototomous endpoint of in-hospital mortality where the death component corresponds to −1 on the OSFD endpoint.

1.4 Vocabulary

- **Domain:** a specific set of competing alternative interventions within a common clinical mode

- **Intervention:** is a treatment option that is subject to variation in clinical practice (comparative effectiveness intervention) or has been proposed for introduction into clinical practice (experimental intervention) and also is being subjected to experimental manipulation within the design of a REMAP.
- **Regimen:** Each patient is assigned a single intervention from each domain. The regimen is the combination of assigned interventions across the domains.
- **Immediate Reveal Domain:** is one for which all participants are eligible, the allocation status is made known, and the intervention is initiated at the time of randomization.
- **Delayed Reveal Domain:** is one for which all participants received a randomization assignment, but the allocation status is only made known and the intervention initiated if and when eligibility occurs. This occurs for example, when a domain is appropriate only for patients in a certain disease state and the patient transitions to that disease state.
- **Deferred Reveal Domain:** is one for which patients receive a randomization assignment and the allocation status is made known based on eligibility criterion known at the time of randomization, but additional information to assess that eligibility becomes known after some time. This occurs for example, when a test results confirming an eligibiltiy criterion are returned after some time.
- **Nest:** A grouping of interventions within a domain that are modeled hierarchically in order to allow for borrowing among the interventions effect estimates.
- **State:** Defined by the disease characteristics of the patient and may change over time as the disease progresses. States are used to define eligibility for certain domains.

1.5 Current Trial Status

The data transfers provided to the SAC (see Section 7 for details) include patients randomized through August 11, 2020 from the combined Spiral and Research Online databases, and patients randomized through June 25, 2020 from the UPMC database. This data include:

- 1340 patients randomized in the REMAP-CAP/REMAP-COVID trial, with:
  - 786 randomized, consented patients with pandemic infection suspected or proven (PISOP),
  - 554 randomized, consented patients with pandemic infection neither suspected nor proven (PIN-SNP).

These counts exclude patients that withdrew consent for the use of their data in the analysis.

Figure 1.1 gives an overview of the interventions, domains, and strata currently being investigated in the COVID-19 pandemic portion of the trial. Each intervention is represented by a colored box, with similar colors used for interventions within the same domain. The figure also indicates features of the statistical model. For example, interactions are represented with an arrow and star (*). Within a domain, interventions that are nested within a hierarchical model are grouped within a curly bracket. Interventions that are closed to enrollment are indicated by an "X".

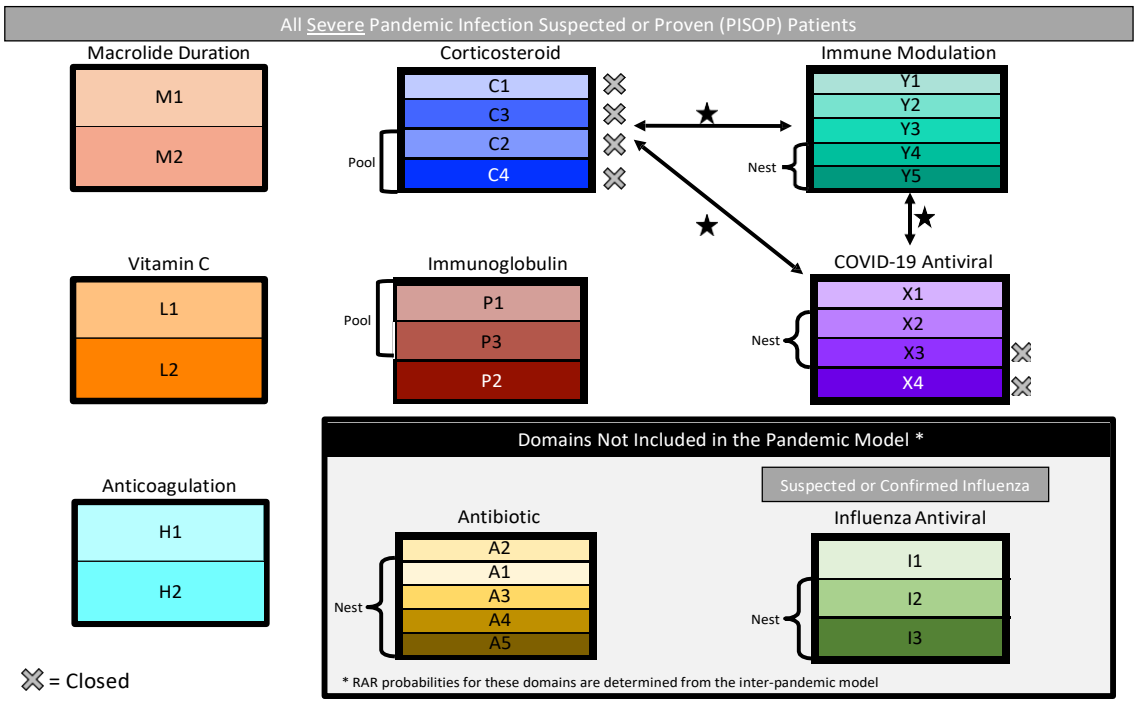

Figure 1.1: Current state of the pandemic REMAP-CAP domains, interventions, and strata. Each colored box represents an intervention, grouped by domain, with similar colors used for interventions within the same domain. Domains connected with an arrow and indicated with a star (*) will have interaction terms fit between the interventions in those domains. Within a domain, interventions that are grouped with a curly bracket are part of a nest whose main effects are estimated with a hierarchical model. Interventions that are closed to enrollment are indicated by an "X"

Table 1.1: List of all interventions to which a patient may be allocated.

Code	Intervention
Antibiotic	
A1	Ceftriaxone + Macrolide
A2	Moxifloxacin or Levofloxacin
A3	Piperacillin-Tazobactam + Macrolide
A4	Ceftaroline + Macrolide
A5	Amoxicillin-Clavulanate + Macrolide
Macrolide Duration	
M1	Standard course (3 to 5 days)
M2	Extended course (14 days)
Corticosteroid	
C1	No corticosteroids
C2	Hydrocortisone (50mg)
C3	Shock dependent hydrocortisone
C4	High-dose hydrocortisone (100mg)
Antiviral	
I1	No antiviral
I2	Oseltamivir 5 days
I3	Oseltamivir 10 days
COVID-19 Antiviral	
X1	No antiviral for COVID-19
X2	Lopinavir/ritonavir
X3	Hydroxychloroquine
X4	Hydroxychloroquine + lopinavir/ritonavir
COVID-19 Immune Modulation	
Y1	No immune modulation for COVID-19
Y2	Interferon-Beta-1a
Y3	Anakinra
Y4	Tocilizumab
Y5	Sarilumab
COVID-19 Immunoglobulin	
P1	No Immunoglobulin against COVID-19
P2	Convalescent plasma
P3	Delayed convalescent plasma
COVID-19 Therapeutic Anticoagulation	
H1	Standard practice thromboprophylaxis
H2	Therapeutic anticoagulation
Vitamin C	
L1	No vitamin C
L2	Vitamin C

1.6 Analysis Population

The SAP for the corticosteroid analysis restricts the analysis population to consented patients randomized on or before June 17, 2020, i.e. the day randomization to the PISOP corticosteroid domain was halted. The SAP further restricts the analysis population to patients in Severe disease state, which includes both patients randomized for the first time while in Severe state and also patients randomized in Moderate state that progressed to Severe state with randomized assignments for Severe state domains revealed on or before June 17, 2020. The patient population breakdown is as follows:

- 786 PISOP consented patients randomized on or before June 17, 2020
  - 587 PISOP consented patients randomized to at least one domain in Severe state on or before June 17, 2020
    - ➔ 576 PISOP consented patients randomized to at least one domain in Severe state on or before June 17, 2020 for whom 21 days have elapsed since randomization and there is a known outcome on the 21-day organ-support free-days endpoint

– 384 PISOP consented patients randomized to the corticosteroid domain in Severe state on or before June 17, 2020

➔ 379 PISOP consented patients randomized to the corticosteroid domain in Severe state on or before June 17, 2020 for whom 21 days have elapsed since randomization and there is a known outcome on the 21-day organ-support free-days endpoint

These counts includes 5 patients who were initially randomized while in Moderate State and later progressed to Severe State with randomized assignments for Severe state domains revealed on or before June 17, 2020.

2 Data Summaries

2.1 Overview of Descriptive Data Summaries

The following summaries are provided within the corticosteroid domain:

Summary of the availability of data:

- **Number Eligible:** Eligibility is assessed both at the domain level and the intervention level. We tabulate the number of patients eligible for the domain, and within each category of domain eligibility, the number of patients eligible for each intervention. Eligibility captures both the patient meeting the inclusion criteria, and the domain or intervention being available and active at their site.
- **Number Assigned:** We tabulate the number of patients assigned to each intervention, by eligibility category. No randomized assignment can be given when a patient is ineligible for a domain, or when a patient is eligible for only one intervention within a domain. A patient must be eligible for at least two interventions within a domain to receive a randomized assignment.
- **Number Revealed:** Among the patients eligible and assigned to each intervention, we tabulate the number of patients whose assignment was revealed. Reveal means that the randomization assignment was made known and the patient then commences treatment according to their assigned intervention.
- **Number Past 21 Days:** Among the patients eligible and assigned to each intervention, we tabulate the number of patients who have had the opportunity to complete the 21 days of follow-up for the primary endpoint. A patient must have been in the trial at least 21 days to be included in the analysis.
- **Number Missing:** Among the patients eligible and assigned to each intervention, we tabulate the number of patients who have completed 21 days of follow-up but do not have an outcome available on the primary endpoint.
- **Number Known:** Among the patients eligible and assigned to each intervention, we tabulate the number of patients who have completed 21 days of follow-up and have a known outcome on the primary endpoint.

Summary of the observed data:

For patients that are eligible for the domain and assigned to an intervention, we repeat the tabulation of the number of patients assigned to an intervention and with a known outcome on the 21-day endpoint. Additionally, we provide summaries of the following:

- **Number Deaths:** The number of in-hospital deaths, where the death corresponds to 1 on the OSFD endpoint.
- **Mortality Rate:** We calculate the observed in-hospital mortality rate as the number of in-hospital deaths out of the total number of patients with a known 21-day outcome.

- **OSFD median (IQR):** Among the patients with a known 21-day outcome, we compute the 25th, 50th, and 75th percentiles of the Organ-Support Free-Days endpoint. The interquartile range (IQR) is shown in parentheses as the range between the 25th and 75th percentiles.
- **Conditional OSFD:** Among the patients with a known 21-day outcome that were not deceased, we compute the 25th, 50th, and 75th percentiles of the Organ-Support Free-Days endpoint. The interquartile range (IQR) is shown in parentheses as the range between the 25th and 75th percentiles.

2.2 Overall Data Summaries

Figure 2.1 displays the distribution of outcomes on the primary endpoint for all patients in the analysis population (including all domains), without respect to treatment assignments. Table 2.1 provides descriptive summaries of the OSFD and in-hospital mortality outcomes for all patients in the analysis population and for all patients in the corticosteroid domain.

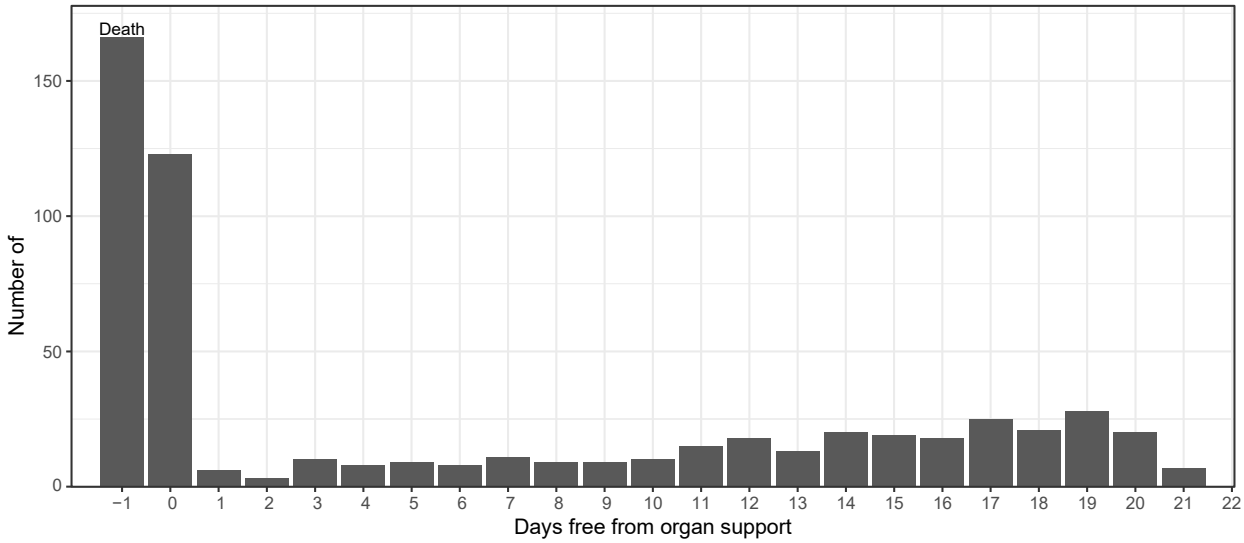

Figure 2.1: Overall distribution of the primary organ support free days endpoint.

Table 2.1: Overall summary of the OSFD and In-Hospital mortality data

Participant Group	Number Assigned (N)	Number Known (n)	Number Deaths (y)	Mortality Rate (y/n)	OSFD median (IQR)	Conditional* OSFD median (IQR)
COVID Severe State	587	576	166	0.288	0.00 (−1.00 − 14.00)	10.00 (0.00 − 16.00)
Corticosteroid Domain	384	379	111	0.293	0.00 (−1.00 − 13.00)	9.00 (0.00 − 16.00)

* Conditional OSFD reports the median and IQR for subjects that did not die.

2.3 Corticosteroid Domain

2.3.1 Description of the Corticosteroid domain

The corticosteroids domain includes 4 interventions. This domain:

- is an immediate reveal domain;
- is only available for patients in the Severe State stratum;

- has no strata identified as being of interest. Analyses and response adaptive randomization are applied to all randomized patients in Severe State;
- has possible interactions modeled with the COVID-19 antiviral domain and with the COVID-19 immune modulation domain. A previous study suggested that the interaction of interferon-β and corticosteroids may be harmful; therefore an informative prior is used to reflect a harmful interaction. Furthermore, initial (burn-in) randomization probabilities were constructed to limit the number of patients randomized to the combination of corticosteroids and interferon-β;
- was originally intended to have one nest, comprised of the 2 fixed duration corticosteroid interventions; Since very few patients were randomized to the high-dose corticosteroid intervention at the time that the domain was closed, the 2 fixed duration interventions will be pooled rather than nested in a hierarchical model.

2.3.2 Observed data within the Corticosteroids domain

In this section, we describe the data at the most granular level, prior to pooling arms together for analysis. Later sections of this report will show data summaries collapsing interventions for analysis.

Table 2.2: Summary of the availability of data (**Corticosteroid** domain)

Intervention	Number Eligible	Number Assigned	Number Revealed	Number Past Day 21	Number Missing	Number Known
Eligible for domain: N=384						
No corticosteroids	314	101	101	101	0	101
Hydrocortisone (50mg)	375	135	135	135	0	135
Shock dependent hydrocortisone	336	146	146	146	5	141
High-dose hydrocortisone (100mg)	15	2	2	2	0	2
Not eligible for domain: N=128						
No assignment		128	125	128	3	125
Domain not active/not available: N=75						
No assignment		75	75	75	3	72

Table 2.3: Summary of the OSFD and In-Hospital mortality data for patients that were eligible for the **Corticosteroid** domain

Intervention	Number Assigned (N)	Number Known (n)	Number Deaths (y)	Mortality Rate (y/n)	OSFD median (IQR)	Conditional* OSFD median (IQR)
No corticosteroids	101	101	33	0.327	0.00 (−1.00 – 11.00)	6.00 (0.00 – 12.00)
Hydrocortisone (50mg)	135	135	41	0.304	0.00 (−1.00 – 15.00)	12.50 (0.00 – 17.00)
Shock dependent hydrocortisone	146	141	37	0.262	0.00 (−1.00 – 13.00)	9.50 (0.00 – 16.00)
High-dose hydrocortisone (100mg)	2	2	0	0.000	5.00 (2.50 – 7.50)	5.00 (2.50 – 7.50)

* Conditional OSFD reports the median and IQR for subjects that did not die.

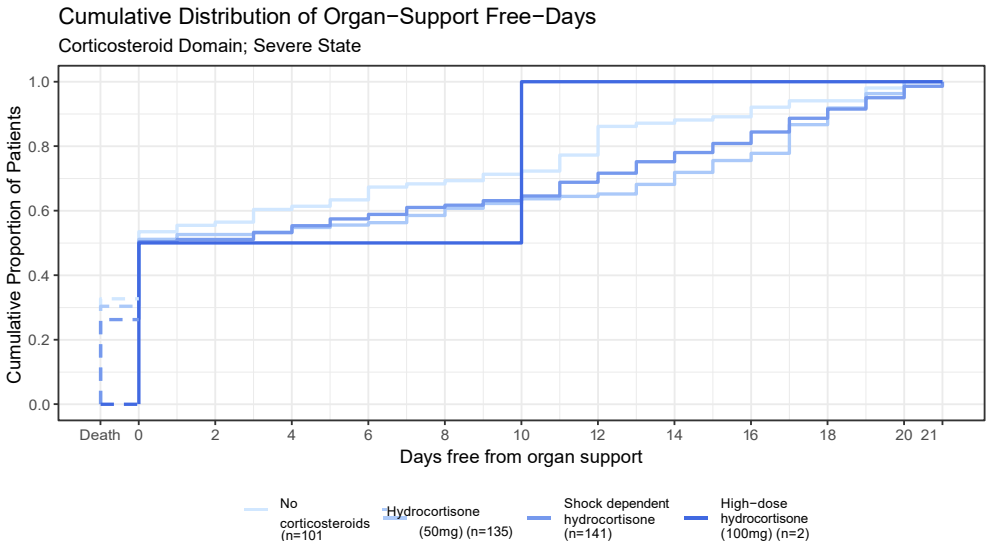

Figure 2.2: Empirical cumulative distribution of organ support free days for each intervention in the **Corticosteroid** domain. This plot is restricted to include only patients who were eligible for the domain.

3 Analysis Results and Conclusions

3.1 Definition of Statistical Triggers

The adaptive design 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 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.

Per communication in the corticosteroids SAP, the primary and secondary OSFD analyses and primary and secondary mortality analyses for the corticosteroid domain do not include formal, intervention-specific futility and inferiority assessments and are not part of the pre-specified result summaries. However, for informational purposes, we do include the futility and inferiority evaluations for the corticosteroid domain interventions as specified in the original statistical analysis plan.

3.2 Analyses pooling the fixed duration steroid arms

For these analyses, the high-dose 7-day hydrocortisone arm will be combined with the 7-day hydrocortisone arm (fixed duration). These interventions were originally intended to be nested within a hiearchical model,

which allowed pooling, and there were very few patients randomized to the high-dose 7-day hydrocortisone arm. Table 3.1 summarizes the observed data on the OSFD and in-hospital mortality endpoints for the combined arms for patients that were eligible for the corticosteroid domain.

Table 3.1: Summary of the OSFD and In-Hospital mortality data for patients that were eligible for the **Corticosteroid** domain (pooling the fixed duration steroid arms)

Intervention	Number Assigned (N)	Number Known (n)	Number Deaths (y)	Mortality Rate (y/n)	OSFD median (IQR)	Conditional* OSFD median (IQR)
No corticosteroids	101	101	33	0.327	0.00 (−1.00 − 11.00)	6.00 (0.00 − 12.00)
Fixed duration hydrocortisone	137	137	41	0.299	0.00 (−1.00 − 15.00)	11.50 (0.00 − 17.00)
Shock dependent hydrocortisone	146	141	37	0.262	0.00 (−1.00 − 13.00)	9.50 (0.00 − 16.00)

* Conditional OSFD reports the median and IQR for subjects that did not die.

3.2.1 Organ-Support Free Days

Table 3.2: Model-estimated Odds-Ratios for the **OSFD** endpoint (Model pooling the fixed duration steroid arms)

Odds-Ratio Parameter	Mean (SD)	Median	95% Credible Interval
Age ≤ 39	3.01 (0.93)	2.87	1.63 − 5.21
Age 40 − 49	2.19 (0.56)	2.12	1.31 − 3.48
Age 50 − 59	1.43 (0.29)	1.41	0.95 − 2.08
Age 70 − 79	0.41 (0.10)	0.40	0.25 − 0.63
Age ≥ 80	0.63 (0.28)	0.57	0.24 − 1.32
Female	1.23 (0.21)	1.21	0.87 − 1.70
Time Bucket 1	0.91 (0.10)	0.91	0.73 − 1.11
Time Bucket 2	0.85 (0.16)	0.84	0.56 − 1.19
Time Bucket 3	0.86 (0.22)	0.84	0.52 − 1.36
Time Bucket 4	0.89 (0.28)	0.85	0.46 − 1.55
Time Bucket 5	0.98 (0.42)	0.91	0.40 − 2.06
Fixed duration hydrocortisone	1.47 (0.35)	1.43	0.91 − 2.27
Shock dependant hydrocortisone	1.26 (0.31)	1.22	0.76 − 1.94
Fixed duration hydrocortisone vs. Shock dependant hydrocortisone	1.20 (0.28)	1.17	0.75 − 1.83

Note: For Age, Odds-Ratio is relative to the Age 60-90 category. Time bucket X is the Xth 2-week interval prior to the most recent month, and Odds-Ratios are relative to the most recent month.

Table 3.3: Summary of posterior probabilities for the **OSFD** endpoint in the **Corticosteroid** domain (Model pooling the fixed duration steroid arms)

Intervention	Pr(in Optimal)	Pr($OR > 1$)	Pr($OR > 1.2$)	Pr(Equivalent) Shock dependent hydrocortisone
No corticosteroids	0.1090			
Fixed duration hydrocortisone	0.5466	0.9346	0.7744	0.4761
Shock dependent hydrocortisone	0.3444	0.8013	0.5253	

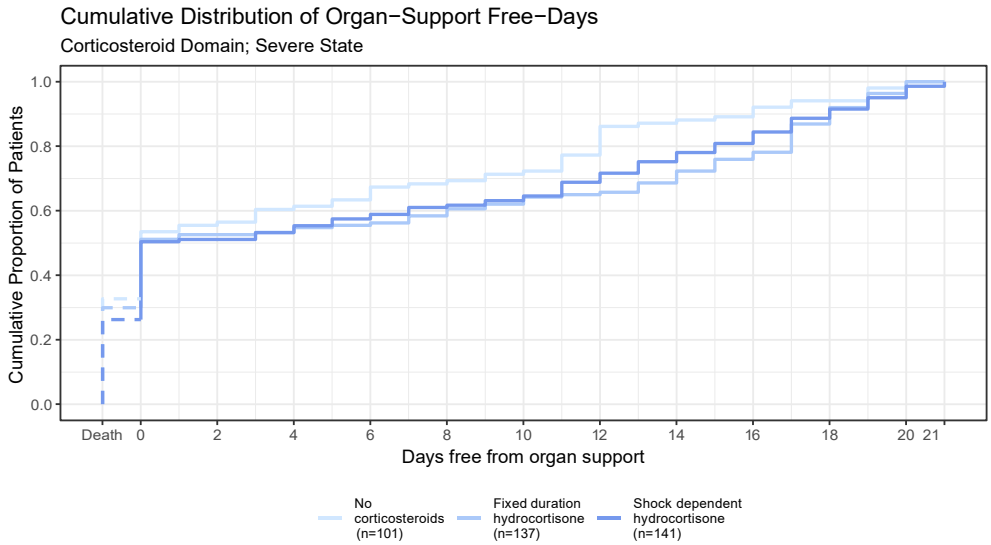

Figure 3.1: Empirical cumulative distribution of organ support free days for each intervention in the **Corticosteroid** domain. This plot is restricted to include only patients who were eligible for the domain.

Table 3.4: Evaluation of Statistical Triggers for the **OSFD** endpoint in the **Corticosteroid** Domain (Model pooling the fixed duration steroid arms)

Decision Quantity	Value	Direction	Threshold	Conclusion
Efficacy				
Pr(OR for C2 > 1)	0.9346	>	0.990	None
Pr(OR for C3 > 1)	0.8013	>	0.990	None
Equivalence				
Pr(C2 equiv C3)	0.4761	>	0.900	None
Futility				
Pr(OR for C2 > 1.2)	0.7744	<	0.050	None
Pr(OR for C3 > 1.2)	0.5253	<	0.050	None
Inferiority				
Pr(C1 in optimal)	0.1090	<	0.005	None
Pr(C2 in optimal)	0.5466	<	0.005	None
Pr(C3 in optimal)	0.3444	<	0.005	None
Superiority				
Pr(C2 in optimal)	0.5466	>	0.990	None
Pr(C3 in optimal)	0.3444	>	0.990	None

C1 = No corticosteroids; C2 = Fixed duration hydrocortisone; C3 = Shock dependent hydrocortisone

3.2.2 In-hospital Mortality

Table 3.5: Model-estimated Odds-Ratios for the **Mortality** endpoint (Model pooling the fixed duration steroid arms)

Odds-Ratio Parameter	Mean (SD)	Median	95% Credible Interval
Age ≤ 39	20.18 (15.37)	15.72	5.20 – 60.56
Age 40 – 49	4.37 (1.99)	3.92	1.83 – 9.48
Age 50 – 59	2.68 (0.79)	2.57	1.45 – 4.56
Age 70 – 79	0.28 (0.08)	0.27	0.16 – 0.46
Age ≥ 80	0.37 (0.20)	0.33	0.12 – 0.88
Female	1.06 (0.26)	1.03	0.65 – 1.64
Time Bucket 1	0.97 (0.12)	0.96	0.75 – 1.21
Time Bucket 2	0.94 (0.24)	0.93	0.51 – 1.45
Time Bucket 3	1.07 (0.35)	1.03	0.50 – 1.87
Time Bucket 4	1.37 (0.58)	1.27	0.55 – 2.79
Time Bucket 5	2.12 (1.45)	1.75	0.60 – 5.72
Fixed duration hydrocortisone	1.08 (0.37)	1.03	0.53 – 1.95
Shock dependant hydrocortisone	1.16 (0.40)	1.10	0.58 – 2.11
Fixed duration hydrocortisone vs. Shock dependant hydrocortisone	0.98 (0.34)	0.93	0.48 – 1.78

Note: For Age, Odds-Ratio is relative to the Age 60-90 category. Time bucket X is the Xth 2-week interval prior to the most recent month, and Odds-Ratios are relative to the most recent month.

Table 3.6: Summary of posterior probabilities for the **Mortality** endpoint in the **Corticosteroid** domain (Model pooling the fixed duration steroid arms)

Intervention	Pr(in Optimal)	Pr(*OR* > 1)	Pr(*OR* > 1.2)	Pr(Equivalent) Shock dependent hydrocortisone
No corticosteroids	0.241			
Fixed duration hydrocortisone	0.294	0.5353	0.3155	0.4208
Shock dependent hydrocortisone	0.465	0.6165	0.3943	

Table 3.7: Evaluation of Statistical Triggers for the **Mortality** endpoint in the **Corticosteroid** Domain (Model pooling the fixed duration steroid arms)

Decision Quantity	Value	Direction	Threshold	Conclusion
Efficacy				
Pr(OR for C2 > 1)	0.5353	>	0.990	None
Pr(OR for C3 > 1)	0.6165	>	0.990	None
Equivalence				
Pr(C2 equiv C3)	0.4208	>	0.900	None
Futility				
Pr(OR for C2 > 1.2)	0.3155	<	0.050	None
Pr(OR for C3 > 1.2)	0.3943	<	0.050	None
Inferiority				
Pr(C1 in optimal)	0.2410	<	0.005	None
Pr(C2 in optimal)	0.2940	<	0.005	None
Pr(C3 in optimal)	0.4650	<	0.005	None
Superiority				
Pr(C2 in optimal)	0.2940	>	0.990	None
Pr(C3 in optimal)	0.4650	>	0.990	None

C1 = No corticosteroids; C2 = Fixed duration hydrocortisone; C3 = Shock dependent hydrocortisone

3.3 Analyses pooling all active steroid arms

For these analyses, the fixed duration hydrocorisone arms and the shock-dependent hydrocortisone arm will be combined. Table 3.8 summarizes the observed data on the OSFD and in-hospital mortality endpoints for the combined arms for patients that were eligible for the corticosteroid domain.

Table 3.8: Summary of the OSFD and In-Hospital mortality data for patients that were eligible for the **Corticosteroid** domain (pooling all active steroid arms)

Intervention	Number Assigned (N)	Number Known (n)	Number Deaths (y)	Mortality Rate (y/n)	OSFD median (IQR)	Conditional* OSFD median (IQR)
No corticosteroids	101	101	33	0.327	0.00 (−1.00 − 11.00)	6.00 (0.00 − 12.00)
Any steroid	283	278	78	0.281	0.00 (−1.00 − 14.00)	10.00 (0.00 − 17.00)

* Conditional OSFD reports the median and IQR for subjects that did not die.

3.3.1 Organ-Support Free Days

Table 3.9: Model-estimated Odds-Ratios for the **OSFD** endpoint (Model pooling all active steroid arms)

Odds-Ratio Parameter	Mean (SD)	Median	95% Credible Interval
Age ≤ 39	2.98 (0.89)	2.84	1.63 − 5.10
Age 40 − 49	2.19 (0.56)	2.13	1.29 − 3.47
Age 50 − 59	1.43 (0.28)	1.41	0.95 − 2.05
Age 70 − 79	0.41 (0.10)	0.40	0.25 − 0.62
Age ≥ 80	0.62 (0.28)	0.56	0.23 − 1.31
Female	1.22 (0.21)	1.20	0.87 − 1.68
Time Bucket 1	0.91 (0.09)	0.91	0.73 − 1.11
Time Bucket 2	0.84 (0.16)	0.83	0.55 − 1.17
Time Bucket 3	0.85 (0.21)	0.82	0.51 − 1.31
Time Bucket 4	0.87 (0.27)	0.83	0.45 − 1.51
Time Bucket 5	0.96 (0.40)	0.88	0.41 − 1.97
Any steroid	1.37 (0.29)	1.34	0.88 − 2.02

Note: For Age, Odds-Ratio is relative to the Age 60-90 category. Time bucket X is the Xth 2-week interval prior to the most recent month, and Odds-Ratios are relative to the most recent month.

Table 3.10: Summary of posterior probabilities for the **OSFD** endpoint in the **Corticosteroid** domain (Model pooling all active steroid arms)

Intervention	Pr(in Optimal)	Pr($OR > 1$)	Pr($OR > 1.2$)
No corticosteroids	0.2513		
Any steroid	0.7487	0.9121	0.7031

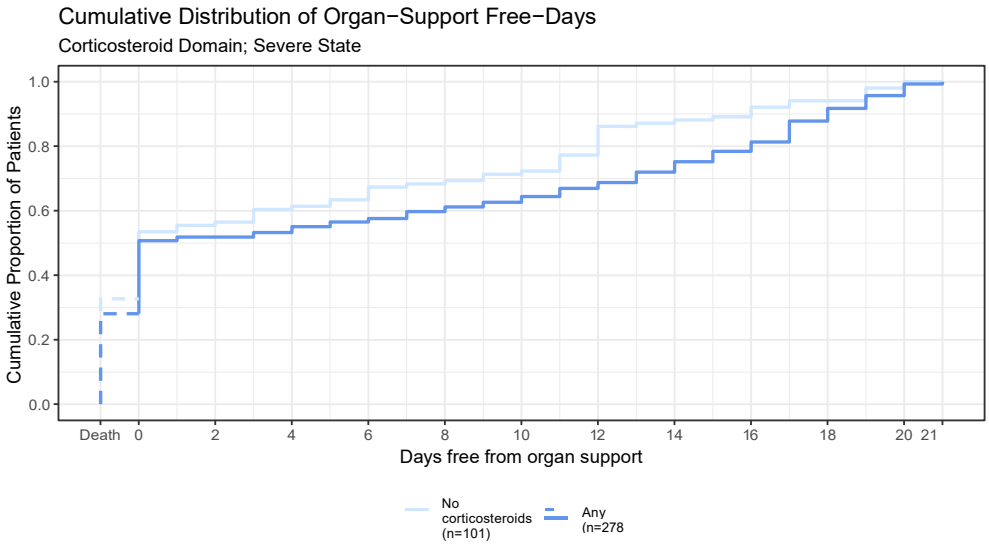

Figure 3.2: Empirical cumulative distribution of organ support free days for each intervention in the **Corticosteroid** domain. This plot is restricted to include only patients who were eligible for the domain.

Table 3.11: Evaluation of Statistical Triggers for the **OSFD** endpoint in the **Corticosteroid** Domain (Model pooling all active steroid arms)

Decision Quantity	Value	Direction	Threshold	Conclusion
Efficacy				
Pr(OR for C2 > 1)	0.9121	>	0.99	None
Futility				
Pr(OR for C2 > 1.2)	0.7031	<	0.05	None
Inferiority				
Pr(C1 in optimal)	0.2513	<	0.01	None
Pr(C2 in optimal)	0.7487	<	0.01	None
Superiority				
Pr(C2 in optimal)	0.7487	>	0.99	None

C1 = No corticosteroids; C2 = Any steroid

3.3.2 In-hospital Mortality

Table 3.12: Model-estimated Odds-Ratios for the **Mortality** endpoint (Model pooling all active steroid arms)

Odds-Ratio Parameter	Mean (SD)	Median	95% Credible Interval
Age ≤ 39	19.09 (14.56)	15.12	4.85 – 57.52
Age 40 – 49	4.55 (2.02)	4.12	1.92 – 9.64
Age 50 – 59	2.67 (0.78)	2.55	1.47 – 4.50
Age 70 – 79	0.28 (0.08)	0.27	0.16 – 0.46
Age ≥ 80	0.38 (0.20)	0.34	0.13 – 0.90
Female	1.06 (0.26)	1.03	0.65 – 1.67
Time Bucket 1	0.95 (0.12)	0.94	0.73 – 1.19
Time Bucket 2	0.89 (0.21)	0.88	0.49 – 1.34
Time Bucket 3	0.99 (0.30)	0.95	0.51 – 1.69
Time Bucket 4	1.24 (0.49)	1.16	0.55 – 2.45
Time Bucket 5	1.92 (1.33)	1.57	0.55 – 5.23
Any steroid	1.12 (0.30)	1.08	0.64 – 1.78

Note: For Age, Odds-Ratio is relative to the Age 60-90 category. Time bucket X is the Xth 2-week interval prior to the most recent month, and Odds-Ratios are relative to the most recent month.

Table 3.13: Summary of posterior probabilities for the **Mortality** endpoint in the **Corticosteroid** domain (Model pooling all active steroid arms)

Intervention	Pr(in Optimal)	Pr($OR > 1$)	Pr($OR > 1.2$)
No corticosteroids	0.4167		
Any steroid	0.5833	0.6117	0.3476

Table 3.14: Evaluation of Statistical Triggers for the **Mortality** endpoint in the **Corticosteroid** Domain (Model pooling all active steroid arms)

Decision Quantity	Value	Direction	Threshold	Conclusion
Efficacy				
Pr(OR for C2 > 1)	0.6117	>	0.99	None
Futility				
Pr(OR for C2 > 1.2)	0.3476	<	0.05	None
Inferiority				
Pr(C1 in optimal)	0.4167	<	0.01	None
Pr(C2 in optimal)	0.5833	<	0.01	None
Superiority				
Pr(C2 in optimal)	0.5833	>	0.99	None

C1 = No corticosteroids; C2 = Any steroid

4 Other Data Summaries

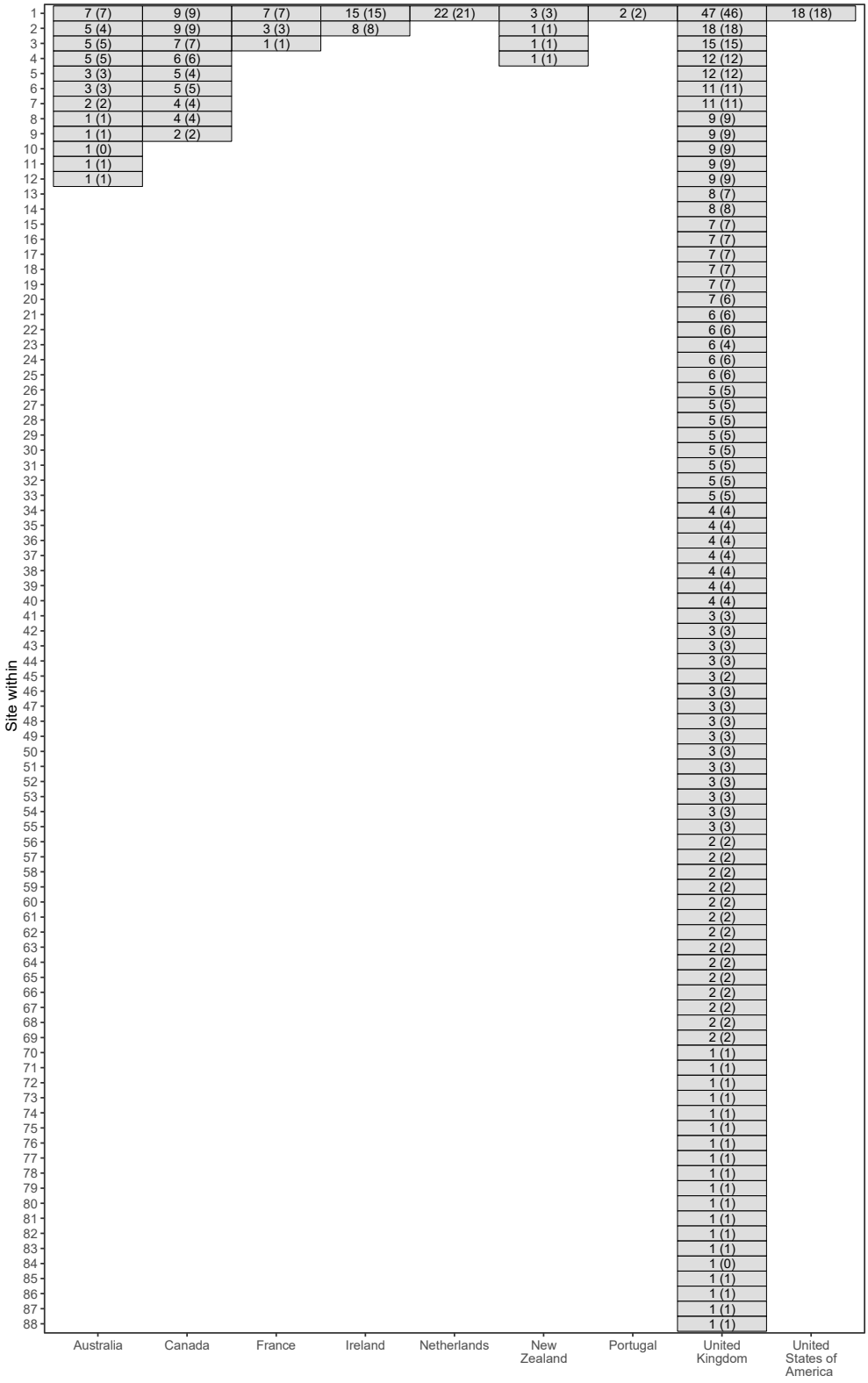

Figure 4.1: Sample size at each site within each country. The values in each cell represent the number of patients randomized to any domain at that site and, in parentheses, the number of patients for whom the outcome on the 21-day outcome is known. Within each country, all sites having fewer than 5 randomized patients are combined into a single site for the statistical model.

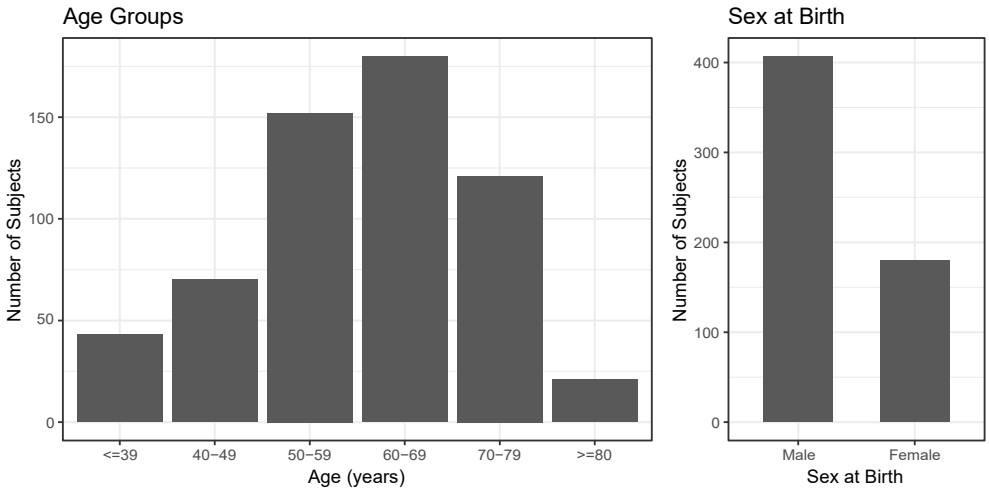

Figure 4.2: Distribution of age groups and sex at birth

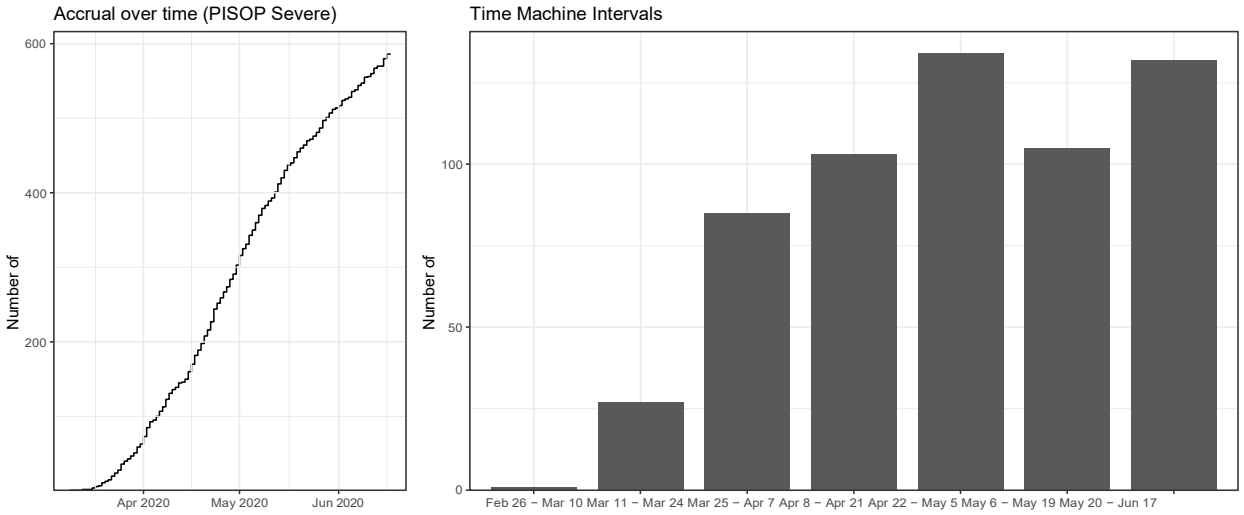

Figure 4.3: Accrual over time and distribution of patients within each of the time buckets used to estimate time trends in the analysis model. The time buckets are derived so that the first bucket is the most recent month going backwards in time from the most recently randomized patient in the dataset that has an outcome. Thereafter, each bucket is defined as the next two-week interval backwards in time.

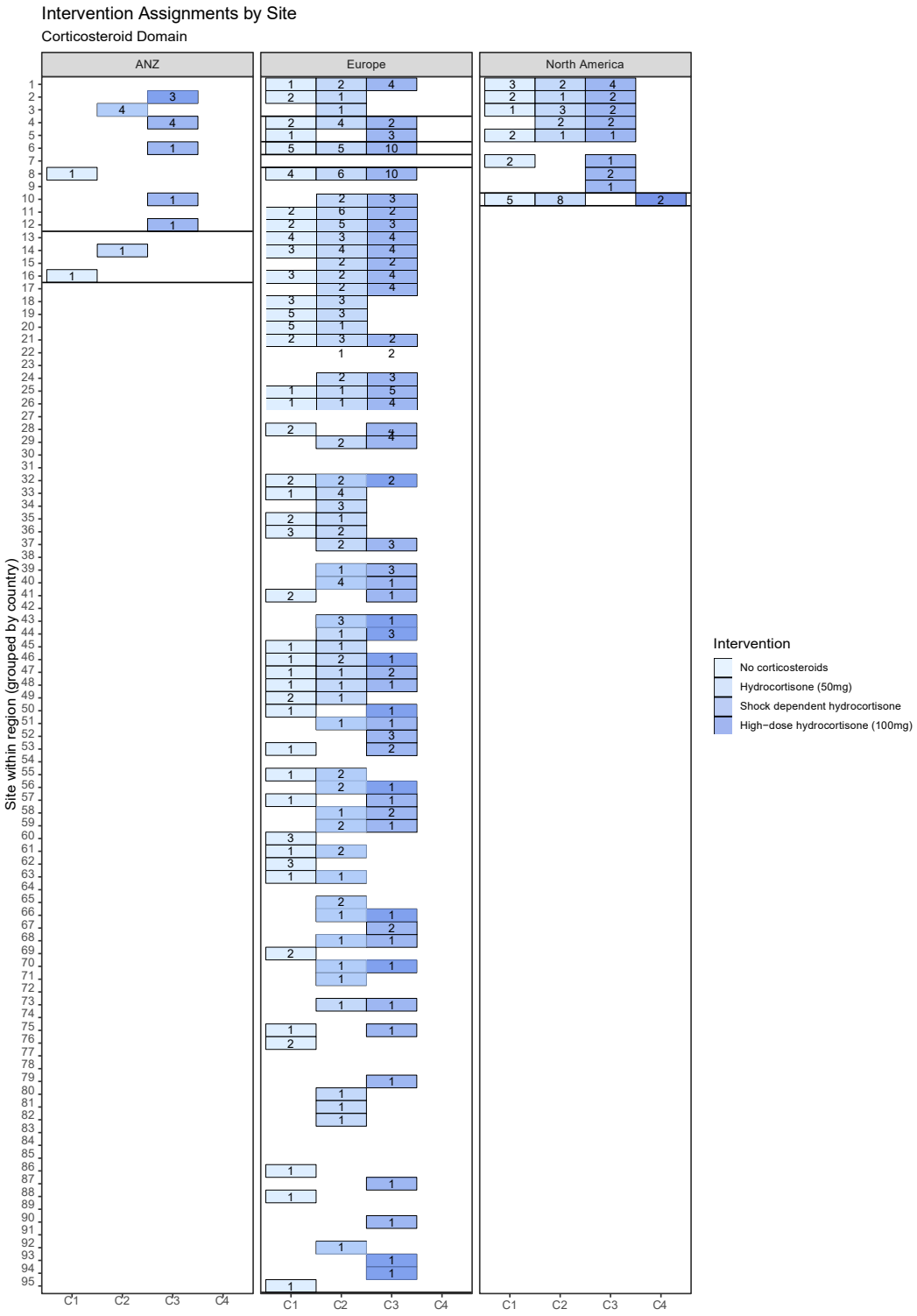

Figure 4.4: Allocation of interventions in the **Corticosteroid domain** by site. The data are summarized in three panels - one for each geographical region. Each panel is a grid with interventions on the x-axis and sites on the y-axis. Each colored cell corresponds to an intervention that has randomized patients at a site. Cells are colored by intervention, with the number in each cell representing how many patients were randomized to the intervention at that site. The solid black horizontal lines distinguish sites located within the same country in the region.

Table 4.1: Summary of the number of sites and patients randomized within each country

Region	Country	All Domains		Steroid Domain	
		Number of Sites	Number of Patients	Number of Sites	Number of Patients
ANZ	Australia	12	35	7	15
	New Zealand	4	6	2	2
Europe	France	3	11	3	11
	Ireland	2	23	2	12
	Netherlands	1	22	1	20
	Portugal	1	2		
	United Kingdom	88	419	70	275
North America	Canada	9	51	8	34
	United States of America	1	18	1	15

Table 4.2: Summary of age groups by sex at birth

	Age Group (years)						
	≤ 39	40 – 49	50 – 59	60 – 69	70 – 79	≥ 80	Total
Male	27	54	104	129	80	13	407
Female	16	16	48	51	41	8	180
Total	43	70	152	180	121	21	587

5 Analysis Conventions

The following conventions were applied to the analyses contained in this report:

- All sites within a country that have < 5 patients randomized in the analysis population will have their results combined into a single site within that country.
- For the estimation of time trends in the model, time buckets with < 5 patients randomized within the bucket were combined with a neighboring bucket.
- Patients with no randomized assignment in any domain were removed from the analysis population.
- Data from some patients who withdrew consent for use of their data in the analysis were included in the data exports received by the SAC. Subsequently, the SAC received a separate file to identify such patients, and they were manually removed from the analysis population by the SAC.
- For some patients whose 21-day outcome was missing in the data export, a supplemental file was provided to the SAC in which some additional outcome data was obtained. These additional outcomes were merged into the analysis dataset by the SAC. For any patients in the supplemental file that had a non-missing outcome recorded in the database, the outcome from the supplemental file was used rather than the database version; however, the SAC verified that all non-missing outcomes were the same between the data export and the supplemental file.
- For unique patient identifiers that exist in both the Research Online and Spiral databases, we generally pull the eligibility and randomization information from the Spiral database and the outcomes from the Research Online database. If outcomes were reported in both places, the reported outcome in Spiral was selected per instructions from the global project manager for the trial (email dated August 6, 2020).
- Within a domain, the analysis convention, as documented in the Current State, is that patients who are ***ineligible*** for the domain, or who have ***no assignment*** within the domain, or whose assignment ***is not revealed*** within the domain will not contribute to the estimate of the treatment effect for that domain.

In some domains (but not in the corticosteroid domain) data inconsistencies have been identified where patients were recorded as *ineligible* or as *domain not active/not available*, but the patient had a randomized assignment that was revealed for that domain. In accordance with the pre-specified analysis convention, these patient outcomes do not inform the treatment effect estimates within their respective domains.

- If any intervention within a domain has no patients with known outcomes, the analysis convention is to set the respective model terms to zero, including any associated interactions terms if they exist.
- The SAC manually corrected the values for one patient for which the respective Moderate and Severe columns had been switched for the variable that identifies whether 21 days have elapsed since randomization. The data error was confirmed with the data center and documented by the SAC in a Note to File.

6 Model Stability

The Bayesian model was computed in R version 4.0.2, using the rstan package version 2.21.2. This package computes the Markov Chain Mote Carlo (MCMC) using the highly efficient Hamiltonian Monte Carlo method. The MCMC used 5 separate chains, with each chain using a burnin of 500 samples, followed by 2000 samples, for a total of 10000 samples. Convergence diagnostics were assessed, and no concerns regarding mixing or convergence were identified. All $\hat{R}$ values were less than 1.05. All model runs used a random number seed of 7292020 for the MCMC initialization.

7 Report Production

All analyses in this report are based on the following documents:

- Statistical Analysis Plan (SAP) for the Corticosteroid Domain, version 1.0, dated July 21, 2020;
- Current State of the Statistical Model: Pandemic Model, dated July 21, 2020;
- Errata Sheet, last updated July 29, 2020;
- Instructions ("Single Source of Truth"), dated July21, 2020.

Berry Consultants performed the analysis using data received from multiple sources. Table 7.1 shows the file names for the data exports from each database along with the names of supplemental files received by the SAC, and the dates on which each file was received by the SAC.

Table 7.1: Summary of data sources.

File Name	Date Received	Description
8.7.2020_UPMC_REMAPCOVID_EXPORT v3.csv	August 7, 2020	UPMC data
remapcap_spiral interimexport 2020-08-11 175520_v10.csv	August 11, 2020	Spiral data
RAR_Unscrambled_RO 20200810_new.csv	August 12, 2020	Research Online data
Patients without consent 27 July 2020.xlsx	July 27, 2020	List of patients that witdrew consent
missing_outcome ID 20200810.xlsx	August 11, 2020	Supplemental 21-day outcome data

All data summaries were completed using the R[1] statistical computing environment R version 3.5.2 (2018-12-20).

[1] R Development Core Team (2005). R: *A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. URL http://www.R-project.org.

eAppendix 4. Technical Report from Berry Consultants for SAP Outcome Analyses 15.5-20

Secondary/Sensitivity Analysis Results of the Corticosteroid Domain for Patients with COVID-19 Pandemic Infection Suspected Or Proven (PISOP)

COVID-19 Corticosteroid Domain Results Version 1.0 dated 13 August 2020

Prepared by the ITSC Analysis Committee

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TABLE OF CONTENTS

1. AUTHORS

Lindsay Berry, Berry Consultants, Austin, TX, USA

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2. INTRODUCTION

This document summarizes the data and the results for the corticosteroid domain for analyses 15.5-15.20 as outlined in the corticosteroid SAP. Results for models 15.1-15.4 are provided in the SAC document "Analysis of the Corticosteroid Domain."

3. 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.

4. 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.

5. 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.

6. 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

7. SPECIFIC PROSPECTIVE ANALYSES

The table below displays the 15 pre-specified prospective analyses completed by the ITSC Analysis Committee.

#	Status	Population	Endpoint	Other
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	Time-to-events modeling
15.18	Secondary	Corticosteroid Domain ITT	Length of Hospital Stay	Time-to-events modeling
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

8. ORGAN SUPPORT FREE DAYS (OSFD)

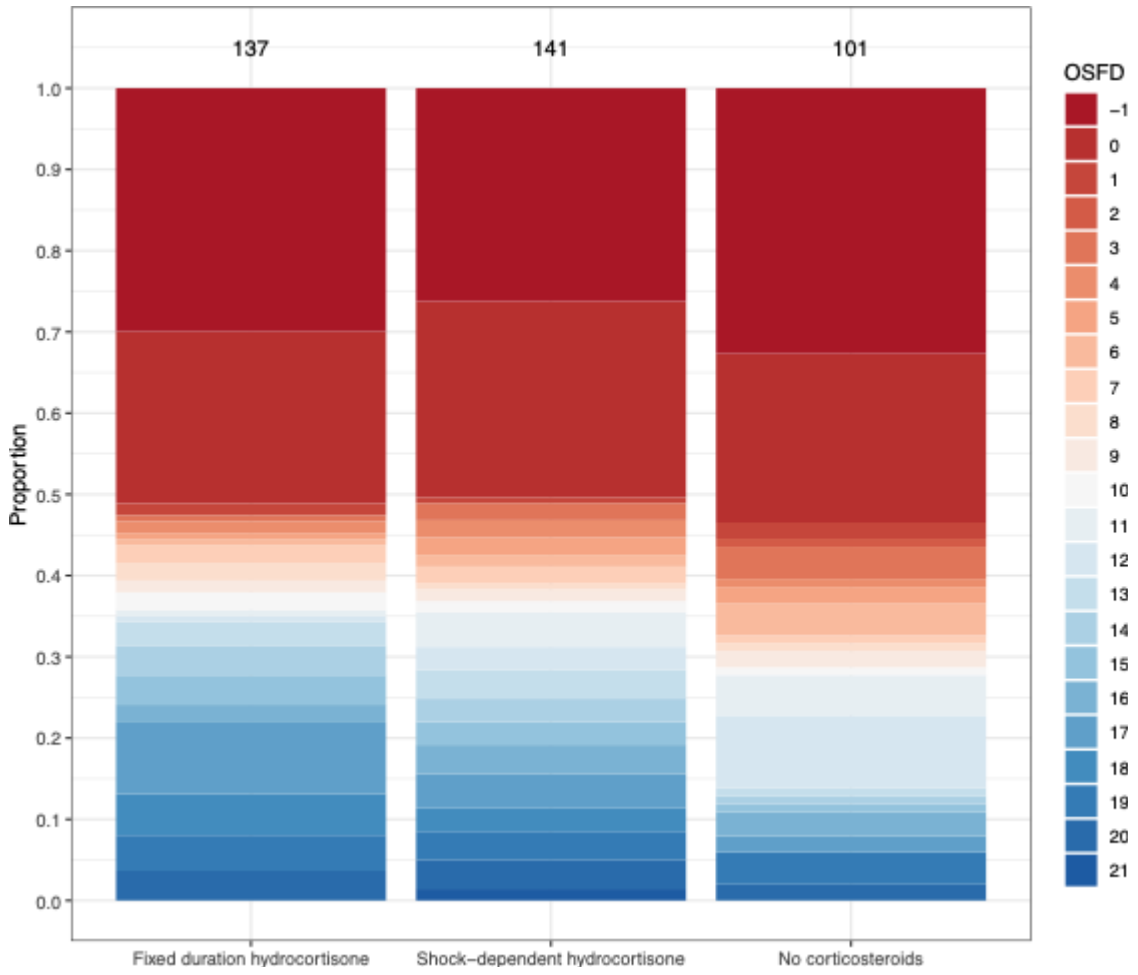

Figure 1: Empirical distribution of OSFD for each intervention in the Corticosteroid domain.

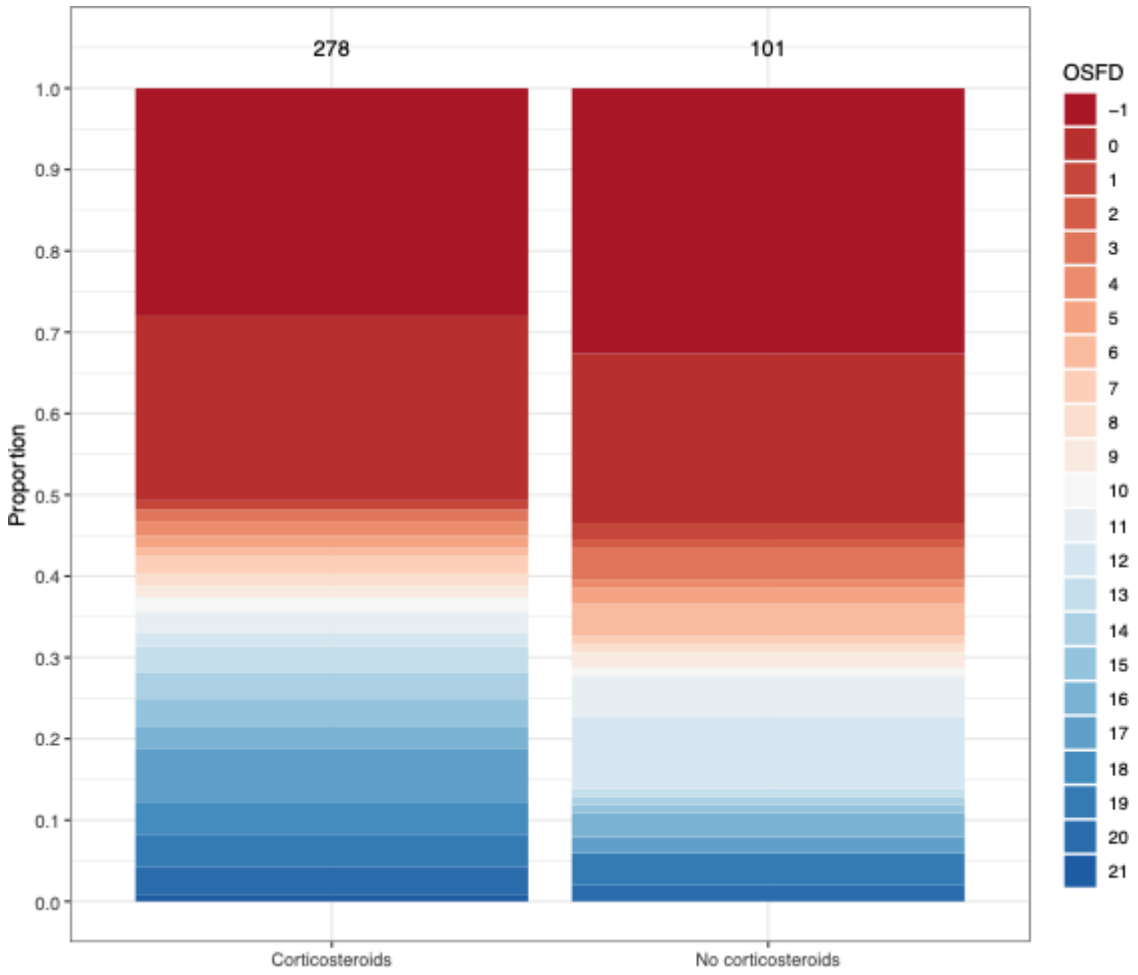

Figure 2: Empirical distribution of OSFD in the Corticosteroid domain for the pooled corticosteroid interventions and the “no corticosteroids” intervention.

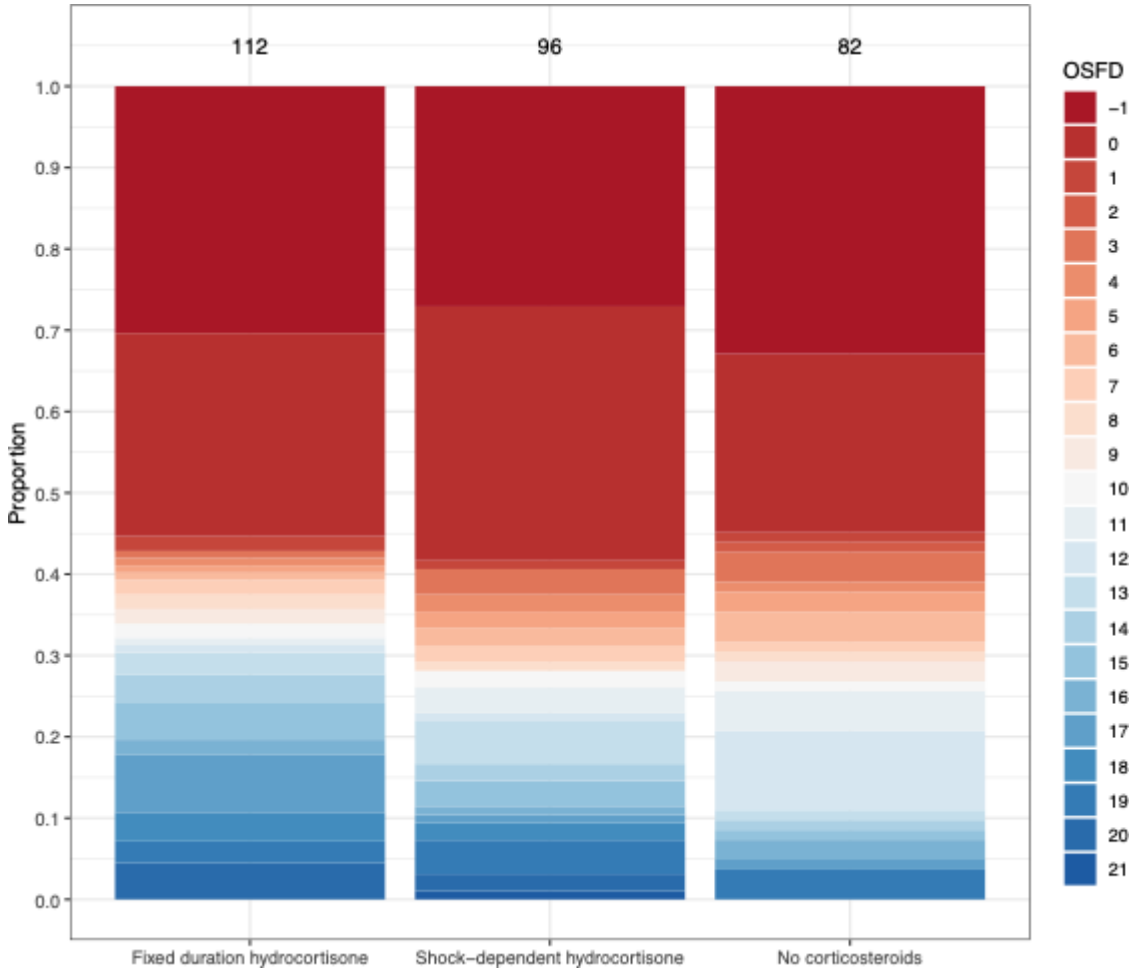

Figure 3: Empirical distribution of OSFD for all interventions in the Corticosteroid domain. Plot restricted to only patients in the Corticosteroid Domain Non-Negative COVID population.

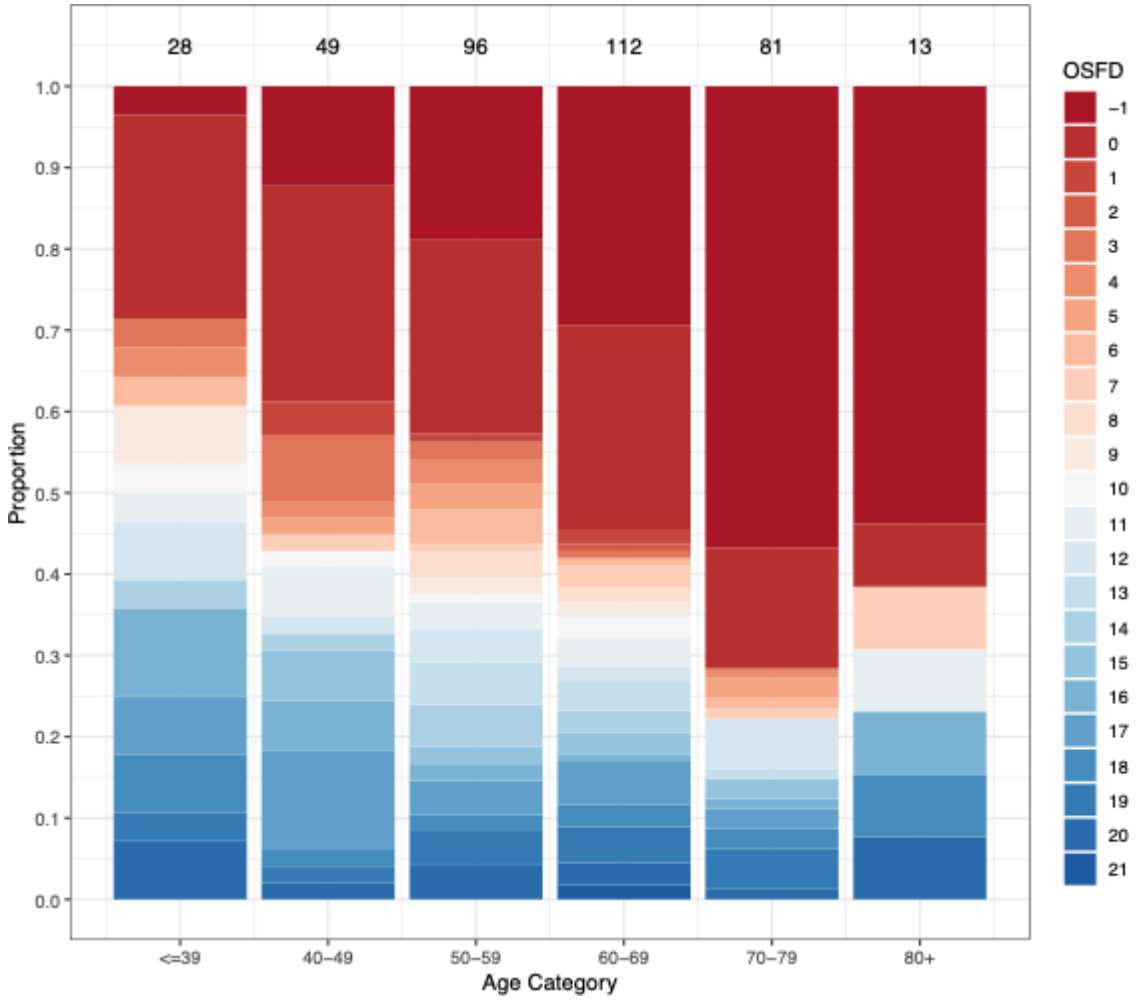

Figure 4: Empirical distribution of OSFD by age category

a. Model 15.5: A secondary analysis of OSFD for 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

1. 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.
2. 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.
3. 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.

Posterior probabilities for the OSFD endpoint in the Corticosteroid Domain ITT population:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.03
Fixed-duration is in the optimal regimen	0.74
Shock-based is in the optimal regimen	0.23
Fixed-duration is superior to control	0.95
Shock-based is superior to control	0.83
Fixed-duration is equivalent to shock-based	0.49

Model 15.5 estimated odds-ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	4.19	1.59	3.93	(1.92, 8.09)
Age 40, 49	2.47	0.72	2.36	(1.35, 4.18)
Age 50, 59	1.96	0.48	1.90	(1.19, 3.06)
Age 70-79	0.42	0.12	0.40	(0.23, 0.68)
Age 80+	0.61	0.35	0.53	(0.19, 1.50)
Female	1.16	0.25	1.14	(0.75, 1.72)
Time Bucket 1	0.89	0.10	0.89	(0.70, 1.10)
Time Bucket 2	0.81	0.17	0.8	(0.48, 1.17)
Time Bucket 3	1.00	0.25	0.97	(0.61, 1.59)
Time Bucket 4	1.16	0.43	1.09	(0.55, 2.23)
Time Bucket 5	1.62	1.15	1.31	(0.46, 4.69)
Fixed-duration Corticosteroids	1.49	0.35	1.45	(0.93, 2.30)
Shock-based Corticosteroids	1.28	0.30	1.24	(0.80, 1.95)
Fixed-duration Corticosteroids/Shock-based Corticosteroids	1.20	0.27	1.16	(0.75, 1.80)

b. Model 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

1. 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.
2. 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.
3. 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.

Posterior probabilities for the OSFD endpoint in the Corticosteroid Domain Non-negative COVID population:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.12
Fixed-duration is in the optimal regimen	0.74
Shock-based is in the optimal regimen	0.14
Fixed-duration is superior to control	0.85
Shock-based is superior to control	0.53
Fixed-duration is equivalent to shock-based	0.35

Model 15.6 estimated odds-ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	4.44	1.94	4.06	(1.79, 9.24)
Age 40, 49	1.92	0.64	1.83	(0.96, 3.40)
Age 50, 59	2.17	0.60	2.09	(1.24, 3.54)
Age 70-79	0.42	0.14	0.40	(0.22, 0.75)
Age 80+	0.87	0.65	0.70	(0.18, 2.56)
Female	0.99	0.24	0.96	(0.60, 1.54)

Time Bucket 1	0.94	0.11	0.94	(0.72, 1.16)
Time Bucket 2	0.97	0.20	0.96	(0.60, 1.41)
Time Bucket 3	1.24	0.37	1.18	(0.69, 2.11)
Time Bucket 4	1.51	0.70	1.37	(0.60, 3.24)
Time Bucket 5	2.01	1.92	1.53	(0.44, 6.46)
Fixed-duration Corticosteroids	1.36	0.36	1.32	(0.79, 2.16)
Shock-based Corticosteroids	1.06	0.29	1.02	(0.60, 1.73)
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids	1.33	0.35	1.28	(0.78, 2.15)

c. Model 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

1. 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.
2. Corticosteroids will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

Posterior probabilities for the OSFD endpoint in the Corticosteroid Domain combining corticosteroid intervention arms:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.07
Corticosteroids use is in the optimal regimen	0.93

Model 15.7 estimated odds-ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	4.17	1.53	3.91	(1.93, 7.86)
Age 40, 49	2.49	0.75	2.38	(1.34, 4.26)
Age 50, 59	1.97	0.48	1.91	(1.20, 3.06)
Age 70-79	0.42	0.12	0.41	(0.24, 0.70)
Age 80+	0.60	0.34	0.53	(0.18, 1.45)
Female	1.16	0.24	1.14	(0.77, 1.71)
Time Bucket 1	0.89	0.10	0.89	(0.70, 1.10)
Time Bucket 2	0.81	0.18	0.80	(0.47, 1.18)
Time Bucket 3	1.00	0.26	0.97	(0.60, 1.59)
Time Bucket 4	1.16	0.42	1.10	(0.55, 2.18)
Time Bucket 5	1.58	1.09	1.32	(0.46, 4.32)
Corticosteroids	1.40	0.30	1.36	(0.91, 2.07)

d. Model 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

1. 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.
2. 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.
3. 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.

Posterior probabilities for the OSFD endpoint in the Corticosteroid Domain ITT population with site and time factors removed:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.02
Fixed-duration is in the optimal regimen	0.59
Shock-based is in the optimal regimen	0.39
Fixed-duration is superior to control	0.95
Shock-based is superior to control	0.93
Fixed-duration is equivalent to shock-based	0.59

Model 15.8 estimated odds-ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	3.37	1.19	3.18	(1.65, 6.28)
Age 40, 49	1.98	0.56	1.90	(1.12, 3.28)
Age 50, 59	1.61	0.38	1.56	(0.99, 2.45)
Age 70-79	0.45	0.12	0.44	(0.26, 0.73)
Age 80+	0.70	0.39	0.61	(0.22, 1.67)
Female	1.15	0.23	1.13	(0.77, 1.68)

Fixed-duration Corticosteroids	1.50	0.34	1.46	(0.94, 2.26)
Shock-based Corticosteroids	1.42	0.31	1.38	(0.90, 2.12)
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids	1.08	0.23	1.06	(0.70, 1.61)

9. IN-HOSPITAL MORTALITY

Table 1: Summary of in-hospital mortality for patients in the Corticosteroid ITT and Corticosteroid Non-negative COVID populations for each intervention in the Corticosteroid domain

Population	Intervention	Number with Known Outcome	Number of Deaths	Mortality rate
Corticosteroids ITT	No corticosteroids	101	33	0.33
	Fixed Duration Corticosteroids	137	41	0.30
	Shock-based Corticosteroids	141	37	0.26
	Corticosteroid (Pooled)	278	78	0.28
	Overall	379	111	0.29
Corticosteroids Non-negative ITT	No corticosteroids	82	27	0.33
	Fixed Duration Corticosteroids	112	34	0.30
	Shock-based Corticosteroids	96	26	0.26
	Corticosteroid (Pooled)	208	60	0.29
	Overall	290	87	0.30

a. Model 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

1. 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.
2. 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.
3. 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.

Posterior probabilities for the in-hospital mortality endpoint in the Corticosteroid Domain ITT population:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.17
Fixed-duration is in the optimal regimen	0.33
Shock-based is in the optimal regimen	0.49
Fixed-duration is superior to control	0.64
Shock-based is superior to control	0.71
Fixed-duration is equivalent to shock-based	0.43

Model 15.9 estimated odds-ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	13.95	10.86	10.99	(3.41, 41.40)
Age 40, 49	5.32	2.72	4.68	(2.06, 12.31)
Age 50, 59	2.94	1.03	2.76	(1.47, 5.42)
Age 70-79	0.29	0.10	0.28	(0.15, 0.52)

Age 80+	0.34	0.21	0.29	(0.09, 0.88)
Female	1.08	0.32	1.04	(0.59, 1.83)
Time Bucket 1	0.99	0.12	0.98	(0.76, 1.23)
Time Bucket 2	0.99	0.23	0.97	(0.56, 1.48)
Time Bucket 3	1.24	0.41	1.17	(0.64, 2.23)
Time Bucket 4	1.59	0.85	1.39	(0.59, 3.73)
Time Bucket 5	2.93	6.71	1.75	(0.49, 12.15)
Fixed-duration Corticosteroids	1.17	0.37	1.11	(0.60, 2.05)
Shock-based Corticosteroids	1.26	0.41	1.19	(0.65, 2.21)
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids	0.98	0.31	0.93	(0.51, 1.70)

b. Model 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

1. 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.
2. 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.
3. 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.

Posterior probabilities for the in-hospital mortality endpoint in the Corticosteroid Domain Non-negative COVID population:

Quantity of Interest	**Posterior Probability**

Control arm is in the optimal regimen	0.26
Fixed-duration is in the optimal regimen	0.25
Shock-based is in the optimal regimen	0.49
Fixed-duration is superior to control	0.49
Shock-based is superior to control	0.64
Fixed-duration is equivalent to shock-based	0.37

Model 15.10 estimated odds-ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	10.96	9.76	8.31	(2.39, 35.12)
Age 40, 49	3.95	2.11	3.46	(1.40, 9.41)
Age 50, 59	3.05	1.17	2.84	(1.43, 5.91)
Age 70-79	0.27	0.11	0.25	(0.12, 0.53)
Age 80+	0.60	0.50	0.46	(0.11, 1.88)
Female	0.97	0.33	0.92	(0.49, 1.73)
Time Bucket 1	1.02	0.12	1.01	(0.79, 1.28)
Time Bucket 2	1.10	0.26	1.08	(0.66, 1.67)
Time Bucket 3	1.39	0.54	1.29	(0.65, 2.70)
Time Bucket 4	1.93	1.65	1.53	(0.54, 5.83)
Time Bucket 5	4.41	22.54	1.76	(0.36, 18.33)
Fixed-Duration Corticosteroids	1.05	0.36	0.99	(0.50, 1.90)
Shock-based Corticoteroids	1.21	0.44	1.13	(0.56, 2.29)
Shock-based Corticoteroids vs. Fixed-Duration Corticosteroids	0.93	0.34	0.88	(0.44, 1.75)

c. Model 15.11: 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

1. 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.
2. Corticosteroids will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

Posterior probabilities for the in-hospital mortality endpoint in the Corticosteroid Domain ITT population with the steroid interventions combined:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.29
Corticosteroid use is in the optimal regimen	0.71

Model 15.11 estimated odds ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	14.25	11.46	11.05	(3.35, 44.91)
Age 40, 49	5.28	2.70	4.66	(2.01, 12.05)
Age 50, 59	2.92	1.03	2.73	(1.46, 5.35)
Age 70-79	0.29	0.10	0.28	(0.15, 0.52)
Age 80+	0.34	0.20	0.29	(0.09, 0.84)
Female	1.09	0.32	1.04	(0.59, 1.84)
Time Bucket 1	0.98	0.12	0.98	(0.76, 1.23)
Time Bucket 2	0.98	0.23	0.96	(0.55, 1.49)
Time Bucket 3	1.22	0.41	1.15	(0.64, 2.24)

Time Bucket 4	1.57	0.86	1.37	(0.58, 3.71)
Time Bucket 5	3.66	18.16	1.71	(0.47, 14.40)
Corticosteroids	1.21	0.34	1.17	(0.67, 2.00)

d. Model 15.12: 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

1. 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.
2. 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.
3. 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.

Posterior probabilities for the in-hospital mortality endpoint in the Corticosteroid Domain ITT COVID population with site and time removed:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.08
Fixed-duration is in the optimal regimen	0.24
Shock-based is in the optimal regimen	0.68
Fixed-duration is superior to control	0.71
Shock-based is superior to control	0.88
Fixed-duration is equivalent to shock-based	0.41

Model 15.12 estimated odds ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval

Age < 39	11.42	9.07	8.95	(2.76, 34.48)
Age 40, 49	4.06	1.94	3.63	(1.66, 8.98)
Age 50, 59	2.22	0.70	2.11	(1.18, 3.90)
Age 70-79	0.39	0.11	0.38	(0.22, 0.66)
Age 80+	0.51	0.29	0.44	(0.16, 1.24)
Female	1.11	0.29	1.07	(0.66, 1.80)
Fixed-duration Corticosteroids	1.22	0.35	1.17	(0.67, 2.03)
Shock-based Corticosteroids	1.45	0.42	1.39	(0.80, 2.43)
Shock-based Corticosteroids vs. Fixed-duration corticosteroids	0.88	0.25	0.84	(0.48, 1.47)

10. MORTALITY

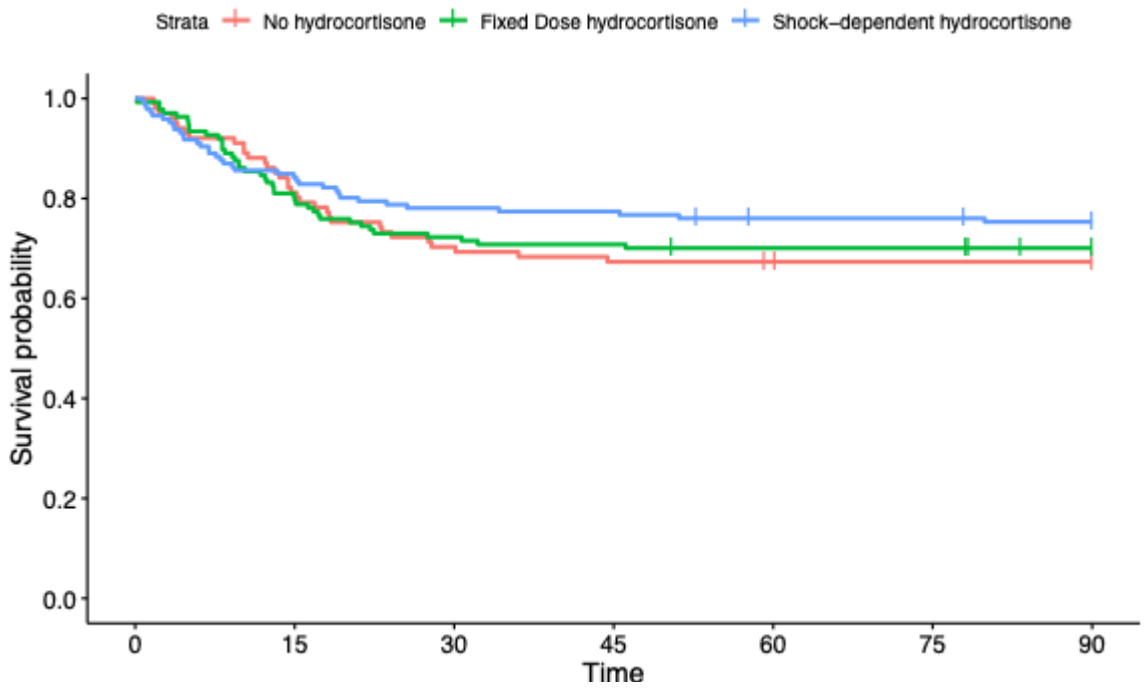

Figure 5: Kaplan Meier curve of 90-day mortality for each intervention in the Corticosteroid domain

Table 2: Summary of 2.5th, 10th, 25th percentiles from the Kaplan-Meier estimates for mortality. Displaying only the percentiles that are observed for this outcome.

	2.5th percentile	10th percentile	25th percentile
No corticosteroids	2.21	10.22	23.03
Fixed Duration Corticosteroids	2.63	8.19	21.26
Shock-based Corticosteroids	1.44	6.91	NA

a. Model 15.13: A secondary analysis of Mortality

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

Notes

1. 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.
2. 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.
3. 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.

Posterior probabilities for the time to mortality endpoint in the Corticosteroid Domain ITT population:

Quantity of Interest	Posterior Probability
Control arm is in the optimal regimen	0.38
Fixed-duration is in the optimal regimen	0.27
Shock-based is in the optimal regimen	0.35
Fixed-duration is superior to control	0.40
Shock-based is superior to control	0.47

Fixed-duration is equivalent to shock-based	0.53

Model 15.13 estimated odds-ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	11.36	9.47	8.68	(2.79, 35.57)
Age 40, 49	4.08	1.86	3.68	(1.73, 8.83)
Age 50, 59	2.31	0.67	2.20	(1.31, 3.93)
Age 70-79	0.33	0.07	0.32	(0.21, 0.49)
Age 80+	0.40	0.21	0.35	(0.14, 0.92)
Female	1.02	0.23	1.00	(0.65, 1.54)
Time Bucket 1	0.94	0.11	0.94	(0.75, 1.16)
Time Bucket 2	0.88	0.19	0.87	(0.54, 1.27)
Time Bucket 3	1.16	0.30	1.11	(0.70, 1.86)
Time Bucket 4	1.55	0.72	1.38	(0.69, 3.31)
Time Bucket 5	5.86	174.49	1.83	(0.58, 13.05)
Fixed-duration Corticosteroids	0.97	0.22	0.94	(0.61, 1.46)
Shock-based Corticosteroids	1.01	0.23	0.98	(0.63, 1.54)
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids	0.99	0.25	0.96	(0.59, 1.56)

11. PROGRESSION TO INTUBATION, ECMO, OR DEATH

Table 3: Summary of progression to intubation, ECMO, or death displayed for patients in the Corticosteroid ITT population for each intervention in the steroid domain and overall.

	Number of patients not on MV or ECMO at baseline	Number of progressions of intubation, ECMO, or death	Rate of progression to intubation, ECMO, or death
No corticosteroids	48	37	0.77
Fixed Duration Corticosteroids	50	23	0.46
Shock-based Corticosteroids	70	42	0.60
Overall	168	102	0.61

a. Model 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

1. 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.
2. 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.
3. 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.

Posterior probabilities for the progression to intubation, ECMO, or death endpoint:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.01
Fixed-duration is in the optimal regimen	0.97
Shock-based is in the optimal regimen	0.03
Fixed-duration is superior to control	0.99
Shock-based is superior to control	0.70
Fixed-duration is equivalent to shock-based	0.06

Model 15.14 estimated odds-ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	13.16	11.09	10.09	(2.68, 41.9)
Age 40, 49	3.00	1.57	2.66	(1.02, 6.95)
Age 50, 59	0.99	0.43	0.91	(0.40, 2.02)
Age 70-79	0.61	0.30	0.55	(0.21, 1.35)
Age 80+	0.69	0.60	0.53	(0.12, 2.17)
Female	0.60	0.24	0.56	(0.25, 1.18)
Time Bucket 1	0.98	0.13	0.98	(0.75, 1.25)
Time Bucket 2	1.04	0.29	1.02	(0.54, 1.70)
Time Bucket 3	1.44	0.74	1.27	(0.57, 3.27)
Time Bucket 4	2.39	2.92	1.6	(0.47, 9.25)
Fixed-duration Corticosteroids	3.02	1.40	2.74	(1.18, 6.56)
Shock-based Corticosteroids	1.36	0.59	1.24	(0.56, 2.82)
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids	2.40	1.06	2.20	(0.99, 5.04)

12. DAYS-FREE OF VASOPRESSOR/INOTROPES USE

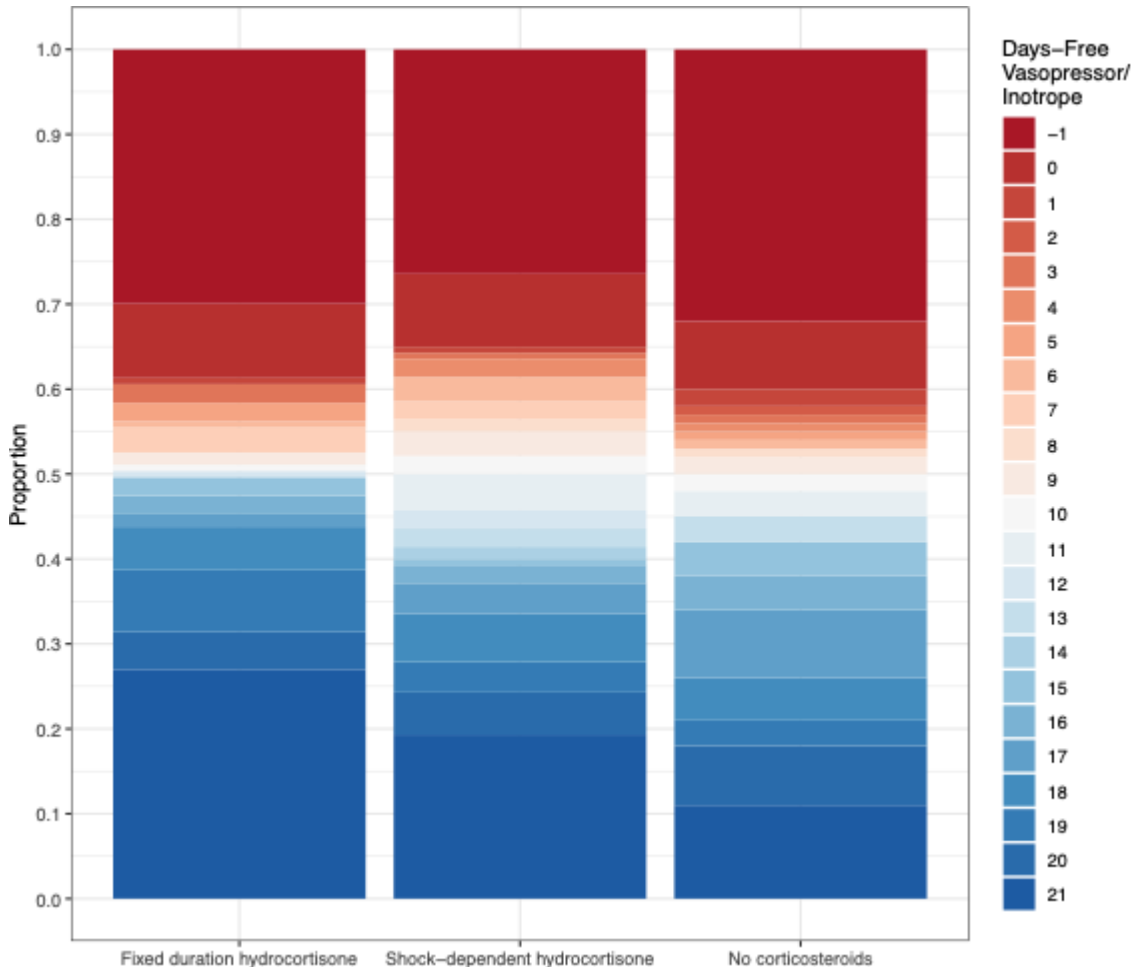

Figure 6: Empirical distribution of days-free of vasopressor/inotropes for each intervention in the Corticosteroid domain.

a. Model 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

1. 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.
2. 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.

3. 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.

Posterior probabilities for the days-free of vasopressor/inotropes use endpoint in the Corticosteroid Domain ITT population:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.01
Fixed-duration is in the optimal regimen	0.85
Shock-based is in the optimal regimen	0.14
Fixed-duration is superior to control	0.98
Shock-based is superior to control	0.86
Fixed-duration is equivalent to shock-based	0.36

Model 15.15 estimated odds-ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	3.90	1.45	3.63	(1.83, 7.34)
Age 40, 49	3.09	0.94	2.95	(1.65, 5.32)
Age 50, 59	2.04	0.50	1.99	(1.23, 3.17)
Age 70-79	0.41	0.11	0.40	(0.23, 0.67)
Age 80+	0.57	0.32	0.49	(0.17, 1.43)
Female	1.20	0.25	1.17	(0.78, 1.76)
Time Bucket 1	0.92	0.10	0.91	(0.74, 1.12)
Time Bucket 2	0.81	0.16	0.81	(0.51, 1.15)
Time Bucket 3	0.84	0.21	0.82	(0.51, 1.32)
Time Bucket 4	0.86	0.29	0.82	(0.43, 1.57)
Time Bucket 4	1.00	0.62	0.85	(0.33, 2.59)
Fixed-duration Corticosteroids	1.68	0.40	1.63	(1.03, 2.59)
Shock-based Corticosteroids	1.32	0.31	1.29	(0.81, 2.02)

Shock-based Corticosteroids vs. Fixed-duration Corticosteroids	1.30	0.30	1.27	(0.81, 1.97)

13. DAYS-FREE OF VENTILATION

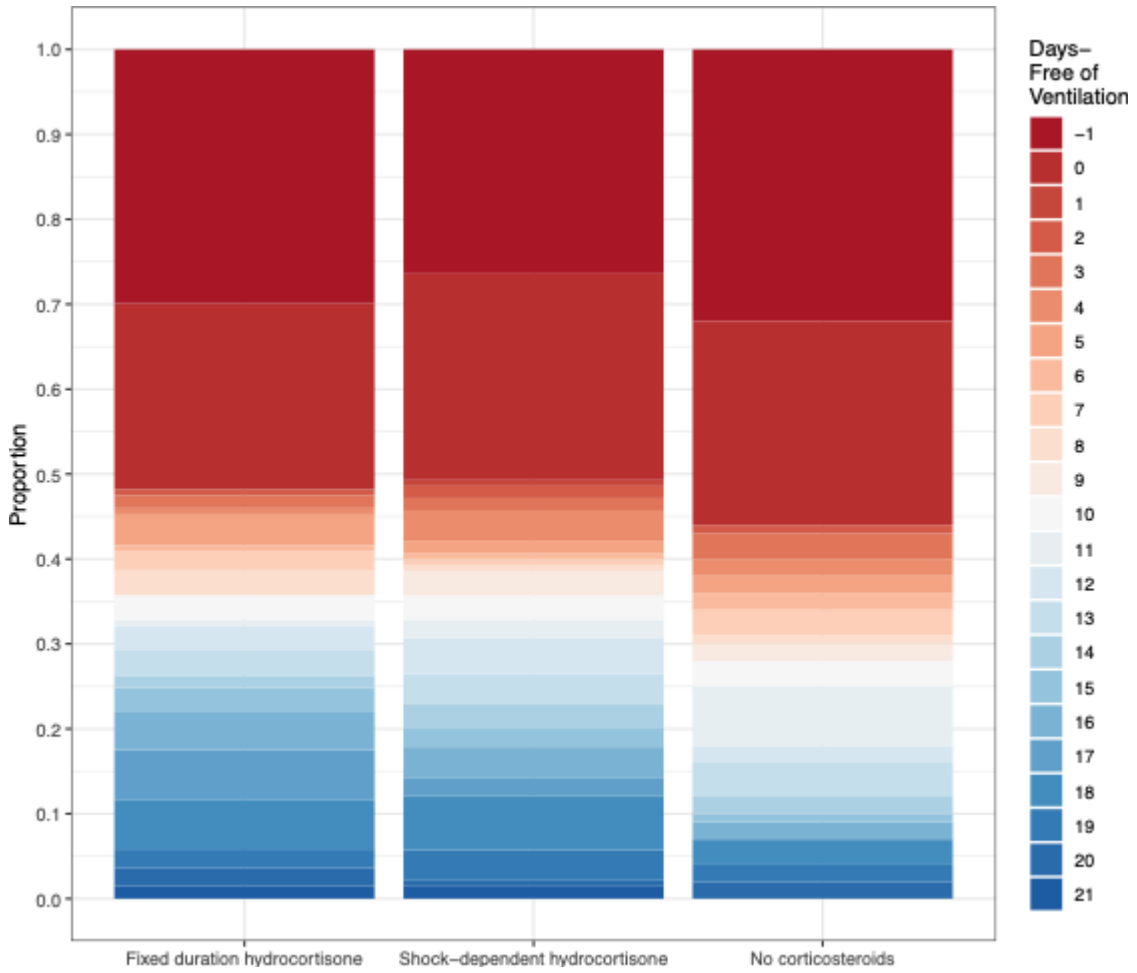

Figure 7: Empirical distribution of days-free of ventilation for each intervention in the Corticosteroid domain.

a. Model 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

1. 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.
2. 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.
3. 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.

Posterior probabilities for the days-free of ventilation endpoint in the Corticosteroid Domain ITT population:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.03
Fixed-duration is in the optimal regimen	0.66
Shock-based is in the optimal regimen	0.30
Fixed-duration is superior to control	0.94
Shock-based is superior to control	0.85
Fixed-duration is equivalent to shock-based	0.54

Model 15.16 estimated odds ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	4.45	1.63	4.19	(2.12, 8.27)
Age 40, 49	2.44	0.73	2.33	(1.33, 4.19)
Age 50, 59	1.94	0.48	1.88	(1.18, 3.04)
Age 70-79	0.42	0.12	0.40	(0.23, 0.69)
Age 80+	0.55	0.31	0.48	(0.16, 1.36)
Female	1.19	0.25	1.17	(0.78, 1.76)
Time Bucket 1	0.89	0.1	0.89	(0.71, 1.1)
Time Bucket 2	0.81	0.17	0.80	(0.49, 1.17)

Time Bucket 3	0.99	0.25	0.96	(0.60, 1.56)
Time Bucket 4	1.16	0.42	1.09	(0.56, 2.18)
Time Bucket 5	1.66	1.20	1.33	(0.48, 4.95)
Fixed-duration Corticosteroids	1.45	0.34	1.42	(0.90, 2.24)
Shock-based Corticosteroids	1.31	0.30	1.28	(0.81, 2.00)
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids	1.14	0.26	1.11	(0.72, 1.72)

14. LENGTH OF ICU STAY

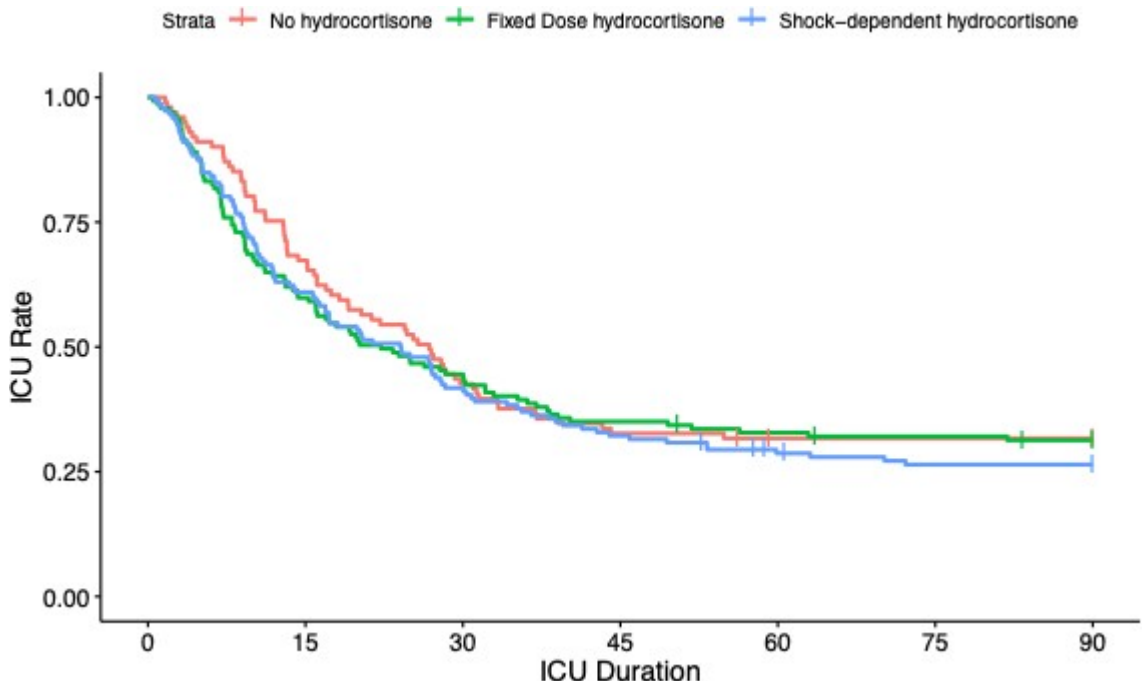

Figure 8: Kaplan Meier curve of ICU duration for each intervention in the Corticosteroid domain

Table 4: Summary of 2.5th, 10th, 25th and 50th percentiles from the Kaplan-Meier estimates for duration of ICU stay. Displaying only the percentiles that are observed for this outcome.

	2.5th percentile	10th percentile	25th percentile	50th percentile
No corticosteroids	2.23	7.15	12.89	26.80
Fixed Duration Corticosteroids	2.02	4.04	8.01	22.21
Shock-based Corticosteroids	1.63	3.97	9.05	24.09

a. Model 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

1. 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.
2. 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.
3. 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.

Posterior probabilities for the length of ICU stay endpoint in the Corticosteroid Domain ITT population:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.65
Fixed-duration is in the optimal regimen	0.27
Shock-based is in the optimal regimen	0.09
Fixed-duration is superior to control	0.29
Shock-based is superior to control	0.14
Fixed-duration is equivalent to shock-based	0.68

Model 15.17 estimated hazard-ratios:

Hazard-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	2.76	0.66	2.68	(1.68, 4.24)
Age 40, 49	2.23	0.44	2.19	(1.49, 3.19)
Age 50, 59	1.53	0.25	1.51	(1.10, 2.07)
Age 70-79	0.49	0.10	0.48	(0.33, 0.70)
Age 80+	0.86	0.32	0.82	(0.38, 1.61)
Female	1.11	0.16	1.10	(0.83, 1.45)
Time Bucket 1	0.84	0.09	0.83	(0.67, 1.02)
Time Bucket 2	0.70	0.12	0.70	(0.49, 0.97)
Time Bucket 3	0.96	0.20	0.94	(0.65, 1.41)
Time Bucket 4	0.90	0.24	0.87	(0.51, 1.44)
Time Bucket 5	2.16	1.40	1.76	(0.66, 5.87)
Fixed-duration Corticosteroids	0.93	0.14	0.92	(0.68, 1.24)
Shock-based Corticosteroids	0.86	0.13	0.85	(0.62, 1.15)
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids	1.10	0.17	1.09	(0.79, 1.48)

15. LENGTH OF HOSPITAL STAY

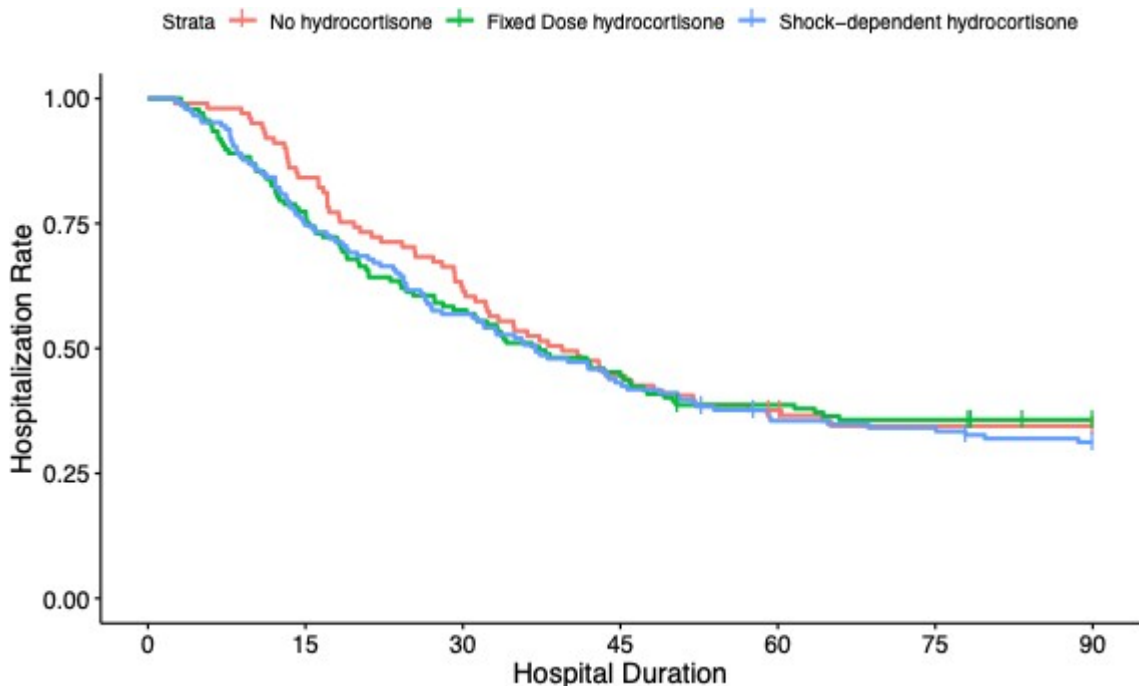

Figure 9: Kaplan Meier curve of hospital duration for each intervention in the Corticosteroid domain

Table 5: Summary of 2.5th, 10th, 25th and 50th percentiles from the Kaplan-Meier estimates for duration of hospital stay. Displaying only the percentiles that are observed for this outcome.

	2.5th percentile	10th percentile	25th percentile	50th percentile
No corticosteroids	8.91	13.18	19.64	39.45
Fixed Duration Corticosteroids	4.86	7.36	15.34	37.28
Shock-based Corticosteroids	4.10	8.44	14.92	36.93

a. Model 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

1. 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.
2. 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.
3. 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.

Posterior probabilities for the length of hospital stay endpoint in the Corticosteroid Domain ITT population:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.47
Fixed-duration is in the optimal regimen	0.35
Shock-based is in the optimal regimen	0.18
Fixed-duration is superior to control	0.43
Shock-based is superior to control	0.31
Fixed-duration is equivalent to shock-based	0.74

Model 15.18 estimated hazard-ratios:

Hazard-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	2.97	0.72	2.9	(1.79, 4.58)
Age 40, 49	2.55	0.5	2.51	(1.71, 3.66)
Age 50, 59	1.63	0.27	1.61	(1.17, 2.25)
Age 70-79	0.54	0.11	0.53	(0.35, 0.79)
Age 80+	0.62	0.25	0.59	(0.25, 1.21)
Female	0.96	0.14	0.95	(0.72, 1.26)
Time Bucket 1	0.84	0.09	0.84	(0.68, 1.02)
Time Bucket 2	0.68	0.12	0.67	(0.46, 0.94)
Time Bucket 3	0.85	0.16	0.83	(0.58, 1.21)

Time Bucket 4	0.93	0.26	0.9	(0.53, 1.52)
Time Bucket 5	1.81	1.18	1.49	(0.59, 4.89)
Fixed-duration Corticosteroids	0.99	0.16	0.97	(0.72, 1.32)
Shock-based Corticosteroids	0.94	0.15	0.93	(0.69, 1.26)
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids	1.06	0.17	1.05	(0.77, 1.42)

16. WHO Ordinal Scale

A 7-level approximation of the WHO ordinal scale was pre-specified for this analysis. This version of the WHO scale has a single level for patients discharged from the hospital. The WHO ordinal scale is assessed on *Study Day 14* and is defined as follows:

- 0 = discharged from hospital prior to day 14
- 3 = still in hospital but discharged from ICU on day 14
- 4 = in ICU on day 14 but not requiring any HFNO, NIV or invasive ventilation
- 5 = in ICU on day 14 and requiring HFNO or NIV
- 6 = in ICU on day 14 and requiring IMV (Only) without ECMO/ECCOR and without vasopressors and without RRT
- 7 = in ICU on day 14 and requiring IMV with ECMO/ECCOR or with vasopressors / inotropes or with RRT
- 8 = deceased before day 14.

Two patients were in the ICU on day 14 but had no data on organ support, so their WHO ordinal outcome was defined using the last ICU status carried forward. Both subjects were defined as WHO level 5. Three patients had no available data on ICU/hospital discharge dates or organ support, so they were excluded from the WHO analysis.

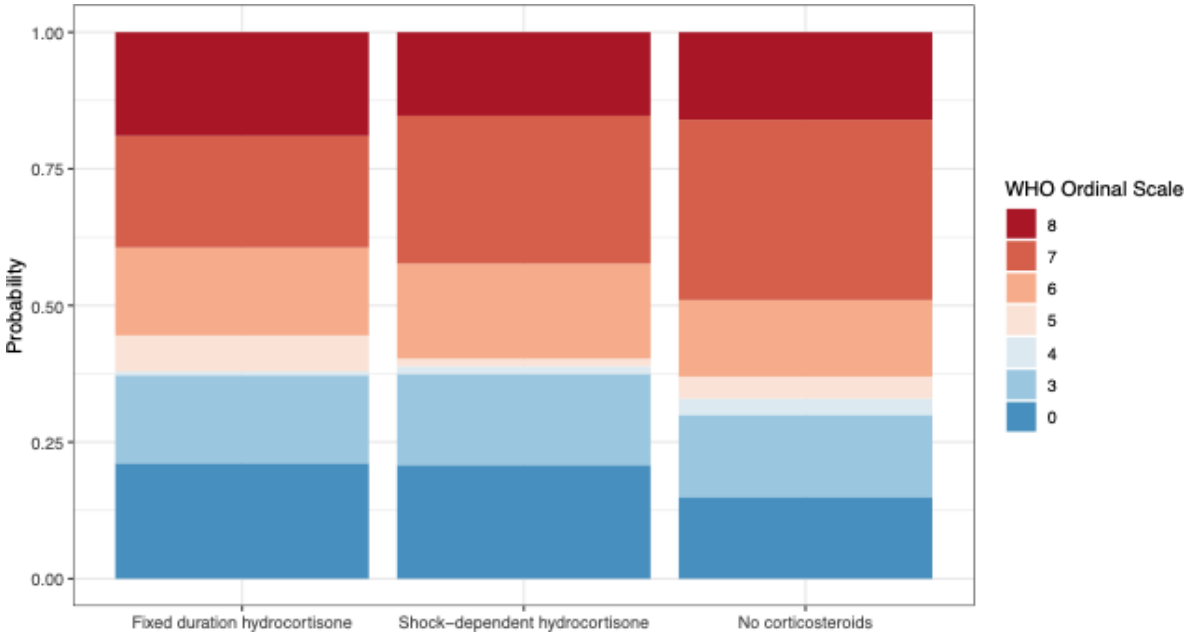

Figure 10: Empirical distribution of the WHO ordinal scale for each intervention in the Corticosteroid domain.

a. Model 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

1. 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.
2. 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.
3. 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.

Posterior probabilities for the WHO ordinal scale endpoint in the Corticosteroid Domain ITT population:

Quantity of Interest	**Posterior Probability**
Control arm is in the optimal regimen	0.11
Fixed-duration is in the optimal regimen	0.76
Shock-based is in the optimal regimen	0.13
Fixed-duration is superior to control	0.87

Shock-based is superior to control	0.55
Fixed-duration is equivalent to shock-based	0.39

Model 15.19 estimated odds-ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39	3.13	1.22	2.91	(1.38, 6.09)
Age 40, 49	1.91	0.59	1.82	(1.03, 3.30)
Age 50, 59	1.35	0.32	1.31	(0.83, 2.08)
Age 70-79	0.43	0.12	0.41	(0.25, 0.69)
Age 80+	0.62	0.35	0.54	(0.19, 1.56)
Female	1.11	0.23	1.08	(0.72, 1.62)
Time Bucket 1	0.86	0.10	0.85	(0.67, 1.06)
Time Bucket 2	0.72	0.17	0.71	(0.41, 1.06)
Time Bucket 3	0.87	0.22	0.85	(0.52, 1.38)
Time Bucket 4	1.06	0.40	0.99	(0.50, 2.05)
Time Bucket 5	1.87	1.66	1.39	(0.45, 6.13)
Fixed-duration Corticosteroids	1.33	0.32	1.29	(0.83, 2.05)
Shock-based Corticosteroids	1.06	0.26	1.03	(0.65, 1.65)
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids	1.29	0.29	1.25	(0.81, 1.95)

17. SERIOUS ADVERSE EVENTS

Table 6: Summary of serious adverse events displayed for patients in the Corticosteroid ITT population for each intervention in the steroid domain and overall.

	Number of patients	Number of SAEs	Rate of SAEs
No corticosteroids	101	1	0.01
Fixed Duration Corticosteroids	137	4	0.03
Shock-based Corticosteroids	141	5	0.04
Overall	379	10	0.03

a. Model 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

1. 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
2. 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.

Posterior probabilities for the Serious Adverse Events endpoint in the Corticosteroid Domain ITT population:

Quantity of Interest	**Posterior Probability**
Fixed-duration is superior to control	0.45
Shock-based is superior to control	0.39

Model 15.20 estimated odds-ratios:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval

Age < 39	9.70	11.08	6.35	(1.17, 38.93)
Age 40, 49	4.46	4.56	3.16	(0.73, 15.97)
Age 50, 59	4.16	3.67	3.18	(0.85, 13.28)
Age 70-79	2.02	1.62	1.58	(0.45, 6.35)
Age 80+	1.90	1.99	1.33	(0.27, 7.08)
Female	1.93	1.46	1.53	(0.45, 5.80)
Fixed-duration Corticosteroids	1.13	0.80	0.92	(0.27, 3.16)
Shock-based Corticosteroids	1.04	0.76	0.83	(0.23, 3.04)
Shock-based Corticosteroids vs. Fixed-duration Corticosteroids	1.43	1.19	1.09	(0.27, 4.51)

eAppendix 5. The REMAP-CAP Investigators

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St. James's University Hospital and Leeds General Infirmary: Elankumaran Paramasivam, FRCP, Matthew Powell, FFICM, Richard Gould, FFICM, Elizabeth Wilby, RGN, Clare Howcroft, RGN;

St. Mary's Hospital: Anthony Gordon, MD; Dorota Banach, BSc, Ziortza Fernández de Pinedo Artaraz, BN, Leilani Cabreros, BSN;

St. Peter's Hospital, Chertsey: Ian White, FFICM, Maria Croft, BSc(Hons), Nicky Holland, BN(Hons), Rita Pereira, MPharm;

Stepping Hill Hospital, Stockport: Ahmed Zaki, PhD, David Johnson, MPhil, Matthew Jackson, MBChB, Hywel Garrard, BMBS, Vera Juhaz, MD;

Sunderland Royal Hospital: Alistair Roy, MBChB, Anthony Rostron, PhD, Lindsey Woods, BSc, Sarah Cornell, BSc;

Swansea Bay University Health Board: Suresh Pillai, FFCIM, Rachel Harford, RN, Tabitha Rees, MSc, Helen Ivatt, FRCA, Ajay Sundara Raman, MBBS;

Tunbridge Wells Hospital: David Golden, FFICM, Miriam Davey, PGDip;

United Lincolnshire NHS Trust: Kelvin Lee, PhD, Russell Barber, FRCA, Manish Chablani, FRCA;

University Hospital of North Tees: Farooq Brohi, FFARCSI, Vijay Jagannathan, FRCA, Michele Clark, MA, Sarah Purvis, Dip, Bill Wetherill, MSc;

University Hospital Southampton NHS Foundation Trust: Ahilanandan Dushianthan, PhD, Rebecca Cusack, MD, Kim de Courcy-Golder, PGDip, Simon Smith, BN, Susan Jackson, BSc;

Warwick Hospital: Ben Attwood, MBBCh, Penny Parsons, BSc;

Watford General Hospital: Valerie J Page, MBBCh, Xiao Bei Zhao, BSc, Deepali Oza, MPharm;

Western General Hospital, Edinburgh: Jonathan Rhodes, PhD, Tom Anderson, MBChB, Sheila Morris;

Whipps Cross Hospital: Charlotte Xia Le Tai, MBChB, Amy Thomas, MSc, Alexandra Keen, MSc;

Worcester Royal Hospital: Stephen Digby, MBBS, Nicholas Cowley, MD, Laura Wild, BSc(Hons), Jessica Thrush, RGN, Hannah Wood, BSc(Hons)

Wrexham Maelor Betsi Cadwaladr University Hospital: David Southern, FFICM, Harsha Reddy, FFICM, Andy Campbell, FFICM, Claire Watkins, PGDip, Sara Smuts, BN;

Wrexham Park Hospital: Omar Touma, MD, Nicky Barnes;

Wythenshawe Hospital: Peter D G Alexander, FFICM, Tim Felton, FFICM, Susan Ferguson, BSc, Katharine Sellers, BSc, Joanne Bradley-Potts, BSc;

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