REMAP-CAP (REMAP-COVID)

Analysis of COVID-19 Immunoglobulin Domain

May 30, 2021

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

This report contains the final analysis of the COVID-19 Immunoglobulin domain for both Moderate and Severe disease states.

The international trial steering committee (ITSC) halted randomization to the COVID-19 Immunoglobulin domain in the PISOP stratum Severe state on January 11, 2021 following the disclosure from the Data and Safety Monitoring Board (DSMB) that the pre-specified threshold for futility had been met in Severe state. Enrollment to the moderate state of the Immunoglobulin domain was halted on January 18th, 2021 following the press release of results from the RECOVERY trial of no evidence of benefit. The ITSC prepared a statistical analysis plan (SAP) for the COVID-19 Immunoglobulin domain and provided this plan to the Statistical Analysis Committee (SAC).

Although the ITSC will be unblinded to the interventions within the COVID-19 Immunoglobulin domain, they will not be unblinded to the other domains to which patients have been randomized (except the corticosteroid domain, the COVID-19 antiviral domain, the therapeutic anticoagulation domain, and the two IL-6ra interventions within the COVID-19 Immune Modulation domain, which were previously unblinded). The fully unblinded SAC performed the set of 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 Immunoglobulin domain interventions resulting from the analyses using the full statistical model. This report is restricted to summaries and results pertaining to the unblinded interventions. Summaries and results for other ongoing 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 is organ support-free days (OSFD) (days alive and free of ICU-based respiratory or cardiovascular support) within 21 days, where patients who die before discharge from the index hospitalization, and before day 90, were assigned a -1 day, even if the death occurred after day 21. The cumulative hours of organ support are computed and then rounded to the nearest day. 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. An outcome of 21 organ-support free-days is only possible in the Severe state if the patient had less than 12 hours of organ support.

1.3.2 Secondary Endpoint: In-Hospital Mortality

The secondary endpoint is a dichotomous endpoint of in-hospital mortality, i.e. those patients with a -1 for 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

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". Table 1.1 is a companion to the current state figure, and provides the mapping of intervention codes to the actual intervention names (e.g. X2 = Lopinavir/ritonavir).

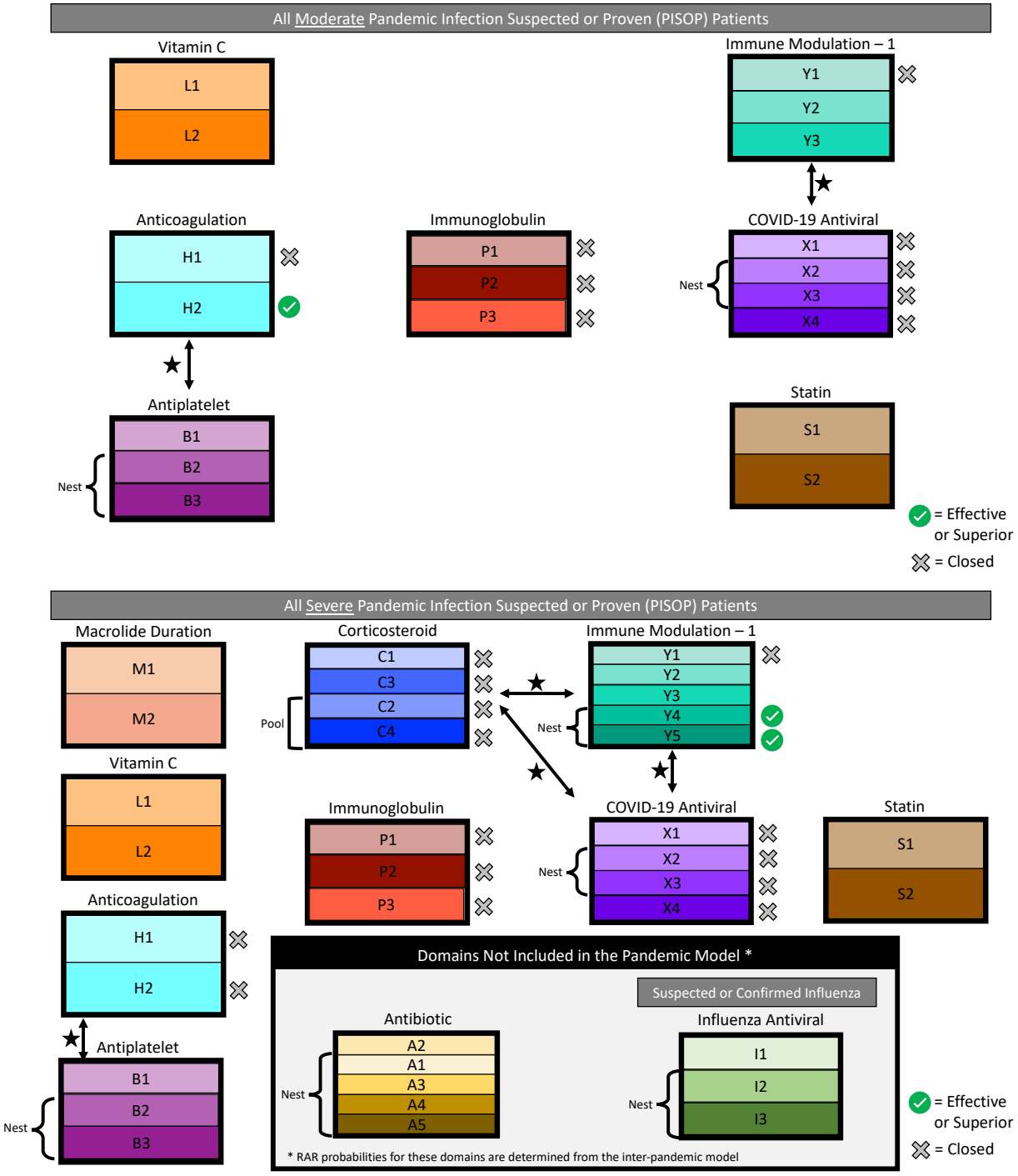

Figure 1.1: Current state of the **Moderate State** and **Severe State** pandemic domains and interventions. Each colored box represents an intervention, grouped by domain, with similar colors used for interventions within the same domain. Domains connected with an arrow and indicated with a star (★) 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 a grey "X". Interventions that have met an Efficacy or Superiority trigger are indicated by a green checkmark. Closure of the Antiviral domain occurred simultaneously with the closure of the control arm (Y1) in the Immune Modulation domain and the superiority trigger of tocilizumab (Y4). The superiority trigger for sarilumab (Y5) occurred subsequently and results were publicly disclosed along with tocilizumab.

Table 1.1: List of all interventions to which a patient may be allocated, by disease state.

Code	Intervention	Moderate	Severe
Antibiotic			
A1	Ceftriaxone + Macrolide	Not Available	
A2	Moxifloxacin or Levofloxacin	Not Available	
A3	Piperacillin-Tazobactam + Macrolide	Not Available	
A4	Ceftaroline + Macrolide	Not Available	
A5	Amoxicillin-Clavulanate + Macrolide	Not Available	
Macrolide Duration			
M1	Standard course (3 to 5 days)	Not Available	
M2	Extended course (14 days)	Not Available	
Corticosteroid			
C1	No corticosteroids	Not Available	Closed
C2	Hydrocortisone (50mg)	Not Available	Closed
C3	Shock dependent hydrocortisone	Not Available	Closed
C4	High-dose hydrocortisone (100mg)	Not Available	Closed
Influenza Antiviral			
I1	No antiviral	Not Available	
I2	Oseltamivir 5 days	Not Available	
I3	Oseltamivir 10 days	Not Available	
COVID-19 Antiviral			
X1	No antiviral for COVID-19	Closed	Closed
X2	Lopinavir/ritonavir	Closed	Closed
X3	Hydroxychloroquine	Closed	Closed
X4	Hydroxychloroquine + lopinavir/ritonavir	Closed	Closed
COVID-19 Immune Modulation			
Y1	No immune modulation for COVID-19		Closed
Y2	Interferon Beta-1a		
Y3	Anakinra		
Y4	Tocilizumab	Not Available	Effective
Y5	Sarilumab	Not Available	Effective
COVID-19 Immunoglobulin			
P1	No Immunoglobulin against COVID-19	Closed	Closed
P2	Convalescent plasma	Closed	Closed
P3	Delayed convalescent plasma	Closed	Closed
COVID-19 Therapeutic Anticoagulation			
H1	Standard practice thromboprophylaxis	Closed	Closed
H2	Therapeutic anticoagulation	Effective	Closed
Vitamin C			
L1	No vitamin C		
L2	Vitamin C		
Statin Therapy			
S1	No simvastatin		
S2	Simvastatin		
COVID-19 Antiplatelet			
B1	No antiplatelet therapy		
B2	Aspirin		
B3	P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor)		

1.6 Analysis Population

This report restricts the analysis population to consented patients with pandemic infection suspected or proven (PISOP) that were randomized, including both Moderate and Severe disease states, on or before January 18, 2021. This population is defined as the **REMAP-CAP COVID-19 severe and moderate state ITT population**. The patient population breakdown is as follows:

- 512 PISOP consented patients randomized initially in **Moderate** disease state (inclusive of 19 patients initially randomized while in Moderate disease state that later met the criteria for Severe disease state

and had additional randomization for Severe state domains), on or before January 18, 2021;

➔ 512 PISOP consented patients randomized for the first time in Moderate state for whom 21 days have elapsed since randomization and there is a known outcome on the 21-day organ-support free-days endpoint;

- 4190 PISOP consented patients randomized in **Severe** disease state (inclusive of 19 patients initially randomized while in Moderate disease state that later met the criteria for Severe disease state and had additional randomization for Severe state domains), on or before January 18, 2021;

  ➔ 4150 PISOP consented patients randomized in Severe state 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 exclude patients that withdrew consent for the use of their data. The patients who withdrew consent do not appear in the SAC data export, so no information is available to the SAC regarding when in the process (e.g. before or after eligibility assessment) consent was withdrawn.

Thus the analysis model is run on the 4662 outcomes for all PISOP patients (512 Moderate and 4150 Severe) for whom 21 days have elapsed since randomization and there is a known outcome on the 21-day OSFD endpoint. A patient randomized in both disease states is expected to have an outcome in each disease state (thus two outcomes in the model).

Although the full statistical model is run on the population defined above, the report only presents data summaries and results for the Immunoglobulin domain.

2 Data Summaries

2.1 Overview of Descriptive Data Summaries

Data for the PISOP patient population will be summarized, both across all patients, by disease state (without respect to intervention assignments), and at the intervention level for the interventions in the COVID-19 Immunoglobulin domain. A description of each of the summary tables and figures is provided here.

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 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.

- For the subjects that are eligible for the domain, a stacked bar chart summarizes the number and percent of patients assigned to each intervention.

Summary of the observed outcomes 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.
- For the subjects that are eligible for the domain, we show a plot of the cumulative distribution function for the OSFD endpoint for each intervention within the domain.
- For the subjects that are eligible for the domain, we show a stacked bar plot for the OSFD outcomes for each intervention within the domain. Red represents worse outcomes and blue represents better outcomes.

2.2 Overall Summaries

Figure 2.1 displays the distribution of outcomes on the primary endpoint for all patients in the analysis population (across 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.

Table 2.1: Overall summary of the OSFD and In-Hospital mortality data (REMAP-CAP COVID-19 severe and moderate state ITT population)

Participant Group	Number Assigned (N)	Number Past Day 21	Number Known (n)	Number Deaths (y)	Mortality Rate (y/n)	OSFD median (IQR)	Conditional* OSFD median (IQR)
Moderate State	512	512	512	56	0.109	22.00 (22.00 – 22.00)	22.00 (22.00 – 22.00)
Severe State	4190	4190	4150	1481	0.357	2.00 (−1.00 – 16.00)	14.00 (4.00 – 18.00)

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

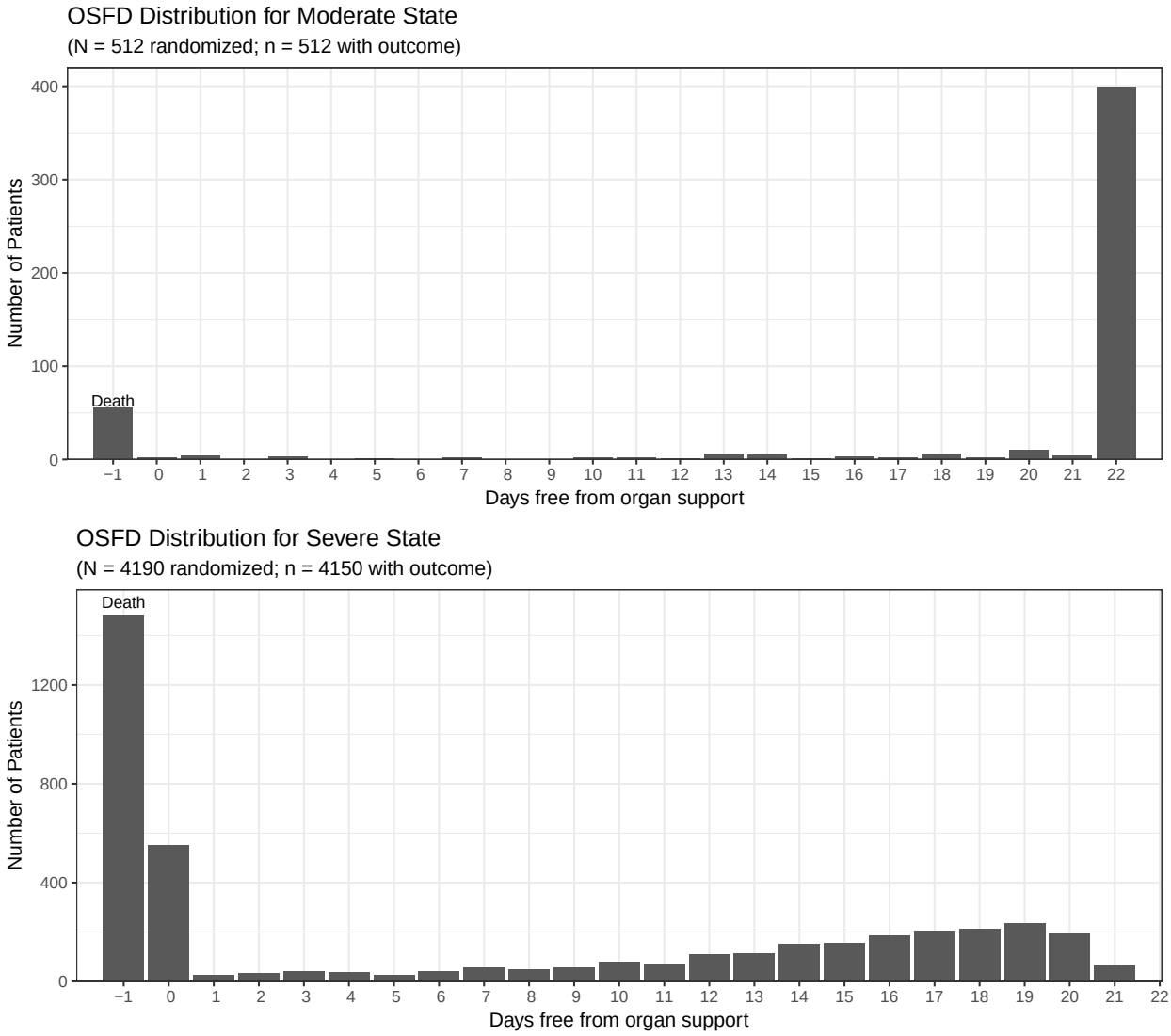

Figure 2.1: Overall distribution of the primary organ support free days endpoint for **Moderate** (top) and **Severe** (bottom) disease states.

2.3 COVID-19 Immunoglobulin Domain

2.3.1 Description of the COVID-19 Immunoglobulin domain

The COVID-19 Immunoglobulin domain includes a total of 3 interventions. This domain:

- started enrollment on May 5, 2020;
- was available for randomization in both Moderate and Severe disease states;
- closed randomization in Severe state on January 11, 2021 after meeting a futility trigger at an interim. Randomization in Moderate state was closed on January 18, 2021;
- was a deferred reveal domain;
- had no strata identified as being of interest. Analyses and response adaptive randomization were applied to all randomized patients, by disease state;
- had no modeled interactions with any other domains;
- had no nests;
- included borrowing at the intervention level between the Moderate and Severe disease states;
- included one intervention, only active at US sites, defined as "Delayed" convalescent plasma administered only if the treating clinician did not think the patient was improving. This intervention was available only temporarily in the United States resulting from FDA emergency use authorization. Randomization within this domain was initially between convalescent plasma and delayed convalescent plasma until the control arm became available. For analysis purposes, the delayed convalescent plasma intervention has a main effect in the model; however, no statistical triggers were evaluated.

2.3.2 Observed data within the COVID-19 Immunoglobulin domain

Table 2.2 shows the number of patients assigned to each intervention within the Immunoglobulin domain, by eligibility category within each disease state. The category "Eligibility not assessed in this state" refers to patients had randomization assignments in one or more domains in both disease states. For example, of the 512 patients in moderate disease state, 8 patients had assignments in other moderate domains, but their assignment the immunoglobulin domain occurred when they were in severe disease state. Similarly, of the 4190 patients in with severe state randomizations, there were 6 patients whose randomization within the immunoglobulin domain occurred while in moderate state.

Table 2.2: Summary of the availability of data (**COVID-19 Immunoglobulin** domain)

Intervention	Number Eligible	Number Assigned	Number Past Day 21	Number Missing	Number Known
Moderate State: N = 512					
Eligible for domain: N=87					
No assignment		1	1	0	1
No Immunoglobulin against COVID-19	42	24	24	0	24
Convalescent plasma	87	42	42	0	42
Delayed convalescent plasma	45	20	20	0	20
Not eligible for domain: N=12					
No assignment		12	12	0	12
Domain not active/not available: N=405					
No assignment		405	405	0	405
Eligibility not assessed in this state: N=8					
No assignment		8	8	0	8
Severe State: N = 4190					
Eligible for domain: N=2178					
No assignment		180	180	3	177
No Immunoglobulin against COVID-19	2155	909	909	5	904
Convalescent plasma	2178	1078	1078	3	1075
Delayed convalescent plasma	23	11	11	0	11
Not eligible for domain: N=321					
No assignment		321	321	0	321
Domain not active/not available: N=1685					
No assignment		1368	1368	24	1344
Immunoglobulin domain closed		317	317	5	312
Eligibility not assessed in this state: N=6					
No assignment		6	6	0	6

Table 2.3: Summary of the OSFD and In-Hospital mortality data for patients that were eligible for the **COVID-19 Immunoglobulin** domain

Intervention	Number Assigned (N)	Number Known (n)	Number of Deaths (y)	Mortality Rate (y/n)	OSFD median (IQR)	Conditional* OSFD median (IQR)
Moderate State						
No Immunoglobulin against COVID-19	24	24	7	0.292	14.00 (−1.00 – 22.00)	20.00 (14.00 – 22.00)
Convalescent plasma	42	42	5	0.119	22.00 (21.25 – 22.00)	22.00 (22.00 – 22.00)
Delayed convalescent plasma	20	20	3	0.150	22.00 (20.25 – 22.00)	22.00 (22.00 – 22.00)
Severe State						
No Immunoglobulin against COVID-19	909	904	347	0.384	3.00 (−1.00 – 16.00)	14.00 (7.00 – 18.00)
Convalescent plasma	1078	1075	401	0.373	0.00 (−1.00 – 16.00)	14.00 (3.00 – 18.00)
Delayed convalescent plasma	11	11	6	0.545	−1.00 (−1.00 – 0.00)	0.00 (0.00 – 0.00)

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

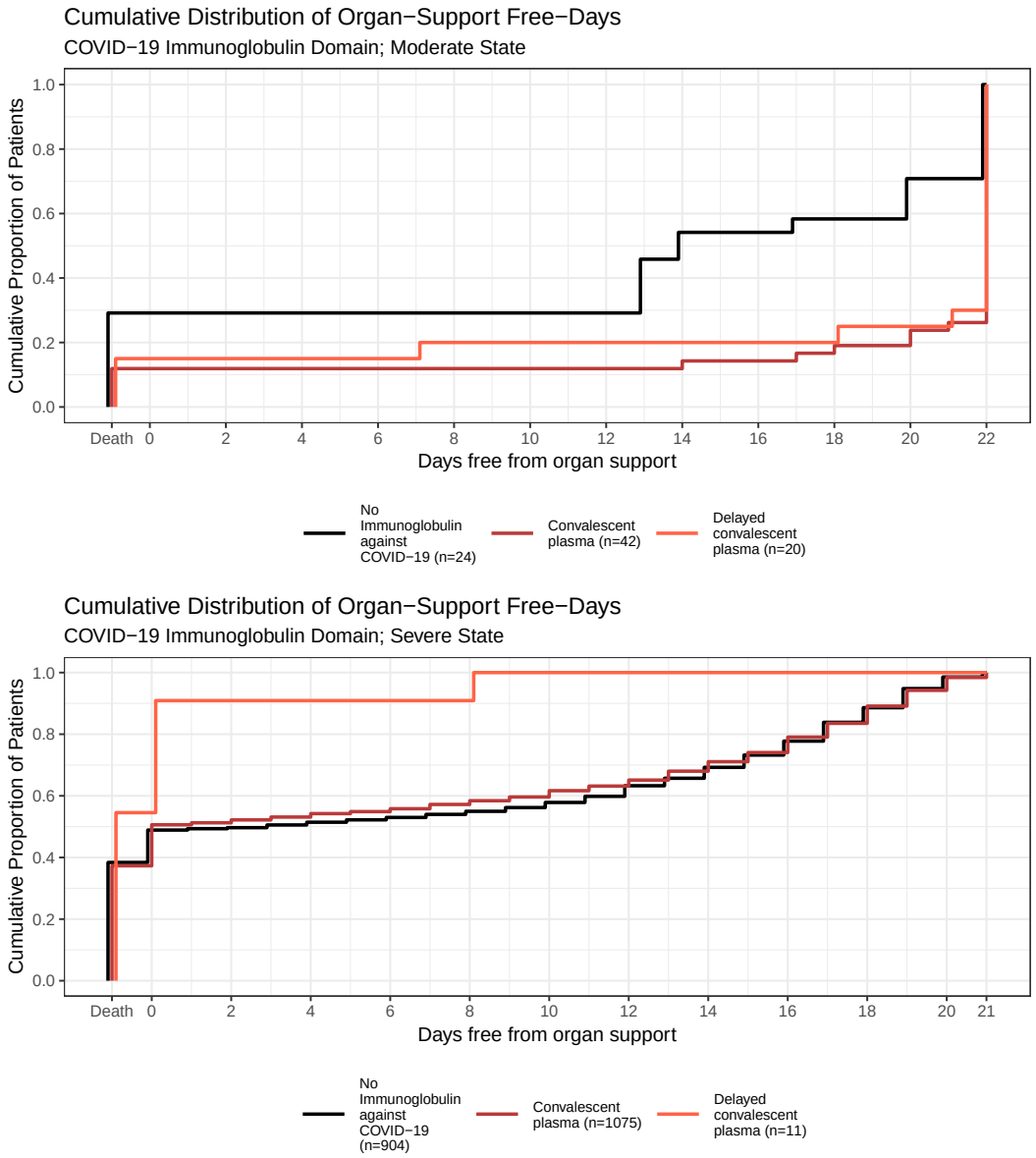

Figure 2.2: Empirical cumulative distribution of organ support free days for each intervention in the **COVID-19 Immunoglobulin** domain. This plot is restricted to patients who were eligible for the domain and had a revealed assignment.

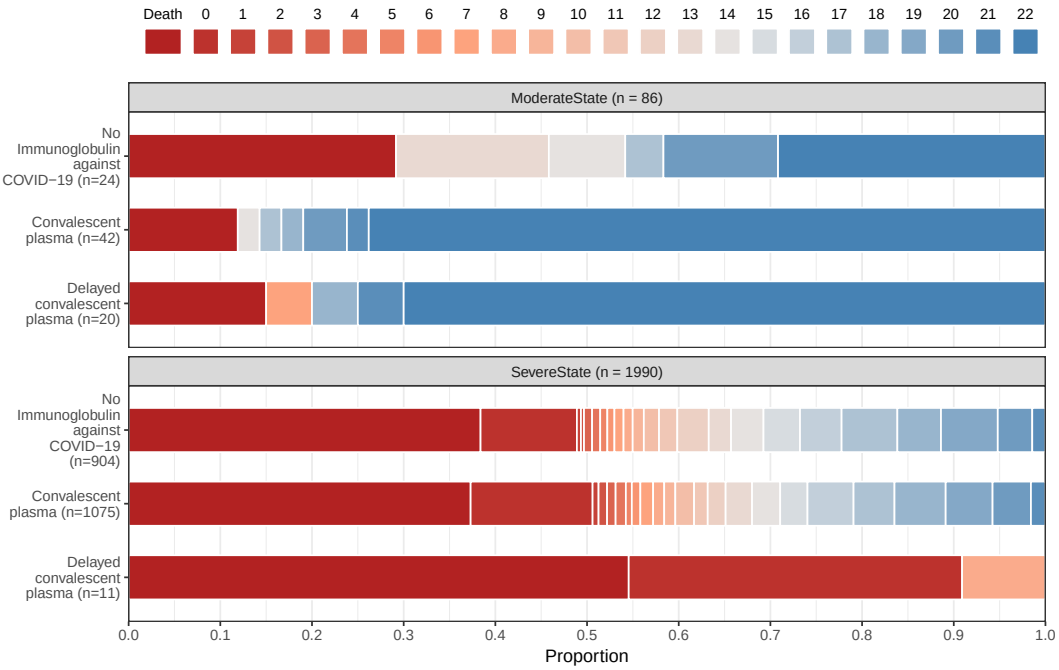

Figure 2.3: Stacked proportion of organ support free days for each intervention in the **COVID-19 Immunoglobulin** domain. Red represents worse outcomes and blue represents better outcomes. This plot is restricted to patients who were eligible for the domain and have a revealed assignment in the domain.

Given the small number of patients randomized to the delayed convalesent plasma intervention, we reproduce the plots removing the intervention.

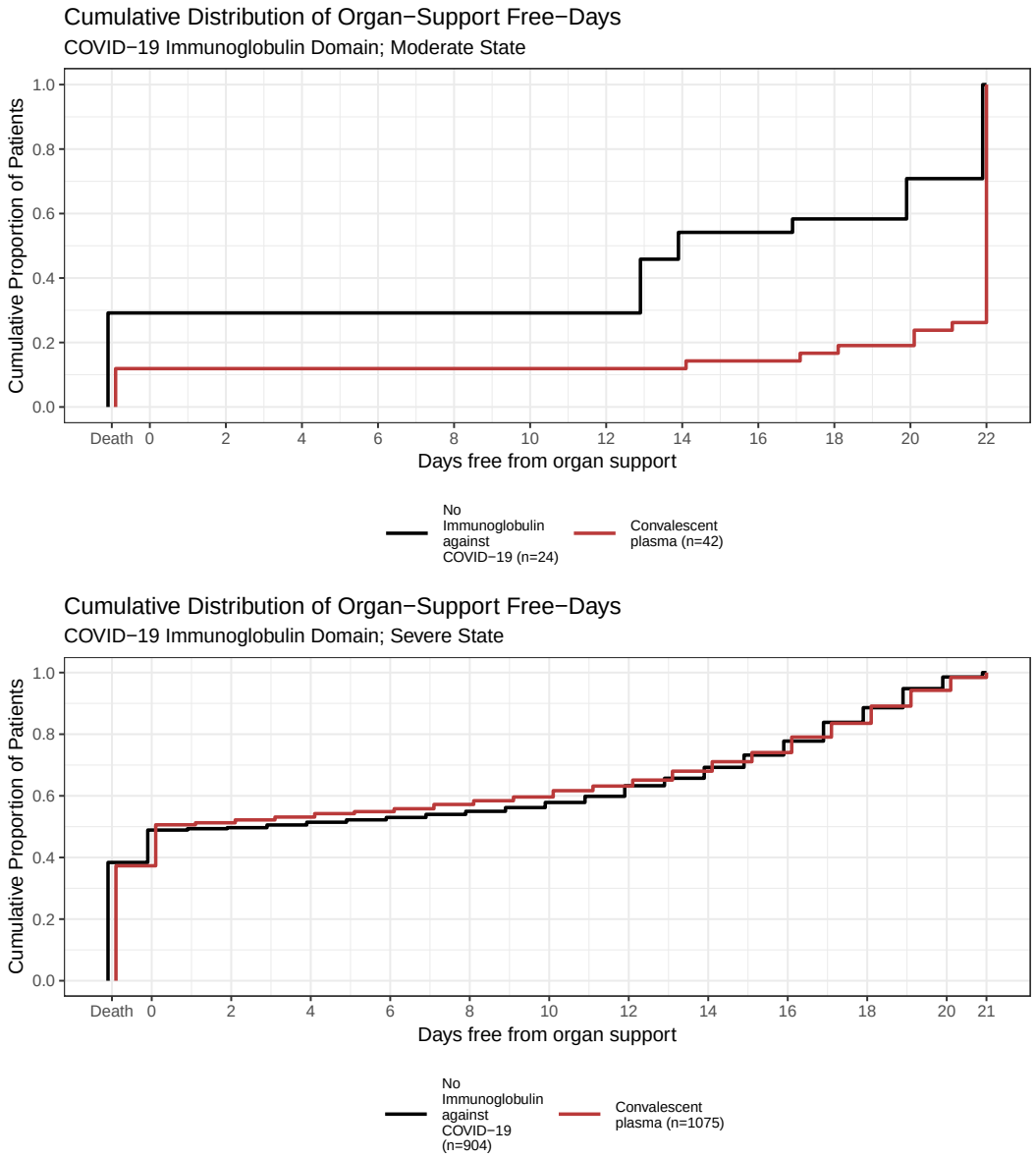

Figure 2.4: Empirical cumulative distribution of organ support free days for each intervention in the **COVID-19 Immunoglobulin** domain. This plot is restricted to patients who were eligible for the domain and had a revealed assignment for either Convalescent plasma or No Immunoglobulin against COVID-19.

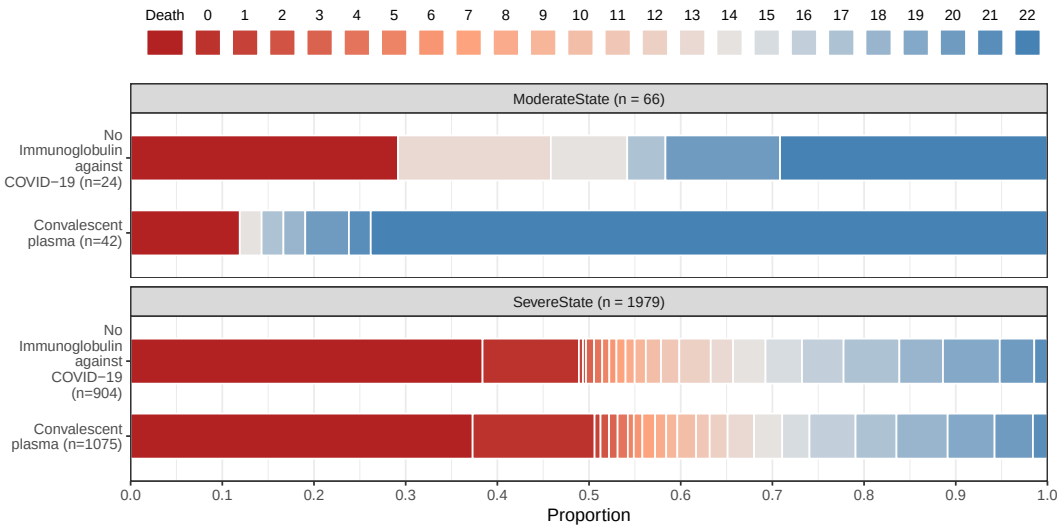

Figure 2.5: Stacked proportion of organ support free days for each intervention in the **COVID-19 Immunoglobulin** domain. Red represents worse outcomes and blue represents better outcomes. This plot is restricted to patients who were eligible for the domain and have a revealed assignment for either Convalescent plasma or No Immunoglobulin against COVID-19.

3 Analysis Results and Conclusions

3.1 Overview of the Statistical Model

The primary analysis model is a Bayesian cumulative logistic model for the ordinal primary endpoint. The full statistical model includes data from all interventions within all domains; however this report shows results only for the immunoglobulin domain. The model adjusts for age, sex, site (nested within country), domain ineligibility, randomization within each domain, and time epochs. Borrowing of information between moderate and severe disease states is accomplished through hierarchical modeling. Additionally, the model includes a term for patients that transition from moderate to severe disease state. The model is constructed so that odds-ratios greater than 1 indicate improved outcomes.

3.2 Definition of Statistical Triggers

The adpative design defines several statistical triggers within the trial, that at any analysis of the trial would result in public disclosure and declaration of a platform conclusion. The following statistical triggers were defined for the COVID-19 Immunoglobulin domain:

1. **Domain Superiority.** If a single intervention within a 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 superiority of that intervention.

2. **Intervention Futility.** If an intervention is deemed to have less than 5% posterior probability of at least a 20% odds ratio improvement compared to the control, then a declaration of futility of that intervention would be declared. This statistical trigger is active for each of the non-control arms in the domain.

3.3 Overview of the model results

The OSFD endpoint is an ordered categorical endpoint that is modeled with a cumulative logistic model. The median and 95% Bayesian credible intervals for the odds-ratios are presented for each intervention, relative to the control intervention in the domain. The model is structured so that an odds-ratio greater than 1 implies patient benefit. We also present the posterior mean and standard deviation, but caution that the mean tends to be higher than the median due to the skewed nature of the posterior distribution.

3.4 Primary analysis for OSFD

Table 3.1 summarizes the model-estimated odds-ratios for the covariates in the model, including age categories, sex at birth, and time effects.

Table 3.1: Model-estimated Odds-Ratios for the **OSFD** endpoint; REMAP-CAP COVID-19 severe and moderate state ITT population

Odds-Ratio Parameter	Moderate State			Severe State		
	Median	95% Credible Interval	Mean (SD)	Median	95% Credible Interval	Mean (SD)
≤ 39	2.28	0.94 – 5.95	2.58 (1.31)	3.99	3.18 – 5.00	4.01 (0.46)
40-49	3.40	1.43 – 8.88	3.85 (1.99)	2.36	1.97 – 2.84	2.37 (0.22)
50-59	1.31	0.73 – 2.39	1.38 (0.43)	1.74	1.50 – 2.02	1.75 (0.13)
60-69 (referent)	1.00	$NA - NA$	1.00 (NA)	1.00	$NA - NA$	1.00 (NA)
70-79	0.64	0.34 – 1.18	0.67 (0.22)	0.53	0.45 – 0.63	0.53 (0.05)
80+	0.43	0.20 – 0.90	0.46 (0.18)	0.32	0.23 – 0.44	0.32 (0.05)
Male (referent)	1.00	$NA - NA$	1.00 (NA)	1.00	$NA - NA$	1.00 (NA)
Female	1.49	0.93 – 2.44	1.54 (0.39)	1.14	1.01 – 1.29	1.15 (0.07)
Time Epoch-0 (referent)	1.00	$NA - NA$	1.00 (NA)	1.00	$NA - NA$	1.00 (NA)
Time Epoch-1	0.99	0.81 – 1.22	1.00 (0.10)	1.06	0.94 – 1.20	1.07 (0.07)
Time Epoch-2	0.95	0.68 – 1.38	0.97 (0.18)	1.14	0.95 – 1.37	1.14 (0.11)
Time Epoch-3	0.90	0.56 – 1.48	0.93 (0.23)	1.19	0.95 – 1.48	1.19 (0.13)
Time Epoch-4	0.83	0.46 – 1.48	0.87 (0.26)	1.21	0.94 – 1.55	1.22 (0.16)
Time Epoch-5	0.75	0.38 – 1.43	0.79 (0.27)	1.24	0.94 – 1.64	1.25 (0.18)
Time Epoch-6	0.70	0.32 – 1.43	0.75 (0.29)	1.28	0.95 – 1.73	1.30 (0.20)
Time Epoch-7	0.67	0.29 – 1.50	0.73 (0.31)	1.37	1.00 – 1.89	1.39 (0.23)
Time Epoch-8	0.66	0.26 – 1.57	0.73 (0.34)	1.49	1.07 – 2.11	1.52 (0.27)
Time Epoch-9	0.67	0.26 – 1.70	0.75 (0.38)	1.59	1.12 – 2.26	1.62 (0.29)
Time Epoch-10	0.72	0.26 – 1.97	0.82 (0.45)	1.65	1.15 – 2.34	1.67 (0.31)
Time Epoch-11	0.78	0.26 – 2.35	0.91 (0.57)	1.69	1.18 – 2.40	1.72 (0.31)
Time Epoch-12	0.86	0.26 – 2.82	1.03 (0.71)	1.72	1.21 – 2.45	1.75 (0.32)
Time Epoch-13	0.94	0.25 – 3.52	1.17 (0.90)	1.71	1.20 – 2.44	1.74 (0.32)
Time Epoch-14	1.03	0.25 – 4.37	1.35 (1.17)	1.65	1.15 – 2.36	1.68 (0.31)
Time Epoch-15	1.15	0.24 – 5.63	1.58 (1.55)	1.51	1.05 – 2.17	1.54 (0.29)
Time Epoch-16	1.29	0.24 – 7.42	1.92 (2.21)	1.39	0.94 – 2.01	1.41 (0.27)
Time Epoch-17	1.47	0.23 – 10.32	2.44 (3.57)	1.29	0.87 – 1.89	1.32 (0.26)
Time Epoch-18	1.70	0.21 – 15.81	3.33 (6.97)	1.25	0.84 – 1.85	1.27 (0.26)
Time Epoch-19				1.23	0.80 – 1.88	1.26 (0.28)
Time Epoch-20				1.20	0.72 – 2.01	1.24 (0.33)
ModToSevere				1.31	0.61 – 2.85	1.42 (0.58)
Convalescent Plasma	1.58	0.82 – 5.95	2.07 (1.47)	0.97	0.83 – 1.15	0.98 (0.08)

Note: For referent categories, the Odds-Ratio is 1.0 by definition. 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 3.2: Posterior Probabilities for the **OSFD** endpoint; REMAP-CAP COVID-19 severe and moderate state ITT population

Quantity of Interest	Posterior Probability
Moderate	
Prob(OR > 1)	0.86255
Prob(OR < 1.2)	0.30795
Severe	
Prob(OR > 1)	0.37840
Prob(OR < 1.2)	0.99400

3.5 Primary analysis for in-hospital mortality

Table 3.3: Model-estimated Odds-Ratios for the **Mortality** endpoint; REMAP-CAP COVID-19 severe and moderate state ITT population

	Moderate State			Severe State		
Odds-Ratio Parameter	Median	95% Credible Interval	Mean (SD)	Median	95% Credible Interval	Mean (SD)
≤ 39	9.91	2.40 – 51.21	14.11 (14.32)	7.93	5.37 – 12.17	8.13 (1.74)
40-49	4.22	1.38 – 15.73	5.32 (3.94)	3.41	2.65 – 4.43	3.44 (0.46)
50-59	3.42	1.43 – 8.91	3.87 (2.00)	2.26	1.85 – 2.75	2.27 (0.23)
60-69 (referent)	1.00	$NA - NA$	1.00 (NA)	1.00	$NA - NA$	1.00 (NA)
70-79	0.54	0.26 – 1.13	0.58 (0.23)	0.47	0.39 – 0.57	0.47 (0.05)
80+	0.34	0.14 – 0.78	0.37 (0.16)	0.27	0.19 – 0.38	0.27 (0.05)
Male (referent)	1.00	$NA - NA$	1.00 (NA)	1.00	$NA - NA$	1.00 (NA)
Female	2.10	1.10 – 4.04	2.22 (0.76)	1.20	1.03 – 1.40	1.20 (0.10)
Time Epoch-0 (referent)	1.00	$NA - NA$	1.00 (NA)	1.00	$NA - NA$	1.00 (NA)
Time Epoch-1	0.95	0.77 – 1.18	0.96 (0.10)	1.08	0.95 – 1.23	1.08 (0.07)
Time Epoch-2	0.88	0.59 – 1.31	0.90 (0.18)	1.17	0.96 – 1.45	1.18 (0.12)
Time Epoch-3	0.80	0.47 – 1.40	0.84 (0.24)	1.26	0.98 – 1.64	1.27 (0.17)
Time Epoch-4	0.73	0.37 – 1.42	0.77 (0.27)	1.33	1.00 – 1.80	1.35 (0.20)
Time Epoch-5	0.66	0.29 – 1.45	0.71 (0.30)	1.38	1.00 – 1.93	1.40 (0.24)
Time Epoch-6	0.61	0.24 – 1.48	0.67 (0.32)	1.43	1.01 – 2.06	1.46 (0.27)
Time Epoch-7	0.58	0.22 – 1.54	0.66 (0.35)	1.52	1.04 – 2.24	1.55 (0.31)
Time Epoch-8	0.56	0.19 – 1.62	0.65 (0.38)	1.64	1.10 – 2.47	1.68 (0.35)
Time Epoch-9	0.55	0.17 – 1.74	0.65 (0.42)	1.75	1.16 – 2.68	1.79 (0.39)
Time Epoch-10	0.55	0.16 – 1.91	0.67 (0.48)	1.84	1.21 – 2.86	1.89 (0.42)
Time Epoch-11	0.55	0.14 – 2.08	0.69 (0.55)	1.92	1.26 – 2.99	1.97 (0.44)
Time Epoch-12	0.55	0.13 – 2.31	0.71 (0.62)	2.00	1.31 – 3.09	2.05 (0.46)
Time Epoch-13	0.55	0.11 – 2.56	0.74 (0.71)	2.06	1.34 – 3.19	2.11 (0.47)
Time Epoch-14	0.54	0.10 – 2.92	0.77 (0.82)	2.08	1.35 – 3.26	2.14 (0.49)
Time Epoch-15	0.54	0.09 – 3.39	0.82 (0.98)	2.04	1.31 – 3.23	2.10 (0.49)
Time Epoch-16	0.53	0.07 – 4.03	0.90 (1.21)	1.94	1.22 – 3.10	2.00 (0.48)
Time Epoch-17	0.54	0.06 – 5.04	1.02 (1.64)	1.86	1.15 – 3.01	1.92 (0.48)
Time Epoch-18	0.55	0.05 – 6.77	1.24 (2.56)	1.84	1.12 – 3.07	1.91 (0.50)
Time Epoch-19				1.88	1.08 – 3.33	1.96 (0.58)
Time Epoch-20				1.93	0.98 – 3.86	2.05 (0.74)
ModToSevere				1.21	0.47 – 3.32	1.39 (0.77)
Convalescent Plasma	1.20	0.70 – 4.54	1.55 (1.15)	1.04	0.85 – 1.27	1.04 (0.11)

Note: For referent categories, the Odds-Ratio is 1.0 by definition. 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 3.4: Posterior Probabilities for the **Mortality** endpoint; REMAP-CAP COVID-19 severe and moderate state ITT population

Quantity of Interest	Posterior Probability
Moderate	
Prob(OR > 1)	0.75605
Prob(OR < 1.2)	0.50040
Severe	
Prob(OR > 1)	0.64520
Prob(OR < 1.2)	0.91830

3.6 Sensitivity analysis of the proportional odds assumption

An assumption of the ordinal logistic regression model being used to analyze OSFD is that effects have a *proportional* effect on log-odds. That is, a treatment effect that increases the log-odds of OSFD being greater than X is the same for all values of X. In order to assess this modeling assumption, a logistic regression model is fit to dichotomized versions of the OSFD values ($\leq X$ versus $> X$) across the possible range of OSFD values, to see if the estimated treatment effect is nearly constant. The prior distribution for the dichotomized outcomes is constructed in like manner, converting the Dirichlet distribution across OSFD values to a Beta distribution by summing across the parameter values for the corresponding OSFD ranges.

The logistic regression model is subject to poor estimation when categories in the model contain only a single outcome type (e.g. all observations are $\leq X$). With the large number of covariate effects being used in the current model, some categories of these covariate crossings may contain single outcomes, particularly as the dichotomization goes to the higher end of the OSFD values with low frequencies. The Bayesian model uses informative priors and thus a model fit can always be constructed. However, because many of the prior distributions in the model are relatively non-informative, the MCMC fitting algorithms can perform poorly in the more extreme dichotomizations. Some poor MCMC behavior was observed for dichotomizations at ≥ 15 OSFD and higher.

For this analysis, only the OSFD endpoint for the severe state was dichotomized; the moderate state OSFD endpoint remains as pre-specified (a 7-level ordinal outcome) in each sensitivity analysis. The convalescent plasma odds ratio relative to control is reported for each dichotomization of OSFD in the severe state only.

Table 3.5: Sensitivity analysis of proportional odds assumption. Values are Odds-Ratio estimates for the **OSFD** endpoint for different dichotomizations of OSFD; REMAP-CAP COVID-19 ITT population (**Severe State**)

OSFD Dichotomization	Median	95% Credible Interval	Mean (SD)
≤-1 vs ≥0	1.05	0.86 – 1.29	1.05 (0.11)
≤0 vs ≥1	0.92	0.75 – 1.11	0.92 (0.09)
≤1 vs ≥2	0.90	0.74 – 1.10	0.91 (0.09)
≤2 vs ≥3	0.88	0.73 – 1.07	0.89 (0.09)
≤3 vs ≥4	0.88	0.73 – 1.07	0.89 (0.09)
≤4 vs ≥5	0.88	0.72 – 1.07	0.88 (0.09)
≤5 vs ≥6	0.88	0.73 – 1.07	0.89 (0.09)
≤6 vs ≥7	0.87	0.72 – 1.06	0.88 (0.09)
≤7 vs ≥8	0.86	0.71 – 1.04	0.86 (0.08)
≤8 vs ≥9	0.84	0.70 – 1.02	0.85 (0.08)
≤9 vs ≥10	0.85	0.69 – 1.03	0.85 (0.09)
≤10 vs ≥11	0.83	0.69 – 1.01	0.84 (0.08)
≤11 vs ≥12	0.85	0.70 – 1.04	0.85 (0.09)
≤12 vs ≥13	0.91	0.75 – 1.11	0.92 (0.09)
≤13 vs ≥14	0.89	0.72 – 1.08	0.89 (0.09)
≤14 vs ≥15	0.90	0.73 – 1.12	0.91 (0.10)
≤15 vs ≥16	0.97	0.78 – 1.20	0.97 (0.11)
≤16 vs ≥17	0.94	0.74 – 1.18	0.94 (0.11)
≤17 vs ≥18	1.05	0.81 – 1.35	1.06 (0.14)
≤18 vs ≥19	0.99	0.73 – 1.32	1.00 (0.15)
≤19 vs ≥20	1.23	0.82 – 1.83	1.25 (0.26)
≤20 vs ≥21	1.43	0.68 – 2.77	1.51 (0.54)

4 Other Data Summaries

This section provides summary tables and graphics for variables that are included as covariates in the model, including age, sex at birth, sites within country, and time effects.

Table 4.1: Summary of age groups by sex at birth (REMAP-CAP COVID-19 severe and moderate state ITT population)

	Age Group (years)							
	≤ 39	40 – 49	50 – 59	60 – 69	70 – 79	≥ 80	Missing	Total
Moderate State								
Male	20	35	76	82	51	30	0	294
Female	18	31	53	48	43	25	0	218
Sum	38	66	129	130	94	55	0	512
Severe State								
Male	184	365	676	869	598	138	1	2831
Female	114	179	348	388	264	66	0	1359
Total	298	544	1024	1257	862	204	1	4190

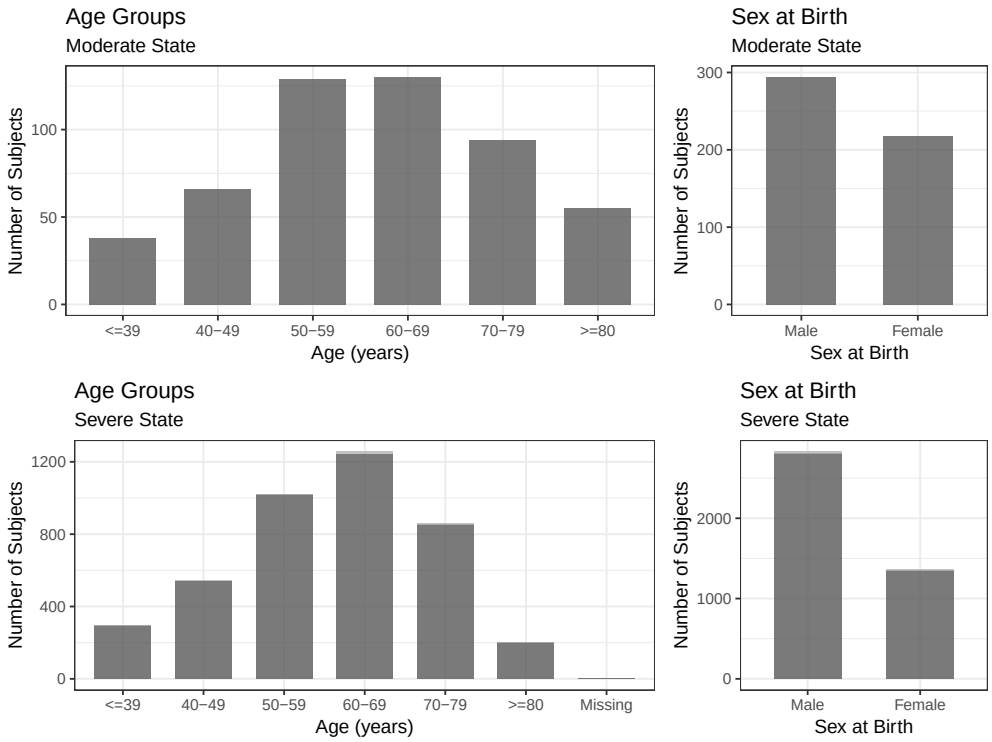

Figure 4.1: Distribution of age groups and sex at birth (REMAP-CAP COVID-19 severe and moderate state ITT population). The total height of each bar represents the number of patients in each category. The darker shaded area indicates the number of patients for whom 21 days have elapsed since randomization and have a known OSFD outcome. The lighter shaded area indicates the number of patients who do not have a known OSFD outcome.

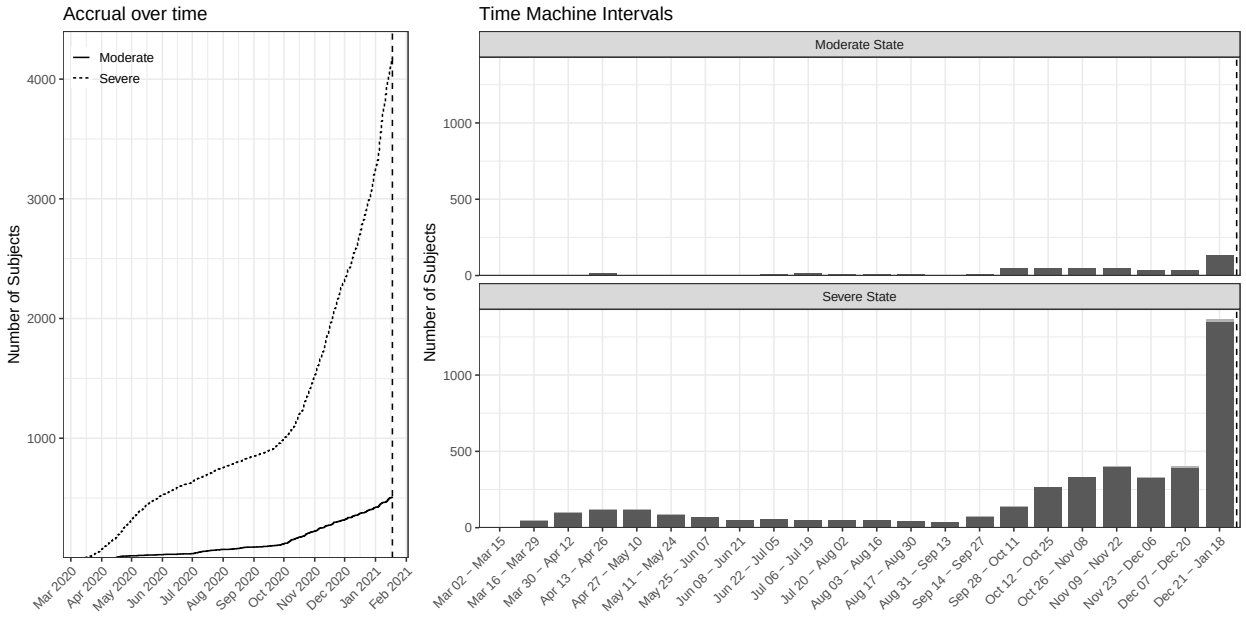

Figure 4.2: Accrual over time and distribution of patients within each of the time buckets used to estimate time trends in the analysis model for the REMAP-CAP COVID-19 severe and moderate state ITT population. The time buckets are derived so that the first bucket is the most recent month going backwards 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. The total height of each bar represents the number of patients in each category. The darker shaded area indicates the number of patients for whom 21 days have elapsed since randomization and have a known OSFD outcome. The lighter shaded area indicates the number of patients who do not have a known OSFD outcome. The vertical dashed line indicates the randomization date for the last patient who has passed 21 days and has a known outcome on the primary endpoint at the time of this analysis.

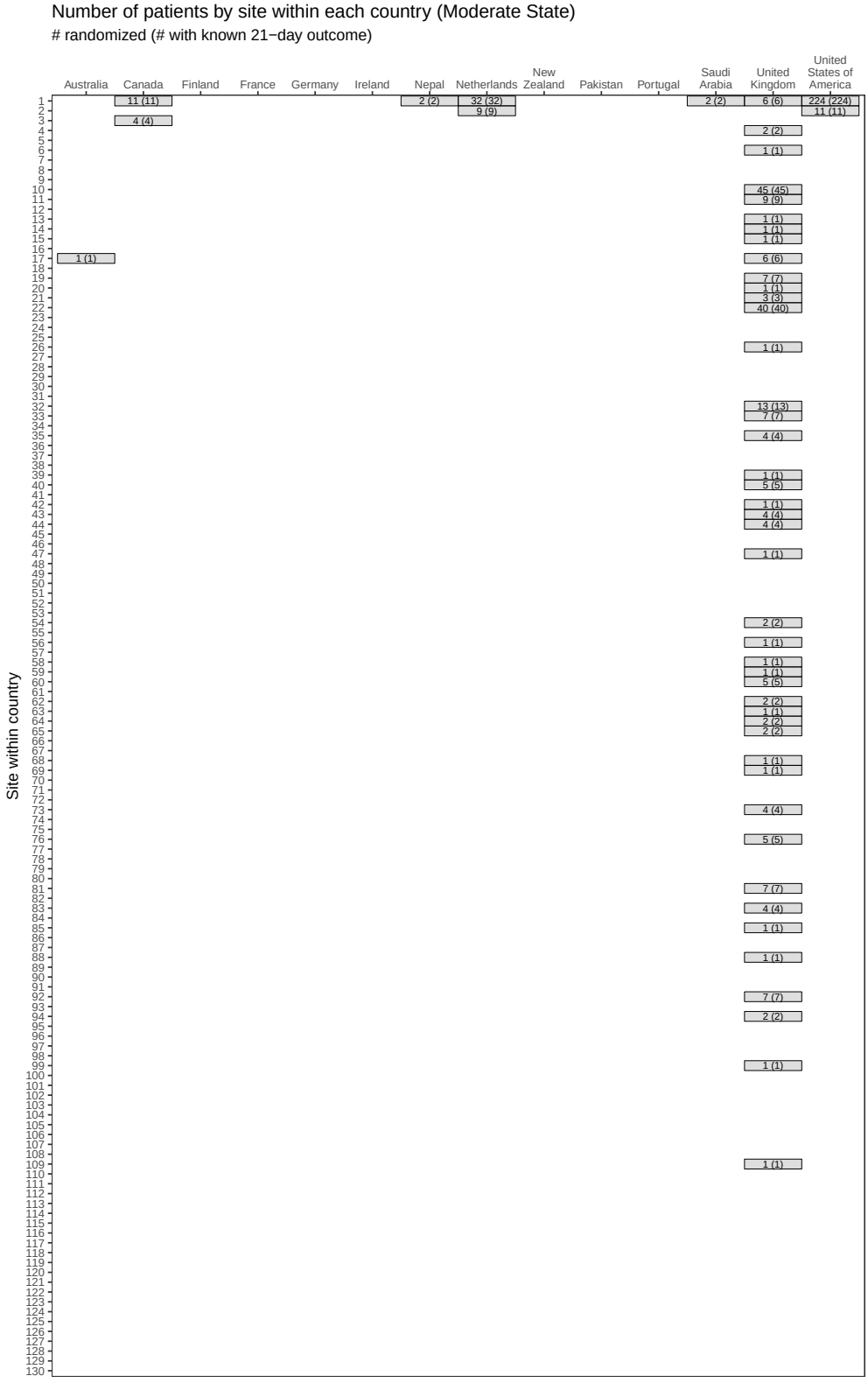

Figure 4.3: Sample size at each site within each country (**Moderate** State). The values in each cell represent the number of patients randomized to any domain at that site and, in parentheses, the number of patients for whom the outcome on the 21-day endpoint is known. Within each country, all sites having fewer than 5 randomized patients are combined into a single site for the statistical model.

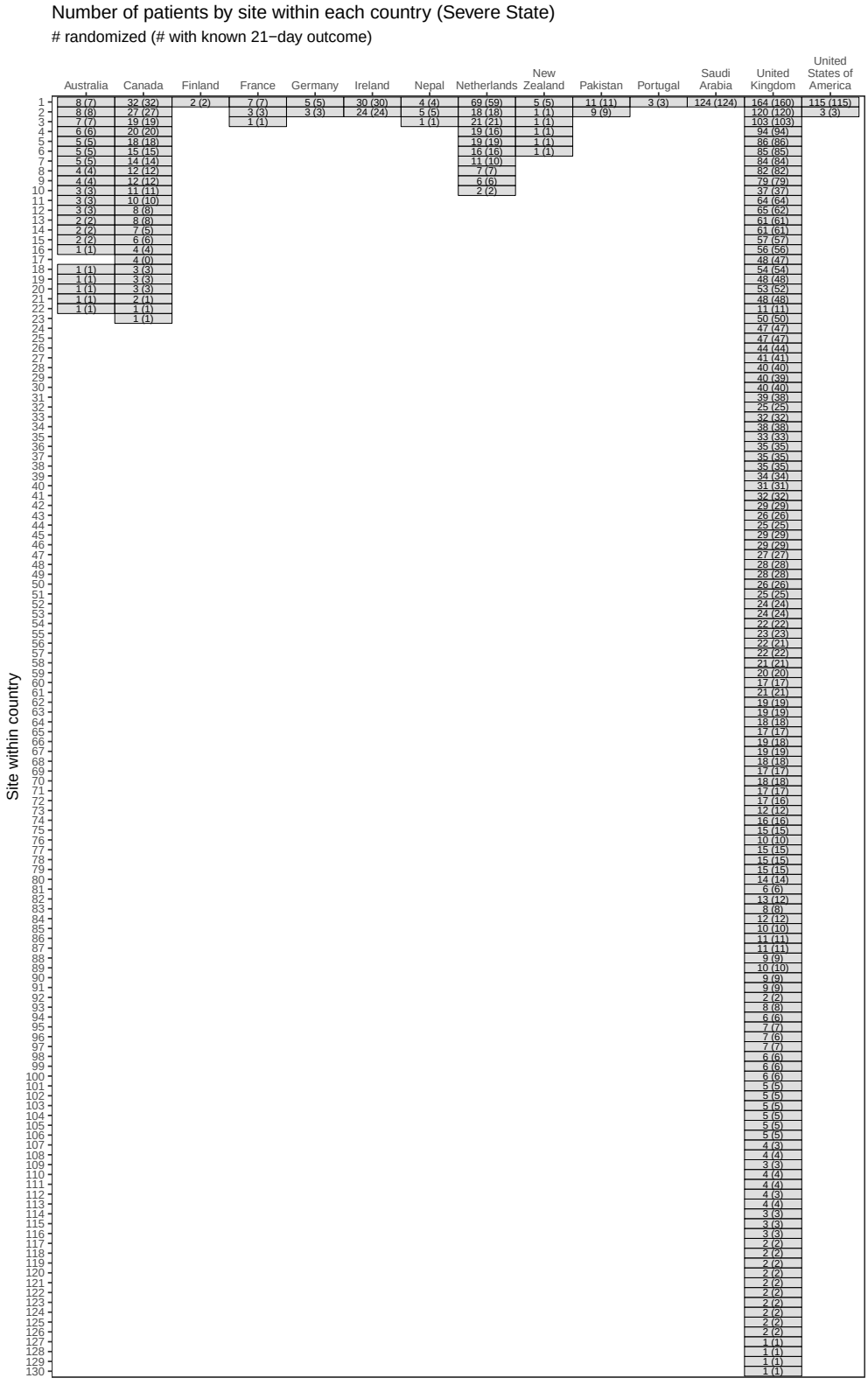

Figure 4.4: Sample size at each site within each country (**Severe** State).

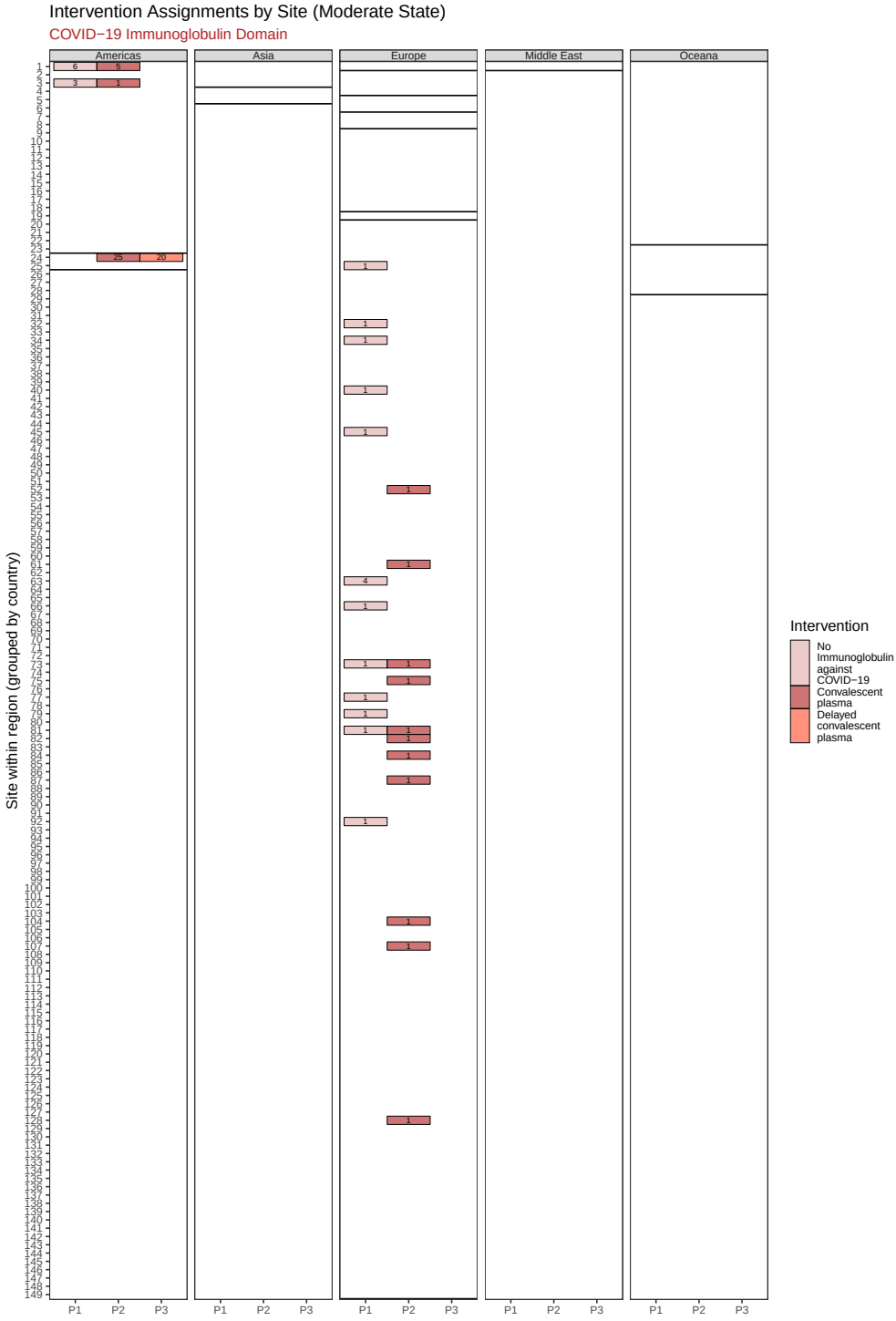

Figure 4.5: Allocation of **Moderate State** interventions in the **COVID-19 Immunoglobulin** domain by site. The data are summarized in three panels — one for each geographical region. Each panel is a grid with interventions on the x-axis and sites on the y-axis. Each colored cell corresponds to an 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.

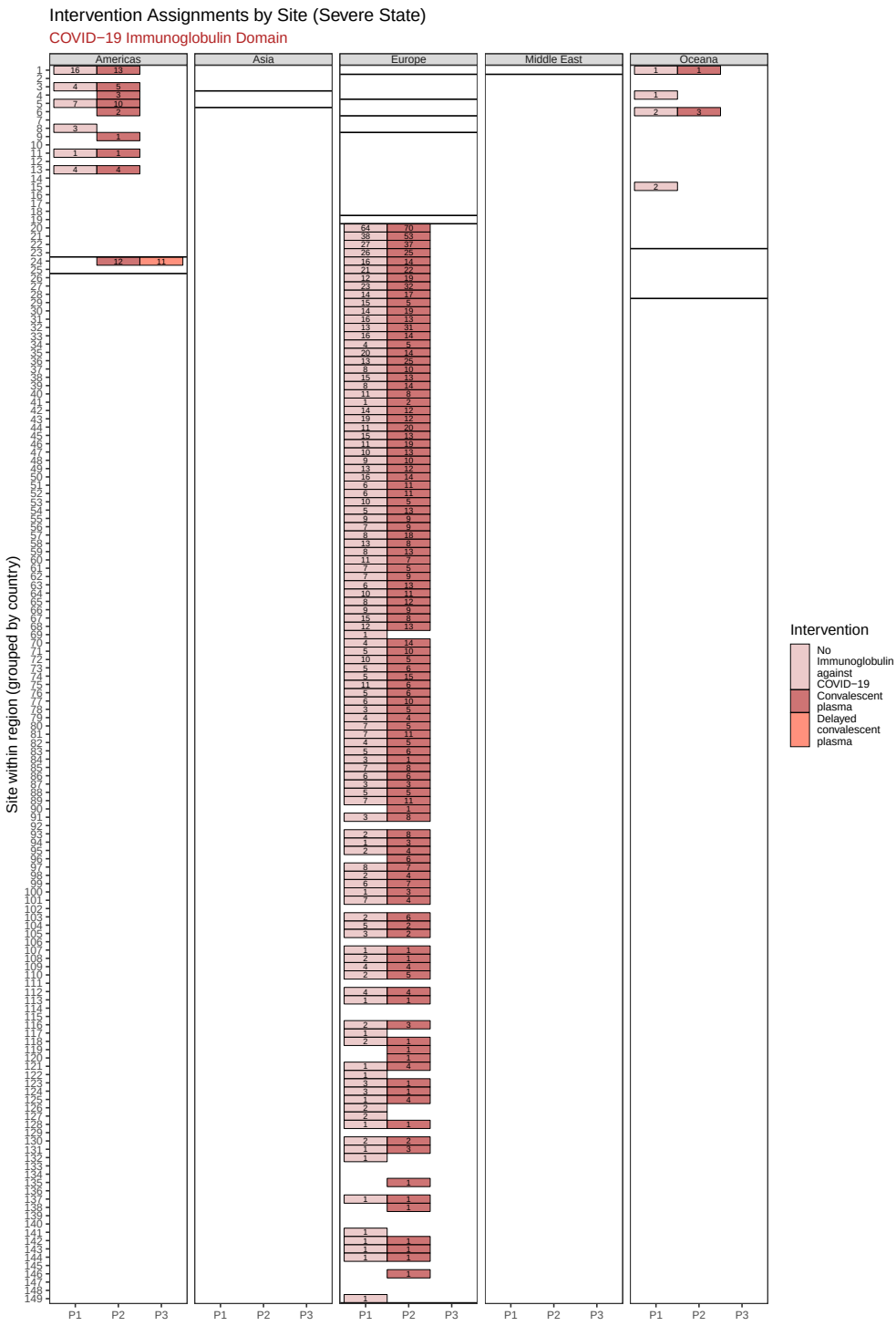

Figure 4.6: Allocation of **Severe State** interventions in the **COVID-19 Immunoglobulin** domain by site.

Table 4.2: Summary of the number of sites and patients randomized within each country (**Moderate** State)

		All Domains			COVID-19 Immunoglobulin Domain		
Region	Country	Number of Sites	Number of Patients Randomized	Number of Patients w/ Outcomes	Number of Sites	Number of Patients Randomized	Number of Patients w/ Outcomes
Americas	Canada	2	15	15	2	15	15
	United States of America	2	235	235	1	45	45
Asia	Nepal	1	2	2			
Europe	Netherlands	2	41	41			
	United Kingdom	44	216	216	21	26	26
Middle East	Saudi Arabia	1	2	2			
Oceana	Australia	1	1	1			

Table 4.3: Summary of the number of sites and patients randomized within each country (**Severe** State)

		All Domains			COVID-19 Immunoglobulin Domain		
Region	Country	Number of Sites	Number of Patients Randomized	Number of Patients w/ Outcomes	Number of Sites	Number of Patients Randomized	Number of Patients w/ Outcomes
Americas	Canada	23	240	233	9	74	74
	United States of America	2	118	118	1	23	23
Asia	Nepal	3	10	10			
	Pakistan	2	20	20			
Europe	Finland	1	2	2			
	France	3	11	11			
	Germany	2	8	8			
	Ireland	2	54	54			
	Netherlands	10	188	174			
	Portugal	1	3	3			
	United Kingdom	130	3329	3311	115	1891	1883
Middle East	Saudi Arabia	1	124	124			
Oceana	Australia	21	73	72	4	10	10
	New Zealand	6	10	10			

5 Analysis Conventions

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

- The ITSC closed randomization to the Corticosteroid domain within the PISOP stratum on June 17, 2020. This decision was made following the release of the RECOVERY trial results on June 16, 2020 which reported strong positive effects of dexamethasone. Following this decision, the results from the Corticosteroid domain in REMAP-CAP were publicly disclosed. Patients who are randomized within the PISOP stratum after June 17 receive no randomized assignment within the Corticosteroid domain; however it is asssumed they likely receive fixed duration steroid. Thus, for the statistical model, patients randomized after June 17 are coded identically to patients randomized to fixed duration steroid.
- All sites within a country that have < 5 patients randomized in the analysis population within a disease state 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 within a disease state were combined with a neighboring bucket.
- All interactions between the shock-based steroid arm and other domains are dropped (assumed to be zero) per the SAP.
- Patients with no randomized assignment in any domain are included in the analysis population when the OSFD outcome is known. Thus these patients contribute to estimates of covariate effects (but no treatment effects) in the model.

- Some patients in the Research Online database have missing randomization assignments for some domains. These patients are treated as having "no assignment" within the respective domains. Only 6 patients are affected.
- Data provided to the SAC only include patients who consented for use of their data.
- Some patients for whom 21 days have elapsed since randomization have missing 21-day OSFD outcomes in the data export. A supplemental file was provided to the SAC in which some additional outcome data was obtained based on a manual review.
- For unique patient identifiers that exist in both the Research Online and Spiral databases, the analysis generally pulls 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).
- There are some patients with a missing value for the age covariate. For modeling purposes, these patients are coded as the referent age category, $60 - 69$.

6 Model Stability

The Bayesian model was computed in R version 4.0.5 (2021-03-31), using the rstan package version 2.21.0. This package computes the Markov Chain Monte Carlo (MCMC) using the highly efficient Hamiltonian Monte Carlo method. The MCMC used 10 separate chains, with each chain using a burnin of 500 samples, followed by 2000 samples, for a total of 20000 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 4222021 for the MCMC initialization.

7 Report Production

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

- Statistical Analysis Appendix for REMAP-COVID, version 1, dated August 18, 2020;
- Statistical Analysis Plan for the Immunoglobulin Domain for Patients with COVID-19 Pandemic Infection Suspected or Proven (PISOP), version 1.1, dated February 23, 2021;
- Current State of the Statistical Model: Pandemic Model, version 3.1, dated March 1, 2021;
- Errata Sheet for the Immunoglobulin Domain SAP, Version 1.0, last updated March 18, 2021.

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
UPMC_SACDataExport_04192021_2031.csv	April 19, 2021	UPMC data
remapcap_spiral_interimexport_2021-04-19_070121_v10.2.3.csv	April 19, 2021	Spiral data
RAR_Unscrambled_RO_20201214_v3.csv	December 14, 2020	Research Online data
missingOSFD_PISOPModerateSevereModeling_forCPFinalAnalysis2021-04-21_CG.xlsx	April 22, 2021	Supplemental OSFD 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.