ASCOT Statistical Analysis Report

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2022-12-06

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1 Introduction

1.1 Purpose

The trial steering committee (TSC) closed randomisation to the anticoagulation domain on 8 April 2022. The blinded statistical analysis working group prepared a statistical analysis plan (SAP) for reporting the results of the anticoagulation domain. The unblinded team of statisticians undertook the analyses using the relevant records as extracted from the database on 2022-06-06.

Subsequently, the TSC closed randomisation to the antiviral domain on X XXXX 2022. The blinded statistical analysis group prepared a SAP for reporting the results of the antiviral domain. Given all study domains have closed, the unblinded team of statisticians undertook final analyses using the relevant records as extracted from the database on 2022-10-xx

This report summarises the data and results of the analyses for the ascot trial. The report focuses on the antiviral domain but also reports on the anticoagulation domain for completeness sake.

1.2 Interventions

There were two mutually exclusive interventions in the antiviral domain. They were:

- no specific antiviral (standard of care, control)
- Nafamostat

There were four mutually exclusive interventions in the anticoagulation domain. They were:

- low-dose thromboprophylaxis (control)
- intermediate-dose thromboprophylaxis

- low-dose thromboprophylaxis with aspirin
- therapeutic-dose thromboprophylaxis

For full details of the interventions, refer to the domain specific appendices to the protocol.

1.3 Outcomes

For details on the primary and secondary outcomes, refer to the core protocol. For details on the domain specific outcomes refer to the anticoagulation domain-specific appendix.

1.4 Modelling

1.4.1 General Considerations

All binary outcomes were analysed using a logistic regression model, ordinal outcomes by a cumulative logistic model with proportional odds, and the time to recovery outcome by a discrete-time competing-risk (death) time-to-event model (multinomial logistic regression). Weakly informative priors were specified for all models.

The (pre-specified) primary model for all outcomes included fixed terms for:

- anticoagulation intervention
- antiviral intervention
- intervention ineligibility
- age group (< 60, ≥ 60 years of age)
- sex (male, female)
- oxygen requirement (did not require supplemental oxygen, did require supplemental oxygen)
- region of enrolment (India, Australia/New Zealand, Nepal)

Hierarchical terms were also included for:

- site of enrolment (nested within region)
- epoch of enrolment (4-week groupings)

Outcomes are coded such that an odds ratio less than 1 implies a decrease in the outcome, for example, lower odds of 28 day mortality, fewer days alive and free of hospital, etc. Therefore, depending on the outcome, an odds ratio less than 1 may imply benefit or harm, but this will be made clear for each outcome.

In general, the reference group (to which the model intercept(s) or baseline hazard applies) was taken to be a patient who was:

- randomised to the anticoagulation domain (equal weighting across all interventions)
- *not* randomised to the antiviral domain
- eligible for all anticoagulation interventions
- less than 60 years of age
- was male
- did not require supplemental oxygen
- enrolled in India during the most recent epoch

based on the most prevalent level of each covariate.

Bayesian models were computed using Stan via `cmdstanr` (0.5.2 and cmdstan version 2.30.1) in R (4.2.2). For each model, 8 chains were used with a warm-up of 1000 iterations and sampling for 2500 iterations per chain resulting in 20,000 posterior draws per model. Standard diagnostics were assessed for each model (divergent transitions, trace plots, R-hat). If an issue was identified (e.g. divergent transitions) then the default sampling parameters may have been adjusted (e.g. increasing target acceptance rate or increasing maximum tree depth). If any convergence issues resulted for the pre-specified models, then they are reported along with the model results. If the model was amended in any way to satisfy convergence criteria (e.g. aggregation of groups, removal of model terms) then this is reported in the relevant section. Sampling was run using a different (randomly selected) random seed for each model, and these were recorded for replication.

Due to the small number of enrolments at New Zealand sites, in models where country of enrolment were included as a term, Australia and New Zealand were combined into one region. The hierarchical site effects for centres in Australia and New Zealand were nested within this joint region rather than each country individually. For models where site was included as a random effect, sites with less than 5 participants were aggregated within region into an "other sites" grouping. Similarly, for models where epoch was included, epochs with less than 10 participants were aggregated with the adjacent epoch.

Missing outcome data were not imputed for any of the models (with the exception of the deterministic imputation used in the best-case/worst-case sensitivity analyses). The only baseline covariate of interest which had missing values was oxygen requirement. For the primary analyses, participants with missing information for oxygen requirement (25 participants in full analysis set) were assumed to have *not* required supplemental oxygen.

1.4.2 Further Details

For all models, the primary linear predictor was the same. For a participant i with outcome y_i, their region of enrolment is denoted by $r(i) \in \{1, ..., R\}$, their site by $s(i) \in \{1, ..., S_{r(i)}\}$, and their epoch by $t(i) \in \{1, ..., T\}$. Their anticoagulation design vector is denoted by x_{Ci} and their antiviral design vector by x_{Ai}, their aspirin ineligibility by e_i, their age group by a_i, and oxygen requirement o_i, so that

$$\eta_i = x_{Ci}^{\mathsf{T}}\beta_C + x_{Ai}^{\mathsf{T}}\beta_A + \rho_{r(i)} + \xi_{r(i),s(i)} + \tau_{t(i)} + \omega_1 e_i + \omega_2 a_i + \omega_3 o_i,$$

was the linear predictor for the outcome for participant i.

For all models, the prior distribution on the linear components were

$$\begin{aligned}
\beta_C &\overset{\text{iid}}{\sim} \text{Normal}(0, 1) \\
\beta_A &\overset{\text{iid}}{\sim} \text{Normal}(0, 1) \\
\rho_1 = 0, \rho_r &\sim \text{Normal}(0, 1), \quad r = 2, ..., R \\
\tau_1 = 0, \tau_t &\sim \text{Normal}(\tau_{t-1}, \sigma_\tau^2), \quad t = 2, ..., T \\
\sigma_\tau &\sim \text{Student-}t(3, 0, 1) \\
\xi_{r,s} &\sim \text{Normal}(0, \sigma_{\xi_r}^2), \quad s = 1, ..., S_r, \quad r = 1, ..., R \\
\sigma_{\xi_r} &\sim \text{Student-}t(3, 0, 1), \quad r = 1, ..., R \\
\omega_1 &\sim \text{Normal}(0, 10^2) \\
\omega_2 &\sim \text{Normal}(0, 2.5^2) \\
\omega_3 &\sim \text{Normal}(0, 2.5^2).
\end{aligned}$$

For **binary outcomes**, $y_i \in \{0, 1\}$, the model was

$$\begin{aligned} \pi(\eta) &= \text{logit}^{-1}(\beta_0 + \eta) \\ y_i &\sim \text{Bernoulli}(\pi(\eta_i)) \end{aligned}$$

with $\beta_0 \sim \text{Normal}(0, 2.5^2)$.

For **ordinal outcomes** with K levels, $y_i \in \{1, ..., K\}$, the model was

$$\begin{aligned} \pi_k(\eta) &= \begin{cases} 1 - \text{logit}^{-1}(\eta - \alpha_1) & k = 1 \\ \text{logit}^{-1}(\eta - \alpha_{k-1}) - \text{logit}^{-1}(\eta - \alpha_k) & k = 2, ..., K-1 \\ \text{logit}^{-1}(\eta - \alpha_{K-1}) & k = K \end{cases} \\ y_i &\sim \text{Categorical}(\pi_k(\eta_i)) \end{aligned}$$

where $\alpha_k < \alpha_{k+1}$ for $k \in \{1, ..., K-2\}$ and $\pi(0) \sim \text{Dirichlet}(2/K, \cdots, 2/K)$.

For the **time-to-clinical-recovery outcome**, where $d_i \in \{1, ..., 28\}$ denotes the day of first event (or censoring at day 28) and $m \in \{0, 1, 2\}$ indicates event types (unrecovered, recovered, died), and $y_{id} = (y_{id0}, y_{id1}, y_{id2})$ with $y_{itm} \in \{0, 1\}$ indicates the status of patient i at day $d \leq d_i$, then the model was

$$\begin{aligned} \lambda_m(d, \eta) &= \frac{\exp(\alpha_{dm} + \eta_m)}{1 + \sum_{l=1}^{M} \exp(\alpha_{dl} + \eta_l)}, \quad m = 1, 2 \\ y_{id} &\sim \text{Multinomial}\left(1, \left(1 - \sum_{l=1}^{2} \lambda_l(d, \eta_i), \lambda_1(d, \eta_i), \lambda_2(d, \eta_i)\right)\right), \quad d \leq d_i, \end{aligned}$$

where $\eta = (\eta_1, \eta_2)$ contains the event-specific linear predictors with event-specific parameters in the same structure as previously introduced, and with priors

$$\begin{aligned} \alpha_{1m} &\sim \text{Normal}(0, 10^2) \\ \alpha_{dm} &\sim \text{Normal}(\alpha_{d-1,m}, \sigma_\alpha^2) \end{aligned}, \quad m = 1, 2,$$

on the event-specific baseline-hazard terms.

1.5 Trial Decision Criteria

As per the statistical appendix to the core protocol, the following decision quantities were of interest in the anticoagulation domain for the primary outcome model:

- **Superiority**: superiority was assessed using the posterior probability that the intervention has the lowest odds of the outcome amongst all interventions in the domain. If a single intervention had probability exceeding 0.99 superiority would be triggered for that intervention.
- **Effectiveness**: effectiveness was assessed relative to the low-dose arm as the posterior probability that the intervention reduces the odds of the outcome. If any intervention had probability exceeding 0.99 then effectiveness would be triggered for that intervention.
- **Futility**: futility was assessed relative to the low-dose arm as the posterior probability that the intervention reduces the odds of the outcome by no more than a factor of 1/1.1. If any intervention had probability exceeding 0.95 than futility would be triggered for that intervention.
- **Equivalence**: equivalence was assessed relative to the low-dose arm as the posterior probability that the intervention alters the odds of the outcome by a factor bounded by $(1/1.1, 1.1)$.

2 Results

2.1 Study Population

2.1.1 Summary

At the time of database lock for the antiviral domain, 1,606 participants had been enrolled onto the study platform. Of these enrolees, 1,574 were randomised to the anticoagulation domain and 159 were randomised to the antiviral domain (127 to both domains, 32 to antiviral only, and 1,447 to anticoagulation only). The first participant was randomised on 2021-02-08, the last participant enrolled into the anticoagulation domain was randomised on 2022-03-29, and the last participant enrolled into the antiviral domain was randomised on 2022-08-04.

From the 1,606 enrolled participants, 18 withdrew consent for follow-up, leaving 1,588 participants with expected follow-up.

2.1.2 Analysis Sets

Table 2.1: Overview of the analysis sets used in this report.

Name	Definition
FAS-ITT	All participants who were randomised to at least one study domain. Participants will be analysed as randomised, irrespective of withdrawal from treatment, treatment compliance, or other protocol deviations.
ACS-ITT	Subset of FAS-ITT who were randomised to the anticoagulation domain.
AVS-ITT	Subset of FAS-ITT who were randomised to the antiviral domain.

Name	Definition
FAS-PP	All participants who were randomised to at least one study domain and satisfied platform, domain, and intervention protocol requirements.
ACS-PP	All participants who were randomised to the anticoagulation domain and satisfied platform, domain, and intervention protocol requirements.
AVS-PP	All participants who were randomised to the antiviral domain and satisfied platform, domain, and intervention protocol requirements.

The following sections summarise the distribution of treatment allocations for participants included in each of the above sets.

2.1.2.1 FAS-ITT

Table 2.2: Distribution of intervention assignments for participants in the FAS-ITT set. Brackets indicate the number of participants in that cell with missing primary outcome due to withdrawal from the study, loss-to-follow-up, or missing data.

	Antiviral			
Anticoagulation	Not randomised A	SoC	Nafamostat	Total
Not randomised C	0 (0)	18 (3)	14 (1)	32 (4)
Low	569 (19)	26 (1)	24 (3)	619 (23)
Intermediate	566 (13)	19 (0)	35 (6)	620 (19)
Low with aspirin	278 (6)	6 (0)	1 (0)	285 (6)
Therapeutic	35 (0)	4 (0)	11 (0)	50 (0)
Total	1448 (38)	73 (4)	85 (10)	1606 (52)

2.1.2.2 ACS-ITT

Table 2.3: Distribution of intervention assignments for participants in the ACS-ITT set. Brackets indicate the number of participants in that cell with missing primary outcome due to withdrawal from the study, loss-to-follow-up, or missing data.

	Antiviral			
Anticoagulation	Not randomised A	SoC	Nafamostat	Total
Low	569 (19)	26 (1)	24 (3)	619 (23)
Intermediate	566 (13)	19 (0)	35 (6)	620 (19)
Low with aspirin	278 (6)	6 (0)	1 (0)	285 (6)
Therapeutic	35 (0)	4 (0)	11 (0)	50 (0)
Total	1448 (38)	55 (1)	71 (9)	1574 (48)

2.1.2.3 AVS-ITT

Table 2.4: Distribution of intervention assignments for participants in the AVS-ITT set. Brackets indicate the number of participants in that cell with missing primary outcome due to withdrawal from the study, loss-to-follow-up, or missing data.

	Antiviral		
Anticoagulation	SoC	Nafamostat	Total
Not randomised C	18 (3)	14 (1)	32 (4)
Low	26 (1)	24 (3)	50 (4)
Intermediate	19 (0)	35 (6)	54 (6)
Low with aspirin	6 (0)	1 (0)	7 (0)
Therapeutic	4 (0)	11 (0)	15 (0)
Total	73 (4)	85 (10)	158 (14)

2.1.3 Disposition

Of the 1,606 participants randomised to the trial, 18 withdrew consent for follow-up (16 on study day 1 and 2 on study day 2) leaving 1,588 participants continuing to study day 28. The analyses and summaries included in this report exclude data on participants who withdrew consent for follow-up.

Platform and domain specific flow diagrams is shown in in Figure 2.1 and Figure 2.2.

Figure 2.3 presents overall platform enrolments by calendar time with timing of intervention availabilities and interim analyses. Due to an insufficient number of participants on the therapeutic anticoagulation arm, the initial allocation ratios were not changed during recruitment to the anticoagulation domain. Therefore, the only trial adaptations which occurred were the cessation of the standard dose plus aspirin intervention in the anticoagulation domain, the opening of the antiviral domain, and the introduction of the therapeutic dose intervention into the anticoagulation domain. Despite this, the timing of interim analyses are indicated on the Figures.

2.1.4 Intervention Allocations

Response adaptive randomisation (RAR) was never activated in the anticoagulation domain. This was due to the therapeutic intervention never exceeding the minimum sample size of 50, and the fixed allocation to control. Therefore, target allocations to the interventions were uniform across all available interventions from trial start to trial closure. However, the available interventions did change over time and availability varied by region and site. Similarly, RAR was never activated in the antiviral domain due to insufficient sample size.

The following figures summarise treatment allocations by country, site, and calendar time.

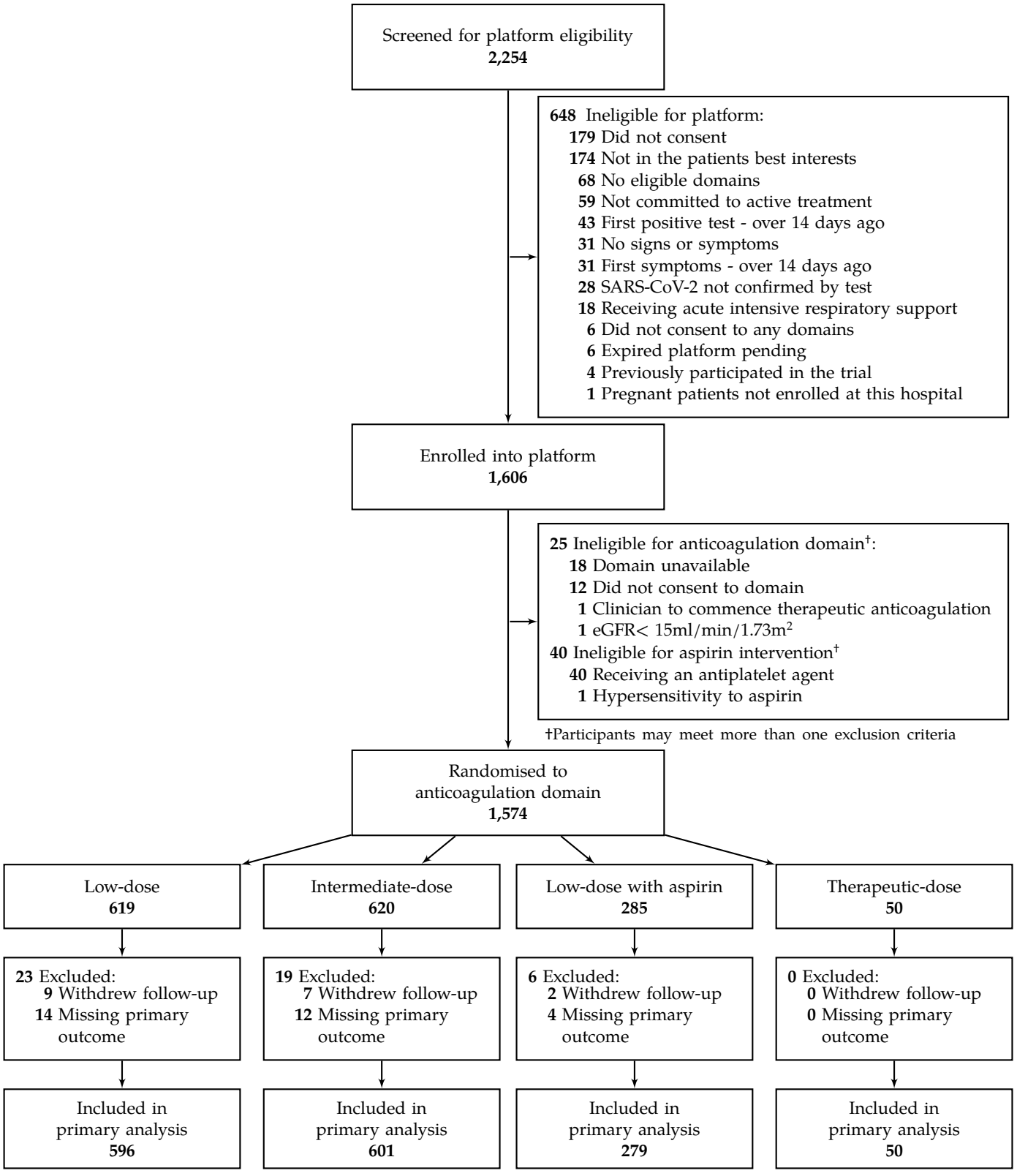

Figure 2.1: Combined domain flowchart for anticoagulation.

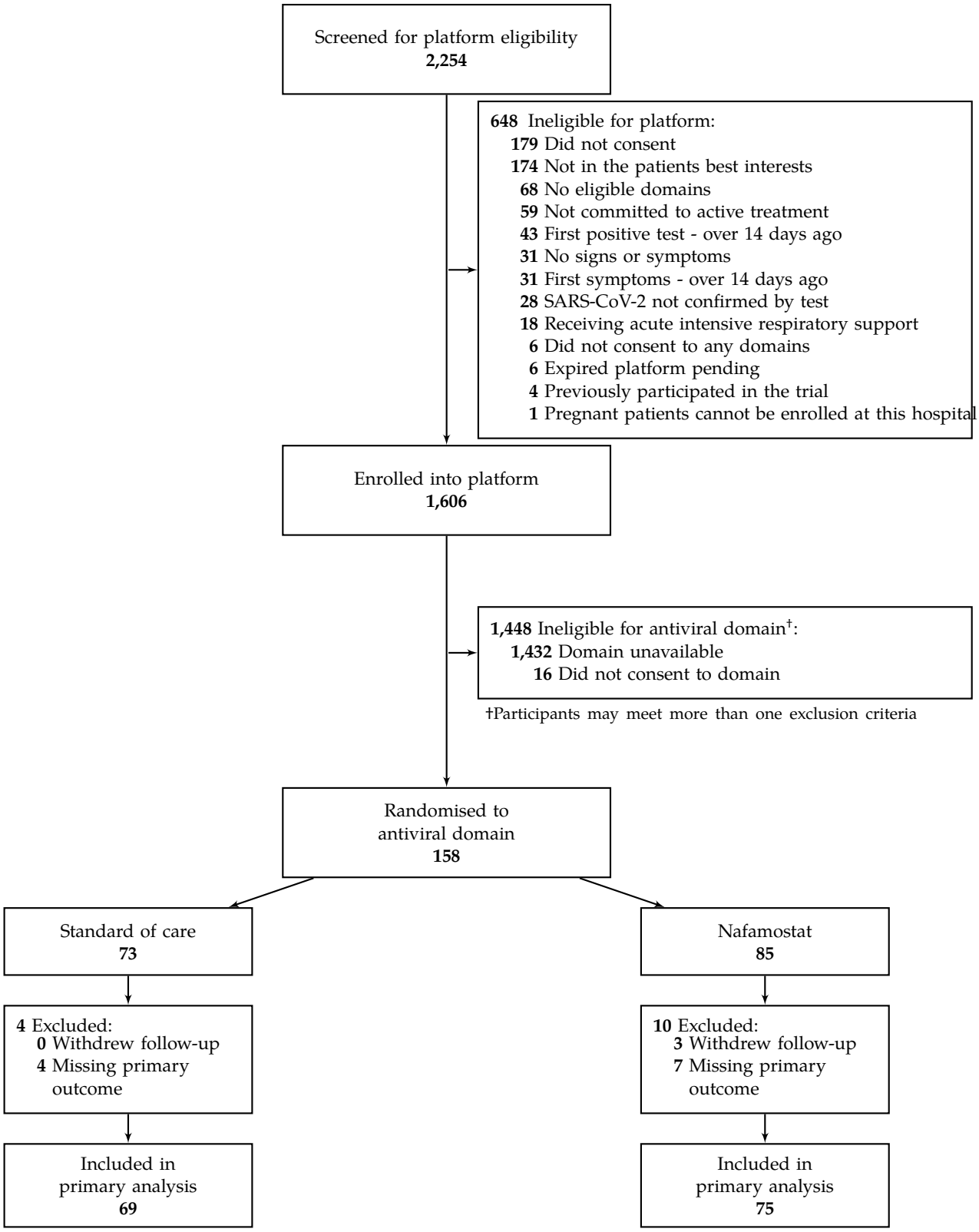

Figure 2.2: Combined domain flowchart for antiviral.

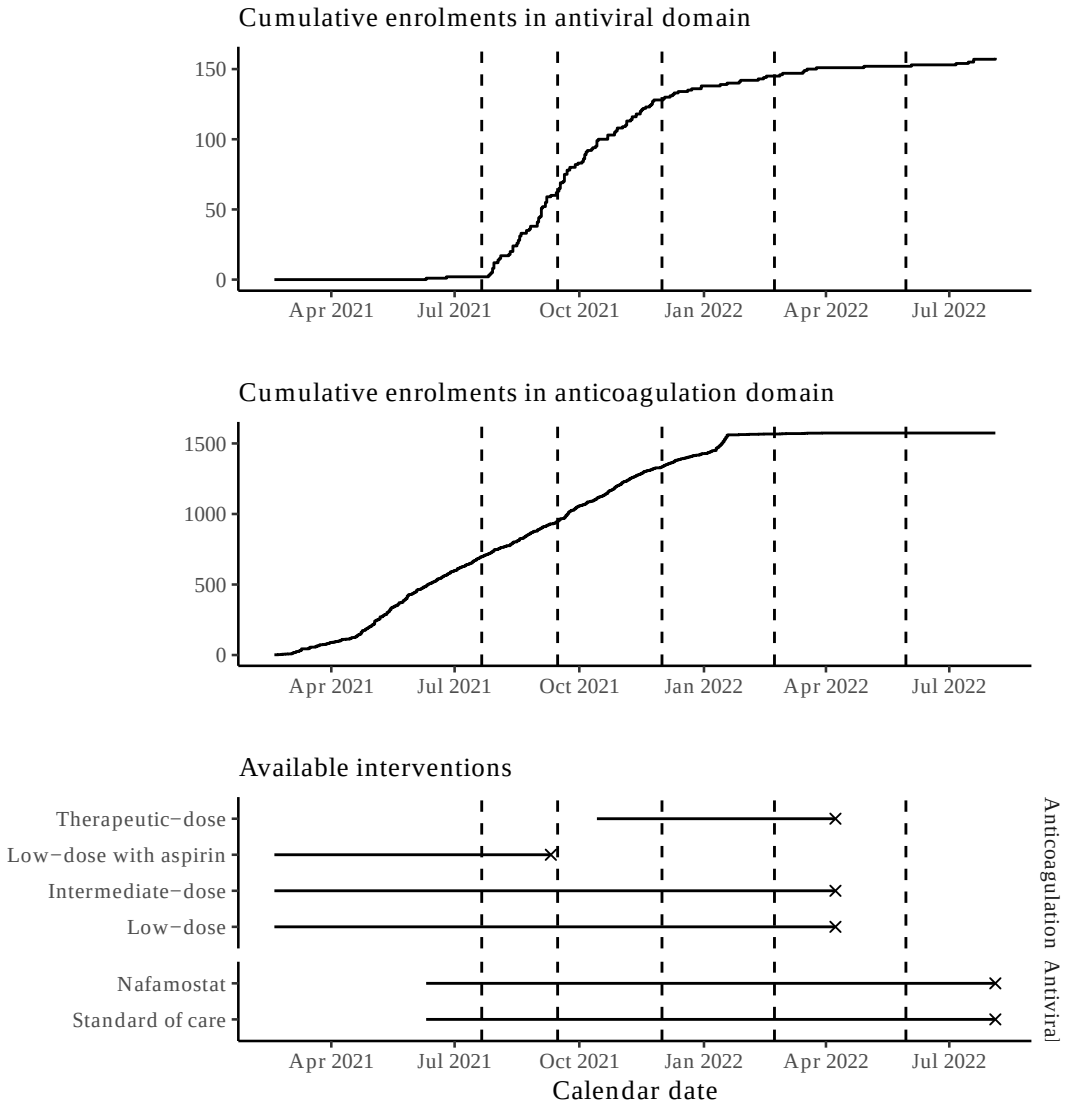

Figure 2.3: Overall enrolment to the study by domain with intervention availability. Vertical dashed lines indicate timing of interim analyses.

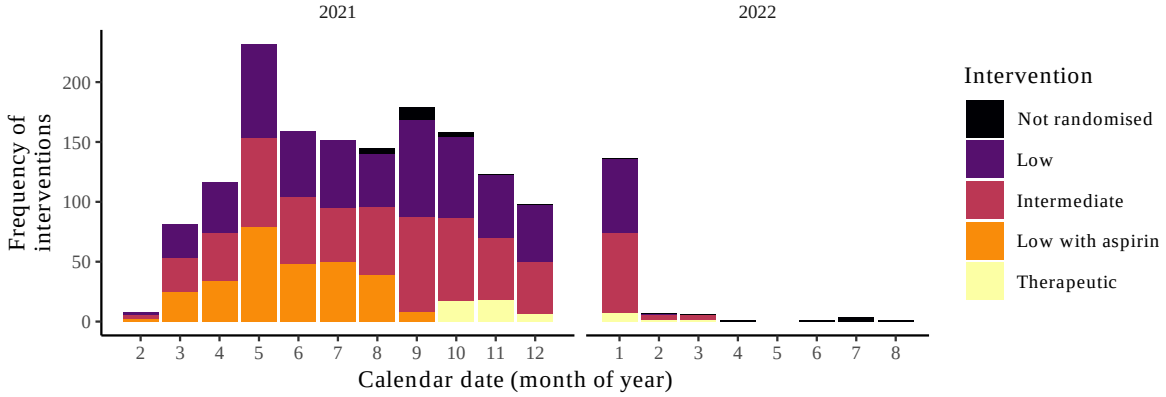

Figure 2.4: Intervention allocations by calendar time (month) for anticoagulation domain.

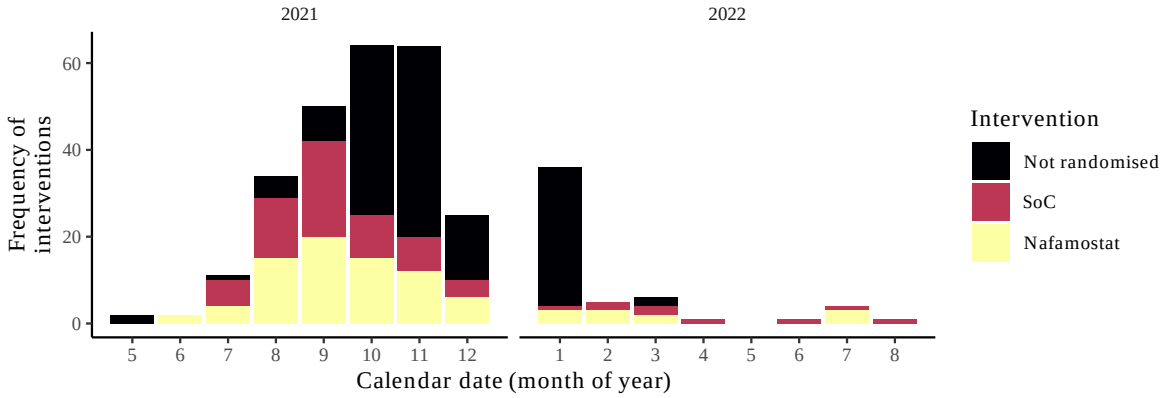

Figure 2.5: Intervention allocations by calendar time (month) for antiviral domain (excludes India as antiviral domain not available).

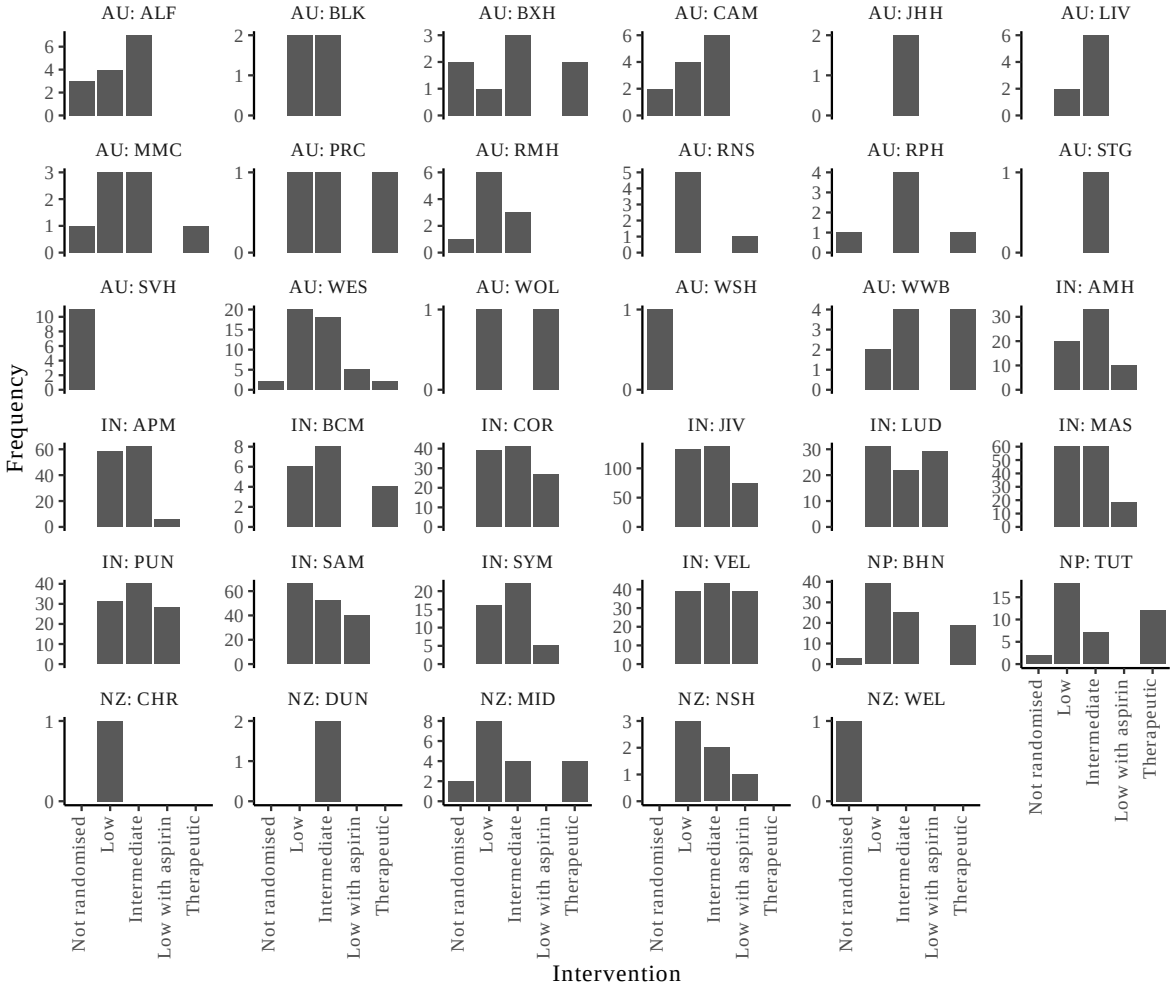

Figure 2.6: Intervention allocations by study site for anticoagulation domain.

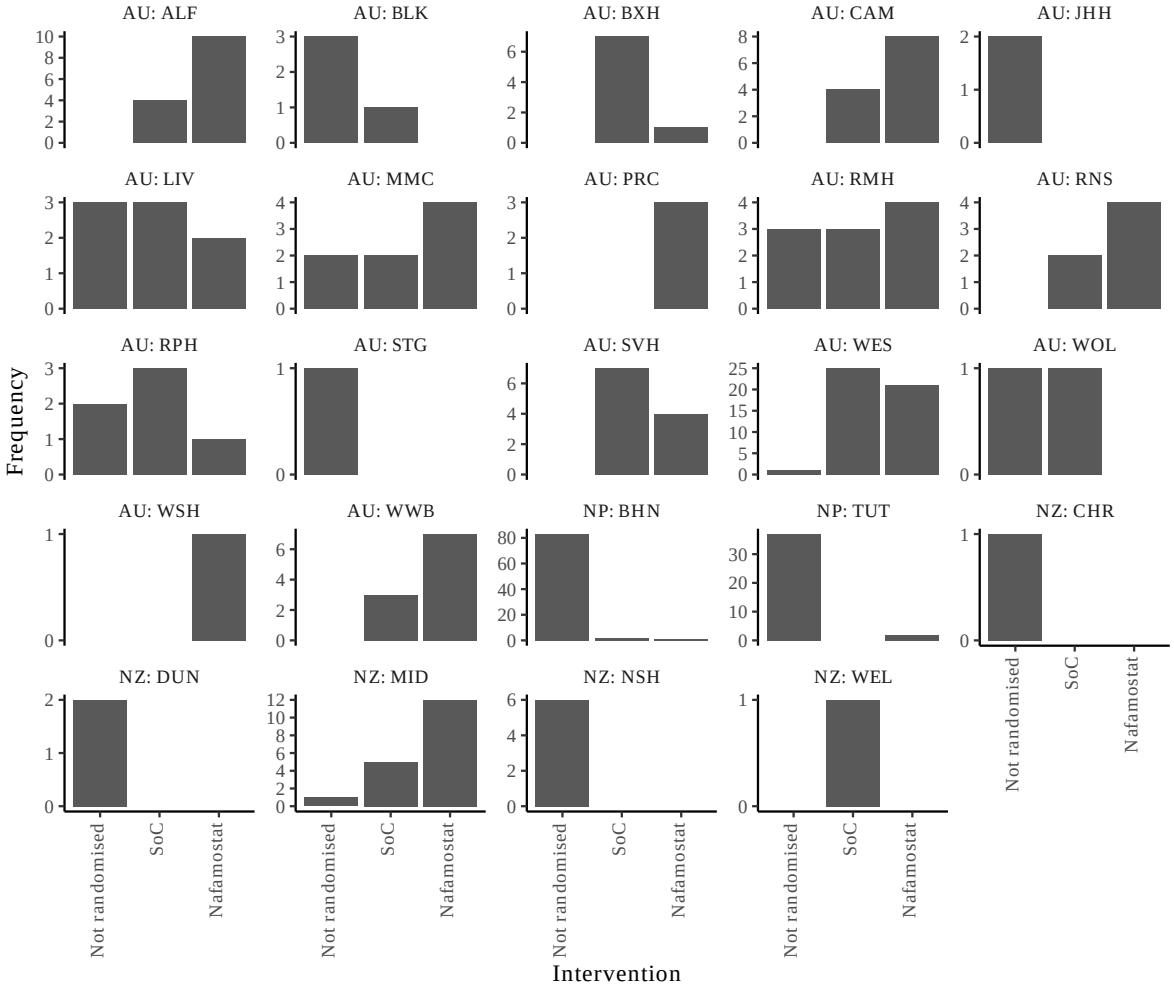

Figure 2.7: Intervention allocations by study site for antiviral domain.

2.1.5 Compliance

There were two participants who received the wrong dosage (according to the antiviral domain specific appendix) on at least one day given their baseline weight:

- One participant reportedly had 3 days of 500 mg/day instead of 350 mg/day (baseline weight of 65 kg). This participant was determined to not be per-protocol.
- Another participant reportedly had 2 days of 350 mg/day instead of 250 mg/day (baseline weight of 60 kg). This participant was determined to be per-protocol.

Figure 2.8 presents the distribution of Nafamostat infusion duration for each study day amongst participants assigned to receive Nafamostat. Table 2.5 presents summaries of treatment compliance for participants assigned to Nafamostat. Table 2.6 outlines the number of participants who were not per-protocol and the associated reason by their assigned antiviral intervention.

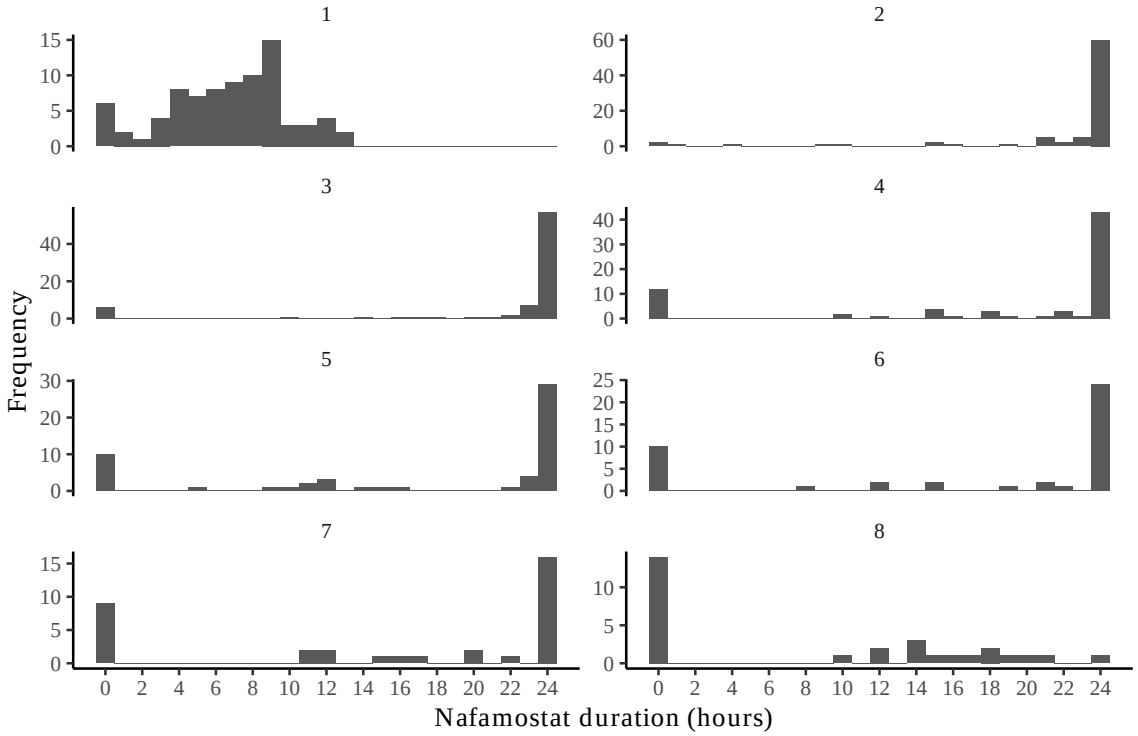

Figure 2.8: Distribution of Nafamostat infusion duration by study day (1 to 8) amongst participants assigned to Nafamostat.

Table 2.5: Compliance to Nafamostat.

Summary	Value
Days on study treatment	
Median (IQR)	5 (3 - 7)
Min, Max	0, 8
Missing	0
Days off study treatment	
Median (IQR)	0 (0 - 1)
Min, Max	0, 7
Missing	0
Total hours receiving infusion	
Median (IQR)	89.7 (57.8 - 138.8)
Min, Max	0.0, 176.6
Missing	0
Hours per day on infusion	
Median (IQR)	17.6 (14.3 - 19.7)
Min, Max	0.0, 22.1
Missing	0
Proportion of days admitted to hospital with infusion $\geq$ 21/24 hours[1]	
Median (IQR)	0.55 (0.50 - 0.71)
Min, Max	0.00, 0.88
Missing	0
Days with 21/24 hours infusion	
Median (IQR)	3 (2 - 5)
Min, Max	0, 7
Missing	0
Days without 21/24 hours infusion	
Median (IQR)	0 (0 - 1)
Min, Max	0, 7
Missing	0

Days on study treatment is any part day on drug.
Days off treatment is any day when no Nafamostat was administered.
Days without 21/24 excludes day 1 and day of discharge.
[1] up to 7 days while hospitalised

Table 2.6: Per-protocol status for antiviral domain

Antiviral	Per Protocol?	Reason	Count
Standard of care	Not Per Protocol	withdrawn from antiviral & anticoagulation treatment (by patient)	1
Standard of care	Per Protocol	NA	72
Nafamostat	Not Per Protocol	>3 hr disruption	9
Nafamostat	Not Per Protocol	withdrawn from antiviral treatment (by patient)	7
Nafamostat	Not Per Protocol	>3 hr disruption. Dose was charted incorrectly for patient's weight on days 1 to 4.	1
Nafamostat	Not Per Protocol	Patient received more than allocated dose (up to day 9) with a disruption on day 7 of >3hrs	1
Nafamostat	Not Per Protocol	withdrawn from antiviral treatment (by treating clinician due to nausea and vomitting)	1
Nafamostat	Per Protocol	NA	62
Nafamostat	Per Protocol	withdrawn from antiviral & anticoagulation treatment (by treating clinician due to concerns about haemoptysis)	1

2.1.6 Baseline Characteristics

The following baseline summaries exclude participants who withdrew consent for follow-up.

2.1.6.1 Demographics

The age distribution of participants are presented in Figure 2.9, Figure 2.10, and Figure 2.11.

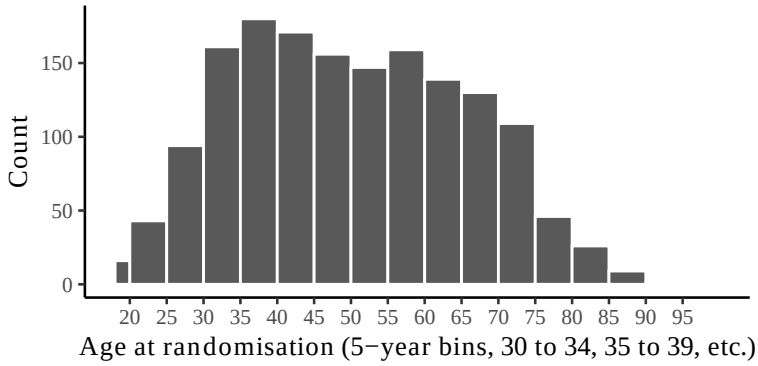

Figure 2.9: Distribution of age amongst participants randomised in the trial.

Baseline demographics stratified by anticoagulation interventions are reported in Table 2.7 and by antiviral interventions in Table 2.8.

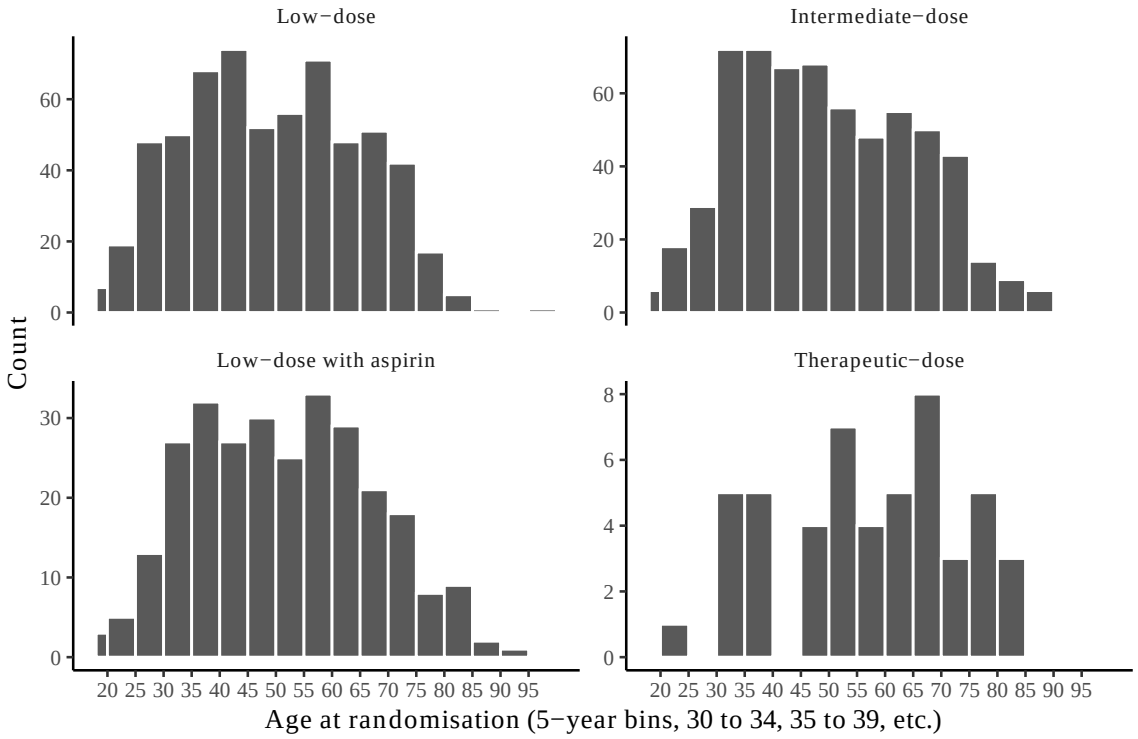

Figure 2.10: Distribution of age amongst participants randomised to the anticoagulation domain.

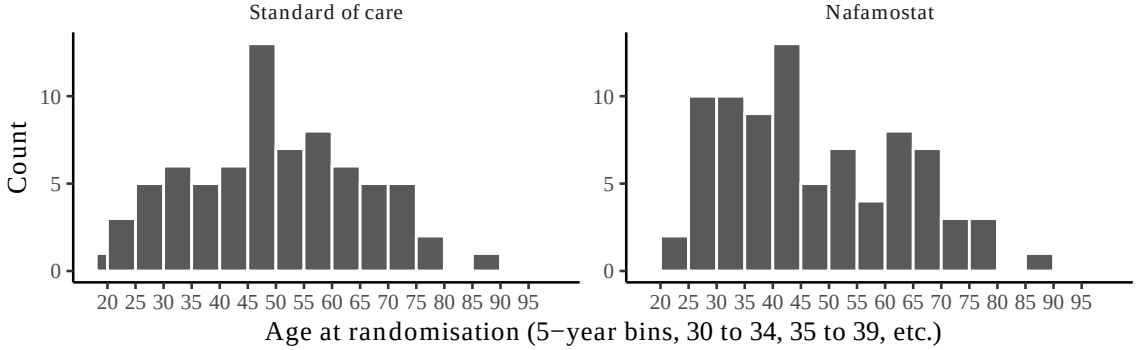

Figure 2.11: Distribution of age amongst participants randomised to the antiviral domain.

Table 2.7: Baseline demographics for participants randomised to the anticoagulation domain.

Variable	Anticoagulation				Overall
	Low dose	Intermediate dose	Low dose with aspirin	Therapeutic dose	
	(n = 610)	(n = 613)	(n = 283)	(n = 50)	(n = 1556)
Age (years), Median (IQR)	48 (37, 60)	48 (37, 61)	50 (38, 62)	58 (46, 69)	49 (37, 61)
Country					
India, n (%)	493 (81)	516 (84)	275 (97)	4 (8)	1288 (83)
Australia, n (%)	49 (8)	59 (10)	7 (2)	11 (22)	126 (8)
Nepal, n (%)	56 (9)	31 (5)	0 (0)	31 (62)	118 (8)
New Zealand, n (%)	12 (2)	7 (1)	1 (0)	4 (8)	24 (2)
Sex					
Male, n (%)	354 (58)	387 (63)	157 (55)	25 (50)	923 (59)
Female, n (%)	256 (42)	226 (37)	126 (45)	25 (50)	633 (41)
Weight (kg)					
Median, (IQR)	68 (62, 76)	70 (62, 77)	68 (62, 76)	66 (57, 80)	69 (62, 76)
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vaccinated[1]					
Yes, n (%)	191 (31)	220 (36)	42 (15)	27 (54)	480 (31)
Missing, n (%)	32 (5)	22 (4)	29 (10)	0 (0)	83 (5)
Ethnicity					
Indian, n (%)	494 (81)	518 (85)	275 (97)	4 (8)	1291 (83)
European, n (%)	21 (3)	18 (3)	4 (1)	4 (8)	47 (3)
Asian, n (%)	20 (3)	12 (2)	1 (0)	10 (20)	43 (3)
Pacific Islander, n (%)	13 (2)	12 (2)	2 (1)	3 (6)	30 (2)
Middle Eastern, n (%)	11 (2)	11 (2)	0 (0)	0 (0)	22 (1)
Maori, n (%)	3 (0)	4 (1)	0 (0)	3 (6)	10 (1)
African, n (%)	1 (0)	0 (0)	1 (0)	0 (0)	2 (0)
Aboriginal, n (%)	0 (0)	1 (0)	0 (0)	1 (2)	2 (0)
Latin American, n (%)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)
Other, n (%)	45 (7)	28 (5)	0 (0)	23 (46)	96 (6)
Unknown, n (%)	8 (1)	9 (1)	0 (0)	3 (6)	20 (1)
Smoking					
Current, n (%)	17 (3)	21 (3)	3 (1)	5 (10)	46 (3)
Former, n (%)	74 (12)	53 (9)	15 (5)	14 (28)	156 (10)
Never, n (%)	519 (85)	539 (88)	265 (94)	31 (62)	1354 (87)
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[1] Site LUD did not have ethics approval for collection of vaccination status.

Table 2.8: Baseline demographics for participants randomised to the antiviral domain.

Variable	Antiviral		Overall
	Standard of care	Nafamostat	
	(n = 73)	(n = 82)	(n = 155)
Age (years), Median (IQR)	46 (37, 60)	44 (34, 60)	45 (35, 60)
Country			
India, n (%)	0 (0)	0 (0)	0 (0)
Australia, n (%)	65 (89)	67 (82)	132 (85)
Nepal, n (%)	2 (3)	3 (4)	5 (3)
New Zealand, n (%)	6 (8)	12 (15)	18 (12)
Sex			
Male, n (%)	39 (53)	56 (68)	95 (61)
Female, n (%)	34 (47)	26 (32)	60 (39)
Weight (kg)			
Median, (IQR)	90 (70, 106)	90 (79, 110)	90 (78, 108)
Missing, n (%)	0 (0)	0 (0)	0 (0)
Vaccinated[1]			
Yes, n (%)	27 (37)	31 (38)	58 (37)
Missing, n (%)	7 (10)	1 (1)	8 (5)
Ethnicity			
Indian, n (%)	1 (1)	1 (1)	2 (1)
European, n (%)	18 (25)	27 (33)	45 (29)
Asian, n (%)	6 (8)	6 (7)	12 (8)
Pacific Islander, n (%)	12 (16)	12 (15)	24 (15)
Middle Eastern, n (%)	9 (12)	11 (13)	20 (13)
Maori, n (%)	1 (1)	7 (9)	8 (5)
African, n (%)	2 (3)	0 (0)	2 (1)
Aboriginal, n (%)	3 (4)	1 (1)	4 (3)
Latin American, n (%)	1 (1)	0 (0)	1 (1)
Other, n (%)	6 (8)	9 (11)	15 (10)
Unknown, n (%)	17 (23)	11 (13)	28 (18)
Smoking			
Current, n (%)	8 (11)	12 (15)	20 (13)
Former, n (%)	22 (30)	16 (20)	38 (25)
Never, n (%)	43 (59)	54 (66)	97 (63)
Missing, n (%)	0 (0)	0 (0)	0 (0)

[1] Site LUD did not have ethics approval for collection of vaccination status.

2.1.6.2 Co-morbidities

Baseline co-morbidities stratified by anticoagulation interventions are reported in Table 2.9 and to by antiviral interventions in Table 2.10.

Table 2.9: Baseline comorbidities for participants randomised to the anticoagulation domain.

Comorbidity	Anticoagulation				Overall (n = 1556)
	Low dose (n = 610)	Intermediate dose (n = 613)	Low dose with aspirin (n = 283)	Therapeutic dose (n = 50)	
None, n (%)	364 (60)	378 (62)	166 (59)	19 (38)	927 (60)
Hypertension, n (%)	147 (24)	140 (23)	68 (24)	14 (28)	369 (24)
Diabetes, n (%)	140 (23)	139 (23)	78 (28)	11 (22)	368 (24)
Obesity, n (%)	23 (4)	22 (4)	3 (1)	5 (10)	53 (3)
Asthma, n (%)	19 (3)	16 (3)	6 (2)	4 (8)	45 (3)
Chronic lung disease, n (%)	16 (3)	13 (2)	1 (0)	7 (14)	37 (2)
Chronic cardiac disease, n (%)	11 (2)	15 (2)	1 (0)	2 (4)	29 (2)
Obstructive sleep apnoea, n (%)	3 (0)	2 (0)	2 (1)	0 (0)	7 (0)
Iatrogenic immunosuppression, n (%)	1 (0)	6 (1)	0 (0)	0 (0)	7 (0)
Chronic kidney disease, n (%)	0 (0)	5 (1)	1 (0)	0 (0)	6 (0)
Malignant neoplasm, n (%)	1 (0)	2 (0)	0 (0)	1 (2)	4 (0)
Moderate or severe liver disease, n (%)	2 (0)	1 (0)	0 (0)	0 (0)	3 (0)
Dialysis, n (%)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)
HIV infection, n (%)	1 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Dementia, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Table 2.10: Baseline comorbidities for participants randomised to the antiviral domain.

Comorbidity	Antiviral		Overall (n = 155)
	Standard of care (n = 73)	Nafamostat (n = 82)	
None, n (%)	31 (42)	34 (41)	65 (42)
Obesity, n (%)	19 (26)	22 (27)	41 (26)
Hypertension, n (%)	16 (22)	17 (21)	33 (21)
Diabetes, n (%)	16 (22)	15 (18)	31 (20)
Asthma, n (%)	10 (14)	10 (12)	20 (13)
Chronic lung disease, n (%)	7 (10)	6 (7)	13 (8)
Chronic cardiac disease, n (%)	3 (4)	6 (7)	9 (6)
Iatrogenic immunosuppression, n (%)	2 (3)	4 (5)	6 (4)
Obstructive sleep apnoea, n (%)	3 (4)	2 (2)	5 (3)
Chronic kidney disease, n (%)	2 (3)	2 (2)	4 (3)
Malignant neoplasm, n (%)	1 (1)	2 (2)	3 (2)
Dialysis, n (%)	0 (0)	0 (0)	0 (0)
Moderate or severe liver disease, n (%)	0 (0)	0 (0)	0 (0)
Dementia, n (%)	0 (0)	0 (0)	0 (0)
HIV infection, n (%)	0 (0)	0 (0)	0 (0)
Missing, n (%)	0 (0)	0 (0)	0 (0)

2.1.6.3 Prognostics

Baseline prognostics stratified by anticoagulation interventions are reported in Table 2.11 and to by antiviral interventions in Table 2.12.

Table 2.11: Baseline prognostics for participants randomised to the anticoagulation domain.

Variable	Anticoagulation				Overall (n = 1556)
	Low dose (n = 610)	Intermediate dose (n = 613)	Low dose with aspirin (n = 283)	Therapeutic dose (n = 50)	
Was the patient on room air for any of the preceding 24 hours?					
Yes, n (%)	460 (75)	460 (75)	224 (79)	39 (78)	1183 (76)
Missing, n (%)	8 (1)	9 (1)	8 (3)	0 (0)	25 (2)
Was the patient's GCS < 15?					
Yes, n (%)	63 (10)	65 (11)	6 (2)	2 (4)	136 (9)
Missing, n (%)	125 (20)	135 (22)	60 (21)	0 (0)	320 (21)
Peripheral oxygen saturation (SpO2) on room air (Lowest)					
Median (IQR)	95 (94, 97)	96 (94, 97)	96 (94, 97)	94 (92, 96)	96 (94, 97)
Missing, n (%)	150 (25)	153 (25)	59 (21)	11 (22)	373 (24)
Highest respiratory rate (breaths/minute)					
Median (IQR)	22 (21, 25)	22 (21, 26)	22 (20, 26)	22 (20, 24)	22 (21, 26)
Missing, n (%)	0 (0)	1 (0)	0 (0)	0 (0)	1 (0)
Highest recorded Urea in the last 24 hours (mmol/L)					
Median (IQR)	4 (3, 5)	5 (4, 6)	4 (3, 6)	4 (3, 6)	4 (3, 6)
Missing, n (%)	30 (5)	33 (5)	16 (6)	1 (2)	80 (5)
Highest recorded CRP in the last 24 hours (mg/L)					
Median (IQR)	70 (37, 190)	75 (38, 220)	77 (44, 223)	68 (33, 129)	73 (39, 200)
Missing, n (%)	74 (12)	59 (10)	18 (6)	29 (58)	180 (12)
APTT[1]					
Median (IQR)	33 (29, 36)	33 (30, 36)	32 (28, 37)	33 (28, 38)	33 (29, 36)
Missing, n (%)	430 (70)	439 (72)	195 (69)	35 (70)	1099 (71)
INR[1]					
Mean (SD)	1.19 (0.39)	1.23 (0.58)	1.32 (1.34)	1.12 (0.18)	1.23 (0.72)
Missing, n (%)	103 (17)	105 (17)	47 (17)	7 (14)	262 (17)
Fibrinogen[1] (g/L)					
Mean (SD)	5.19 (2.01)	5.20 (1.60)	4.75 (1.40)	6.49 (1.52)	5.14 (1.71)
Missing, n (%)	564 (92)	555 (91)	243 (86)	42 (84)	1404 (90)
Prothrombin time[1] (sec)					
Median (IQR)	14 (13, 17)	14 (13, 17)	15 (13, 16)	13 (12, 14)	14 (13, 16)
Missing, n (%)	193 (32)	204 (33)	116 (41)	10 (20)	523 (34)
Taking aspirin					
Yes, n (%)	20 (3)	25 (4)	2 (1)	3 (6)	50 (3)
Missing, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Time from onset of symptoms to hospitalisation					
Median (IQR)	5 (3, 7)	5 (3, 6)	4 (2, 6)	4 (3, 6)	4 (3, 6)
Time from hospitalisation to randomisation					
Median (IQR)	1 (0, 2)	1 (0, 2)	1 (1, 2)	1 (1, 1)	1 (0, 2)
D-dimer					
Test performed, n(%)	494 (81)	514 (84)	247 (87)	17 (34)	1272 (82)
Out of range, n(%)	182 (37)	177 (35)	63 (26)	10 (59)	432 (34)

[1] For APTT, INR, Fibrinogen, and Prothrombin only at least one required.

Table 2.12: Baseline prognostics for participants randomised to the antiviral domain.

Variable	Antiviral		Overall (n = 155)
	Standard of care (n = 73)	Nafamostat (n = 82)	
Was the patient on room air for any of the preceding 24 hours?			
Yes, n (%)	48 (66)	42 (51)	90 (58)
Missing, n (%)	0 (0)	0 (0)	0 (0)
Was the patient's GCS < 15?			
Yes, n (%)	5 (7)	4 (5)	9 (6)
Missing, n (%)	1 (1)	0 (0)	1 (1)
Peripheral oxygen saturation (SpO2) on room air (Lowest)			
Median (IQR)	93 (90, 95)	93 (92, 95)	93 (91, 95)
Missing, n (%)	25 (34)	40 (49)	65 (42)
Highest respiratory rate (breaths/minute)			
Median (IQR)	24 (20, 28)	24 (21, 28)	24 (21, 28)
Missing, n (%)	1 (1)	0 (0)	1 (1)
Highest recorded Urea in the last 24 hours (mmol/L)			
Median (IQR)	5 (4, 7)	5 (4, 7)	5 (4, 7)
Missing, n (%)	4 (5)	4 (5)	8 (5)
Highest recorded CRP in the last 24 hours (mg/L)			
Median (IQR)	68 (32, 114)	55 (28, 84)	58 (28, 108)
Missing, n (%)	5 (7)	11 (13)	16 (10)
APTT[1]			
Median (IQR)	33 (31, 36)	33 (30, 36)	33 (30, 36)
Missing, n (%)	23 (32)	20 (24)	43 (28)
INR[1]			
Mean (SD)	1.09 (0.09)	1.07 (0.11)	1.08 (0.10)
Missing, n (%)	25 (34)	26 (32)	51 (33)
Fibrinogen[1] (g/L)			
Mean (SD)	5.76 (2.08)	5.62 (1.56)	5.68 (1.79)
Missing, n (%)	42 (58)	42 (51)	84 (54)
Prothrombin time[1] (sec)			
Median (IQR)	13 (13, 14)	13 (13, 14)	13 (13, 14)
Missing, n (%)	30 (41)	29 (35)	59 (38)
Taking aspirin			
Yes, n (%)	4 (5)	8 (10)	12 (8)
Missing, n (%)	18 (25)	14 (17)	32 (21)
Time from onset of symptoms to hospitalisation			
Median (IQR)	6 (4, 8)	6 (4, 8)	6 (4, 8)
Time from hospitalisation to randomisation			
Median (IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)
D-dimer			
Test performed, n(%)	54 (74)	51 (62)	105 (68)
Out of range, n(%)	35 (65)	32 (64)	67 (64)

[1] For APTT, INR, Fibrinogen, and Prothrombin only at least one required.

The relative timing (in days) of hospitalisation, symptom onset, randomisation, and first positive test are presented in Figure 2.12.

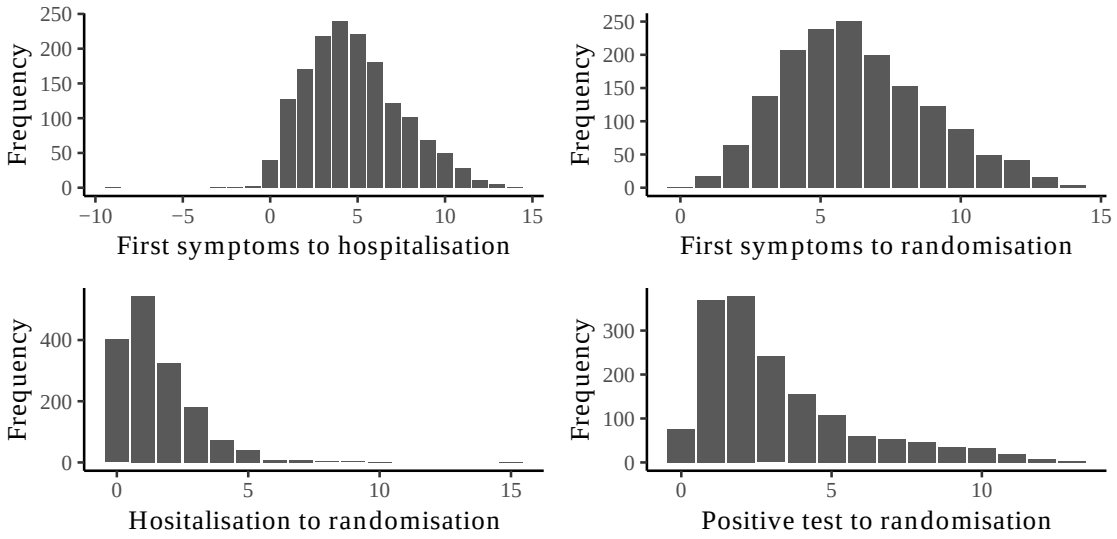

Figure 2.12: Days between events for hospitalisation, randomisation, symptom onset, and first positive test.

2.1.7 Discharge Summaries

2.1.7.1 Drugs Received During Hospital Stay

There were 18 participants without a discharge record (due to withdrawal of consent for follow-up). For the continuing participants, the other medications received during their hospital stay are reported in Table 2.13 and Table 2.14.

Table 2.13: Drugs received during hospital stay for participants randomised to the anticoagulation domain.

Drug received	Anticoagulation				Overall (n = 1556)
	Low dose (n = 610)	Intermediate dose (n = 613)	Low dose with aspirin (n = 283)	Therapeutic dose (n = 50)	
Antibacterial drugs, n (%)	449 (74)	443 (72)	231 (82)	38 (76)	1161 (75)
Antivirals					
No antiviral, n (%)	125 (20)	120 (20)	44 (16)	39 (78)	328 (21)
Camostat, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Favipiravir, n (%)	97 (16)	100 (16)	34 (12)	0 (0)	231 (15)
Doxycycline, n (%)	76 (12)	81 (13)	22 (8)	2 (4)	181 (12)
Ivermectin, n (%)	201 (33)	200 (33)	91 (32)	0 (0)	492 (32)
Remdesivir, n (%)	286 (47)	289 (47)	169 (60)	10 (20)	754 (48)
Other antiviral, n (%)	3 (0)	1 (0)	1 (0)	0 (0)	5 (0)
Immunomodulatory					
No immunomodulatory, n (%)	60 (10)	68 (11)	38 (13)	6 (12)	172 (11)
Anakinra, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Corticosteroids, n (%)	396 (65)	388 (63)	183 (65)	37 (74)	1004 (65)
Sarilumab, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Azithromycin, n (%)	105 (17)	108 (18)	38 (13)	5 (10)	256 (16)
Tocilizumab, n (%)	12 (2)	11 (2)	5 (2)	2 (4)	30 (2)
Baricitinib, n (%)	36 (6)	50 (8)	11 (4)	6 (12)	103 (7)
Ruxolitinib, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tofacitinib, n (%)	11 (2)	13 (2)	5 (2)	0 (0)	29 (2)
Zinc, n (%)	388 (64)	394 (64)	173 (61)	13 (26)	968 (62)
Other immunomodulatory, n (%)	20 (3)	20 (3)	11 (4)	1 (2)	52 (3)

Table 2.14: Drugs received during hospital stay for participants randomised to the anti-viral domain.

Drug received	Antiviral		Overall (n = 155)
	Standard of care (n = 73)	Nafamostat (n = 82)	
Antibacterial drugs, n (%)	33 (45)	38 (46)	71 (46)
Antivirals			
No antiviral, n (%)	28 (38)	36 (44)	64 (41)
Camostat, n (%)	0 (0)	0 (0)	0 (0)
Favipiravir, n (%)	0 (0)	0 (0)	0 (0)
Doxycycline, n (%)	1 (1)	7 (9)	8 (5)
Ivermectin, n (%)	1 (1)	1 (1)	2 (1)
Remdesivir, n (%)	39 (53)	39 (48)	78 (50)
Other antiviral, n (%)	5 (7)	3 (4)	8 (5)
Immunomodulatory			
No immunomodulatory, n (%)	10 (14)	9 (11)	19 (12)
Anakinra, n (%)	0 (0)	0 (0)	0 (0)
Corticosteroids, n (%)	55 (75)	70 (85)	125 (81)
Sarilumab, n (%)	0 (0)	0 (0)	0 (0)
Azithromycin, n (%)	6 (8)	9 (11)	15 (10)
Tocilizumab, n (%)	5 (7)	3 (4)	8 (5)
Baricitinib, n (%)	24 (33)	38 (46)	62 (40)
Ruxolitinib, n (%)	0 (0)	0 (0)	0 (0)
Tofacitinib, n (%)	0 (0)	0 (0)	0 (0)
Zinc, n (%)	1 (1)	2 (2)	3 (2)
Other immunomodulatory, n (%)	3 (4)	3 (4)	6 (4)

2.2 Primary Outcome

2.2.1 Descriptive

The primary outcome is a composite comprised of:

- day 28 mortality
- vasopressor/inotropic support within first 28 days
- new intensive respiratory support within first 28 days.

The definition also allowed for patients who had unknown day 28 status, but were discharged against medical advice (DAMA) and designated as likely to die within 28 days. However, no participants met this criteria (all cases of DAMA and likely to die within 28 days had known day 28 status).

The proportion of participants who met the primary outcome, and rates of missingness, are reported in Table 2.15 and Table 2.16.

A breakdown of the composite, including missingness by component is reported for ACS-ITT and AVS-ITT in Table 2.17 and Table 2.18 respectively. Missingness was predominantly due to unknown patient status at study day 28.

A summary of the primary outcome by each of the baseline covariates pre-specified to be included in the primary model (or as pre-specified subgroup analyses) are presented in the appendix (Section 3.1.1).

Table 2.15: Summary of primary composite outcome by anticoagulation treatment group.

n (%)	Low dose	Intermediate dose	Low dose with aspirin	Therapeutic dose	Overall
Randomised	610	613	283	50	1556
Outcome missing	14 (2.3)	12 (2.0)	4 (1.4)	0 (0.0)	30 (1.9)
Outcome observed	596 (97.7)	601 (98.0)	279 (98.6)	50 (100.0)	1526 (98.1)
Met primary outcome	35 (5.9)	25 (4.2)	20 (7.2)	7 (14.0)	87 (5.7)

Table 2.16: Summary of primary composite outcome by antiviral treatment group.

n (%)	Standard of care	Nafamostat	Overall
Randomised	73	82	155
Outcome missing	4 (5.5)	7 (8.5)	11 (7.1)
Outcome observed	69 (94.5)	75 (91.5)	144 (92.9)
Met primary outcome	8 (11.6)	4 (5.3)	12 (8.3)

Table 2.17: Breakdown of primary composite outcome by anticoagulation treatment group, ACS-ITT.

Outcome	Breakdown	Anticoagulation					Overall
		Not randomised (n = 32)	Low dose (n = 610)	Intermediate dose (n = 613)	Low dose with aspirin (n = 283)	Therapeutic dose (n = 50)	(n = 1588)
Primary outcome							
No		24 (75.0)	561 (92.0)	576 (94.0)	259 (91.5)	43 (86.0)	1463 (92.1)
Yes		4 (12.5)	35 (5.7)	25 (4.1)	20 (7.1)	7 (14.0)	91 (5.7)
Unknown	Total	4 (12.5)	14 (2.3)	12 (2.0)	4 (1.4)	0 (0.0)	34 (2.1)
	Day 28 status	3 (9.4)	13 (2.1)	10 (1.6)	2 (0.7)	0 (0.0)	28 (1.8)
	Vasopressor/inotropes	1 (3.1)	1 (0.2)	2 (0.3)	2 (0.7)	0 (0.0)	6 (0.4)
Total		32 (100.0)	610 (100.0)	613 (100.0)	283 (100.0)	50 (100.0)	1588 (100.0)
Mortality							
Alive at day 28		29 (90.6)	577 (94.6)	588 (95.9)	271 (95.8)	44 (88.0)	1509 (95.0)
Death within 28 days	Total	0 (0.0)	19 (3.1)	15 (2.4)	10 (3.5)	6 (12.0)	50 (3.1)
	Prior to discharge	0 (0.0)	15 (2.5)	11 (1.8)	10 (3.5)	4 (8.0)	40 (2.5)
	Post-discharge	0 (0.0)	4 (0.7)	4 (0.7)	0 (0.0)	2 (4.0)	10 (0.6)
Unknown		3 (9.4)	14 (2.3)	10 (1.6)	2 (0.7)	0 (0.0)	29 (1.8)
Total		32 (100.0)	610 (100.0)	613 (100.0)	283 (100.0)	50 (100.0)	1588 (100.0)
Vasopressor/inotropes							
Not required		27 (84.4)	591 (96.9)	595 (97.1)	273 (96.5)	48 (96.0)	1534 (96.6)
Use within 28 days	Total	1 (3.1)	6 (1.0)	6 (1.0)	6 (2.1)	2 (4.0)	21 (1.3)
	Prior to discharge	1 (3.1)	5 (0.8)	6 (1.0)	6 (2.1)	2 (4.0)	20 (1.3)
	Post-discharge	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	1 (2.0)	3 (0.2)
Unknown		4 (12.5)	13 (2.1)	12 (2.0)	4 (1.4)	0 (0.0)	33 (2.1)
Total		32 (100.0)	610 (100.0)	613 (100.0)	283 (100.0)	50 (100.0)	1588 (100.0)
Ventilation							
Not required		25 (78.1)	562 (92.1)	579 (94.5)	263 (92.9)	43 (86.0)	1472 (92.7)
Use within 28 days	Total	4 (12.5)	35 (5.7)	24 (3.9)	18 (6.4)	7 (14.0)	88 (5.5)
	Prior to discharge	4 (12.5)	29 (4.8)	19 (3.1)	13 (4.6)	5 (10.0)	70 (4.4)
	Post-discharge	0 (0.0)	6 (1.0)	5 (0.8)	5 (1.8)	2 (4.0)	18 (1.1)
Unknown		3 (9.4)	13 (2.1)	10 (1.6)	2 (0.7)	0 (0.0)	28 (1.8)
Total		32 (100.0)	610 (100.0)	613 (100.0)	283 (100.0)	50 (100.0)	1588 (100.0)

Table 2.18: Breakdown of primary composite outcome by antiviral treatment group, AVS-ITT.

Outcome	Breakdown	Antiviral			Overall
		Not randomised to antiviral (n = 1433)	Standard of care (n = 73)	Nafamostat (n = 82)	(n = 1588)
Primary outcome					
No		1331 (92.9)	61 (83.6)	71 (86.6)	1463 (92.1)
Yes		79 (5.5)	8 (11.0)	4 (4.9)	91 (5.7)
Unknown	Total	23 (1.6)	4 (5.5)	7 (8.5)	34 (2.1)
	Day 28 status	18 (1.3)	3 (4.1)	7 (8.5)	28 (1.8)
	Vasopressor/inotropes	5 (0.3)	1 (1.4)	0 (0.0)	6 (0.4)
Total		1433 (100.0)	73 (100.0)	82 (100.0)	1588 (100.0)
Mortality					
Alive at day 28		1364 (95.2)	70 (95.9)	75 (91.5)	1509 (95.0)
Death within 28 days	Total	50 (3.5)	0 (0.0)	0 (0.0)	50 (3.1)
	Prior to discharge	40 (2.8)	0 (0.0)	0 (0.0)	40 (2.5)
	Post-discharge	10 (0.7)	0 (0.0)	0 (0.0)	10 (0.6)
Unknown		19 (1.3)	3 (4.1)	7 (8.5)	29 (1.8)
Total		1433 (100.0)	73 (100.0)	82 (100.0)	1588 (100.0)
Vasopressor/inotropes					
Not required		1391 (97.1)	68 (93.2)	75 (91.5)	1534 (96.6)
Use within 28 days	Total	18 (1.3)	2 (2.7)	1 (1.2)	21 (1.3)
	Prior to discharge	17 (1.2)	2 (2.7)	1 (1.2)	20 (1.3)
	Post-discharge	3 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)
Unknown		24 (1.7)	3 (4.1)	6 (7.3)	33 (2.1)
Total		1433 (100.0)	73 (100.0)	82 (100.0)	1588 (100.0)
Ventilation					
Not required		1339 (93.4)	62 (84.9)	71 (86.6)	1472 (92.7)
Use within 28 days	Total	76 (5.3)	8 (11.0)	4 (4.9)	88 (5.5)
	Prior to discharge	58 (4.0)	8 (11.0)	4 (4.9)	70 (4.4)
	Post-discharge	18 (1.3)	0 (0.0)	0 (0.0)	18 (1.1)
Unknown		18 (1.3)	3 (4.1)	7 (8.5)	28 (1.8)
Total		1433 (100.0)	73 (100.0)	82 (100.0)	1588 (100.0)

2.2.2 Primary Analysis

The primary model was a logistic regression model adjusting for anticoagulation treatment, antiviral treatment, age (≥ 60 or not), oxygen requirement (required supplemental oxygen or not), and region (India (ref), Australia/New Zealand, and Nepal), with random effects for site (nested within country) and epoch (calendar time 4 week intervals, most recent epoch as reference). The three most recent epochs were combined due to small numbers, and the two earliest epochs were combined for the same reason. Sites with fewer than 5 enrolments were combined within region into an "other sites" category. The primary analysis was based on the FAS-ITT set using the full model as specified in the statistical appendix to the core protocol. An odds ratio less than 1 implies a benefit (reduction in the odds of primary outcome).

2.2.2.1 FAS-ITT

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch
- **Set**: FAS-ITT

The trial decision quantities are reported in Table 2.19 and the model parameter posteriors are summarised in Table 2.20 and Figure 2.14.

Table 2.19: Summary of domain decision qauntities for primary outcome model fit to the FAS-ITT set.

Intervention	Posterior	Superior $\Pr(\text{OR} = \min(\text{OR}))$	Effective $\Pr(\text{OR} < 1)$	Futile $\Pr(\text{OR} > 1/1.1)$	Equivalent $\Pr(1/1.1 < \text{OR} < 1.1)$
Antiviral					
SoC	1.00	0.05	-	-	-
Nafamostat	0.36 (0.10, 1.22)	0.95	0.95	0.07	0.03
Anticoagulation					
Low-dose	1.00	0.06	-	-	-
Intermediate-dose	0.71 (0.40, 1.22)	0.67	0.90	0.18	0.13
Low-dose with aspirin	0.85 (0.45, 1.60)	0.27	0.69	0.42	0.21
Therapeutic-dose	2.57 (0.87, 7.07)	0.01	0.04	0.97	0.03

Table 2.20: Summary of model parameters (fixed-effects odds-ratios) for primary outcome model fit to the FAS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.36	(0.10, 1.22)	0.43 (0.31)	0.95
Intermediate-dose	0.71	(0.40, 1.22)	0.73 (0.21)	0.90
Low-dose with aspirin	0.85	(0.45, 1.60)	0.90 (0.30)	0.69
Therapeutic-dose	2.57	(0.87, 7.07)	2.93 (1.65)	0.04
Ineligible aspirin	2.26	(0.61, 7.42)	2.71 (1.80)	0.11
Age ≥ 60	1.75	(1.07, 2.82)	1.80 (0.45)	0.01
Female	0.64	(0.38, 1.03)	0.66 (0.17)	0.97
Oxygen requirement	3.65	(2.21, 6.11)	3.78 (1.01)	0.00
Australia/New Zealand	1.05	(0.25, 4.06)	1.34 (1.06)	0.47
Nepal	1.59	(0.42, 5.81)	1.98 (1.49)	0.24

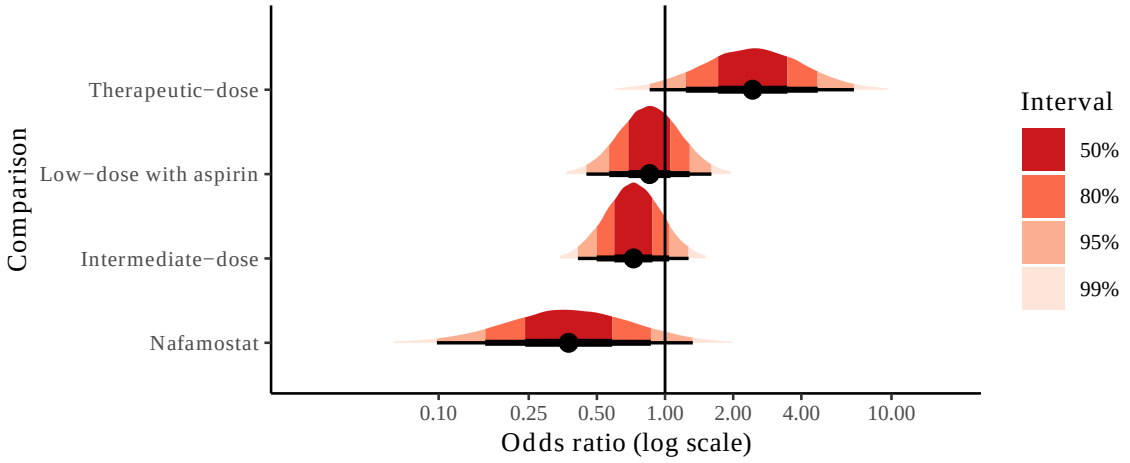

Figure 2.13: Posterior densities for the treatment effect odds ratios, FAS-ITT.

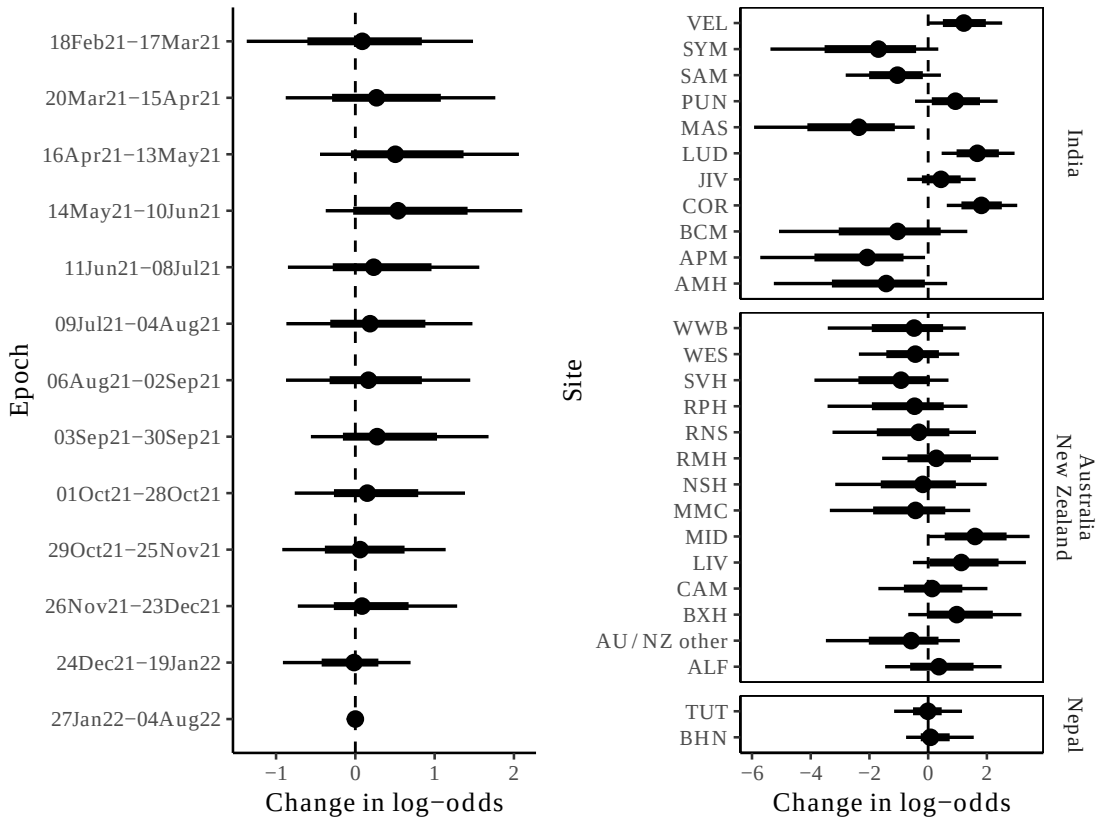

Figure 2.14: Posterior Summaries (point - median, block - 75% CrI, line 0.95% CrI) of odds ratio for epoch and site effects for the primary outcome model fit to the FAS-ITT set.

2.2.2.2 AVS-ITT

The SAP pre-specified that the primary model would be fit using the AVS-ITT including all the pre-specified covariates. This analyses deviated from that specified in the SAP for a number of reasons:

- almost all in AVS-ITT were enrolled in Australia/New Zealand, so region was dropped
- concurrent randomisation to antiviral domain (where available) throughout entire study, so epoch term dropped
- other covariates dropped due to small number of cases and events.

Therefore, the analysis restricted to the AVS-ITT set was based on a antiviral treatment only model. Due to the small number of events, the parameter posteriors will be sensitive to the priors.

In summary, the analysis was based on the following:

- **Model**: logistic regression
- **Terms**: antiviral intervention, anticoagulation intervention, age group, sex, oxygen requirement
- **Set**: AVS-ITT

Table 2.21: Summary of domain decision qauntities for primary outcome model fit to the AVS-ITT set.

Intervention	Posterior	Superior $\Pr(\text{OR} = \min(\text{OR}))$	Effective $\Pr(\text{OR} < 1)$	Futile $\Pr(\text{OR} > 1/1.1)$	Equivalent $\Pr(1/1.1 < \text{OR} < 1.1)$
Antiviral					
SoC	1.00	0.07	-	-	-
Nafamostat	0.43 (0.13, 1.34)	0.93	0.93	0.10	0.05
Anticoagulation					
Low-dose	1.00	0.12	-	-	-
Intermediate-dose	0.82 (0.20, 3.30)	0.23	0.61	0.44	0.10
Low-dose with aspirin	0.61 (0.08, 3.99)	0.47	0.69	0.34	0.06
Therapeutic-dose	0.99 (0.17, 5.25)	0.18	0.50	0.54	0.09

Table 2.22: Summary of model parameters (fixed-effects odds-ratios) for primary outcome model fit to the AVS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.43	(0.13, 1.34)	0.50 (0.32)	0.93
Intermediate-dose	0.82	(0.20, 3.30)	1.06 (0.89)	0.61
Low-dose with aspirin	0.61	(0.08, 3.99)	0.96 (1.13)	0.69
Therapeutic-dose	0.99	(0.17, 5.25)	1.42 (1.50)	0.50
Age ≥ 60	1.17	(0.30, 4.13)	1.43 (1.03)	0.41
Female	0.55	(0.14, 1.84)	0.67 (0.47)	0.82
Oxygen requirement	3.11	(0.73, 19.65)	4.87 (6.29)	0.07

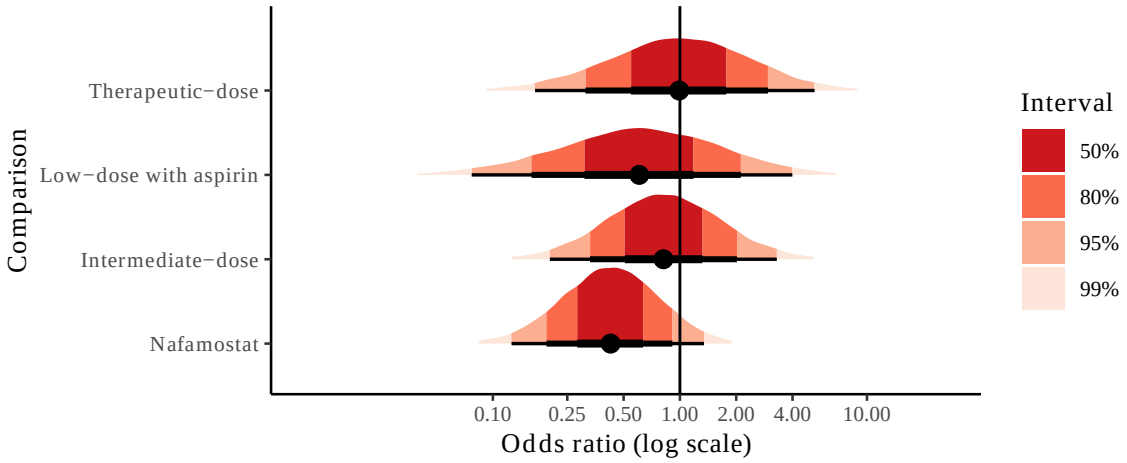

Figure 2.15: Posterior densities for the treatment effect odds ratios, AVS-ITT.

2.2.2.3 ACS-ITT

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch
- **Set**: ACS-ITT

Table 2.23: Summary of domain decision qauntities (relative to standard dose) for primary outcome model fit to the ACS-ITT set.

Intervention	Posterior	Superior Pr(OR = min(OR))	Effective Pr(OR < 1)	Futile Pr(OR > 1/1.1)	Equivalent Pr(1/1.1 < OR < 1.1)
Antiviral					
SoC	1.00	0.03	-	-	-
Nafamostat	0.25 (0.05, 1.06)	0.97	0.97	0.04	0.02
Anticoagulation					
Low-dose	1.00	0.06	-	-	-
Intermediate-dose	0.70 (0.40, 1.21)	0.68	0.90	0.18	0.12
Low-dose with aspirin	0.85 (0.45, 1.60)	0.26	0.69	0.42	0.21
Therapeutic-dose	2.54 (0.88, 7.09)	0.01	0.04	0.97	0.03

Table 2.24: Summary of model parameters (fixed-effects odds-ratios) for primary outcome model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.25	(0.05, 1.06)	0.33 (0.29)	0.97
Intermediate-dose	0.70	(0.40, 1.21)	0.73 (0.21)	0.90
Low-dose with aspirin	0.85	(0.45, 1.60)	0.89 (0.29)	0.69
Therapeutic-dose	2.54	(0.88, 7.09)	2.91 (1.66)	0.04
Ineligible aspirin	2.55	(0.66, 8.57)	3.07 (2.10)	0.08
Age $\geq$ 60	1.75	(1.07, 2.87)	1.81 (0.46)	0.01
Female	0.64	(0.38, 1.05)	0.66 (0.17)	0.96
Oxygen requirement	3.77	(2.24, 6.45)	3.92 (1.09)	0.00
Australia/New Zealand	0.84	(0.19, 3.46)	1.08 (0.88)	0.59
Nepal	1.72	(0.44, 6.21)	2.13 (1.57)	0.21

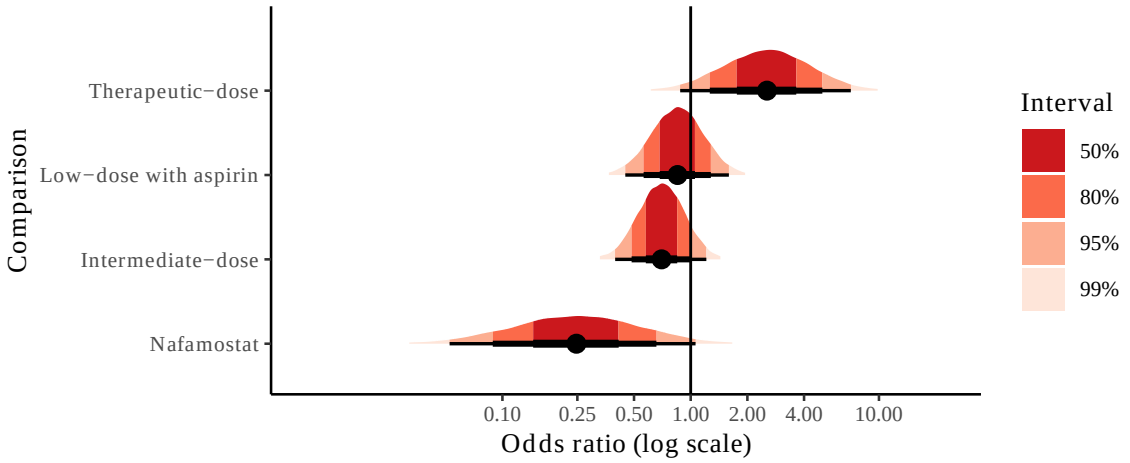

Figure 2.16: Posterior densities for the treatment effect odds ratios, ACS-ITT.

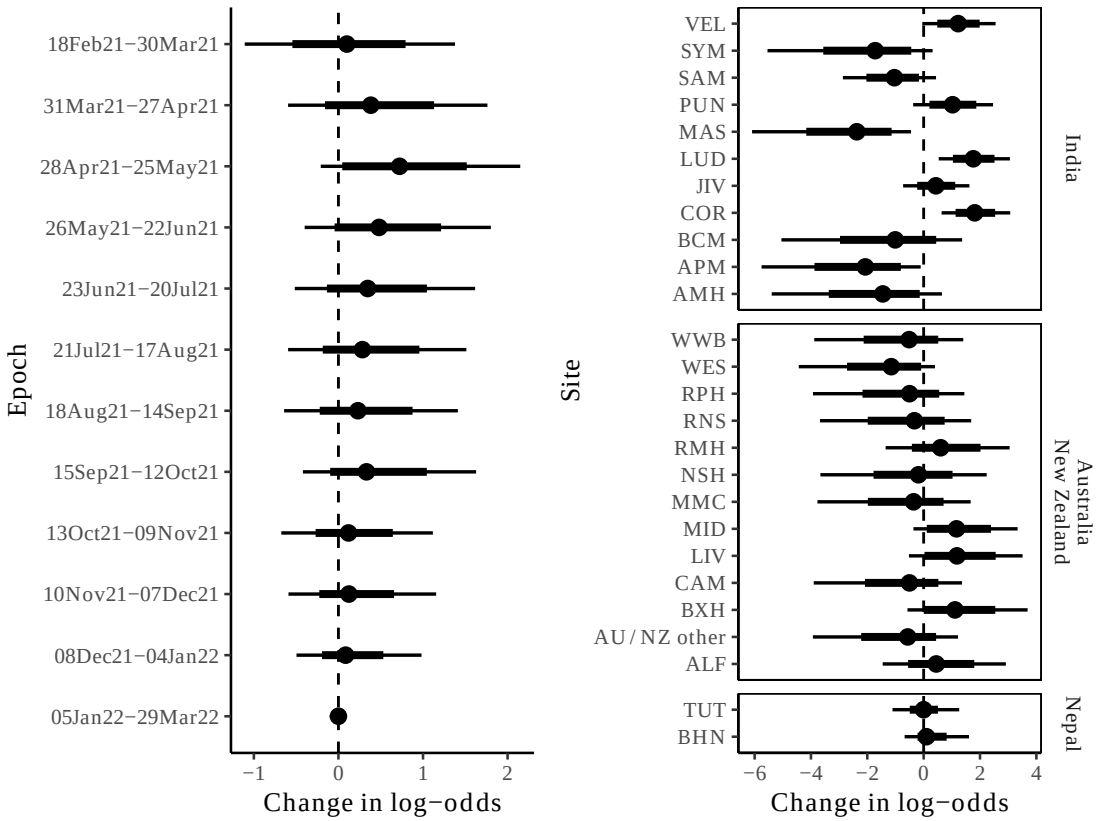

Figure 2.17: Posterior Summaries (point - median, block - 75% CrI, line 0.95% CrI) of odds ratio for epoch and site effects for the primary outcome model fit to the ACS-ITT set.

2.3 Secondary Outcomes

For all secondary outcomes, the primary model (the model adjusting for interventions, age group, country, site, and epoch using the relevant outcome model) was fit to the ACS-ITT set. The only sensitivity analysis conducted was to repeat the analyses restricted to contemporaneous controls using a reduced model.

2.3.1 Time to clinical recovery to day 28

This section reports on the analysis for time to clinical recovery. Time to clinical recovery was taken as the first day from the index admission at which the patient had a WHO outcome score of 3 or less. For participants whose WHO outcome score was greater than 3 on the day of discharge, their day of recovery was counted as the first day after discharge, e.g. if discharged on day 7 with a daily WHO score of 4, then time to recovery was quantified as 8. Death was treated as a competing-risk to recovery. If recovery and death reportedly occurred on the same day (e.g. daily status WHO scale < 4 but discharge outcome of death on same day), then the patient was considered to have died on that day without recovery. No adjustment was made for participants who recovered but then subsequently died (i.e. only the first event was considered; any such patients were just counted as recovered on the relevant day). No allowance was made for participants who discharged against medical advice (treated as recovered following discharge).

The analysis of the time to clinical recovery to day 28 outcome used a discrete-time competing risk time-to-event model (multinomial logistic regression). The events of interest were death or recovery. Baseline cause-specific hazards were modelled separately for death and recovery with some smoothing enforced across adjacent time points via a first order random walk prior on the logit intercept terms.

This modelling approach deviated from that specified in the SAP which did not account for the competing risk of death.

2.3.1.1 FAS-ITT

- **Model**: multinomial logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, epoch
- **Set**: FAS-ITT

Table 2.25: Summary for time to recovery (TTR) or death to day 28, anticoagulation domain, FAS-ITT

Intervention	Randomised	Known	Died	Recovered	Unrecovered	TTR, Median (Q1, Q3)
Not randomised	32	32	0 (0.0)	30 (93.8)	2 (6.2)	6 (5.00, 8.75)
Low	610	610	15 (2.5)	592 (97.0)	3 (0.5)	6 (4.00, 7.00)
Intermediate	613	613	10 (1.6)	598 (97.6)	5 (0.8)	6 (4.00, 7.00)
Low with aspirin	283	283	9 (3.2)	271 (95.8)	3 (1.1)	6 (4.00, 8.00)
Therapeutic	50	50	4 (8.0)	46 (92.0)	0 (0.0)	6 (4.25, 9.00)

Table 2.26: Summary for time to recovery (TTR) or death to day 28, antiviral domain, FAS-ITT

Intervention	Randomised	Known	Died	Recovered	Unrecovered	TTR, Median (Q1, Q3)
Not randomised	1433	1433	38 (2.7)	1386 (96.7)	9 (0.6)	6 (4.00, 7.00)
Standard of care	73	73	0 (0.0)	71 (97.3)	2 (2.7)	6 (5.00, 9.00)
Nafamostat	82	82	0 (0.0)	80 (97.6)	2 (2.4)	6 (5.00, 9.00)

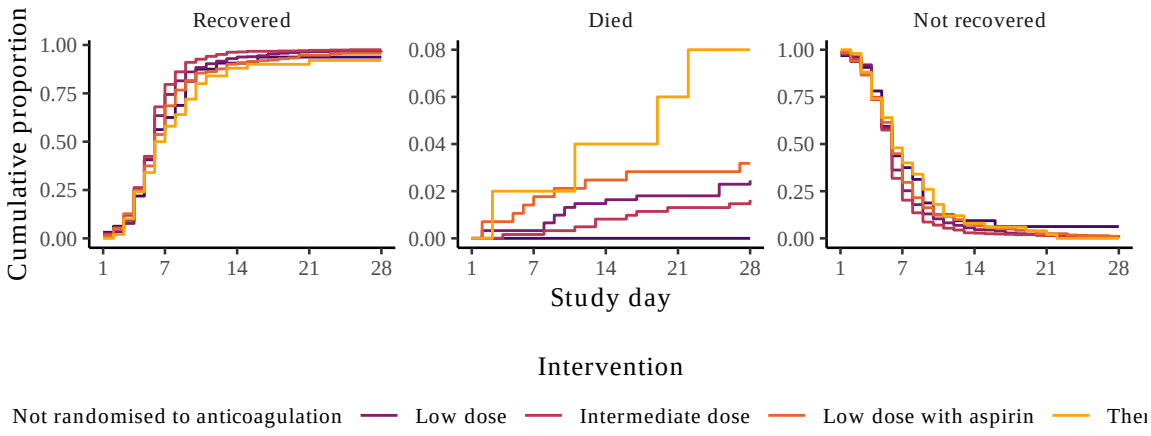

Figure 2.18: Observed progression of patients with respect to death and recovery, anticoagulation domain, FAS-ITT.

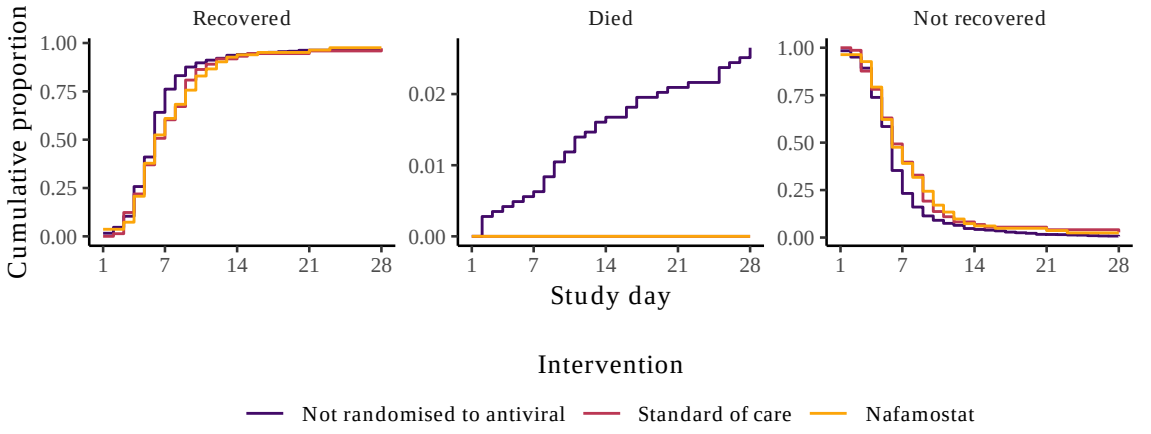

Figure 2.19: Observed progression of patients with respect to death and recovery, antiviral domain, FAS-ITT.

Table 2.27: Posterior summary of cause-specific odds ratios for recovery or death to day 28, FAS-ITT.

Factor	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Recovery				
Nafamostat	1.05	(0.70, 1.51)	1.06 (0.21)	0.58
Intermediate	1.12	(0.98, 1.29)	1.12 (0.08)	0.96
Low with aspirin	1.04	(0.86, 1.24)	1.04 (0.10)	0.66
Therapeutic	0.84	(0.57, 1.22)	0.86 (0.17)	0.19
Ineligible aspirin	0.78	(0.51, 1.16)	0.79 (0.16)	0.11
Age $\geq$ 60	0.67	(0.58, 0.76)	0.67 (0.05)	0.00
Oxygen requirement	0.61	(0.53, 0.70)	0.61 (0.04)	0.00
Australia/New Zealand	0.84	(0.48, 1.50)	0.88 (0.26)	0.27
Nepal	0.78	(0.27, 2.58)	0.93 (0.62)	0.31
Death				
Nafamostat	1.02	(0.10, 10.67)	1.99 (3.04)	0.50
Intermediate	0.67	(0.27, 1.65)	0.74 (0.36)	0.18
Low with aspirin	0.86	(0.35, 2.16)	0.97 (0.51)	0.37
Therapeutic	2.97	(0.82, 10.90)	3.72 (2.84)	0.95
Ineligible aspirin	4.53	(1.16, 16.65)	5.62 (4.13)	0.99
Age $\geq$ 60	0.83	(0.39, 1.72)	0.89 (0.35)	0.32
Oxygen requirement	1.42	(0.66, 3.49)	1.59 (0.76)	0.81
Australia/New Zealand	0.55	(0.11, 2.37)	0.72 (0.62)	0.22
Nepal	1.81	(0.39, 8.68)	2.53 (2.45)	0.79

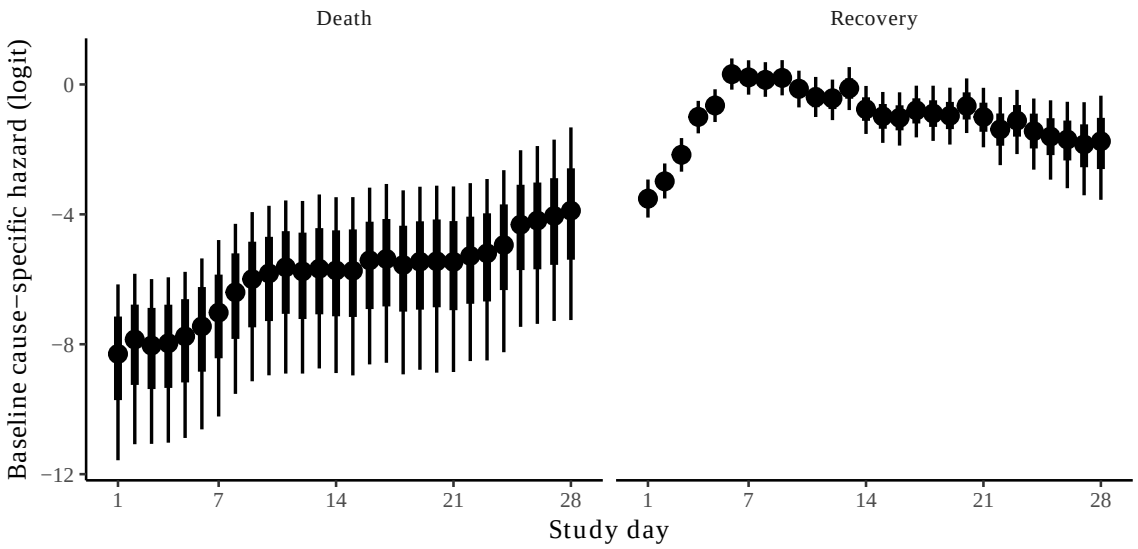

Figure 2.20: Cause-specific baseline hazard posterior summaries, FAS-ITT.

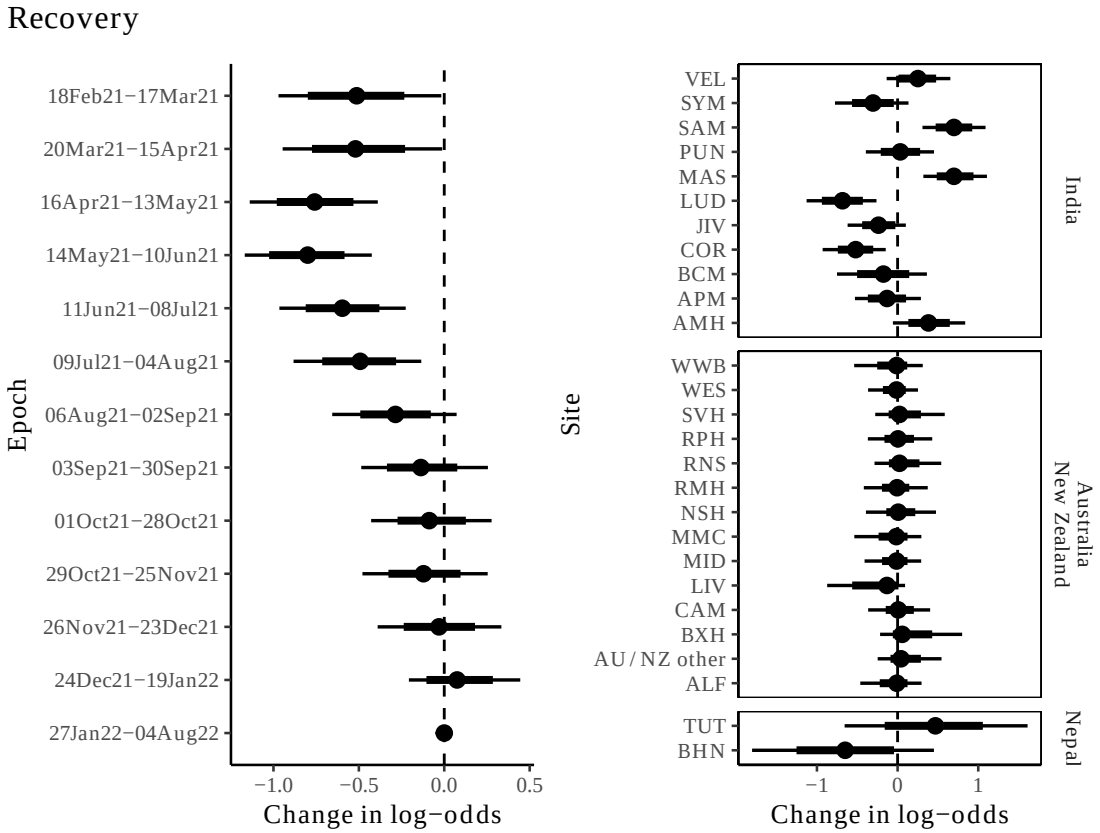

Figure 2.21: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on recovery to day 28 for the outcome model fit to the FAS-ITT set.

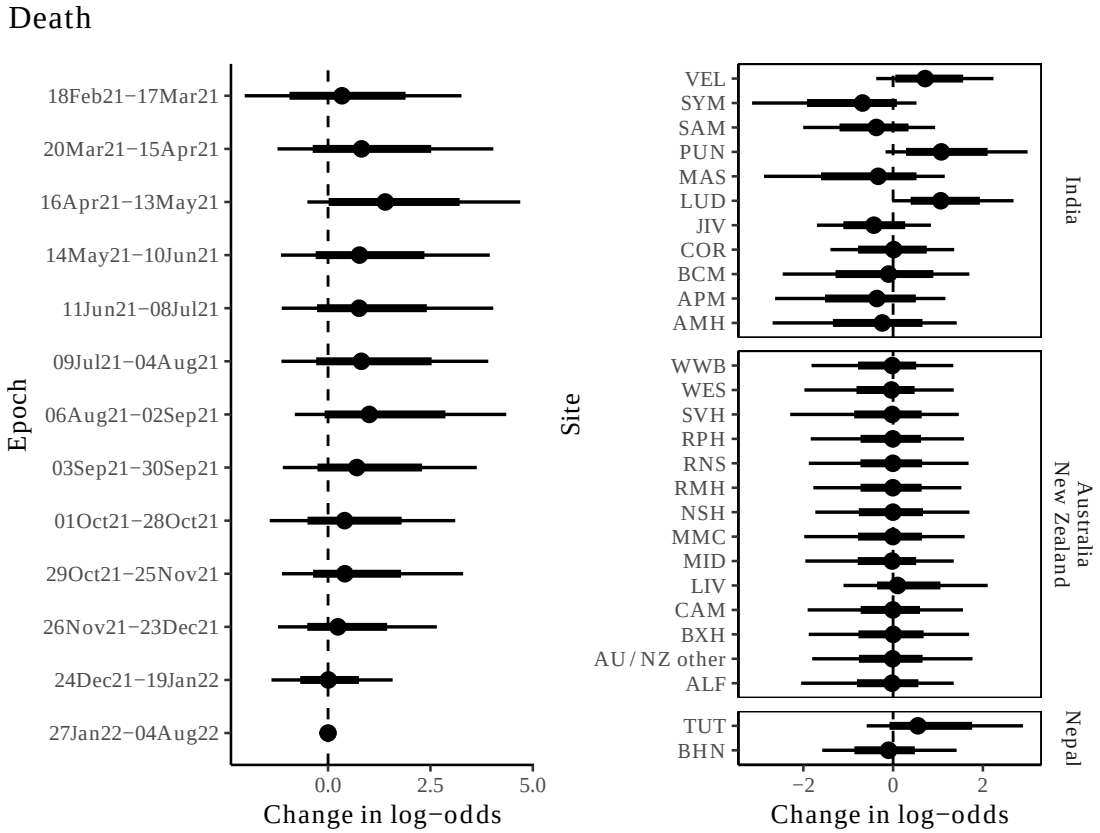

Figure 2.22: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on death to day 28 for the outcome model fit to the FAS-ITT set.

2.3.1.2 AVS-ITT

- **Model**: multinomial logistic regression
- **Terms**: antiviral intervention, anticoagulation intervention, age group, sex, oxygen requirement
- **Set**: AVS-ITT

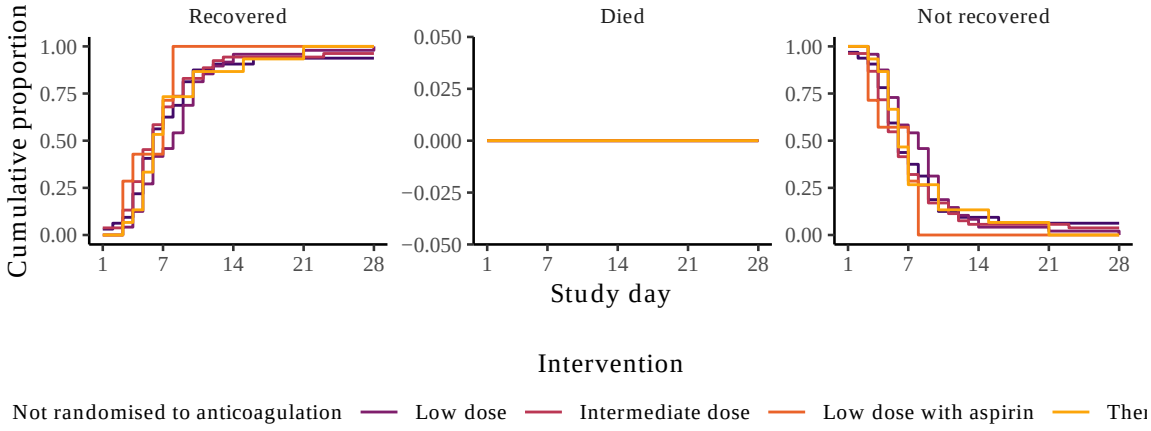

Figure 2.23: Observed progression of patients with respect to death and recovery, anticoagulation domain, AVS-ITT.

Table 2.28: Posterior summary of cause-specific odds ratios for recovery or death to day 28, AVS-ITT.

Factor	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Recovery				
Nafamostat	1.04	(0.72, 1.50)	1.05 (0.20)	0.57
Intermediate	0.75	(0.32, 1.68)	0.81 (0.35)	0.24
Low with aspirin	1.59	(0.55, 4.29)	1.80 (0.98)	0.81
Therapeutic	1.06	(0.43, 2.52)	1.17 (0.54)	0.56
Age ≥ 60	0.32	(0.20, 0.50)	0.33 (0.08)	0.00
Oxygen requirement	0.77	(0.50, 1.18)	0.79 (0.18)	0.12
Death				
Nafamostat	1.00	(0.06, 15.61)	2.60 (6.31)	0.50
Intermediate	1.00	(0.06, 16.32)	2.76 (6.70)	0.50
Low with aspirin	1.07	(0.07, 16.34)	2.80 (5.92)	0.52
Therapeutic	0.98	(0.06, 15.85)	2.65 (5.77)	0.49
Age ≥ 60	0.71	(0.01, 70.20)	11.26 (113.06)	0.44
Oxygen requirement	0.58	(0.01, 61.08)	10.84 (136.99)	0.41

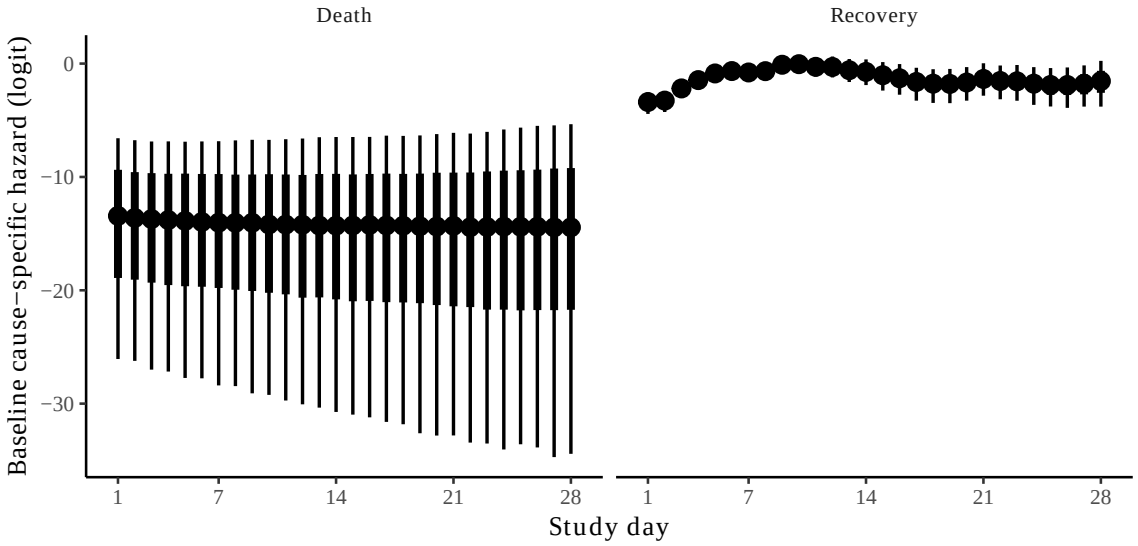

Figure 2.24: Cause-specific baseline hazard posterior summaries, AVS-ITT.

2.3.1.3 ACS-ITT

- **Model**: multinomial logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, epoch
- **Set**: ACS-ITT

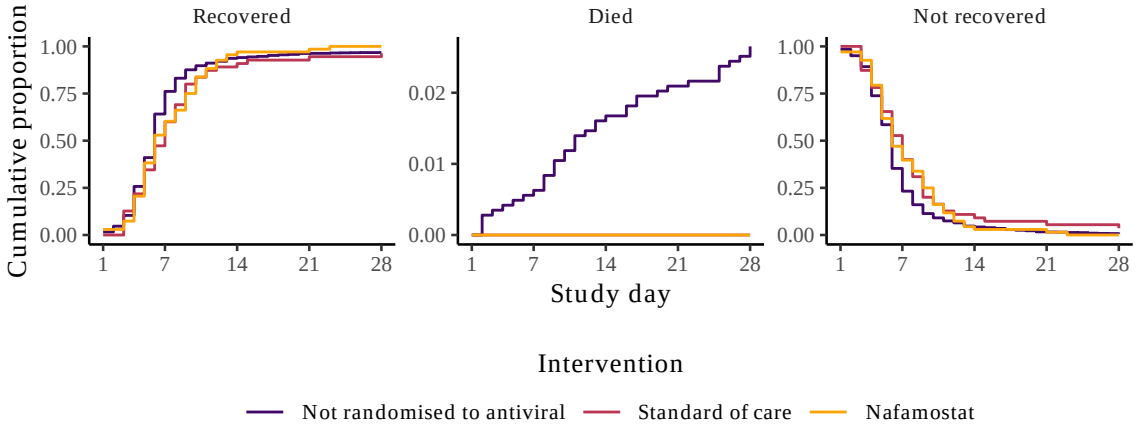

Figure 2.25: Observed progression of patients with respect to death and recovery, antiviral domain, ACS-ITT.

Table 2.29: Posterior summary of cause-specific odds ratios for recovery or death to day 28, ACS-ITT.

Factor	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Recovery				
Nafamostat	1.27	(0.84, 1.90)	1.31 (0.28)	0.87
Intermediate	1.12	(0.97, 1.27)	1.12 (0.08)	0.94
Low with aspirin	1.04	(0.85, 1.23)	1.04 (0.10)	0.64
Therapeutic	0.80	(0.54, 1.18)	0.82 (0.16)	0.14
Ineligible aspirin	0.77	(0.48, 1.18)	0.80 (0.19)	0.15
Age $\geq$ 60	0.68	(0.59, 0.78)	0.68 (0.05)	0.00
Oxygen requirement	0.58	(0.51, 0.67)	0.58 (0.04)	0.00
Australia/New Zealand	0.92	(0.51, 1.68)	0.96 (0.30)	0.38
Nepal	0.80	(0.25, 2.47)	0.92 (0.62)	0.30
Death				
Nafamostat	1.07	(0.11, 11.16)	2.16 (3.58)	0.52
Intermediate	0.62	(0.25, 1.50)	0.69 (0.32)	0.14
Low with aspirin	0.91	(0.39, 2.18)	1.00 (0.45)	0.42
Therapeutic	3.00	(0.72, 11.61)	3.79 (2.94)	0.94
Ineligible aspirin	4.17	(1.08, 14.91)	5.23 (3.65)	0.98
Age $\geq$ 60	0.87	(0.41, 1.87)	0.95 (0.39)	0.38
Oxygen requirement	1.24	(0.56, 2.95)	1.36 (0.62)	0.69
Australia/New Zealand	0.57	(0.11, 2.49)	0.75 (0.65)	0.24
Nepal	1.79	(0.34, 8.89)	2.45 (2.43)	0.77

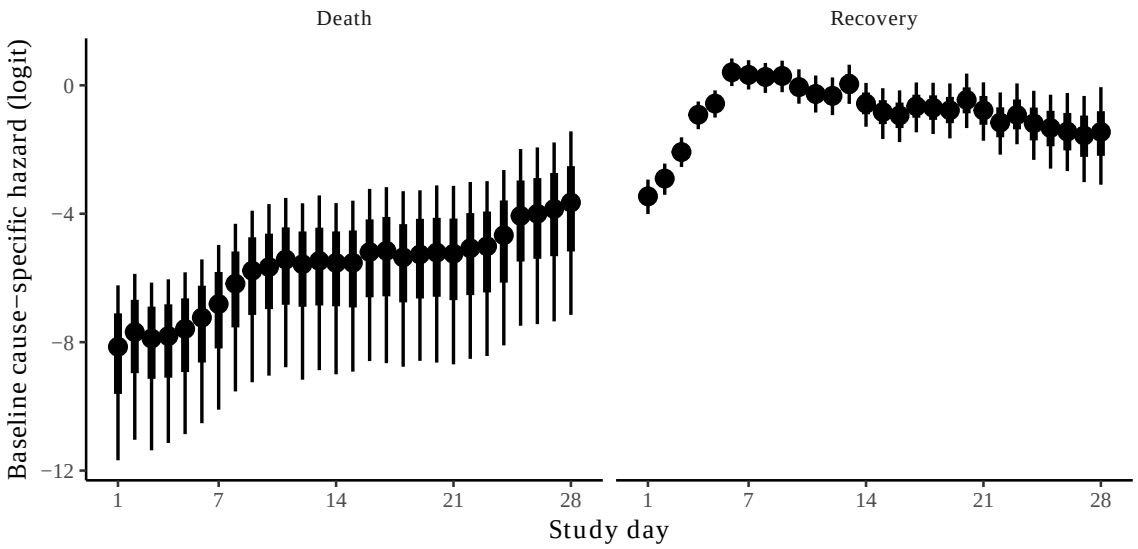

Figure 2.26: Cause-specific baseline hazard posterior summaries, ACS-ITT.

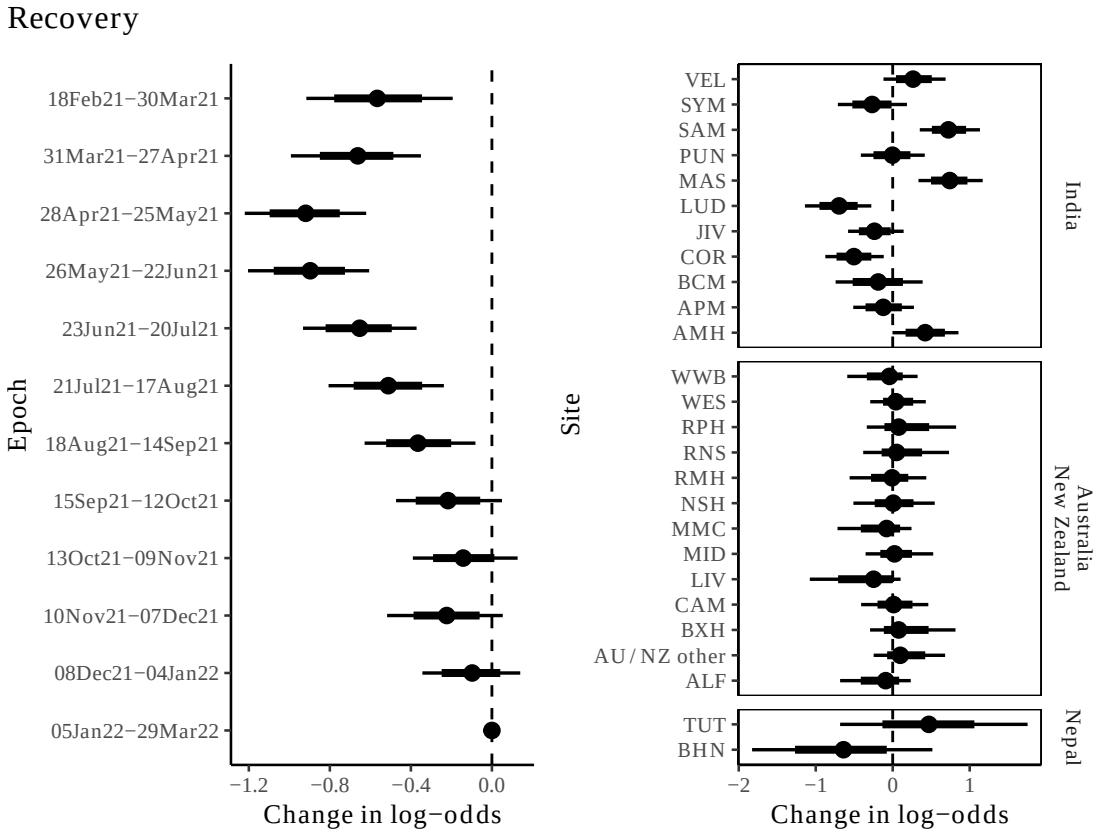

Figure 2.27: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on recovery to day 28 for the outcome model fit to the ACS-ITT set.

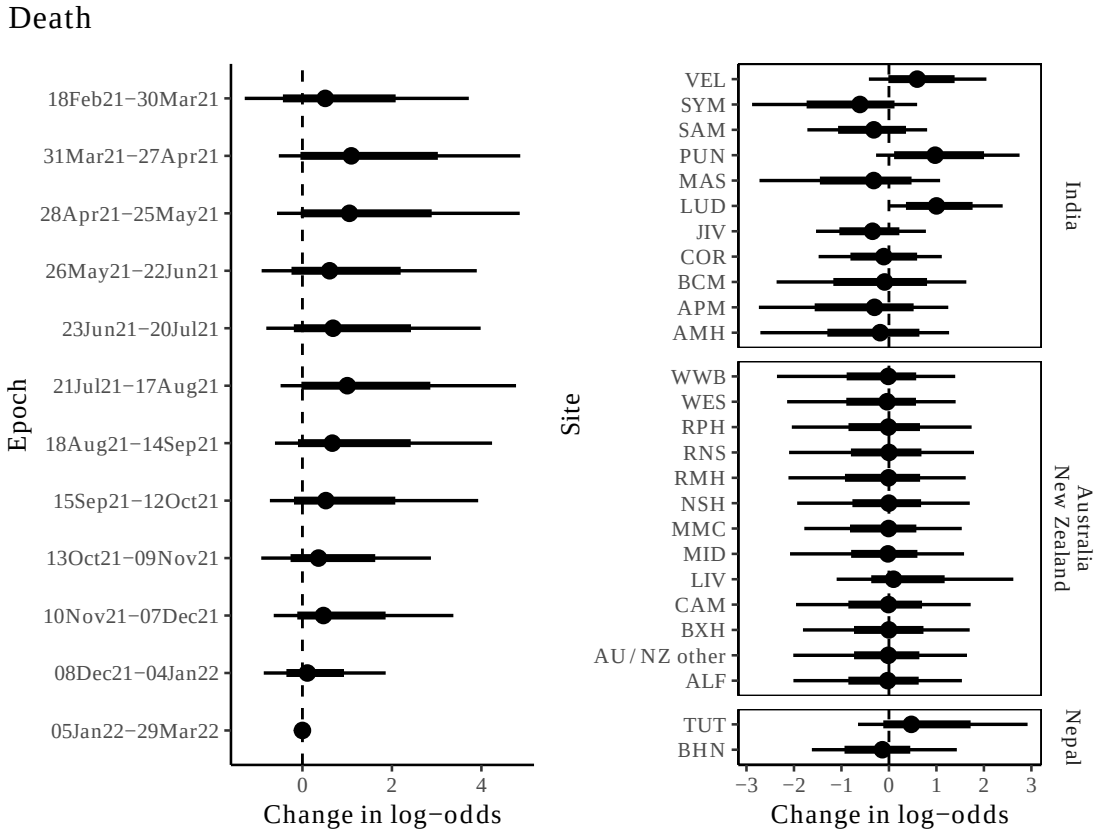

Figure 2.28: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on death to day 28 for the outcome model fit to the ACS-ITT set.

2.3.2 WHO 8-point ordinal outcome scale at day 28

This section reports on the analysis of the secondary outcome: WHO outcome scale at day 28. The model is coded so that an odds ratio less than 1 implies a benefit (reduction in odds of having a higher WHO score at day 28).

Table 2.30 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. Similarly for the antiviral arms in Table 2.31.

Table 2.30: Summary of WHO scale at 28 by anticoagulation treatment group, FAS-ITT.

Anticoagulation intervention	Patients	Known	Deaths	Hospitalised	WHO, Median (Q1, Q3)
Not randomised to anticoagulation	32	29	0 (0%)	4 (14%)	2 (1, 2)
Low-dose	610	596	19 (3%)	7 (1%)	1 (1, 2)
Intermediate-dose	613	603	15 (2%)	5 (1%)	1 (1, 2)
Low-dose with aspirin	283	281	10 (4%)	5 (2%)	1 (1, 2)
Therapeutic-dose	50	50	6 (12%)	1 (2%)	1 (1, 2)
Overall	**1588**	**1559**	**50 (3%)**	**22 (1%)**	**1 (1, 2)**

Table 2.31: Summary of WHO scale at 28 by antiviral treatment group, FAS-ITT.

Antiviral intervention	Patients	Known	Deaths	Hospitalised	WHO, Median (Q1, Q3)
Not randomised to antiviral	1433	1414	50 (4%)	13 (1%)	1 (1, 2)
Standard of care	73	70	0 (0%)	6 (9%)	2 (1, 2)
Nafamostat	82	75	0 (0%)	3 (4%)	1 (1, 2)
Overall	**1588**	**1559**	**50 (3%)**	**22 (1%)**	**1 (1, 2)**

2.3.2.1 FAS-ITT

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch.
- **Set**: FAS-ITT

Figure 2.29 and Figure 2.30 report on the distribution of day 28 WHO score.

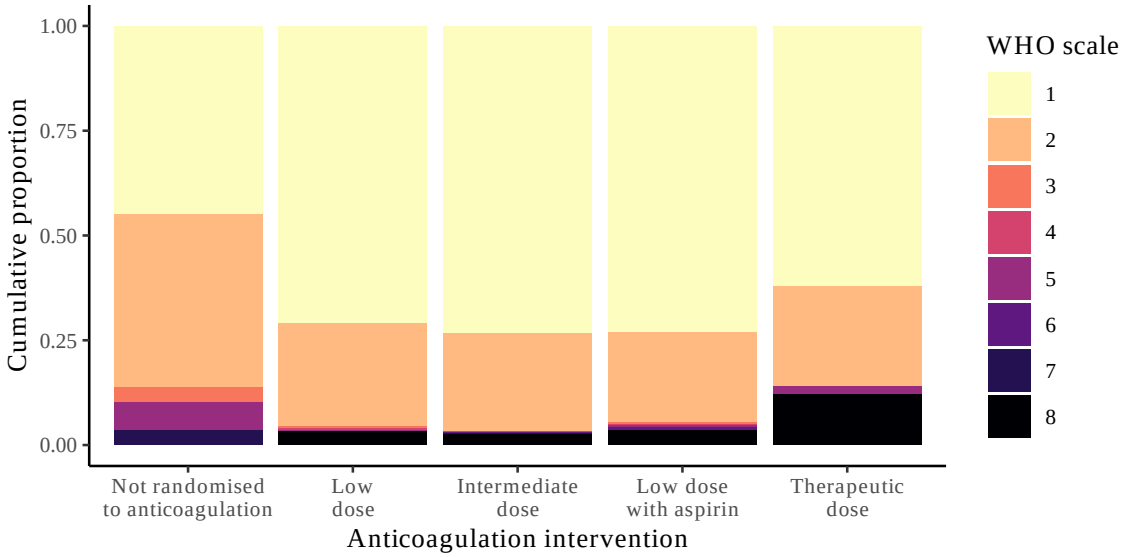

Figure 2.29: Observed distribution of WHO outcome scale at day 28 by anticoagulation treatment group, FAS-ITT.

The model parameters (odds ratios) are summarised in Table 2.32 for the fixed-effect terms and in Figure 2.32 for the site and epoch specific terms.

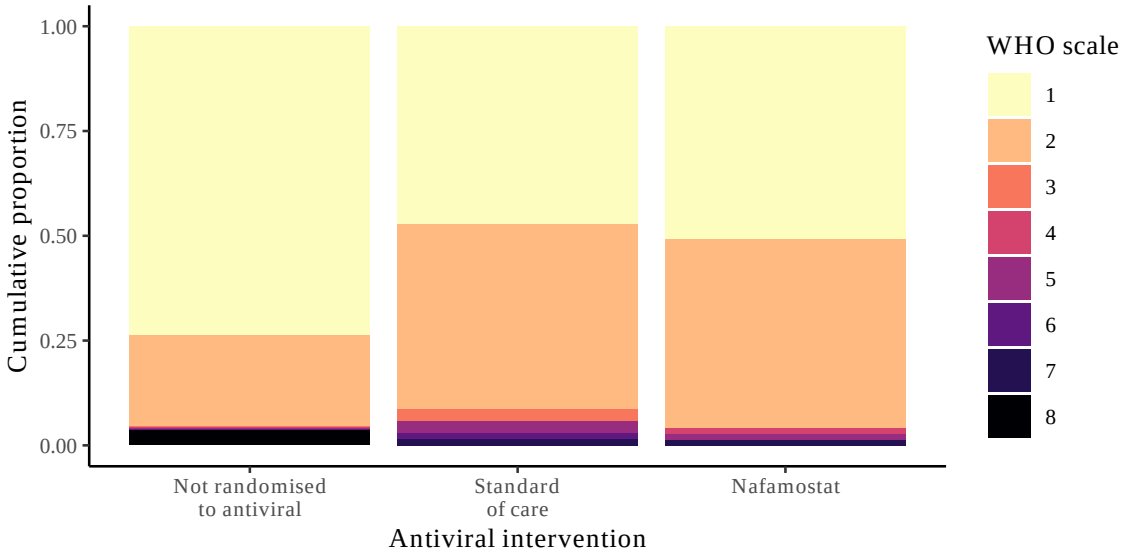

Figure 2.30: Observed distribution of WHO outcome scale at day 28 by antiviral treatment group, FAS-ITT.

Table 2.32: Summary of model parameters (fixed-effects odds-ratios) for WHO outcome scale at day 28 outcome model fit to the FAS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.68	(0.35, 1.32)	0.72 (0.25)	0.88
Intermediate-dose	0.81	(0.61, 1.07)	0.81 (0.12)	0.93
Low-dose with aspirin	0.73	(0.51, 1.05)	0.75 (0.14)	0.95
Therapeutic-dose	1.69	(0.84, 3.37)	1.80 (0.66)	0.07
Ineligible aspirin	1.63	(0.74, 3.51)	1.76 (0.72)	0.11
Age $\geq$ 60	2.50	(1.91, 3.27)	2.52 (0.35)	0.00
Female	0.94	(0.73, 1.20)	0.95 (0.12)	0.70
Oxygen requirement	2.13	(1.59, 2.86)	2.15 (0.32)	0.00
Australia/New Zealand	1.32	(0.42, 4.00)	1.55 (0.95)	0.32
Nepal	0.55	(0.18, 1.95)	0.68 (0.53)	0.83

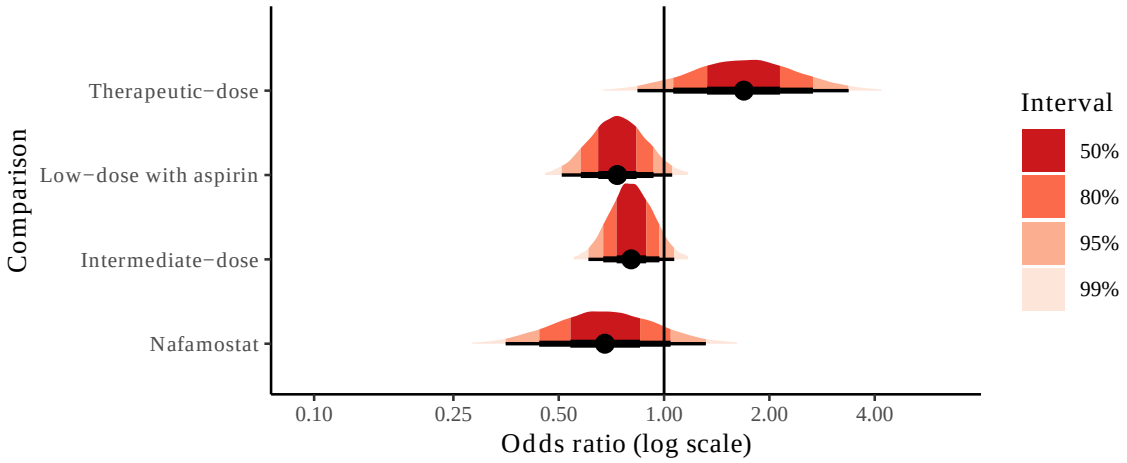

Figure 2.31: Posterior densities for the treatment effect odds ratios, FAS-ITT.

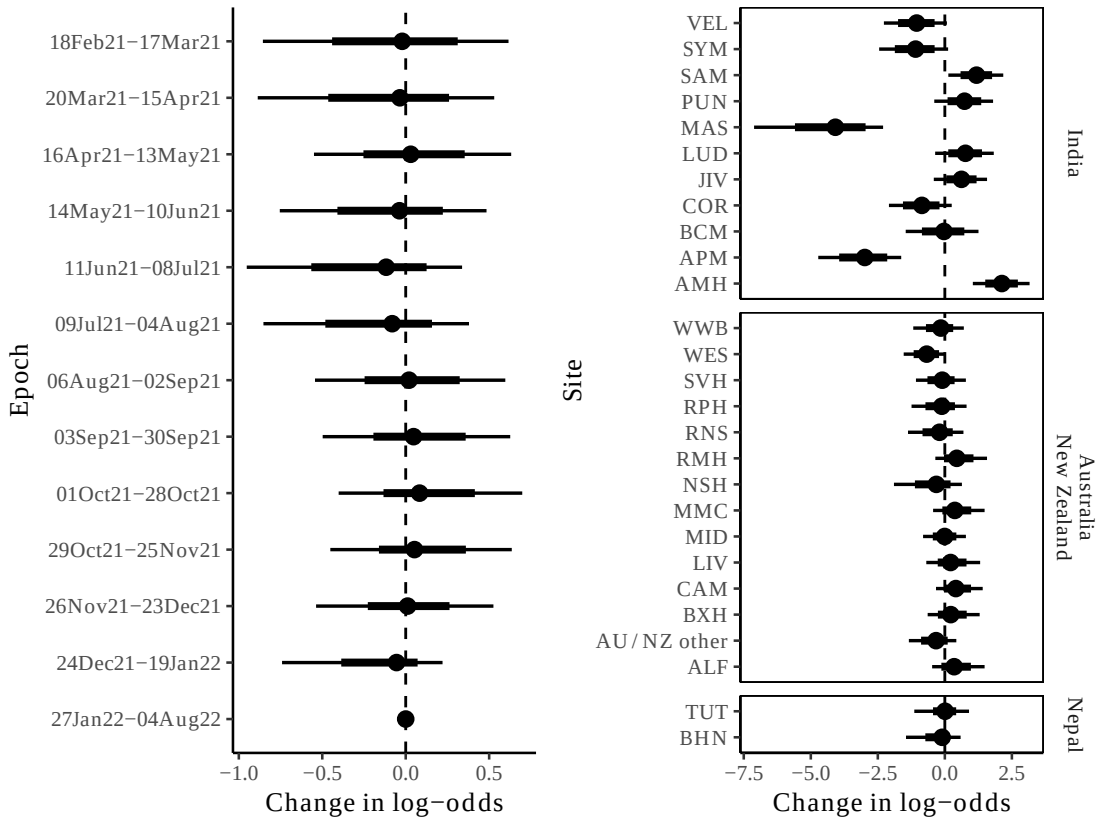

Figure 2.32: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on WHO outcome scale at day 28 for the outcome model fit to the FAS-ITT set.

2.3.2.2 AVS-ITT

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: antiviral intervention, anticoagulation intervention, age group, sex, oxygen requirement
- **Set**: AVS-ITT

Figure 2.33 presents the distribution of day 28 WHO score by anticoagulation intervention for AVS-ITT.

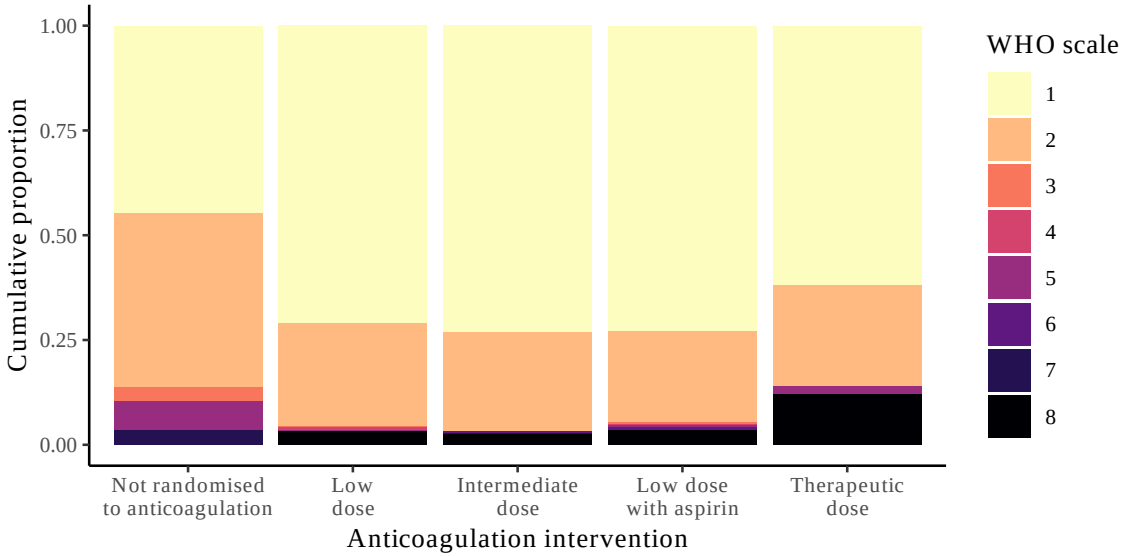

Figure 2.33: Observed distribution of WHO outcome scale at day 28 by anticoagulation treatment group, AVS-ITT.

Table 2.33: Summary of model parameters (fixed-effects odds-ratios) for WHO outcome scale at day 28 outcome model fit to the AVS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.72	(0.36, 1.42)	0.77 (0.27)	0.82
Intermediate-dose	1.35	(0.61, 3.03)	1.47 (0.63)	0.24
Low-dose with aspirin	0.79	(0.19, 3.14)	1.01 (0.81)	0.63
Therapeutic-dose	1.82	(0.60, 5.45)	2.12 (1.29)	0.14
Age ≥ 60	3.88	(1.83, 8.47)	4.21 (1.74)	0.00
Female	1.20	(0.60, 2.40)	1.28 (0.47)	0.30
Oxygen requirement	1.18	(0.56, 2.54)	1.28 (0.51)	0.33

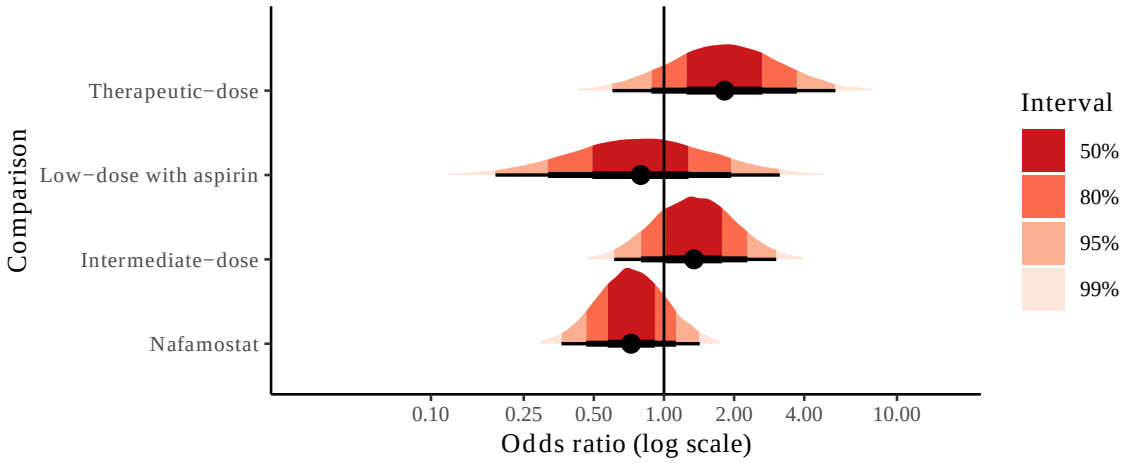

Figure 2.34: Posterior densities for the treatment effect odds ratios, AVS-ITT.

2.3.2.3 ACS-ITT

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch.
- **Set**: ACS-ITT

Figure 2.35 presents the distribution of day 28 WHO score by antiviral intervention for ACS-ITT.

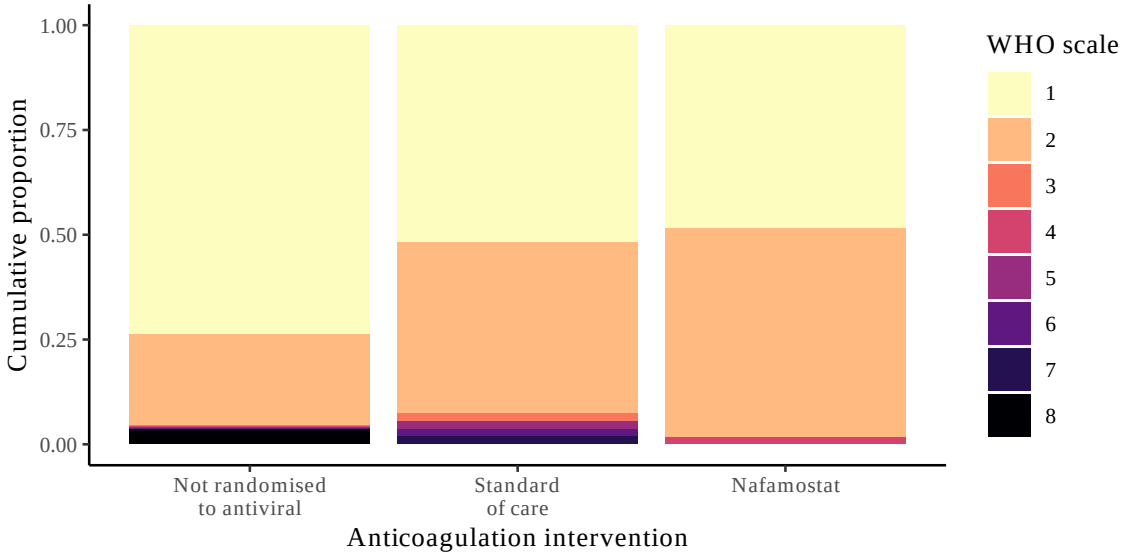

Figure 2.35: Observed distribution of WHO outcome scale at day 28 by antiviral treatment group, ACS-ITT.

Table 2.34: Summary of model parameters (fixed-effects odds-ratios) for WHO outcome scale at day 28 outcome model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.73	(0.34, 1.56)	0.79 (0.31)	0.79
Intermediate-dose	0.81	(0.61, 1.08)	0.82 (0.12)	0.93
Low-dose with aspirin	0.73	(0.51, 1.06)	0.75 (0.14)	0.95
Therapeutic-dose	1.70	(0.84, 3.40)	1.80 (0.66)	0.07
Ineligible aspirin	1.68	(0.76, 3.59)	1.80 (0.74)	0.10
Age ≥ 60	2.37	(1.80, 3.11)	2.39 (0.33)	0.00
Female	0.94	(0.72, 1.21)	0.95 (0.13)	0.69
Oxygen requirement	2.22	(1.65, 2.98)	2.25 (0.34)	0.00
Australia/New Zealand	1.13	(0.35, 3.49)	1.34 (0.84)	0.41
Nepal	0.59	(0.18, 2.07)	0.73 (0.54)	0.81

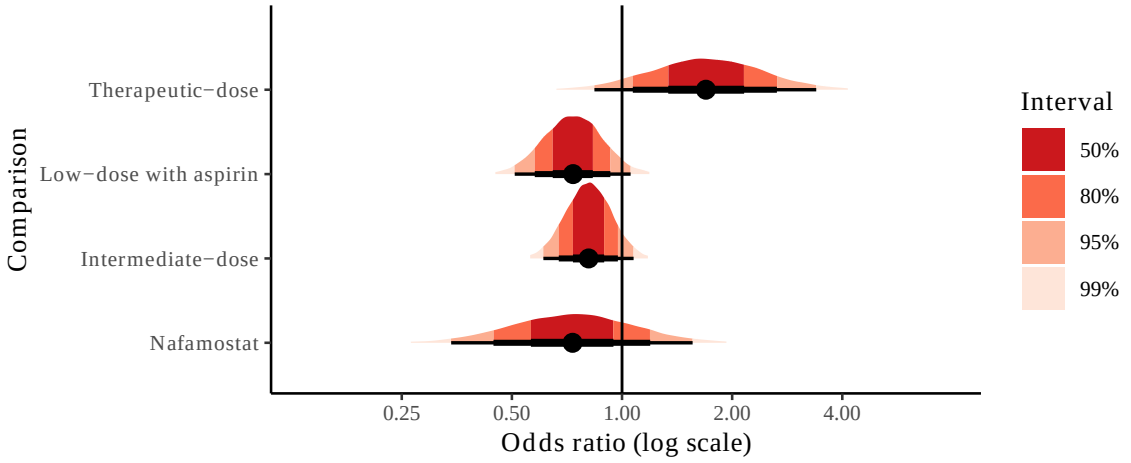

Figure 2.36: Posterior densities for the treatment effect odds ratios, ACS-ITT.

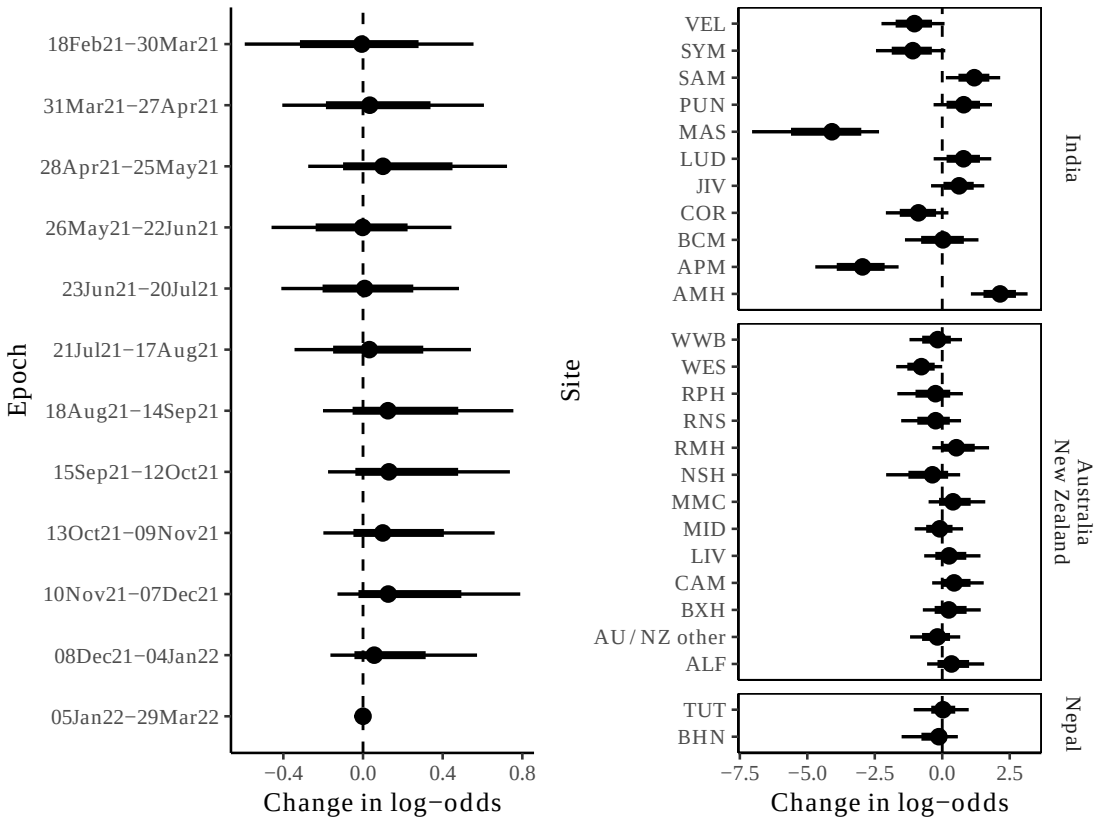

Figure 2.37: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on WHO outcome scale at day 28 for the outcome model fit to the ACS-ITT set.

2.3.3 All-cause mortality to day 28

This section reports on the analysis of the secondary outcome: all-cause mortality to day 28. For this outcome, participants who died within 28 days were coded to have a value of 1, and those who did not, to have a value of 0. The model is coded so that an odds ratio less than 1 implies a benefit (reduction in odds of death by day 28).

2.3.3.1 FAS-ITT

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch.
- **Set**: FAS-ITT

Table 2.35: Summary of model parameters (fixed-effects odds-ratios) for mortality by day 28 primary model fit to the FAS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.87	(0.09, 8.45)	1.69 (2.69)	0.55
Intermediate-dose	0.80	(0.39, 1.61)	0.85 (0.31)	0.74
Low-dose with aspirin	0.80	(0.34, 1.79)	0.87 (0.37)	0.70
Therapeutic-dose	3.91	(1.16, 13.13)	4.73 (3.26)	0.01
Ineligible aspirin	4.67	(1.18, 17.25)	5.84 (4.42)	0.02
Age $\geq$ 60	1.99	(1.06, 3.69)	2.09 (0.68)	0.02
Female	0.35	(0.16, 0.69)	0.37 (0.14)	1.00
Oxygen requirement	3.23	(1.71, 6.32)	3.43 (1.19)	0.00
Australia/New Zealand	0.53	(0.11, 2.35)	0.71 (0.62)	0.80
Nepal	2.45	(0.56, 9.50)	3.10 (2.47)	0.10

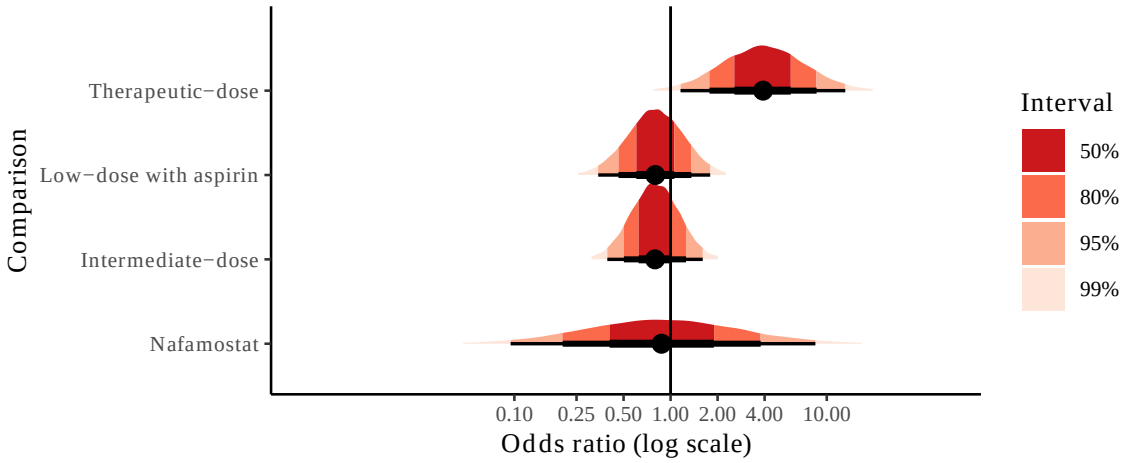

Figure 2.38: Posterior densities for the treatment effect odds ratios, FAS-ITT.

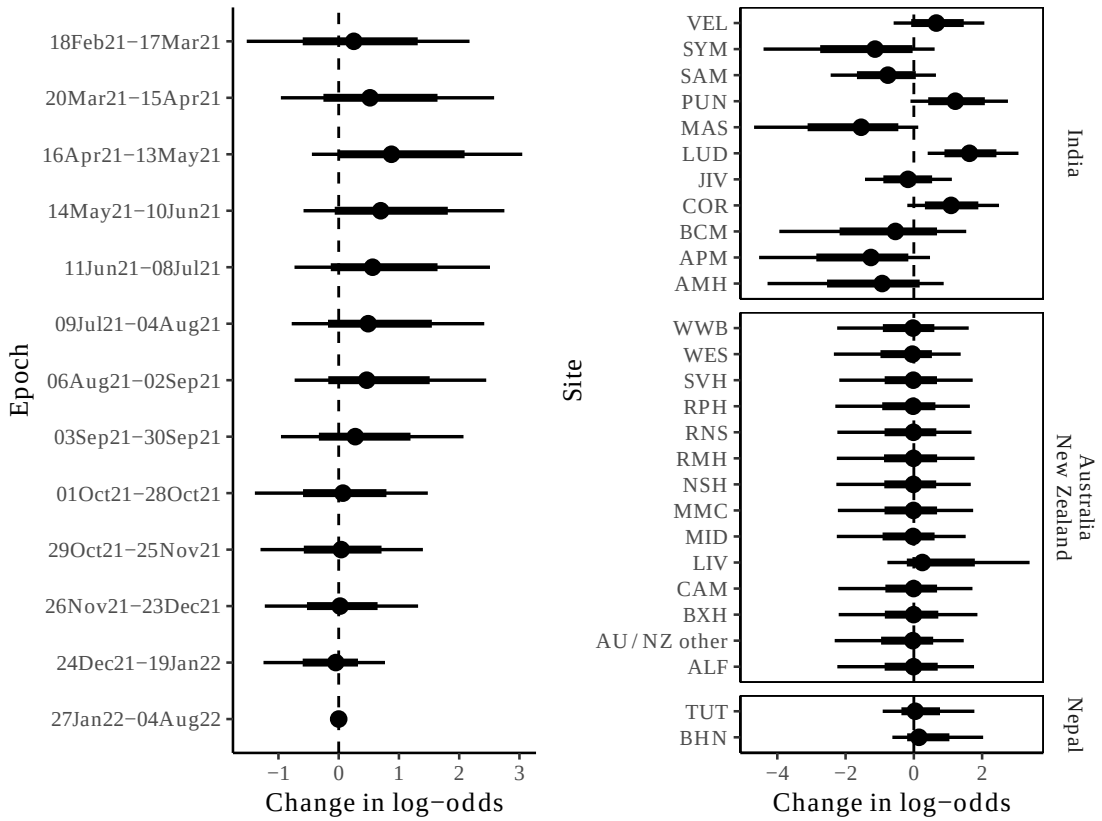

Figure 2.39: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on day 28 mortality for the primary model fit to the FAS-ITT set.

2.3.3.2 AVS-ITT

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, age group, sex, oxygen requirement, region.
- **Set**: AVS-ITT

Table 2.36: Summary of model parameters (fixed-effects odds-ratios) for mortality by day 28 primary model fit to the AVS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	1.00	(0.09, 10.80)	2.11 (4.25)	0.50
Intermediate-dose	1.01	(0.08, 13.15)	2.33 (4.76)	0.50
Low-dose with aspirin	0.82	(0.06, 11.58)	2.02 (4.32)	0.56
Therapeutic-dose	0.87	(0.07, 11.24)	2.08 (4.37)	0.54
Age ≥ 60	2.67	(0.07, 201.24)	40.19 (1462.79)	0.31
Female	3.34	(0.11, 223.37)	44.76 (829.81)	0.25
Oxygen requirement	6.44	(0.24, 324.90)	45.63 (250.72)	0.14

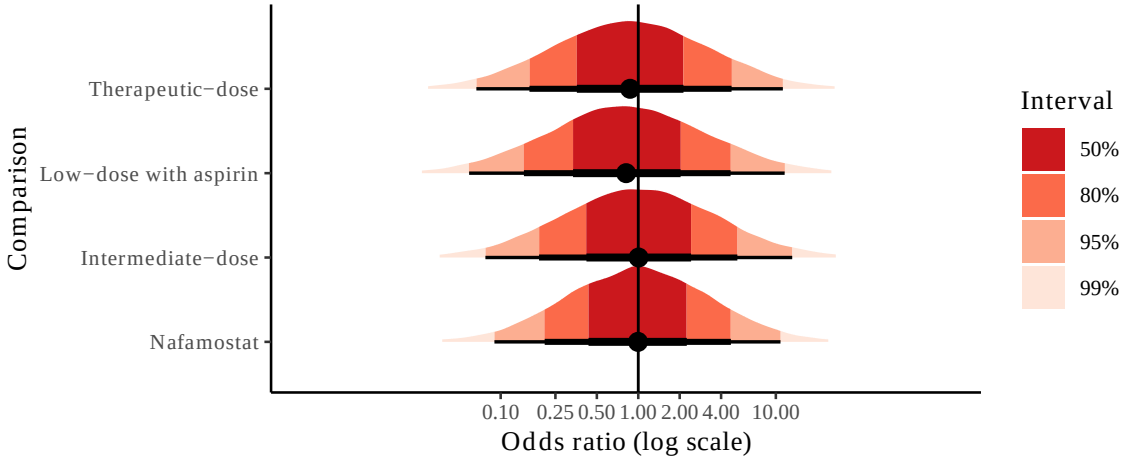

Figure 2.40: Posterior densities for the treatment effect odds ratios, AVS-ITT.

2.3.3.3 ACS-ITT

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch.
- **Set**: ACS-ITT

Table 2.37: Summary of model parameters (fixed-effects odds-ratios) for mortality by day 28 primary model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.83	(0.08, 8.65)	1.70 (3.24)	0.56
Intermediate-dose	0.80	(0.39, 1.61)	0.85 (0.32)	0.74
Low-dose with aspirin	0.82	(0.36, 1.82)	0.89 (0.38)	0.69
Therapeutic-dose	4.03	(1.22, 13.35)	4.85 (3.32)	0.01
Ineligible aspirin	4.51	(1.09, 16.52)	5.59 (4.16)	0.02
Age ≥ 60	2.05	(1.08, 3.86)	2.15 (0.71)	0.01
Female	0.34	(0.16, 0.68)	0.36 (0.14)	1.00
Oxygen requirement	3.24	(1.67, 6.48)	3.45 (1.24)	0.00
Australia/New Zealand	0.54	(0.11, 2.42)	0.72 (0.64)	0.79
Nepal	2.56	(0.56, 9.98)	3.24 (2.61)	0.10

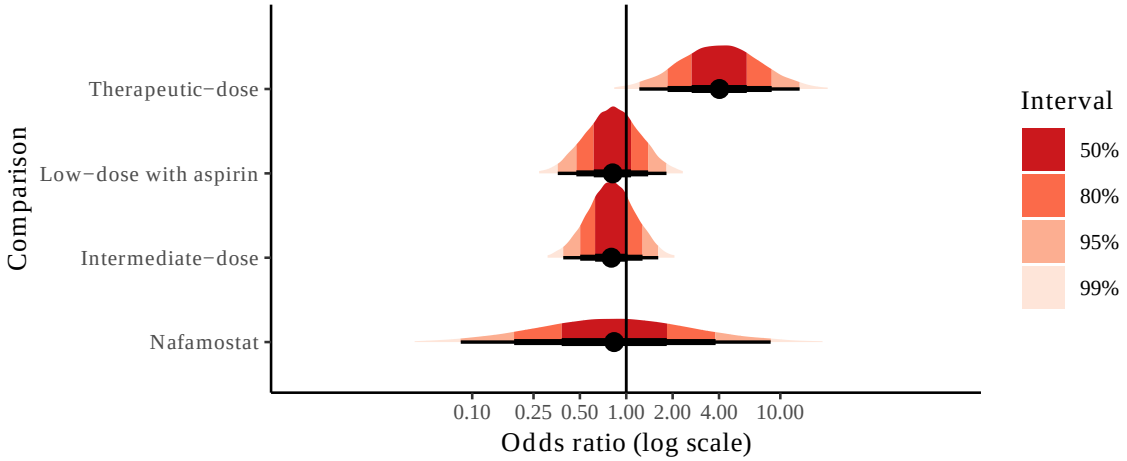

Figure 2.41: Posterior densities for the treatment effect odds ratios, ACS-ITT.

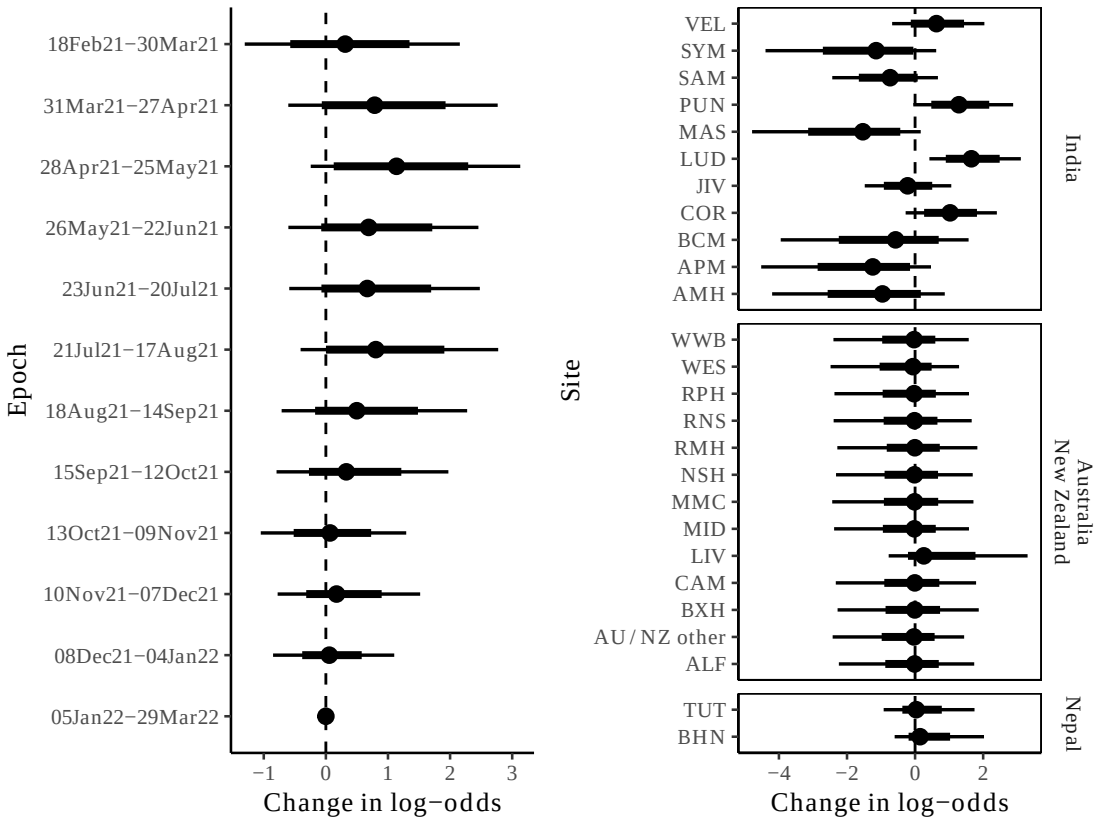

Figure 2.42: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on day 28 mortality for the primary model fit to the ACS-ITT set.

2.3.4 Days alive and free of hospital to day 28

This section reports on the analysis of the secondary outcome: days alive and free of hospital (DAFH) to day 28. For this outcome, participants who died within 28 days were coded to have 0 DAFH. The model is coded so that an odds ratio greater than 1 implies a benefit (increased odds of more days alive and free of hospital).

Table 2.38 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. Similarly, Table 2.39 for the antiviral domain.

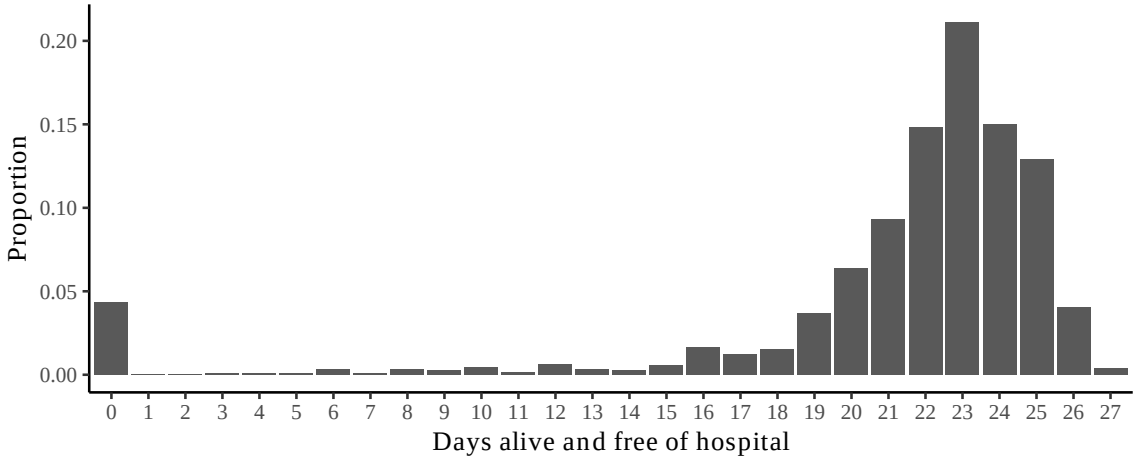

Figure 2.43: Observed overall distribution of days alive and free of hospital at day 28, FAS-ITT.

Table 2.38: Summary of days alive and free of hospital to day 28 by treatment group, FAS-ITT.

Anticoagulation intervention	Patients	Known	Deaths	DAFH, Median (Q1, Q3)
Not randomised to anticoagulation	32	29	0 (0%)	22 (18, 23)
Low-dose	610	595	19 (3%)	23 (21, 24)
Intermediate-dose	613	603	15 (2%)	23 (21, 24)
Low-dose with aspirin	283	280	10 (4%)	22 (20, 24)
Therapeutic-dose	50	50	6 (12%)	22 (19, 24)
Overall	**1588**	**1557**	**50 (3%)**	**23 (21, 24)**

Table 2.39: Summary of days alive and free of hospital to day 28 by treatment group, FAS-ITT.

Antiviral intervention	Patients	Known	Deaths	DAFH, Median (Q1, Q3)
Not randomised to antiviral	1433	1412	50 (4%)	23 (21, 24)
Standard of care	73	70	0 (0%)	22 (20, 24)
Nafamostat	82	75	0 (0%)	22 (19, 24)
Overall	**1588**	**1557**	**50 (3%)**	**23 (21, 24)**

2.3.4.1 FAS-ITT

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch.
- **Set**: FAS-ITT

The observed distribution of DAFH by domain treatment arm is shown in Figure 2.44 and Figure 2.45.

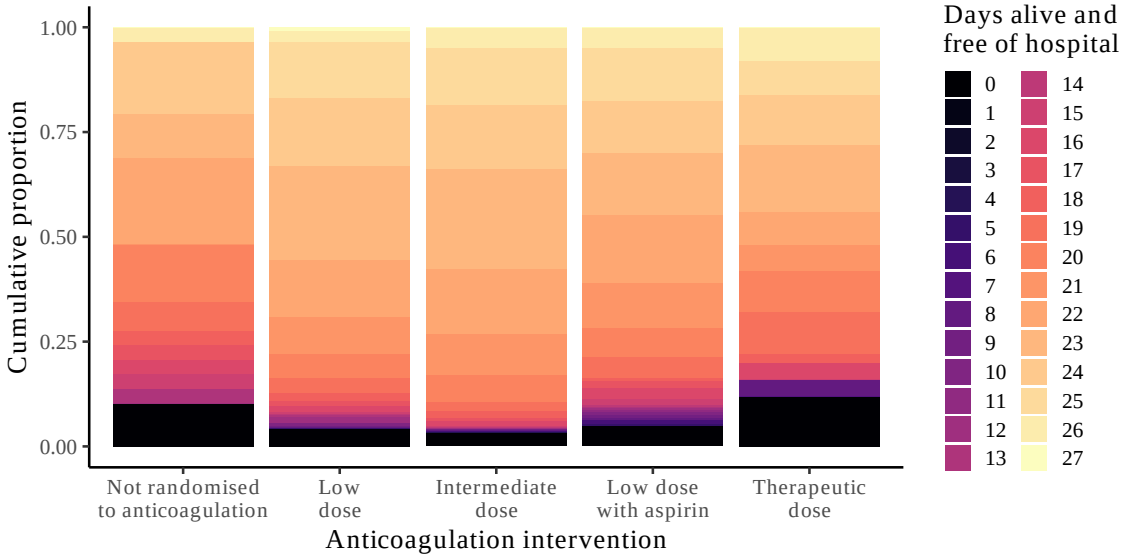

Figure 2.44: Observed distribution of days alive and free of hospital at day 28 by anticoagulation treatment group, FAS-ITT.

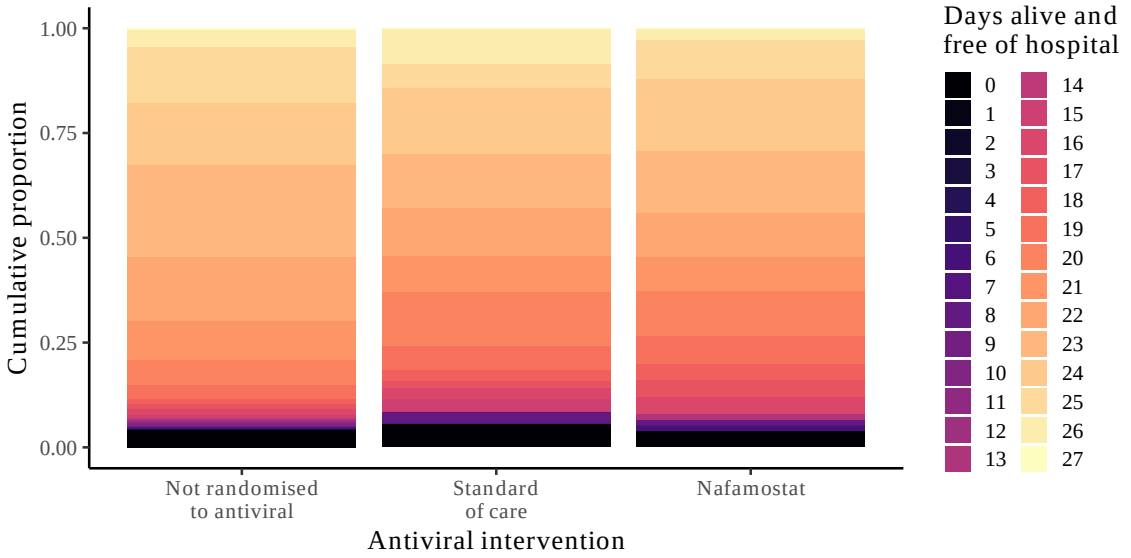

Figure 2.45: Observed distribution of days alive and free of hospital at day 28 by antiviral treatment group, AVS-ITT.

Table 2.40: Summary of model parameters (fixed-effects odds-ratios) for days alive and free of hospital to day 28 outcome model fit to the FAS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Nafamostat	1.02	(0.56, 1.85)	1.07 (0.33)	0.52
Intermediate-dose	1.15	(0.94, 1.41)	1.16 (0.12)	0.92
Low-dose with aspirin	1.06	(0.81, 1.40)	1.08 (0.15)	0.67
Therapeutic-dose	0.65	(0.36, 1.18)	0.68 (0.21)	0.08
Ineligible aspirin	1.09	(0.58, 2.02)	1.14 (0.38)	0.60
Age $\geq$ 60	0.62	(0.50, 0.76)	0.62 (0.07)	0.00
Female	1.13	(0.95, 1.36)	1.14 (0.11)	0.91
Oxygen requirement	0.47	(0.38, 0.58)	0.47 (0.05)	0.00
Australia/New Zealand	0.96	(0.44, 2.16)	1.05 (0.45)	0.46
Nepal	0.85	(0.26, 3.01)	1.04 (0.79)	0.39

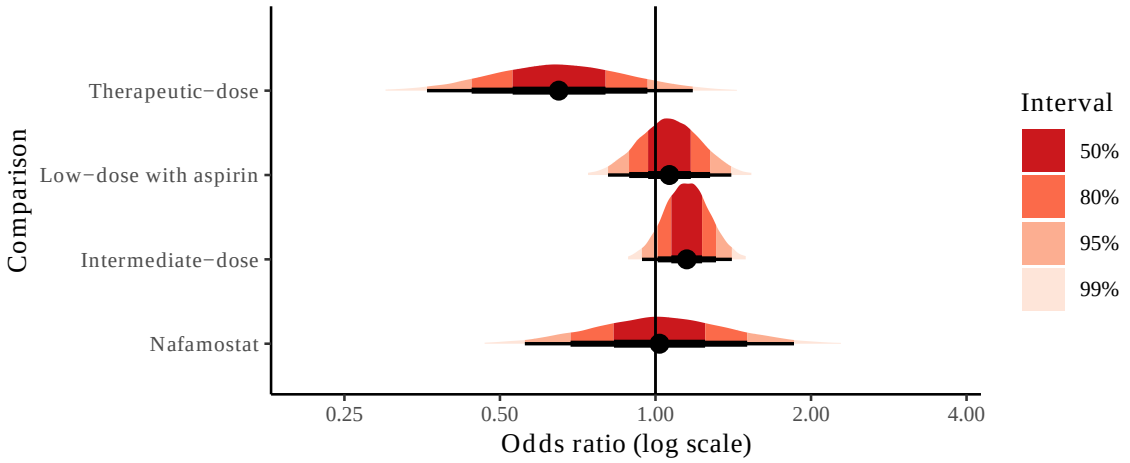

Figure 2.46: Posterior densities for the treatment effect odds ratios, FAS-ITT.

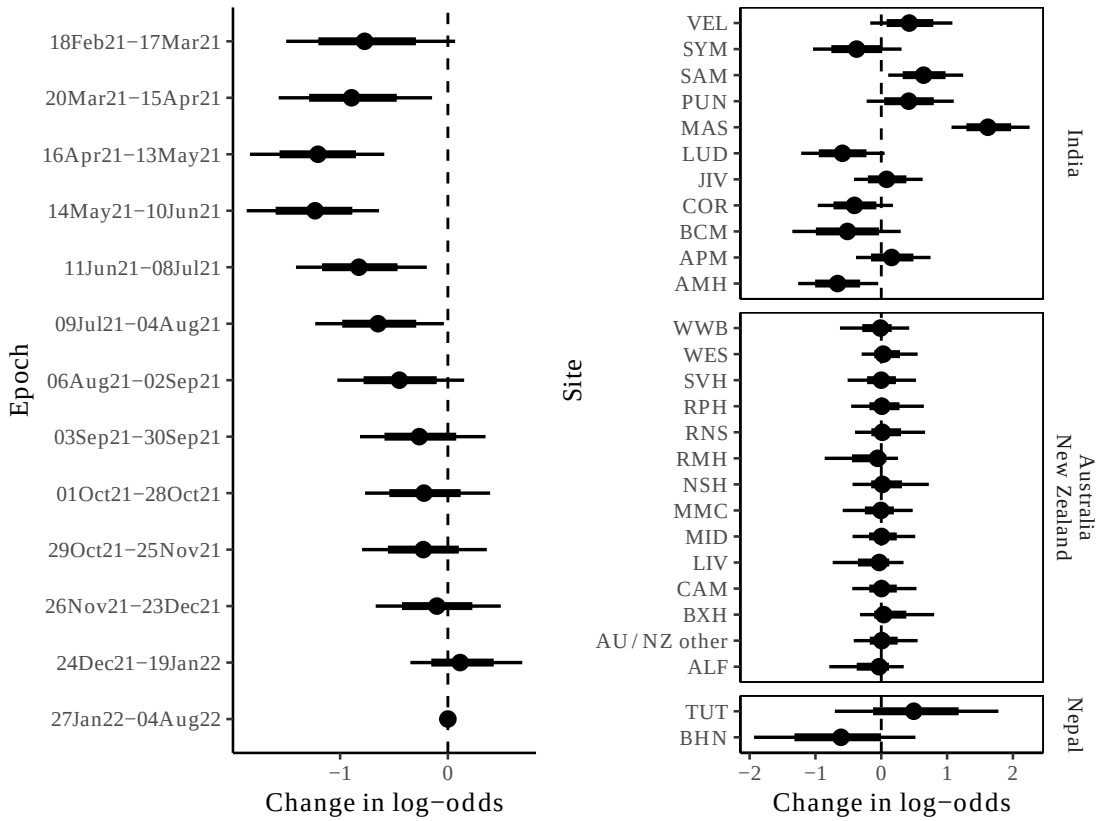

Figure 2.47: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on days alive and free of hospital to day 28 for the outcome model fit to the FAS-ITT set.

2.3.4.2 AVS-ITT

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, age group, sex, oxygen requirement
- **Set**: AVS-ITT

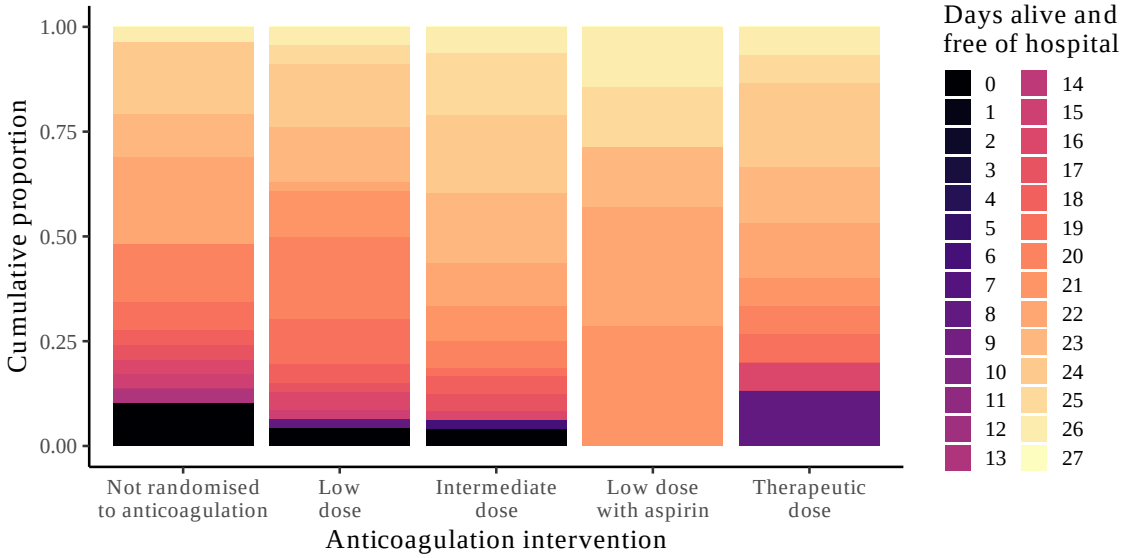

Figure 2.48: Observed distribution of days alive and free of hospital at day 28 by anticoagulation treatment group, AVS-ITT.

Table 2.41: Summary of model parameters (fixed-effects odds-ratios) for days alive and free of hospital to day 28 primary model fit to the AVS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Nafamostat	0.90	(0.49, 1.62)	0.94 (0.29)	0.36
Intermediate-dose	2.57	(1.24, 5.28)	2.75 (1.05)	0.99
Low-dose with aspirin	1.97	(0.57, 6.68)	2.39 (1.67)	0.86
Therapeutic-dose	1.52	(0.59, 3.91)	1.71 (0.88)	0.81
Age $\geq$ 60	0.20	(0.10, 0.41)	0.21 (0.08)	0.00
Female	0.97	(0.53, 1.79)	1.02 (0.32)	0.47
Oxygen requirement	0.73	(0.38, 1.43)	0.78 (0.27)	0.18

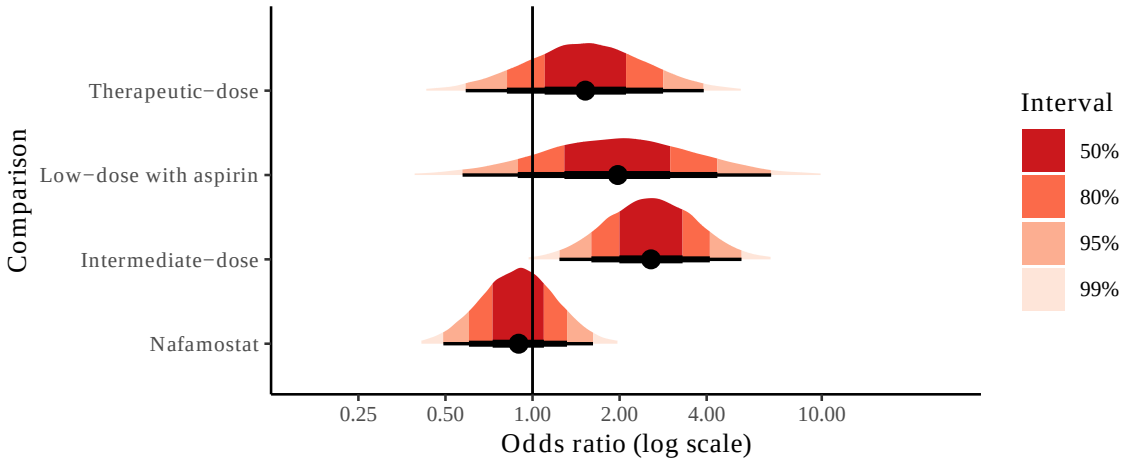

Figure 2.49: Posterior densities for the treatment effect odds ratios, AVS-ITT.

2.3.4.3 ACS-ITT

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch.
- **Set**: ACS-ITT

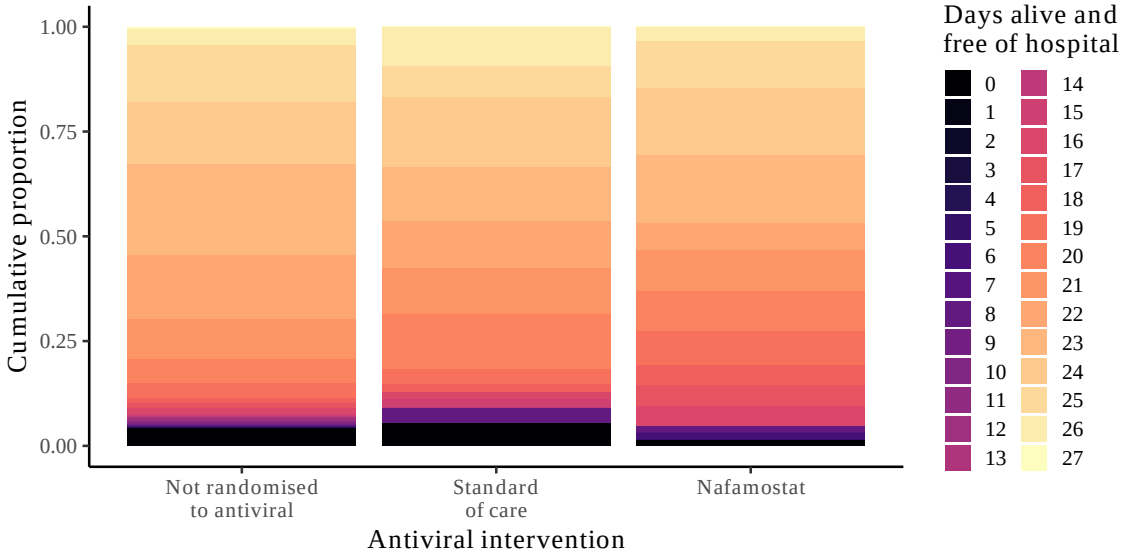

Figure 2.50: Observed distribution of days alive and free of hospital at day 28 by antiviral treatment group, ACS-ITT.

Table 2.42: Summary of model parameters (fixed-effects odds-ratios) for days alive and free of hospital to day 28 primary model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Nafamostat	0.97	(0.48, 1.92)	1.03 (0.37)	0.46
Intermediate-dose	1.15	(0.94, 1.41)	1.16 (0.12)	0.92
Low-dose with aspirin	1.07	(0.81, 1.41)	1.08 (0.15)	0.67
Therapeutic-dose	0.65	(0.36, 1.17)	0.68 (0.21)	0.08
Ineligible aspirin	1.12	(0.59, 2.14)	1.18 (0.40)	0.63
Age $\geq$ 60	0.62	(0.50, 0.76)	0.62 (0.07)	0.00
Female	1.15	(0.96, 1.38)	1.15 (0.11)	0.93
Oxygen requirement	0.47	(0.37, 0.58)	0.47 (0.05)	0.00
Australia/New Zealand	1.12	(0.48, 2.62)	1.24 (0.58)	0.61
Nepal	0.83	(0.25, 3.06)	1.03 (0.81)	0.37

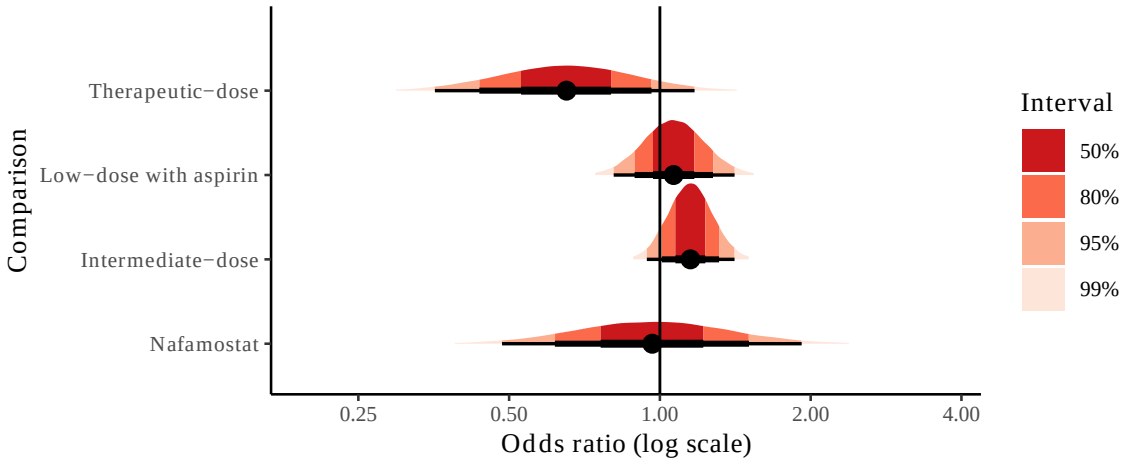

Figure 2.51: Posterior densities for the treatment effect odds ratios, ACS-ITT.

2.3.5 Days alive and free of invasive or non-invasive ventilation to day 28

This section reports on the analysis of the secondary outcome: days alive and free invasive or non-invasive ventilation (DAFV) to day 28. For this outcome, participants who died within 28 days were coded to have 0 DAFV.

Table 2.43 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. Similarly, Table 2.44 for the antiviral domain.

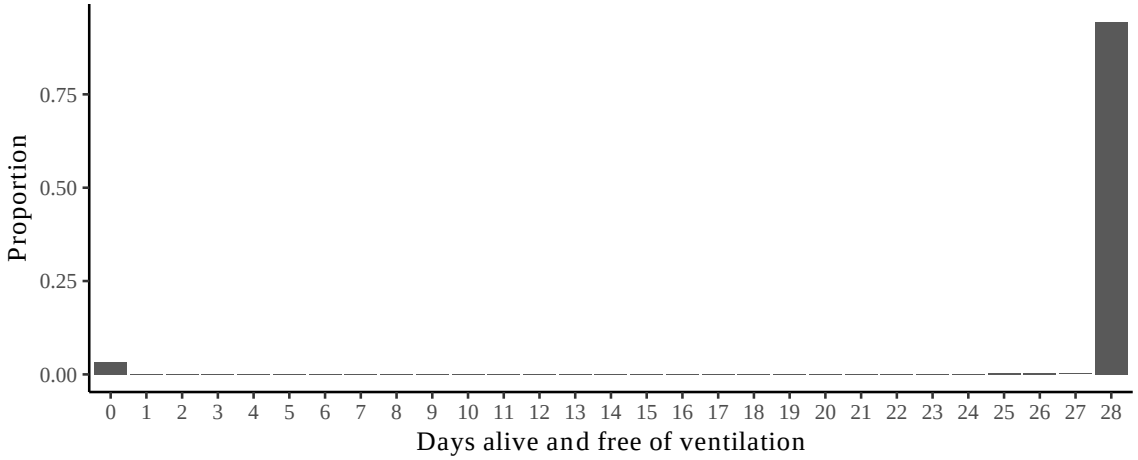

Figure 2.52: Observed overall distribution of days alive and free of hospital at day 28, FAS-ITT.

Table 2.43: Summary of days alive and free of ventilation to day 28 by anticoagulation treatment group, FAS-ITT.

Anticoagulation intervention	Patients	Known	Deaths	Any ventilation	DAFV, Median (Q1, Q3)
Not randomised to anticoagulation	32	25	0 (0%)	4 (15%)	28 (28, 28)
Low-dose	610	596	19 (3%)	34 (6%)	28 (28, 28)
Intermediate-dose	613	603	15 (2%)	23 (4%)	28 (28, 28)
Low-dose with aspirin	283	281	10 (4%)	18 (6%)	28 (28, 28)
Therapeutic-dose	50	50	6 (12%)	7 (14%)	28 (28, 28)
Overall	**1588**	**1555**	**50 (3%)**	**86 (6%)**	**28 (28, 28)**

Table 2.44: Summary of days alive and free of ventilation to day 28 by antiviral treatment group, FAS-ITT.

Antiviral intervention	Patients	Known	Deaths	Any ventilation	DAFV, Median (Q1, Q3)
Not randomised to antiviral	1433	1414	50 (4%)	74 (5%)	28 (28, 28)
Standard of care	73	67	0 (0%)	8 (12%)	28 (28, 28)
Nafamostat	82	74	0 (0%)	4 (5%)	28 (28, 28)
Overall	**1588**	**1555**	**50 (3%)**	**86 (6%)**	**28 (28, 28)**

2.3.5.1 FAS-ITT

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch.
- **Set**: FAS-ITT

The observed distribution of DAFV by domain treatment arm is shown in Figure 2.53 and Figure 2.54.

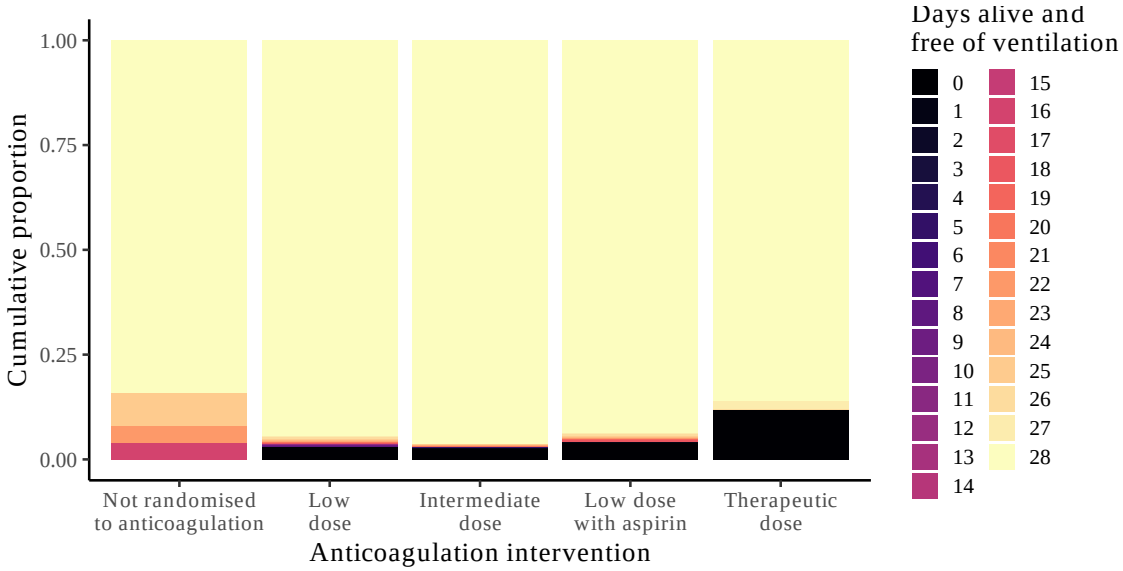

Figure 2.53: Observed distribution of days alive and free of ventilation at day 28 by anticoagulation treatment group, FAS-ITT.

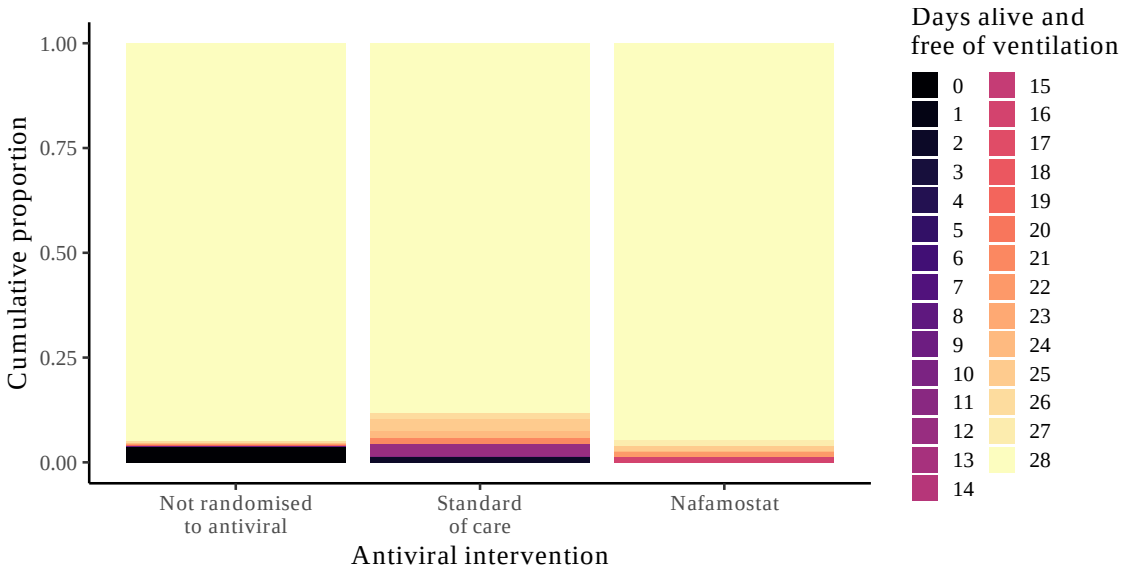

Figure 2.54: Observed distribution of days alive and free of ventilation at day 28 by antiviral treatment group, FAS-ITT.

Table 2.45: Summary of model parameters (fixed-effects odds-ratios) for days alive and free of ventilation to day 28 primary model fit to the FAS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Nafamostat	2.51	(0.77, 8.85)	3.08 (2.17)	0.94
Intermediate-dose	1.48	(0.85, 2.63)	1.55 (0.46)	0.91
Low-dose with aspirin	1.20	(0.63, 2.29)	1.26 (0.43)	0.71
Therapeutic-dose	0.35	(0.13, 1.00)	0.40 (0.23)	0.02
Ineligible aspirin	0.31	(0.10, 1.18)	0.40 (0.37)	0.04
Age $\geq$ 60	0.53	(0.33, 0.87)	0.55 (0.14)	0.01
Female	1.81	(1.11, 3.04)	1.88 (0.50)	0.99
Oxygen requirement	0.27	(0.15, 0.45)	0.27 (0.07)	0.00
Australia/New Zealand	1.10	(0.29, 4.47)	1.42 (1.14)	0.56
Nepal	0.74	(0.21, 2.85)	0.94 (0.74)	0.33

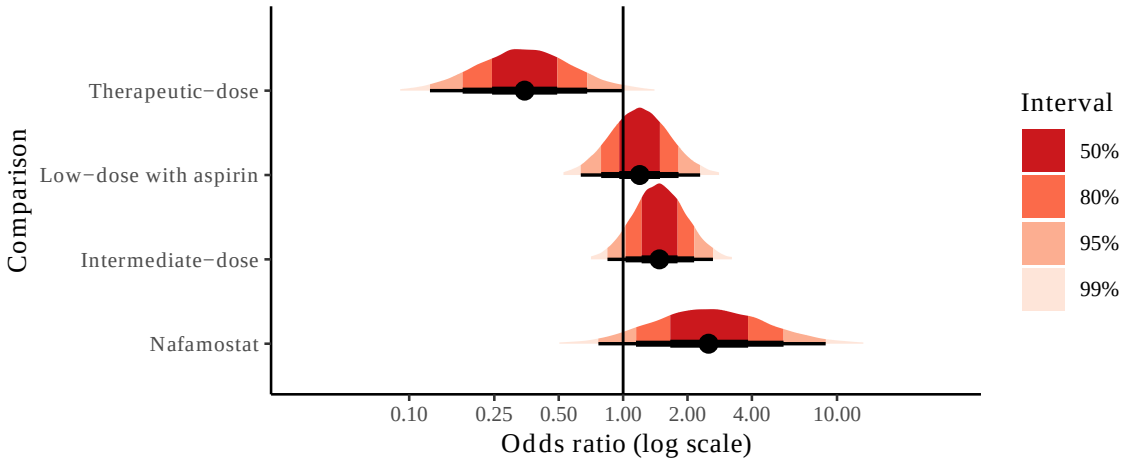

Figure 2.55: Posterior densities for the treatment effect odds ratios, FAS-ITT.

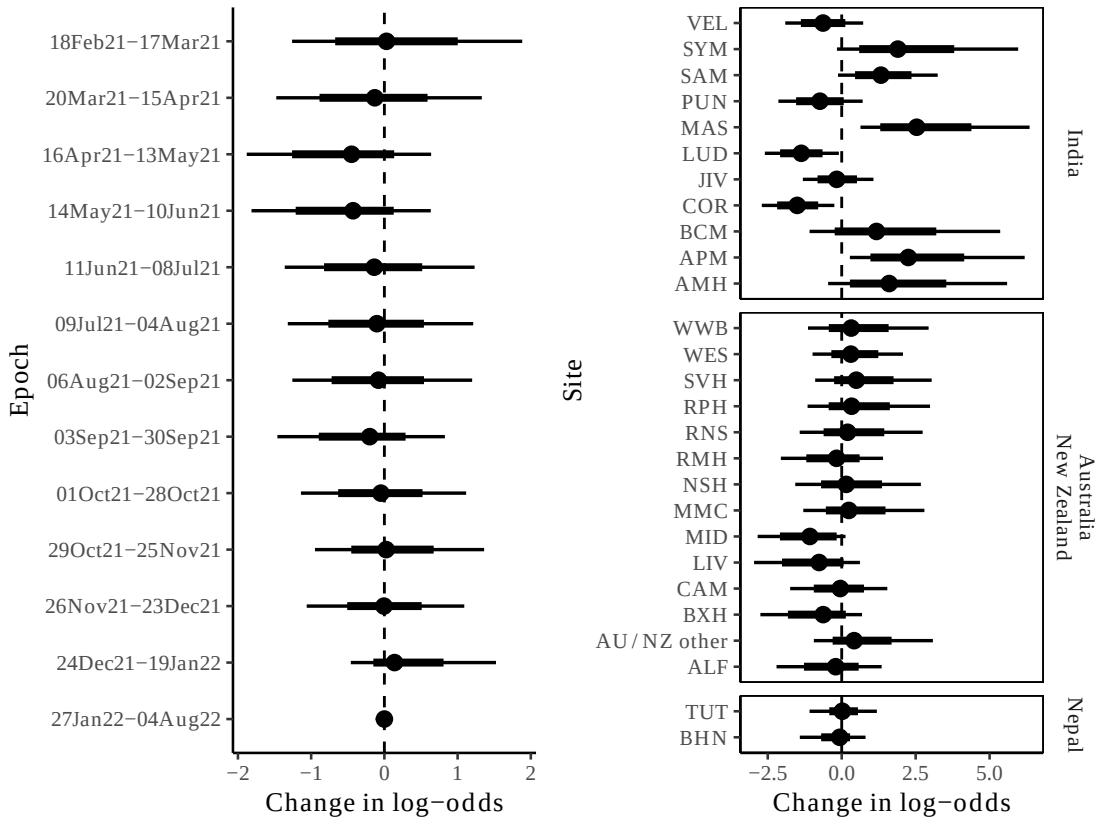

Figure 2.56: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on days alive and free of ventilation to day 28 for the primary model fit to the FAS-ITT set.

2.3.5.2 AVS-ITT

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, age group, sex, oxygen requirement
- **Set**: AVS-ITT

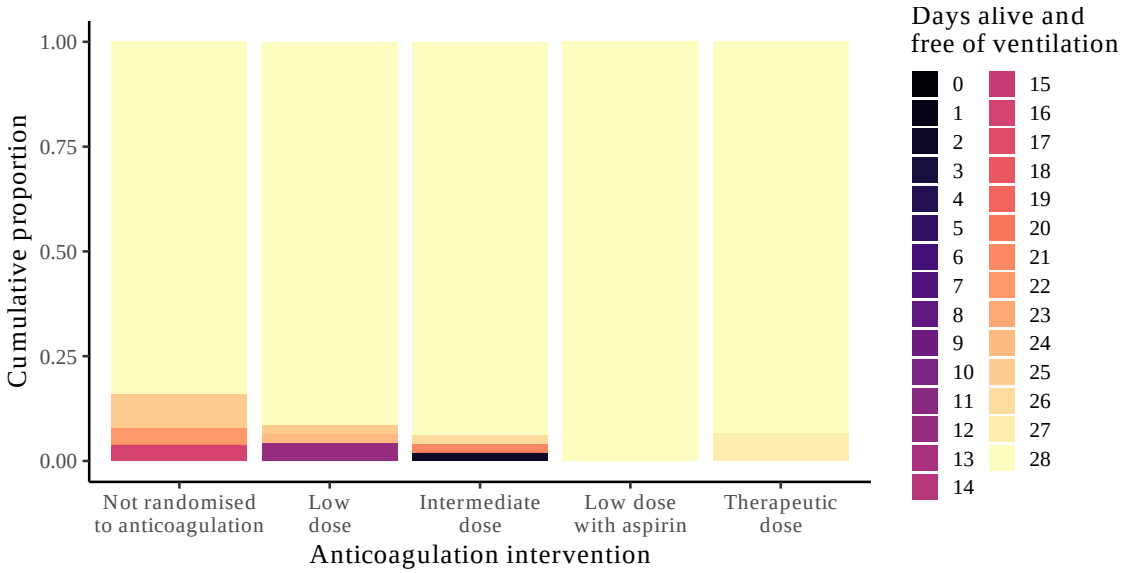

Figure 2.57: Observed distribution of days alive and free of ventilation at day 28 by anticoagulation treatment group, AVS-ITT.

Table 2.46: Summary of model parameters (fixed-effects odds-ratios) for days alive and free of ventilation to day 28 primary model fit to the AVS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Nafamostat	2.52	(0.77, 8.58)	3.08 (2.19)	0.93
Intermediate-dose	1.49	(0.85, 2.65)	1.56 (0.46)	0.92
Low-dose with aspirin	1.29	(0.70, 2.51)	1.37 (0.47)	0.79
Therapeutic-dose	0.34	(0.12, 0.96)	0.39 (0.22)	0.02
Age $\geq$ 60	0.51	(0.31, 0.83)	0.52 (0.13)	0.00
Female	1.84	(1.11, 3.07)	1.90 (0.51)	0.99
Oxygen requirement	0.27	(0.16, 0.45)	0.28 (0.07)	0.00

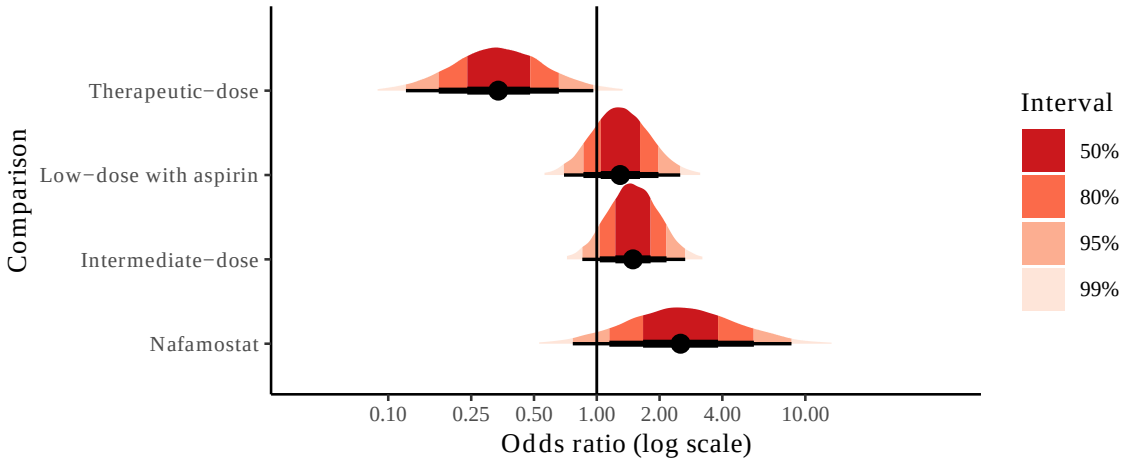

Figure 2.58: Posterior densities for the treatment effect odds ratios, AVS-ITT.

2.3.5.3 ACS-ITT

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch.
- **Set**: ACS-ITT

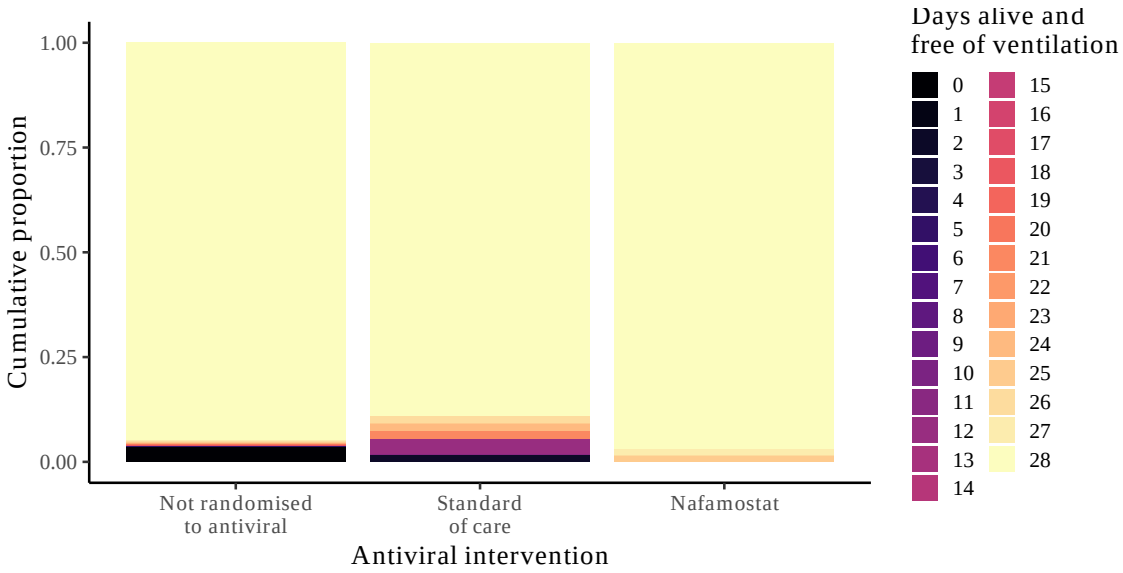

Figure 2.59: Observed distribution of days alive and free of ventilation at day 28 by antiviral treatment group, ACS-ITT.

Table 2.47: Summary of model parameters (fixed-effects odds-ratios) for days alive and free of ventilation to day 28 primary model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR > 1)
Nafamostat	3.80	(0.89, 17.19)	5.09 (4.81)	0.97
Intermediate-dose	1.49	(0.85, 2.63)	1.55 (0.46)	0.92
Low-dose with aspirin	1.20	(0.64, 2.32)	1.27 (0.43)	0.71
Therapeutic-dose	0.35	(0.12, 1.02)	0.40 (0.24)	0.03
Ineligible aspirin	0.28	(0.08, 1.07)	0.35 (0.28)	0.03
Age ≥ 60	0.53	(0.32, 0.88)	0.55 (0.14)	0.01
Female	1.83	(1.11, 3.09)	1.90 (0.51)	0.99
Oxygen requirement	0.26	(0.15, 0.44)	0.27 (0.07)	0.00
Australia/New Zealand	1.40	(0.34, 6.32)	1.88 (1.70)	0.68
Nepal	0.68	(0.18, 2.76)	0.87 (0.72)	0.28

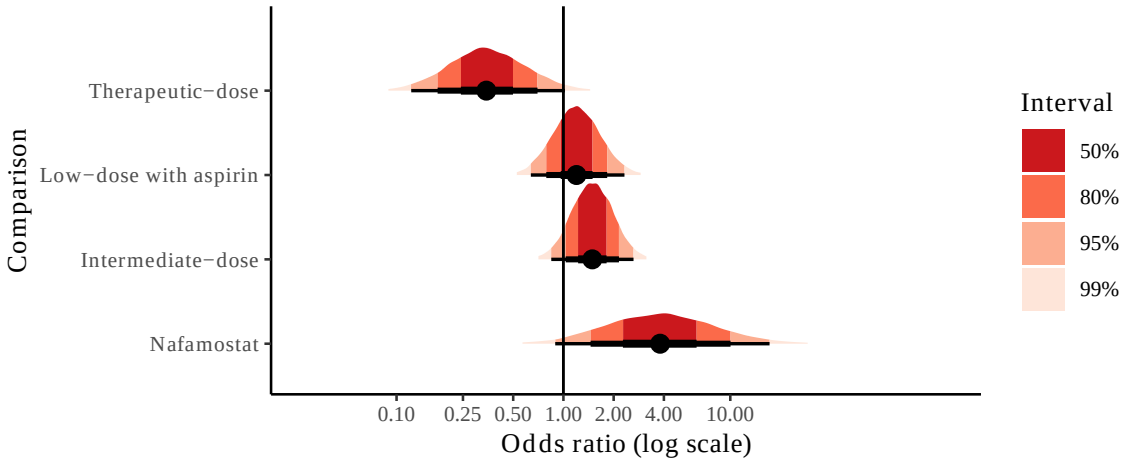

Figure 2.60: Posterior densities for the treatment effect odds ratios, ACS-ITT.

2.3.6 Presence of patient reported shortness of breath at day 28

This section reports on the analysis of the secondary outcome: patient reported shortness of breath at day 28. For this outcome, participants who died within 28 days were coded to have a missing value, so this outcome reflects shortness of breath at day 28 amongst patients who survived to at least day 28. The model is coded so that an odds ratio less than 1 implies a benefit (reduction in odds of shortness of breath at day 28).

Table 2.48 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. Similarly for the antiviral arms in Table 2.49.

Table 2.48: Summary of WHO scale at 28 by anticoagulation treatment group, ACS-ITT.

n (%)	Patients	Known	Missing	Shortness of breath day 28
Low dose	610	577 (94.6)	33 (5.4)	115 (19.9)
Intermediate dose	613	584 (95.3)	29 (4.7)	110 (18.8)
Low dose with aspirin	283	271 (95.8)	12 (4.2)	59 (21.8)
Therapeutic dose	50	44 (88.0)	6 (12.0)	11 (25.0)
Overall	**1556**	**1476 (94.9)**	**80 (5.1)**	**295 (20.0)**

Table 2.49: Summary of WHO scale at 28 by antiviral treatment group, AVS-ITT.

n (%)	Patients	Known	Missing	Shortness of breath day 28
Standard of care	73	67 (91.8)	6 (8.2)	35 (52.2)
Nafamostat	82	73 (89.0)	9 (11.0)	36 (49.3)
Overall	**155**	**140 (90.3)**	**15 (9.7)**	**71 (50.7)**

2.3.6.1 FAS-ITT

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch.
- **Set**: FAS-ITT

Table 2.50: Summary of model parameters (fixed-effects odds-ratios) for shortness of breath at day 28 primary model fit to the FAS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.85	(0.35, 2.07)	0.94 (0.45)	0.64
Intermediate-dose	0.77	(0.54, 1.09)	0.78 (0.14)	0.93
Low-dose with aspirin	1.17	(0.75, 1.83)	1.20 (0.27)	0.24
Therapeutic-dose	0.95	(0.37, 2.39)	1.05 (0.53)	0.55
Ineligible aspirin	1.23	(0.42, 3.42)	1.40 (0.79)	0.35
Age ≥ 60	2.04	(1.45, 2.86)	2.07 (0.36)	0.00
Female	1.02	(0.75, 1.40)	1.04 (0.17)	0.44
Oxygen requirement	1.28	(0.88, 1.86)	1.30 (0.25)	0.10
Australia/New Zealand	2.29	(0.59, 8.51)	2.87 (2.18)	0.11
Nepal	0.50	(0.12, 2.50)	0.70 (0.69)	0.81

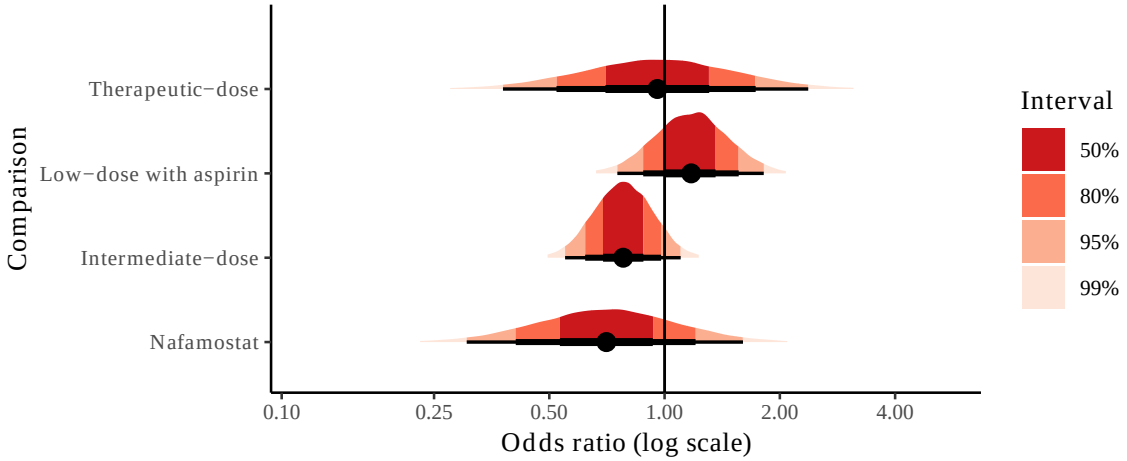

Figure 2.61: Posterior densities for the treatment effect odds ratios, FAS-ITT.

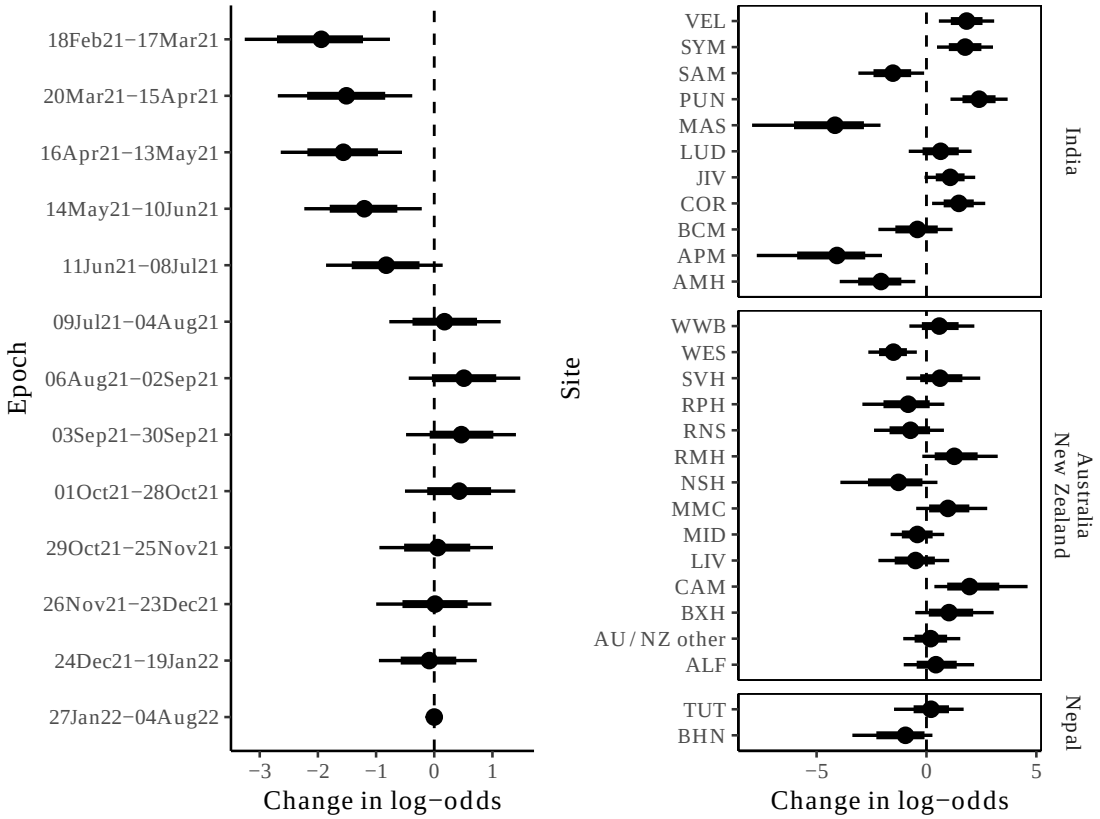

Figure 2.62: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on day 28 shortness of breath for the primary model fit to the FAS-ITT set.

2.3.6.2 AVS-ITT

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, age group, sex, oxygen requirement.
- **Set**: AVS-ITT

Table 2.51: Summary of model parameters (fixed-effects odds-ratios) for shortness of breath at day 28 primary model fit to the AVS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.81	(0.39, 1.67)	0.87 (0.33)	0.71
Intermediate-dose	0.79	(0.33, 1.86)	0.87 (0.40)	0.70
Low-dose with aspirin	0.58	(0.13, 2.45)	0.76 (0.65)	0.77
Therapeutic-dose	1.53	(0.48, 4.93)	1.83 (1.24)	0.24
Age ≥ 60	2.95	(1.29, 7.11)	3.27 (1.52)	0.00
Female	1.17	(0.56, 2.50)	1.26 (0.51)	0.34
Oxygen requirement	2.34	(1.03, 5.56)	2.58 (1.18)	0.02

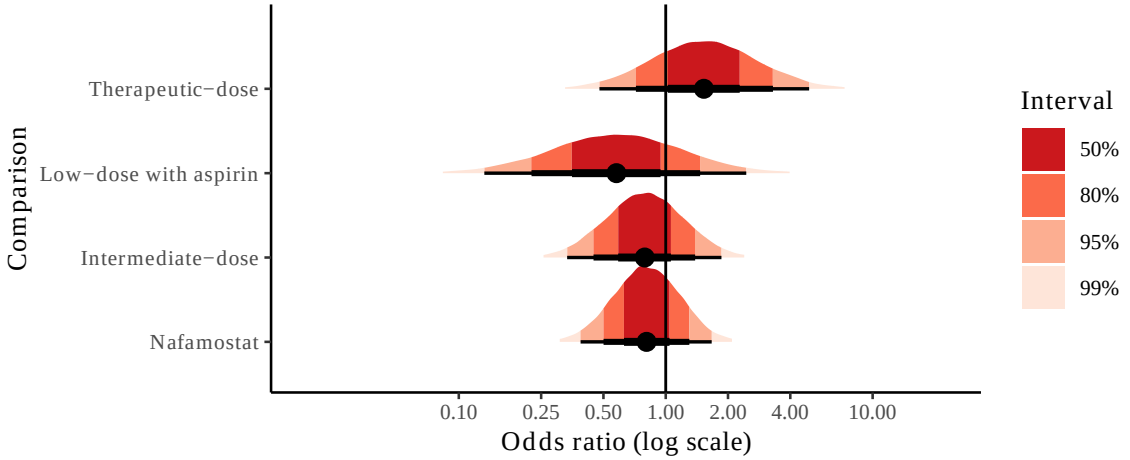

Figure 2.63: Posterior densities for the treatment effect odds ratios, AVS-ITT.

2.3.6.3 ACS-ITT

- **Model**: logistic regression
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch.
- **Set**: ACS-ITT

Table 2.52: Summary of model parameters (fixed-effects odds-ratios) for shortness of breath at day 28 primary model fit to the ACS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.85	(0.35, 2.07)	0.94 (0.45)	0.64
Intermediate-dose	0.77	(0.54, 1.09)	0.78 (0.14)	0.93
Low-dose with aspirin	1.17	(0.75, 1.83)	1.20 (0.27)	0.24
Therapeutic-dose	0.95	(0.37, 2.39)	1.05 (0.53)	0.55
Ineligible aspirin	1.23	(0.42, 3.42)	1.40 (0.79)	0.35
Age ≥ 60	2.04	(1.45, 2.86)	2.07 (0.36)	0.00
Female	1.02	(0.75, 1.40)	1.04 (0.17)	0.44
Oxygen requirement	1.28	(0.88, 1.86)	1.30 (0.25)	0.10
Australia/New Zealand	2.29	(0.59, 8.51)	2.87 (2.18)	0.11
Nepal	0.50	(0.12, 2.50)	0.70 (0.69)	0.81

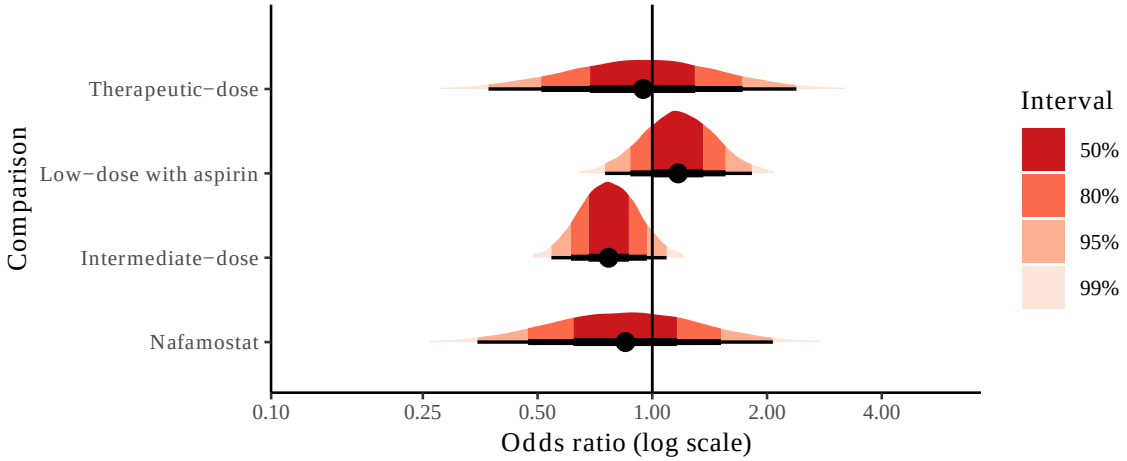

Figure 2.64: Posterior densities for the treatment effect odds ratios, ACS-ITT.

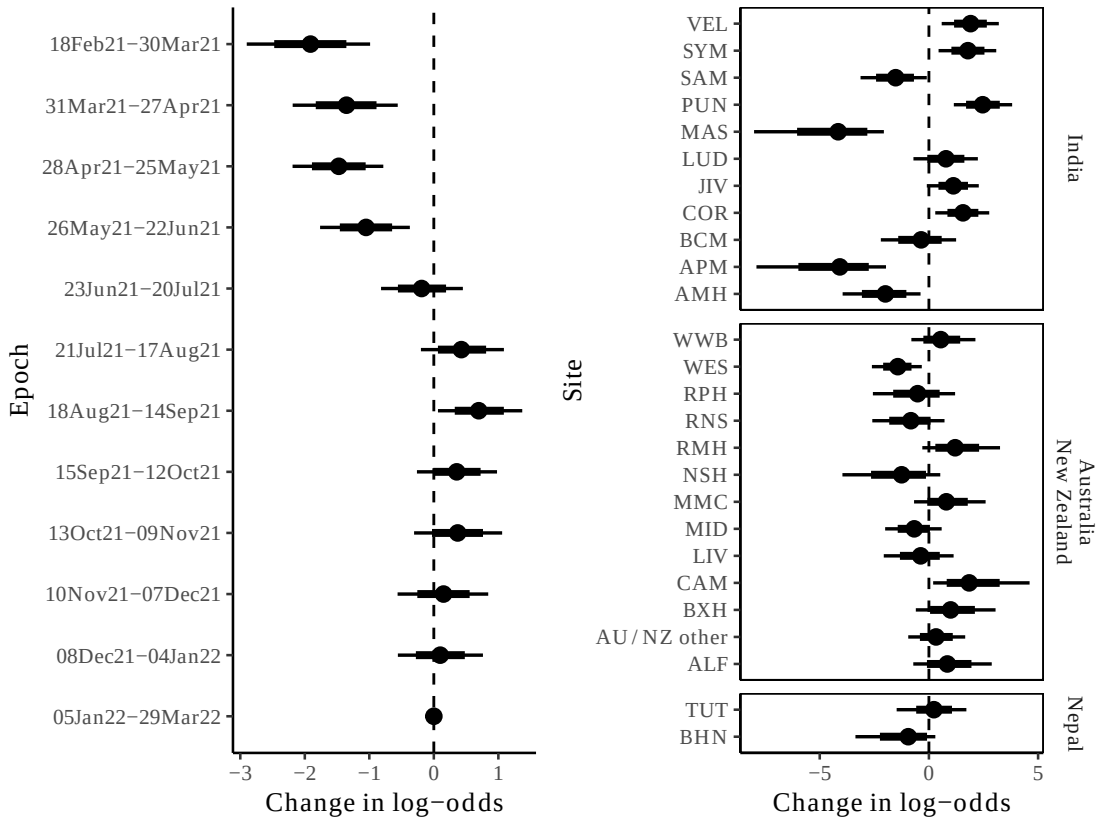

Figure 2.65: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on day 28 shortness of breath for the primary model fit to the ACS-ITT set.

2.3.7 Modified Medical Research Council (mMRC) breathlessness scale at day 28

The mMRC scale was only asked of participants who responded "yes" to the question of new or worsening breathlessness since COVID. Therefore, the distribution of this outcome scale is conditional on the patient responding that they were experiencing new or worse breathlessness since having COVID. In the following tables "Not asked" refers to participants who responded "no" to the question of breathlessness.

Table 2.53: Summary of mMRC scale at day 28 by treatment group, anticoagulation domain, ACS-ITT.

Anticoagulation intervention	Patients	Known	With exercise	Up a slight hill	Slow for age	After 100 metres	Can't leav
Low-dose	610	577	40 (7%)	47 (8%)	12 (2%)	14 (2%)	
Intermediate-dose	613	584	50 (9%)	39 (7%)	11 (2%)	8 (1%)	
Low-dose with aspirin	283	271	26 (10%)	16 (6%)	15 (6%)	1 (0%)	
Therapeutic-dose	50	44	2 (5%)	4 (9%)	3 (7%)	2 (5%)	
Overall	**1556**	**1476**	**118 (8%)**	**106 (7%)**	**41 (3%)**	**25 (2%)**	

Table 2.54: Summary of mMRC scale at day 28 by treatment group, antiviral domain, AVS-ITT.

Antiviral intervention	Patients	Known	With exercise	Up a slight hill	Slow for age	After 100 metres	Can't leave house
Standard of care	73	67	5 (7%)	15 (22%)	5 (7%)	9 (13%)	1 (1%
Nafamostat	82	73	9 (12%)	12 (16%)	5 (7%)	8 (11%)	2 (3%
Overall	**155**	**140**	**14 (10%)**	**27 (19%)**	**10 (7%)**	**17 (12%)**	**3 (2%**

2.3.7.1 FAS-ITT

- **Model**: cumulative logistic (ordinal) regression assuming proportional odds
- **Terms**: anticoagulation intervention, antiviral intervention, aspirin eligibility, age group, sex, oxygen requirement, region, site nested within region, and epoch.
- **Set**: FAS-ITT

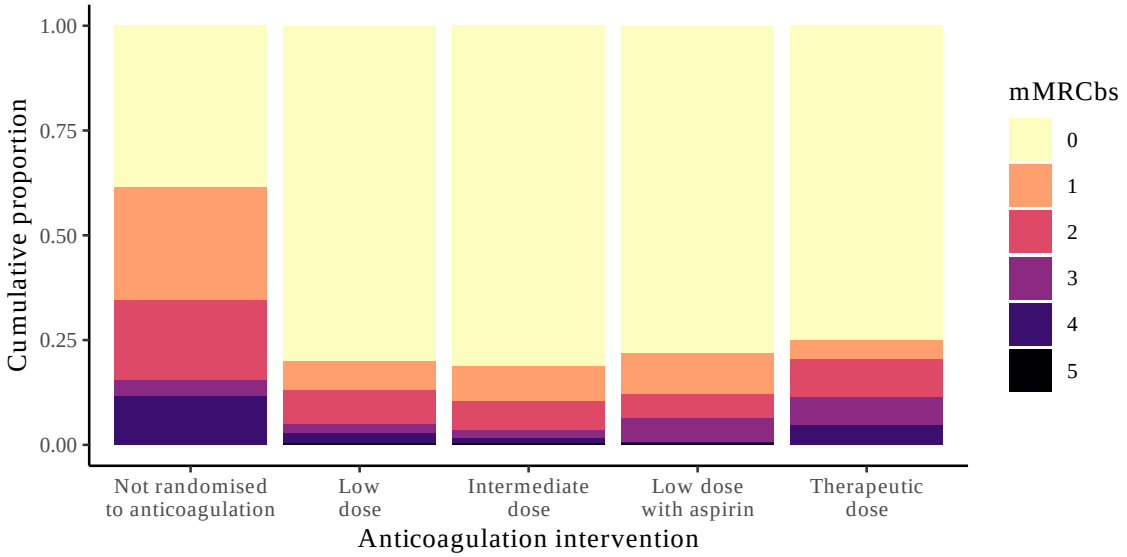

Figure 2.66: Observed distribution of mMRC breathlessness scale (mMRCbs) at day 28 by treatment group, anticoagulation domain, FAS-ITT.

Table 2.55: Summary of model parameters (fixed-effects odds-ratios) for mMRC breathlessness scale at day 28 outcome model fit to the FAS-ITT set.

Parameter	Median	95% CrI	Mean (SD)	Pr(OR < 1)
Nafamostat	0.68	(0.33, 1.39)	0.73 (0.27)	0.86
Intermediate-dose	0.74	(0.53, 1.03)	0.75 (0.13)	0.96
Low-dose with aspirin	1.11	(0.74, 1.68)	1.14 (0.24)	0.31
Therapeutic-dose	0.85	(0.35, 2.01)	0.93 (0.43)	0.64
Ineligible aspirin	1.44	(0.55, 3.51)	1.59 (0.78)	0.23
Age $\geq$ 60	1.98	(1.45, 2.70)	2.01 (0.32)	0.00
Sex	1.03	(0.77, 1.37)	1.04 (0.15)	0.42
Oxygen requirement	1.17	(0.83, 1.63)	1.19 (0.21)	0.18
Australia/New Zealand	2.60	(0.68, 9.38)	3.23 (2.42)	0.08
Nepal	0.44	(0.10, 2.32)	0.63 (0.81)	0.85

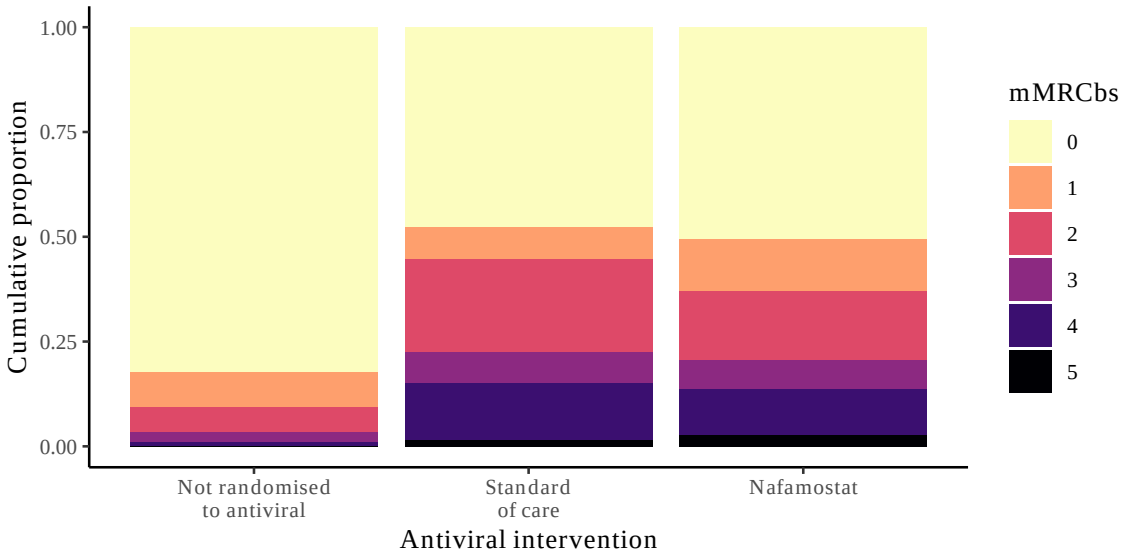

Figure 2.67: Observed distribution of mMRC breathlessness scale (mMRCbs) at day 28 by treatment group, antiviral domain, FAS-ITT.

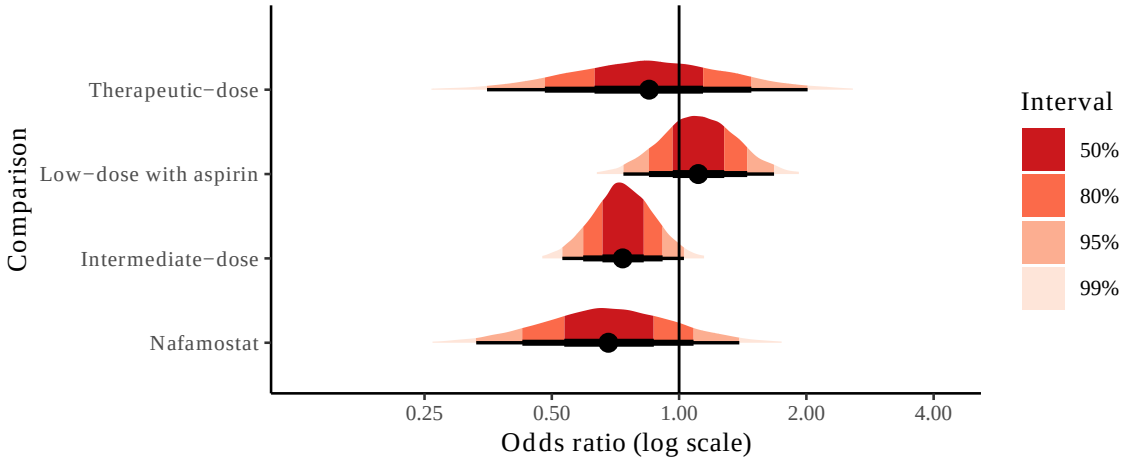

Figure 2.68: Posterior densities for the treatment effect odds ratios, FAS-ITT.

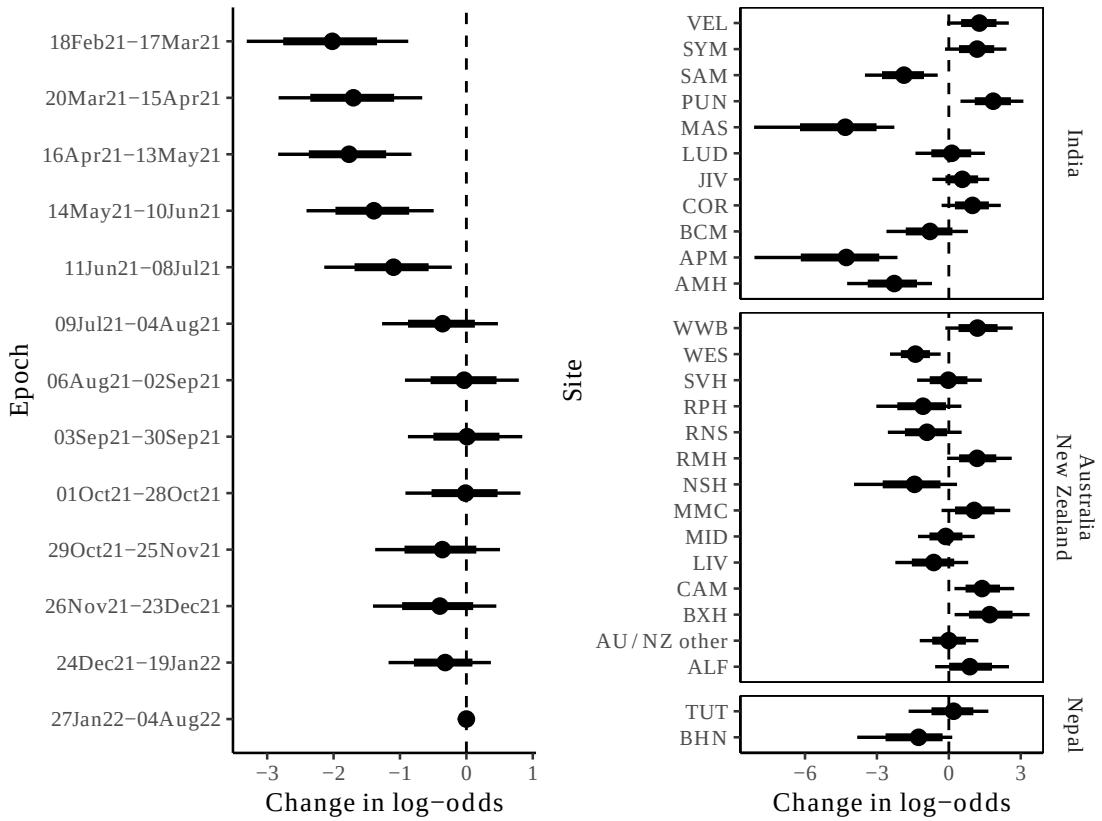

Figure 2.69: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on mMRC breathlessness scale at day 28 for the outcome model fit to the FAS-ITT set.

2.3.8 Quality of life as measured by EQ-5D-5L questionnaire at day 28

The EQ-5D-5L responses are described.

2.4 Domain Specific Outcomes

2.4.1 Antiviral Domain

The antiviral domain-specific outcomes were:

- viral clearance at days 3 and 7
- viral load at days 3 and 7
- safety:
  - elevation of Alanine Transaminase (ALT) or Aspartate Transaminase (AST)
  - elevated of serum potassium (> 5.5 mmol/L)
  - decrease of serum sodium (< 125 mmol/L)
  - major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH)
  - clinically relevant non-major bleeding (as defined by the ISTH)
  - thrombophlebitis/vasculitis at IV line site

The SAP specifies that descriptive summaries are to be reported for the antiviral specific outcomes.

2.4.1.1 Viral Clearance

The SAP specified that viral clearance was to be summarised at days 3 and 7. However, most participants did not have any PCR tests recorded during their hospital stay (Table 2.56), and those that did had inconsistent timing of the tests (Table 2.57).

Table 2.56: Descriptive summary of participant PCR testing.

Variable	Standard of care	Nafamostat
Assigned	73	82
Any tests	33	39
Proportion	0.45	0.48
Total tests	55	67
Mean number of tests	0.75	0.82
Max number of tests	5	8

Table 2.57: Descriptive summary of daily PCR testing, study days 1 to 7.

	Standard of care					Nafamostat				
Day	Patients	Tests	Positive	Negative	Indeterminate	Patients	Tests	Positive	Negative	Indeterminate
1	73	12 (16)	9 (75)	2 (17)	1 (8)	82	9 (11)	8 (89)	1 (11)	0 (0)
2	73	5 (7)	4 (80)	1 (20)	0 (0)	82	5 (6)	4 (80)	0 (0)	1 (20)
3	67	11 (16)	9 (82)	2 (18)	0 (0)	79	12 (15)	11 (92)	1 (8)	0 (0)
4	63	3 (5)	3 (100)	0 (0)	0 (0)	72	8 (11)	7 (88)	1 (12)	0 (0)
5	51	4 (8)	4 (100)	0 (0)	0 (0)	55	4 (7)	2 (50)	2 (50)	0 (0)
6	41	6 (15)	5 (83)	1 (17)	0 (0)	43	6 (14)	5 (83)	1 (17)	0 (0)
7	33	5 (15)	5 (100)	0 (0)	0 (0)	35	10 (29)	10 (100)	0 (0)	0 (0)

2.4.1.2 Viral Load

The SAP specified a descriptive summary of viral load to days 3 and 7, and change in viral load from baseline. Very few participants (24 of 156) had baseline cycle threshold values recorded so there was little data for looking at change in viral load from baseline. Additionally, most participants had no cycle threshold values reported their hospital stay.

Table 2.58: Descriptive summary of participant cycle threshold values.

Variable	Standard of care	Nafamostat
Assigned	73	82
Any Ct values	19 (26)	24 (29)
Total Ct values	27	43
Max number of Ct values	2	6

2.4.1.3 Elevation of Alanine Transaminase (ALT) or Aspartate Transaminase (AST)

The SAP specified that elevation of Alanine Transaminase (ALT) or Aspartate Transaminase (AST) to more than 5 times the upper limit of normal will be summarised. The collected values were reported on IU/L, therefore a threshold of 150 IU/L was used rather than 5 times the upper limit of normal. The number of participants with any ALT/AST tests reported, and the number with values exceeding 150 IU/L are reported in Table 2.59.

Daily summaries are reported in Table 2.60 and Table 2.61.

Table 2.59: Descriptive summary of participant cycle threshold values.

Variable	Standard of care	Nafamostat
Assigned	73	82
Any ALT tests, n (% of assigned)	63 (86)	71 (87)
Any ALT > 150, n (% of tested)	11 (17)	12 (17)
Any AST tests, n (% of assigned)	52 (71)	60 (73)
Any AST > 150, n (% of tested)	2 (4)	6 (10)
Total days	553	586
Total days ALT tested, n (% of days)	275 (50)	316 (54)
Total days ALT > 150, n (% of tests)	33 (12)	35 (11)
Total days AST tested, n (% of days)	185 (33)	254 (43)
Total days AST > 150, n (% of tests)	2 (1)	10 (4)

Table 2.60: Descriptive summary of daily ALT levels (IU/L) and testing.

	Standard of care				Nafamostat			
Study Day	Patients	Tested (% of patients)	Median	> 150 IU/L (% of tests)	Patients	Tested (% of patients)	Median	> 150 IU/L (% of tests)
1	73	43 (59)	40	1 (2)	82	51 (62)	38	1 (2)
2	73	36 (49)	52	2 (6)	82	46 (56)	50	3 (7)
3	67	32 (48)	42	3 (9)	79	42 (53)	50	5 (12)
4	63	29 (46)	57	6 (21)	72	34 (47)	53	4 (12)
5	51	18 (35)	64	3 (17)	55	26 (47)	66	5 (19)
6	41	18 (44)	56	4 (22)	43	22 (51)	52	4 (18)
7	33	17 (52)	81	4 (24)	35	20 (57)	64	6 (30)
8	27	12 (44)	83	3 (25)	29	18 (62)	60	4 (22)
9	17	8 (47)	38	3 (38)	21	6 (29)	36	1 (17)
10	13	6 (46)	36	2 (33)	15	4 (27)	44	0 (0)
11	11	5 (45)	46	1 (20)	11	6 (55)	31	0 (0)
12	9	3 (33)	23	1 (33)	8	6 (75)	40	0 (0)
13	7	4 (57)	30	0 (0)	6	3 (50)	59	0 (0)
14	6	3 (50)	31	0 (0)	5	3 (60)	32	0 (0)
15	5	3 (60)	19	0 (0)	5	2 (40)	25	0 (0)
16	5	3 (60)	45	0 (0)	4	3 (75)	28	0 (0)
17	5	4 (80)	36	0 (0)	4	1 (25)	26	0 (0)
18	5	3 (60)	56	0 (0)	4	2 (50)	36	0 (0)
19	5	4 (80)	40	0 (0)	4	3 (75)	22	0 (0)
20	5	3 (60)	39	0 (0)	4	2 (50)	34	0 (0)
21	4	4 (100)	50	0 (0)	3	2 (67)	40	0 (0)
22	4	4 (100)	68	0 (0)	3	3 (100)	17	0 (0)
23	4	3 (75)	31	0 (0)	2	2 (100)	62	0 (0)
24	4	4 (100)	49	0 (0)	2	2 (100)	88	1 (50)
25	4	1 (25)	43	0 (0)	2	2 (100)	88	0 (0)
26	4	2 (50)	88	0 (0)	2	2 (100)	83	0 (0)
27	4	2 (50)	68	0 (0)	2	1 (50)	160	1 (100)
28	4	1 (25)	39	0 (0)	2	2 (100)	90	0 (0)

Table 2.61: Descriptive summary of daily AST levels (IU/L) and testing.

	Standard of care				Nafamostat			
Study Day	Patients	Tested (% of patients)	Median	> 150 IU/L (% of tests)	Patients	Tested (% of patients)	Median	> 150 IU/L (% of tests)
1	73	35 (48)	42	1 (3)	82	43 (52)	48	2 (5)
2	73	28 (38)	50	1 (4)	82	36 (44)	46	2 (6)
3	67	21 (31)	56	0 (0)	79	35 (44)	41	2 (6)
4	63	22 (35)	50	0 (0)	72	27 (38)	38	1 (4)
5	51	11 (22)	37	0 (0)	55	22 (40)	37	1 (5)
6	41	15 (37)	38	0 (0)	43	17 (40)	37	2 (12)
7	33	12 (36)	38	0 (0)	35	16 (46)	39	0 (0)
8	27	8 (30)	32	0 (0)	29	14 (48)	33	0 (0)
9	17	4 (24)	25	0 (0)	21	5 (24)	25	0 (0)
10	13	3 (23)	23	0 (0)	15	2 (13)	28	0 (0)
11	11	3 (27)	29	0 (0)	11	4 (36)	35	0 (0)
12	9	1 (11)	25	0 (0)	8	5 (62)	48	0 (0)
13	7	2 (29)	25	0 (0)	6	2 (33)	56	0 (0)
14	6	1 (17)	26	0 (0)	5	1 (20)	66	0 (0)
15	5	1 (20)	22	0 (0)	5	1 (20)	51	0 (0)
16	5	1 (20)	20	0 (0)	4	2 (50)	47	0 (0)
17	5	1 (20)	16	0 (0)	4	1 (25)	51	0 (0)
18	5	1 (20)	15	0 (0)	4	2 (50)	38	0 (0)
19	5	2 (40)	18	0 (0)	4	2 (50)	34	0 (0)
20	5	1 (20)	19	0 (0)	4	2 (50)	32	0 (0)
21	4	2 (50)	22	0 (0)	3	2 (67)	38	0 (0)
22	4	2 (50)	22	0 (0)	3	2 (67)	44	0 (0)
23	4	2 (50)	23	0 (0)	2	2 (100)	42	0 (0)
24	4	2 (50)	34	0 (0)	2	2 (100)	60	0 (0)
25	4	1 (25)	44	0 (0)	2	2 (100)	58	0 (0)
26	4	1 (25)	80	0 (0)	2	2 (100)	48	0 (0)
27	4	1 (25)	42	0 (0)	2	1 (50)	78	0 (0)
28	4	1 (25)	56	0 (0)	2	2 (100)	50	0 (0)

2.4.1.4 Serum Potassium

Eight participants had at least one day on which they were tested and had a serum potassium level greater than 5.5 mmol/L, 7 assigned to Nafamostat, and 1 assigned to standard of care (Table 2.62). Six of the participants only had the one day exceeding 5.5 mmol/L, two had 2 days, and one had 3 days. For participants assigned to Nafamostat, all days where serum potassium exceeded 5.5 mmmol/L occurred during the first 8 study days. For the participant assigned to standard of care, the elevated potassium occurred on day 10 (Table 2.63).

Of the seven participants assigned to Nafamostat, one had no reported SAE/SAR which was for hyperkalaemia. For the other six participants details are provided in Table 2.64, Table 2.72, and Table 2.73.

Table 2.62: Descriptive summary of participant serum potassium levels (mmol/L) and testing.

Variable	Standard of care	Nafamostat
Assigned	73	82
Any tests	67	78
Any > 5.5 mmol/L	1	7
Total days	553	586
Total tests	321	361
Total > 5.5 mmol/L	1	11

Table 2.63: Descriptive summary of daily serum potassium levels (mmol/L) and testing.

	Standard of care				Nafamostat			
Study Day	Patients	Tested (% of patients)	Mean	> 5.5 (% of tests)	Patients	Tested (% of patients)	Mean	> 5.5 (% of tests)
1	73	49 (67)	4.05	0 (0)	82	60 (73)	4.07	0 (0)
2	73	44 (60)	3.99	0 (0)	82	48 (59)	4.38	0 (0)
3	67	38 (57)	4.14	0 (0)	79	49 (62)	4.41	1 (2)
4	63	34 (54)	4.05	0 (0)	72	37 (51)	4.50	2 (5)
5	51	24 (47)	4.27	0 (0)	55	29 (53)	4.48	3 (10)
6	41	21 (51)	4.19	0 (0)	43	28 (65)	4.48	1 (4)
7	33	18 (55)	4.14	0 (0)	35	21 (60)	4.40	1 (5)
8	27	12 (44)	4.26	0 (0)	29	20 (69)	4.58	2 (10)
9	17	10 (59)	4.39	0 (0)	21	10 (48)	4.63	0 (0)
10	13	6 (46)	4.60	1 (17)	15	7 (47)	4.07	0 (0)
11	11	8 (73)	4.28	0 (0)	11	7 (64)	4.29	0 (0)
12	9	4 (44)	4.30	0 (0)	8	6 (75)	4.10	0 (0)
13	7	5 (71)	4.18	0 (0)	6	4 (67)	4.12	0 (0)
14	6	4 (67)	4.05	0 (0)	5	2 (40)	4.45	0 (0)
15	5	3 (60)	4.47	0 (0)	5	2 (40)	4.30	0 (0)
16	5	3 (60)	4.53	0 (0)	4	3 (75)	4.57	0 (0)
17	5	4 (80)	4.15	0 (0)	4	2 (50)	3.50	0 (0)
18	5	3 (60)	4.07	0 (0)	4	4 (100)	4.65	1 (25)
19	5	4 (80)	4.25	0 (0)	4	3 (75)	4.47	0 (0)
20	5	3 (60)	4.33	0 (0)	4	2 (50)	4.30	0 (0)
21	4	4 (100)	3.98	0 (0)	3	2 (67)	4.50	0 (0)
22	4	4 (100)	4.00	0 (0)	3	3 (100)	4.53	0 (0)
23	4	3 (75)	4.20	0 (0)	2	2 (100)	4.55	0 (0)
24	4	4 (100)	4.22	0 (0)	2	2 (100)	4.45	0 (0)
25	4	2 (50)	3.75	0 (0)	2	2 (100)	4.65	0 (0)
26	4	3 (75)	4.37	0 (0)	2	2 (100)	4.20	0 (0)
27	4	2 (50)	4.25	0 (0)	2	2 (100)	4.25	0 (0)
28	4	2 (50)	4.45	0 (0)	2	2 (100)	4.35	0 (0)

Table 2.64: Elevated serum potassium SAE notes.

ID	Antiviral	Onset date	SAE Term	Type	Notes from Site
ALF00014	Nafamostat	NA			
CAM00002	Nafamostat	2021-09-20	Hyperkalaemia	SAR	The patient was randomised to nafamostat and standard dose thromboprophylaxis. On Day 5 the patient had hyperkalaemia so nafamostat treatment was ceased.A separate email was sent to clarify whether or not nafamostat should continue after this patient's potassium levels normalised. In this email, I think they may have incorrectly stated it was hypokalaemia not hyperkalaemia. Unable to modify outcome of SAE, as it is locked. I have checked the pathology values following the SAE, and Potassium was restored to within normal range the following day (21/9/21), following cessation of IMP. SAE paper CRF was marked as resolved/recovered. Measured again on 23/9/21 and was within normal range. Measured again on 24/9/21 at 5.5 (higher than normal), and participant was discharged home the following day (25/9/21). No further blood test values available.
CAM00012	Nafamostat	2021-12-30	Hyperkalaemia	SAR	Nafamostat course finished on 30/12. K+ levels were noted to be at 5.9 on 30/12 and again on 31/12. Repeat K+ test on 31/12 showed K+ level of 5.2. PI has reported the hyperkalaemia is likely secondary to nafamostat as no other clinical reason for hyperkalaemia. not reported as an SAE as did not require any interventions or prolonged hospitalisaition or complications and K+ levels returned naturally
MID00010	Standard of care	NA			
MMC00078	Nafamostat	2021-11-17	Hyperkalaemia	SAE	Patient had been experiencing elevated potassium levels- 6.2 mmol/L. Nafamostat ceased and patient successfully treated with resonium. A protocol breach was also submitted regarding this patient receiving the drug incorrectly (charted and administered 500mg per day from 12th to 15h Nov). The error was then discovered and the dose reduced to 375mg until the 17th November when the SAE occured and nafamostat was ceased.
MMC00079	Nafamostat	2021-11-23	Hyperkalaemia	SAR	This patient was randomised to nafamostat and intermediate dose thromboprophylaxis. They experienced hyperkalaemia (6.0) on day 6 (23-Nov-2021) of their treatment. Their baseline potassium was 5.1. They have a number of comorbidities (obesity, diabetes, chronic kidney disease, Iatrogenic immunosuppression). They were treated with Sodium Polystyrene (15mg x2 daily) on 23-Nov-21 and have since recovered. Treatment continued however the patient only received 12 hours of the infusion on day 7 due to poor IV access.
RNS00002	Nafamostat	2021-08-05	Hyperkalaemia	SAR	Serum potassium levels were 6.1 mmol/L on the 05Aug2021 - Day 4 post randomisation 05 Aug 2021, K 6.1 – ECG was normal with normal P and T waves. Pt was given Resonium A 30g po 06 Aug 2021, K 5.7, given a further Resonium A 30g po 07 Aug 2021 K 4.8 The patient was on Nafamostat 350mg IV continuously from the 02Aug2021 to 09Aug2021 The pt was discharged on no medications.
SVH00002	Nafamostat	2021-09-02	Hyperkalaemia	SAR	Clinical Synopsis / Significant Events 21/8/21 - PCR Covid +ive 25/8/21 - hospital admission 27/8/21 - ICU admission -> HFNP. 28/8/21 - . Ongoing HFNP requirement 30/8/21 - self-proning overnight 31/8/21 - Remains on HFNP, supine throughout day, self-proning encouraged overnight 2/9/21- Dex changed to Hydrocort as ? contributing to HypoNa/HyperK 3/9/21 -Urine culters UTI 1/9 E Coli and Pseudomonas aeruginosa, started Tazocin from Augmentin to cover Pseudomonas aeruginosa 6/9/21 - Remains on HFNP 50L 50% 8/9/21 - Ongoing slow wean of HFNP 9/9/21 - Transitioned to NP, cleared for ward Dose was finished prior to high K+

2.4.1.5 Serum Sodium

One participant had any days on which they were tested and had a serum sodium level less than 125 mmol/L. This participant had serum sodium less than 125 mmol/L on two consecutive days (study days 26 and 27). They were assigned to standard of care in the antiviral domain.

Most participants had at least one test during their hospital admission (Table 2.65). A summary of serum sodium testing by study day is presented in Table 2.66.

Table 2.65: Descriptive summary of participant serum sodium levels (mmol/L) and testing.

Variable	Standard of care	Nafamostat
Assigned	73	82
Any tests	67	78
Any < 125 mmol/L	1	0
Total days	553	586
Total tests	325	367
Total < 125 mmol/L	2	0

Table 2.66: Descriptive summary of daily serum sodium levels (mmol/L) and testing.

Study Day	Standard of care				Nafamostat			
	Patients	Tested (% of patients)	Mean	< 125 (% of tests)	Patients	Tested (% of patients)	Mean	< 125 (% of tests)
1	73	49 (67)	136.14	0 (0)	82	60 (73)	137.13	0 (0)
2	73	44 (60)	137.41	0 (0)	82	50 (61)	137.50	0 (0)
3	67	39 (58)	137.23	0 (0)	79	49 (62)	136.43	0 (0)
4	63	34 (54)	137.38	0 (0)	72	39 (54)	135.62	0 (0)
5	51	25 (49)	137.20	0 (0)	55	29 (53)	134.66	0 (0)
6	41	22 (54)	137.45	0 (0)	43	28 (65)	135.25	0 (0)
7	33	18 (55)	136.33	0 (0)	35	22 (63)	136.32	0 (0)
8	27	12 (44)	136.08	0 (0)	29	20 (69)	133.95	0 (0)
9	17	10 (59)	136.40	0 (0)	21	10 (48)	134.60	0 (0)
10	13	6 (46)	134.67	0 (0)	15	7 (47)	134.00	0 (0)
11	11	8 (73)	136.12	0 (0)	11	7 (64)	135.14	0 (0)
12	9	4 (44)	134.25	0 (0)	8	6 (75)	134.50	0 (0)
13	7	5 (71)	135.80	0 (0)	6	4 (67)	136.50	0 (0)
14	6	4 (67)	136.00	0 (0)	5	3 (60)	136.00	0 (0)
15	5	3 (60)	134.00	0 (0)	5	2 (40)	139.00	0 (0)
16	5	3 (60)	136.33	0 (0)	4	3 (75)	136.67	0 (0)
17	5	4 (80)	137.50	0 (0)	4	2 (50)	133.50	0 (0)
18	5	4 (80)	136.50	0 (0)	4	4 (100)	136.50	0 (0)
19	5	4 (80)	134.75	0 (0)	4	3 (75)	137.33	0 (0)
20	5	3 (60)	134.33	0 (0)	4	2 (50)	136.50	0 (0)
21	4	4 (100)	135.75	0 (0)	3	2 (67)	137.00	0 (0)
22	4	4 (100)	136.00	0 (0)	3	3 (100)	137.33	0 (0)
23	4	3 (75)	136.33	0 (0)	2	2 (100)	136.50	0 (0)
24	4	4 (100)	136.00	0 (0)	2	2 (100)	137.00	0 (0)
25	4	2 (50)	137.50	0 (0)	2	2 (100)	136.00	0 (0)
26	4	3 (75)	133.67	1 (33)	2	2 (100)	138.00	0 (0)
27	4	2 (50)	132.50	1 (50)	2	2 (100)	140.50	0 (0)
28	4	2 (50)	133.50	0 (0)	2	2 (100)	141.00	0 (0)

2.4.1.6 Major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH)

One participant randomised to the antiviral domain experienced a major bleeding event (Table 2.67). Two events were recorded for this participant on study days 5 and 6. This participant was also assigned to the *intermediate-dose* intervention in the anticoagulation domain.

An SAR was recorded for this event (onset date 2021-08-30), details are provided in Table 2.68 and Table 2.73.

Table 2.67: Descriptive summary of major bleeding (ISTH) events.

Variable	Standard of care	Nafamostat
Assigned	73	82
Total days in hospital	553	586
Any major bleeding (patient)	0	1
Total major bleeding (days)	0	2

Table 2.68: Major bleeding SARS notes.

Patient ID	Onset Date	Notes from Site
WES00039	2021-08-30	Bleed was diagnosed on CT scan performed 30/8 at 13:49. The last dose of enoxaparin was given at 08:53 on 30/8. Nafamostat was ceased at 14:18 on 30/8. The Hb was 149 on 26/8 at 00:01 (prior to randomization on 26/8), 135 on 27/8 at 02:00, 125 on 29/8 at 04:07 and 123 on 30/9 at 09:28. The onset of abdominal pain was the morning of 30/8. The Nadir Hb was 106 on 31/8 at 00:09, and has risen to 118 on 31/8 at 07:40 post transfusion. 4 units of FFP and 2 units of PRBCs given in the early hours of 31/8. Additionally 20mg protamine given 30/8 at 20:16. antiXa levels: 0.3 U/ml on 30/8 at 16:46, 0.15 U/ml on 30/8 at 21:02 and 0.12 U/ml on 31/8 at 07:40 At 09:28 on 30/8, PT was 14s, APTT 40s, INR 1.2, PLT 193, Creatinine 63 umol/l, eGR>90 and urea 6.8 mmol/l.

2.4.1.7 Clinically relevant non-major bleeding (as defined by the ISTH)

Two participants randomised to the antiviral domain had clinically relevant non-major bleeding reported on their day 28 form (Table 2.69). One participant was assigned to Nafamostat and intermediate-dose anticoagulation. The other was assigned to standard of care in the antiviral domain and therapeutic-dose anticoagulation.

An SAR was recorded for both of these events, details are provided in Table 2.70 and Table 2.73.

Table 2.69: Descriptive summary of clinically relevant non-major bleeding (ISTH) events reported at day 28.

Variable	Standard of care	Nafamostat
Assigned	73	82
Missing	18	14
Any non-major bleeding	1	1

Table 2.70: Major bleeding SARS notes.

Patient ID	Onset Date	Notes from Site
MID00009	2021-09-23	Patient was randomised to nafamostat and intermediate dose anticoagulation and they developed a minor bleed. The clinical team made the decision to reduce the heparin dose (60mg to 40mg), and there were no further issues after this. Even though it is was a minor bleed and the patient outcome not serious, it warranted a clinical response. It was felt that the bleeding was mild but persistent and increasing over a couple of days and was a potential warning sign of a life threatening event as she would not have tolerated a major pulmonary haemorrhage – she was for ward based ceiling of care despite young age because of her co-morbidities. Happily the bleeding resolved with a reduction in enoxaparin dose – I don't know whether it was going to resolve anyway.
RPH00005	2022-03-25	The patient was randomised, and began treatment, on the 16 March 2022. They were randomised to antiviral SoC, and therapeutic anticoagulation * The patient developed haemoptysis on 25 March 2022, which persisted up to 27 March 2022. * Anticoagulation treatment was ceased on the 25 March 2022. * The PI and respiratory team decided to stop anticoagulation treatment and have withdrawn the patient from the study, as they are scheduled for discharge

2.4.1.8 Thrombophlebitis/vasculitis at IV line site

Six participants assigned to Nafamostat had reported thrombophlebitis/vasculitis at IV line site (Table 2.71).

Table 2.71: Descriptive summary of thrombophlebitis/vasculitis at IV line site events.

Variable	Standard of care	Nafamostat
Assigned	73	82
Thrombophlebitis/vasculitis at IV line site (%)	0 (0)	6 (7)

2.5 Safety Listings

Listings of serious adverse events (SAEs) and serious adverse reactions (SARs) for participants randomised to the antiviral domain are included in Table 2.72 and Table 2.73.

2.5.1 SAEs

Table 2.72: SAE listing.

Patient ID	Onset date	SAE Term	Grade	Association with Study Drug	Protocol Treatment Start Date	Protocol Treatment End Date	Action Taken	Outcome	Resolution date
RNS00002	2021-08-05	Hyperkalaemia	1	Unlikely	2021-08-02	2021-08-04	None	Recovered/resolved	2021-08-06
SVH00002	2021-09-02	Hyperkalaemia	1	Possible	2022-08-26	2022-09-01	None	Recovered/Resolved	2022-09-03
CAM00002	2021-09-20	Hyperkalaemia	1	Possible	2021-09-16	2021-09-21	Intervention interupted	Recovered/Resolved	2021-09-21
ALF00013	2021-10-16	Nausea/Vomitting	NA	Possible	NA	NA	intervention withdrawn	NA	NA
CAM00008	2021-10-28	Hospital acquired pneumonia and empyema	3	Unlikely	2021-10-05	2021-10-12	None	Recovered/resolved	NA
ALF00014	2021-10-28	Small volume haemoptysis	NA	Possible	NA	NA	intervention withdrawn	NA	NA
MMC00079	2021-11-23	Hyperkalaemia	2	Probable	2021-11-15	2021-11-21	None	Recovered/resolved	2021-11-24
CAM00011	2021-11-28	elevated transaminases	2	Possible	2021-11-25	2021-11-28	intervention withdrawn	Recovered/Resolved	2021-11-30
CAM00012	2021-12-30	Hyperkalaemia	NA	Possible	2021-12-23	2021-12-30	None	Recovered/resolved	2021-12-31

2.5.2 SARs

Table 2.73: SAR listing.

Patient ID	Onset date	SAE Term	Grade	Association with Study Drug	SUSAR	Protocol Treatment Start Date	Protocol Treatment End Date	Action Taken	Outcome	Resolution date
WES00039	2021-08-30	Left retroperitoneal haemotoma	4	Probable	No	2021-08-26	2021-08-30	Intervention interupted	Recovered/resolved	2021-09-04
MID00009	2021-09-23	Haemoptysis	1	Possible	No	2021-09-20	2021-09-23	Dose reduced	Recovered/Resolved	2021-09-24
MMC00078	2021-11-17	Hyperkalaemia	3	Probable	No	2021-11-12	2021-11-17	intervention withdrawn	Recovered/resolved	2021-11-18
RPH00005	2022-03-25	Haemoptysis	2	Definite	No	2022-03-16	2022-03-25	intervention withdrawn	Recovered/resolved	2022-03-28

3 Appendix

3.1 Outcomes by Model Covariates (FAS-ITT)

3.1.1 Primary Outcome by Model Covariates (FAS-ITT)

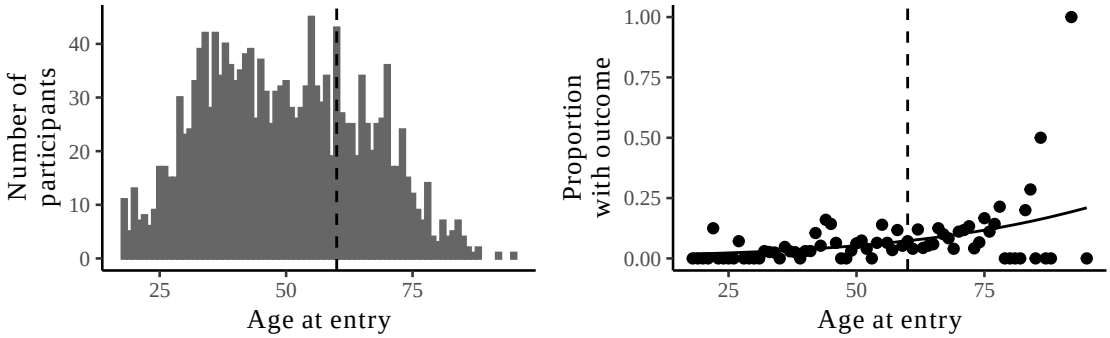

Figure 3.1: Proportion of participants satisfying primary outcome criteria by age at randomisation, FAS-ITT. Vertical dashed line indicates the pre-specified cut-point of 60 years of age.

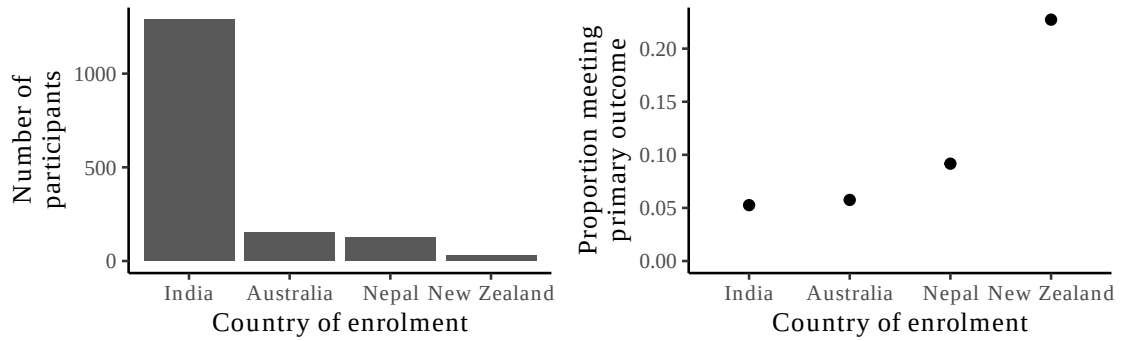

Figure 3.2: Proportion of participants satisfying primary outcome criteria by country of randomisation, FAS-ITT.

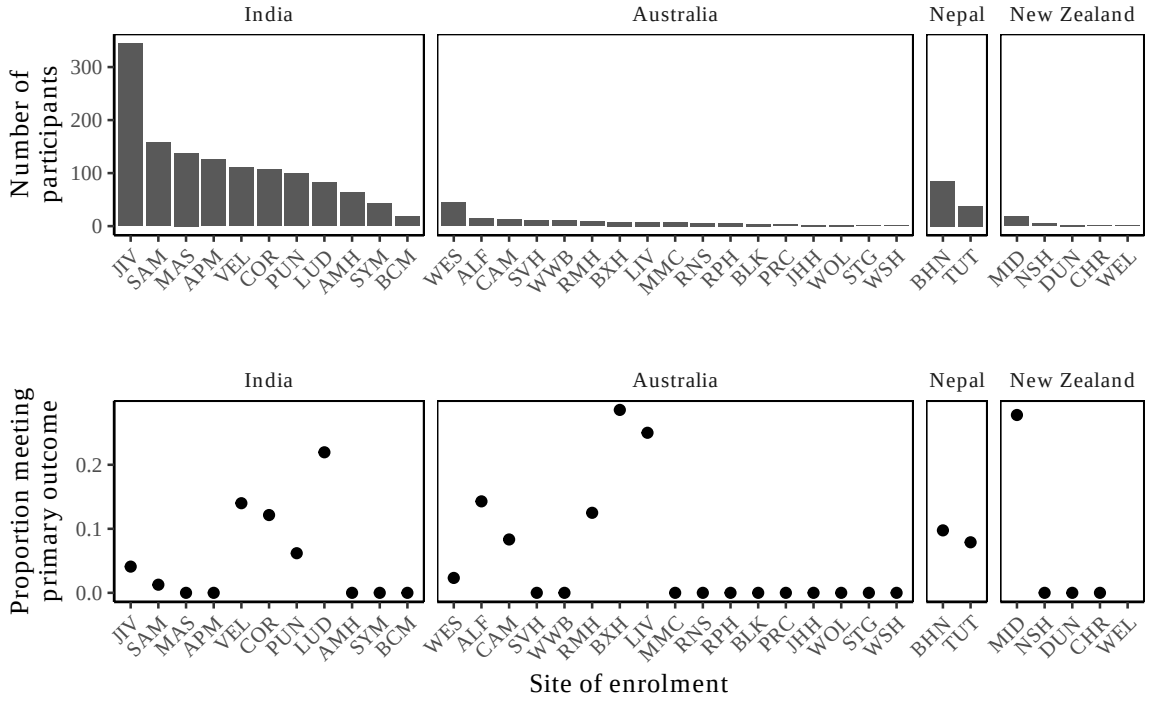

Figure 3.3: Proportion of participants satisfying primary outcome criteria by country and site of randomisation, FAS-ITT.

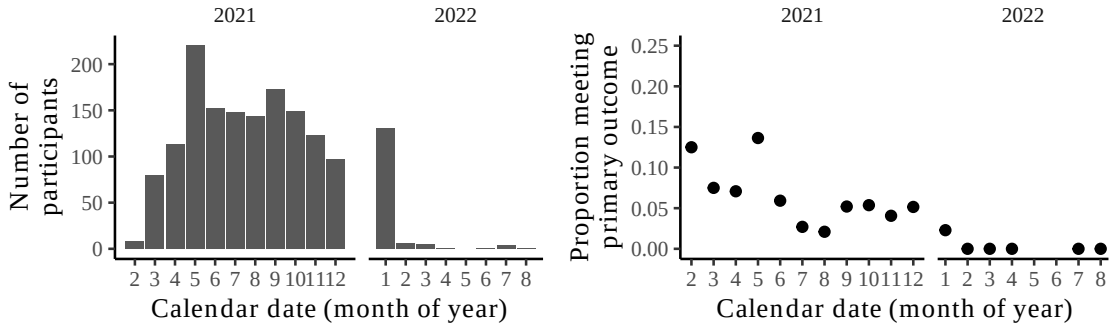

Figure 3.4: Proportion of participants satisfying primary outcome criteria by calendar time (month) of randomisation, FAS-ITT.

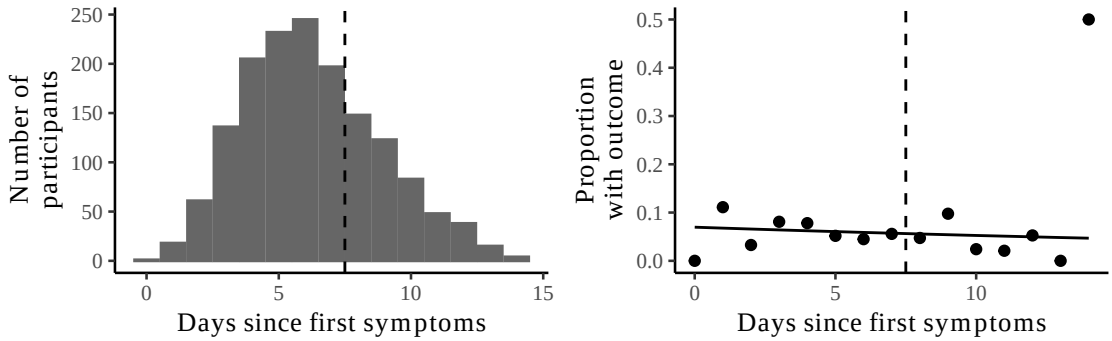

Figure 3.5: Proportion of participants satisfying primary outcome criteria by days since first symptoms at randomisation, FAS-ITT. Vertical dashed line indicates the pre-specified cut-point of 7 days.

3.1.2 Time to recovery to day 28 by model covariates (FAS-ITT)

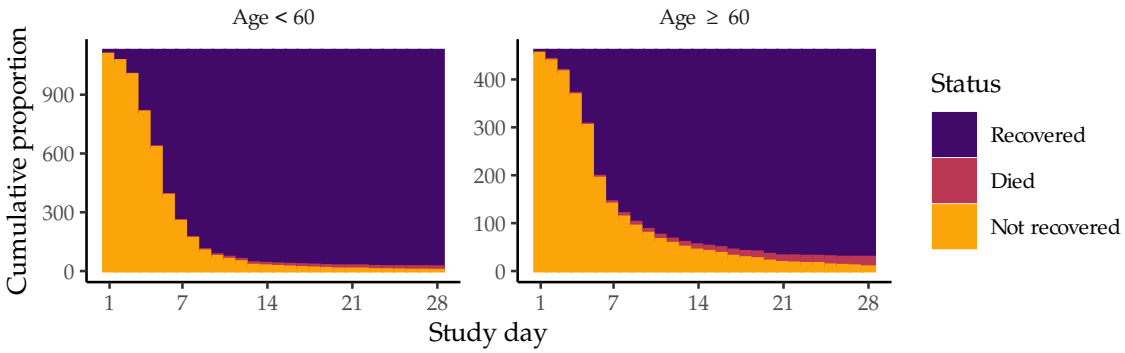

Figure 3.6: Time to clinical recovery to day 28 by age group at randomisation, FAS-ITT.

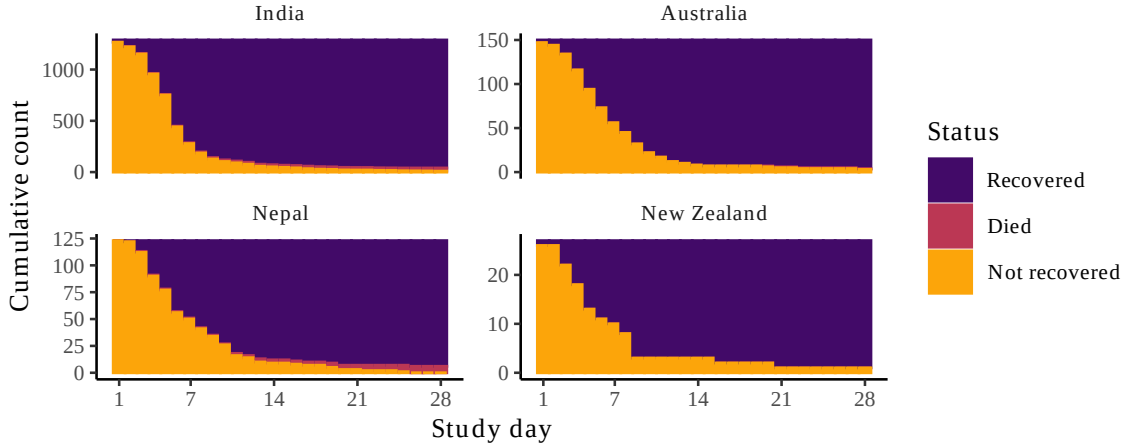

Figure 3.7: Time to clinical recovery to day 28 by country of randomisation, FAS-ITT.

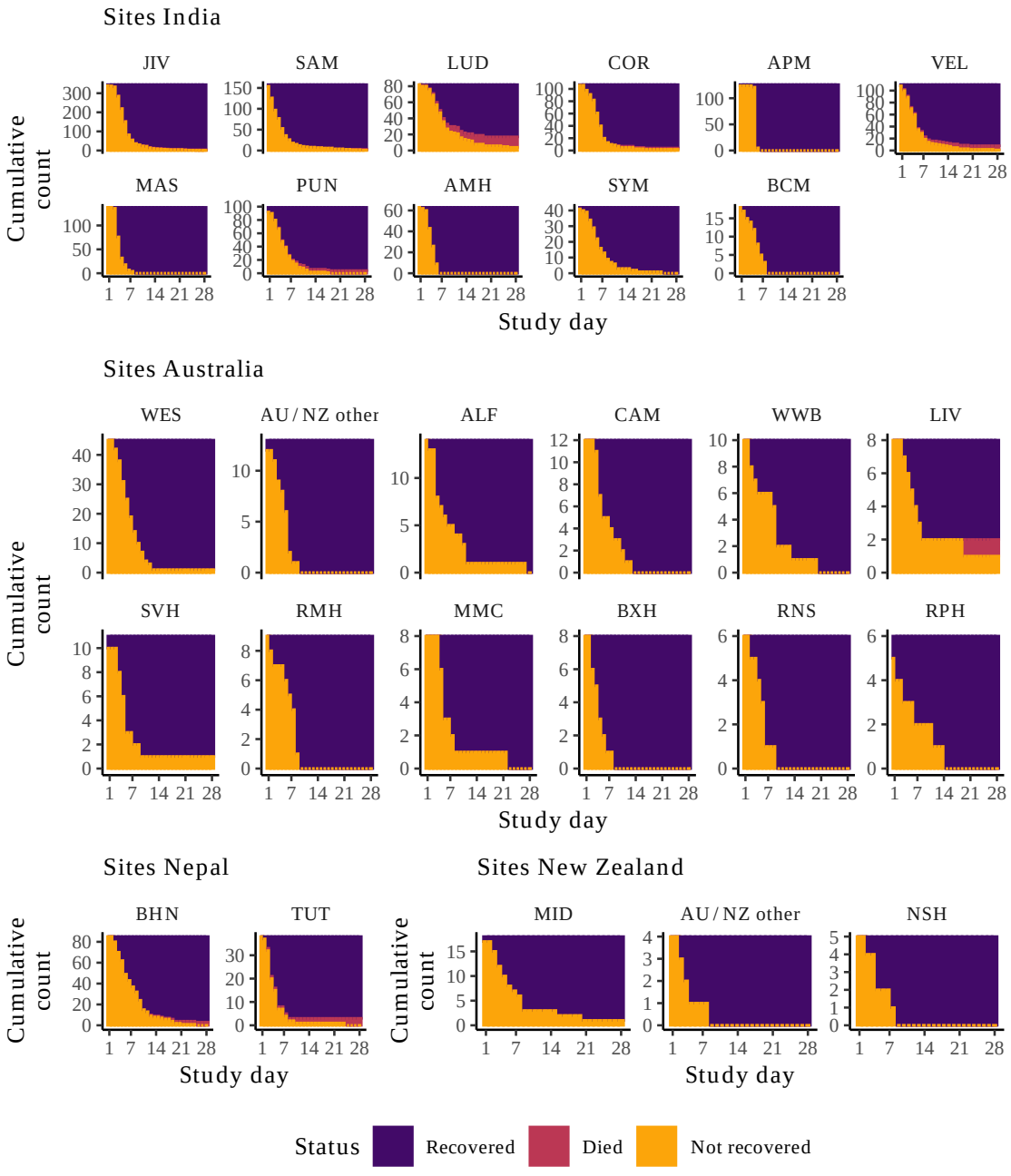

Figure 3.8: Time to clinical recovery to day 28 by country and site of randomisation, FAS-ITT.

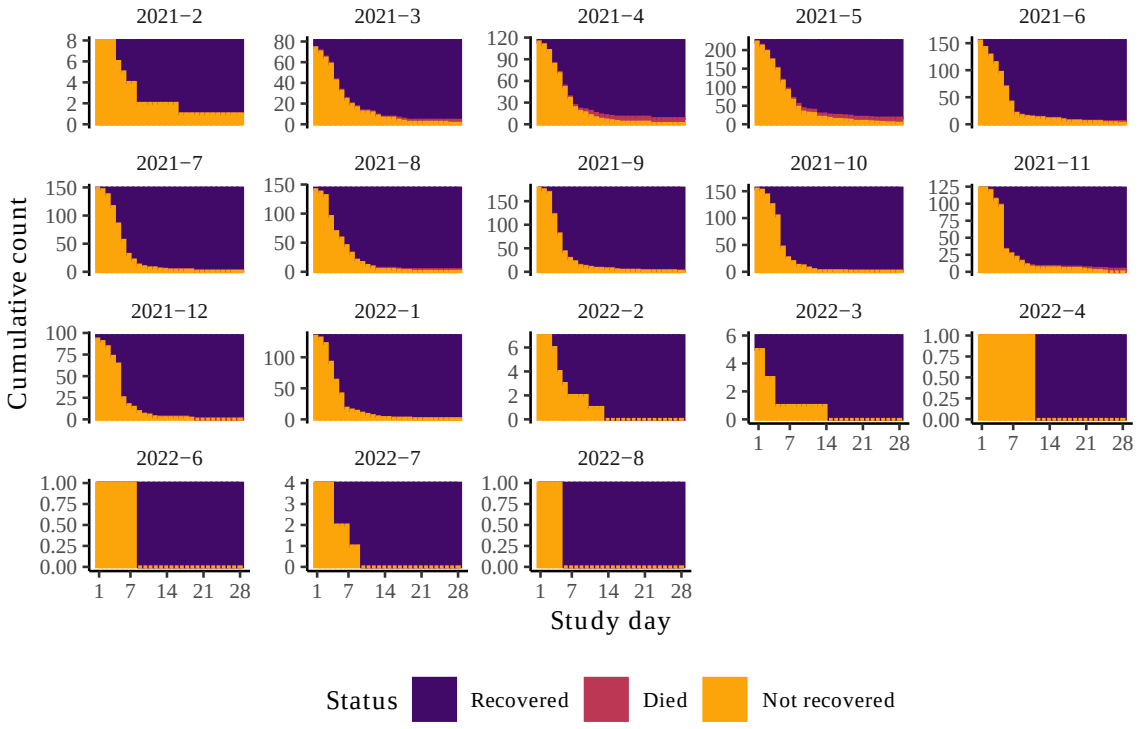

Figure 3.9: Time to clinical recovery to day 28 by calendar time (month) of randomisation, FAS-ITT.

3.1.3 WHO outcome scale at day 28 by model covariates (FAS-ITT)

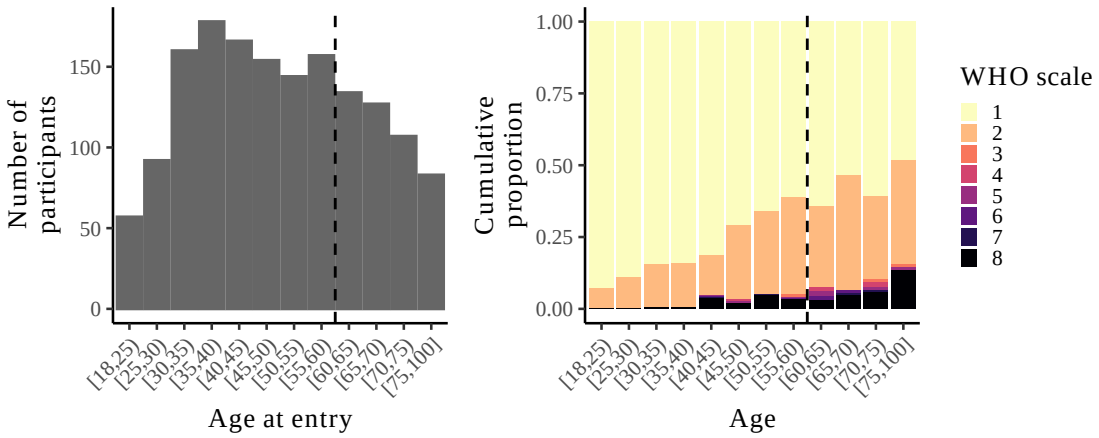

Figure 3.10: Distribution of WHO outcome scale day 28 by age at randomisation, FAS-ITT. Vertical dashed line indicates the pre-specified cut-point of 60 years of age.

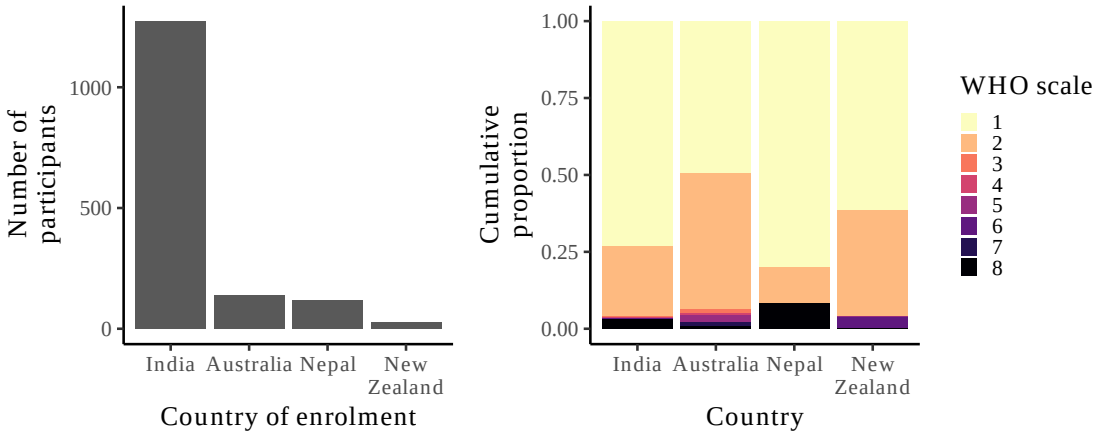

Figure 3.11: Distribution of WHO scale at day 28 by country of randomisation, FAS-ITT.

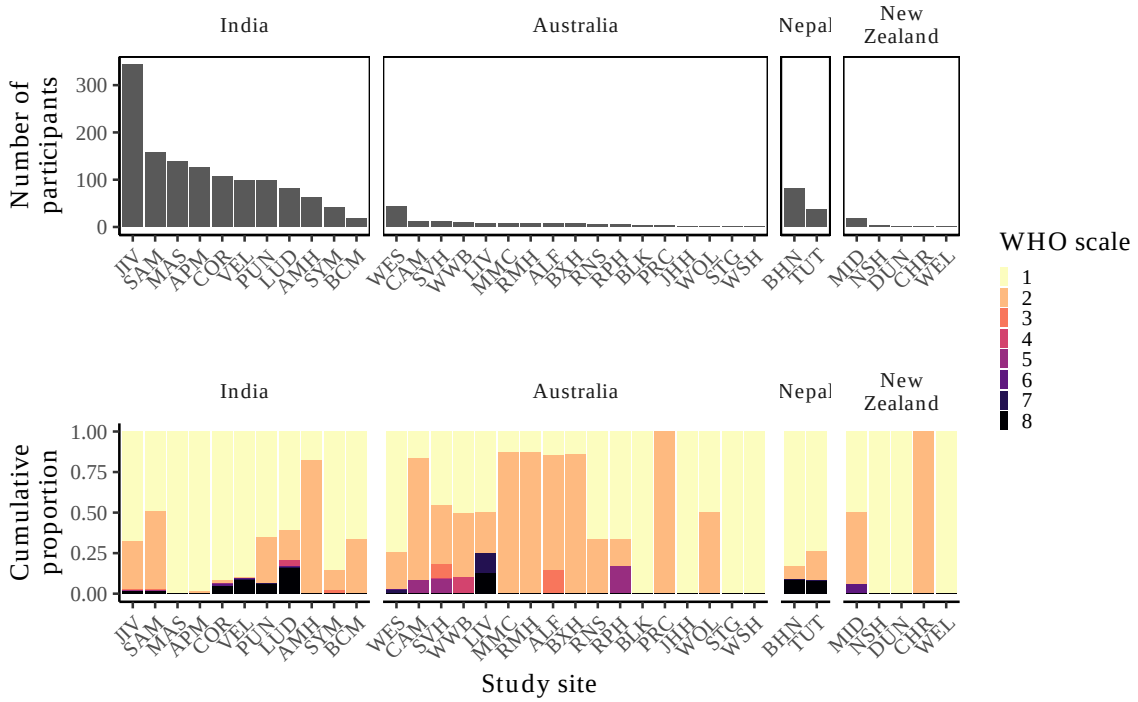

Figure 3.12: Distribution of WHO scale at day 28 by country and site of randomisation, FAS-ITT.

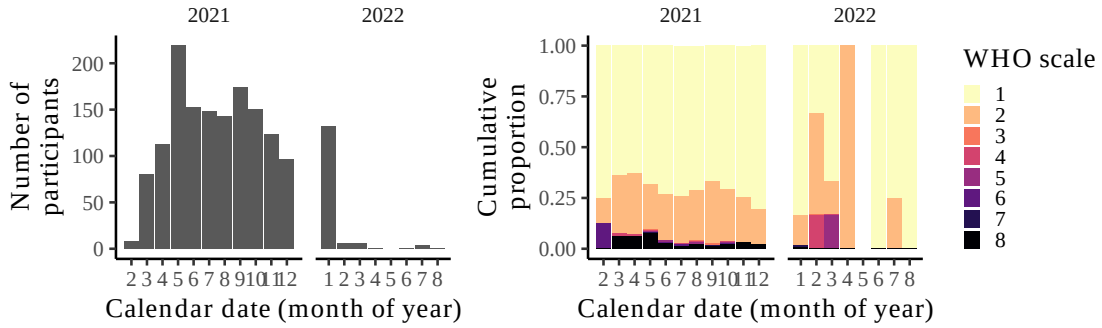

Figure 3.13: Distribution of WHO scale at day 28 by calendar time (month) of randomisation, FAS-ITT.

3.1.4 Mortality to day 28 by Model Covariates (FAS-ITT)

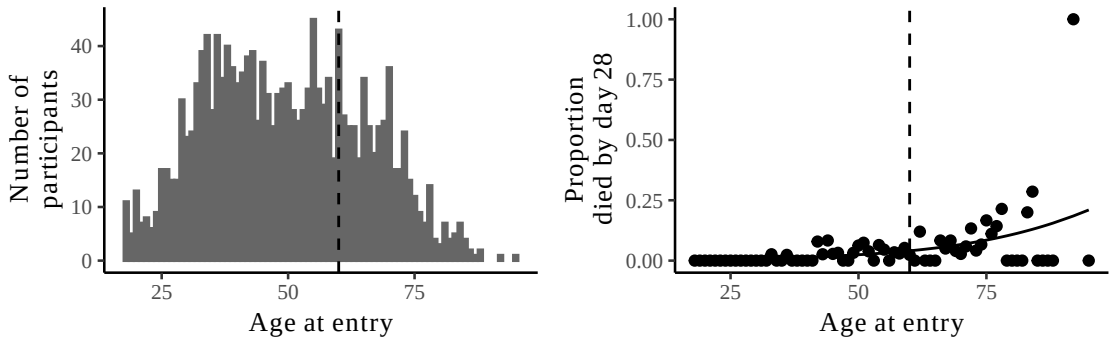

Figure 3.14: Proportion of participants who died by day 28 by age at randomisation, FAS-ITT. Vertical dashed line indicates the pre-specified cut-point of 60 years of age.

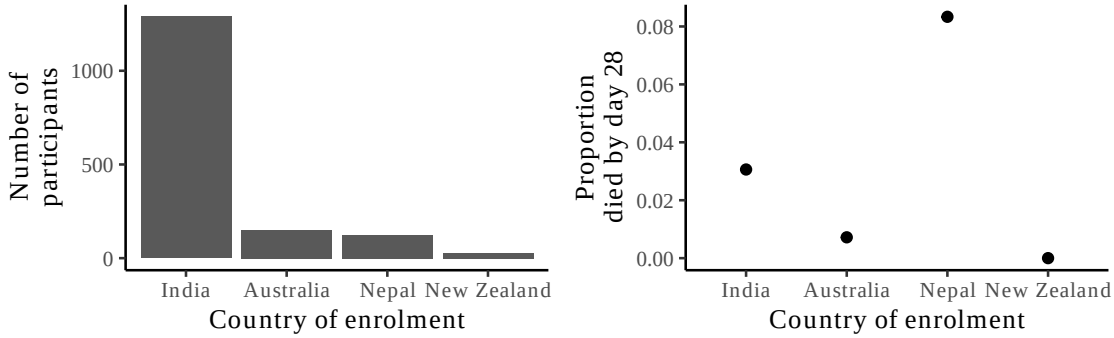

Figure 3.15: Proportion of participants who died by day 28 by country of randomisation, FAS-ITT.

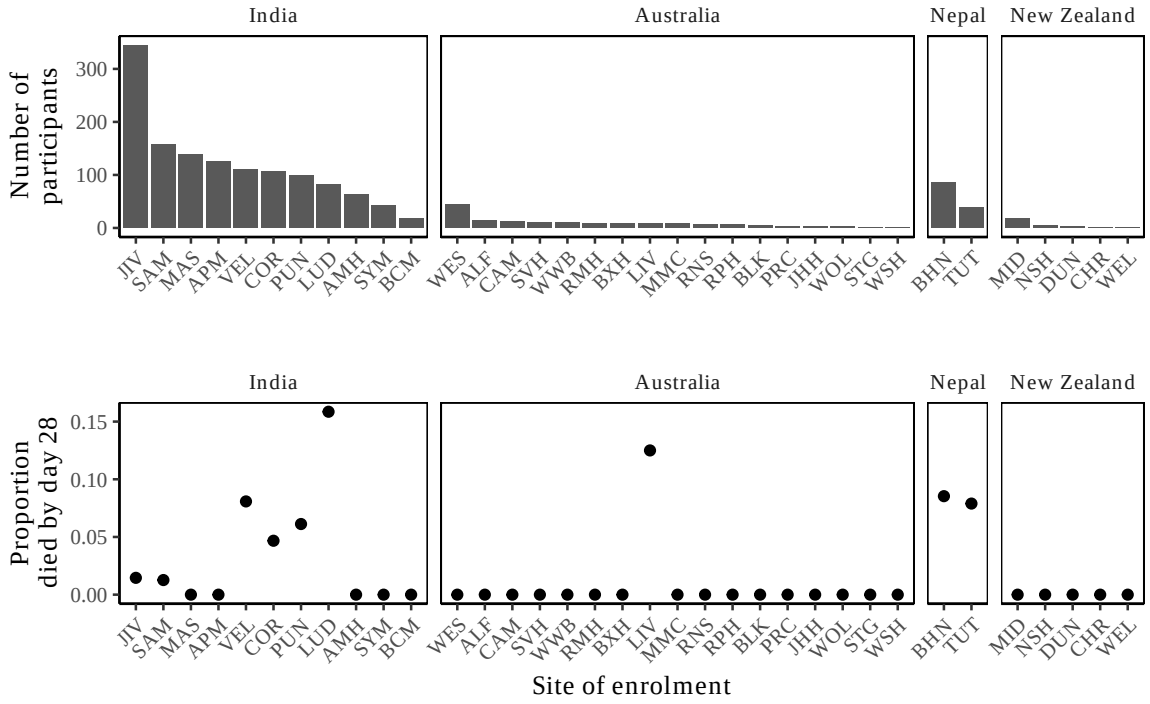

Figure 3.16: Proportion of participants who died by day 28 by country and site of randomisation, FAS-ITT.

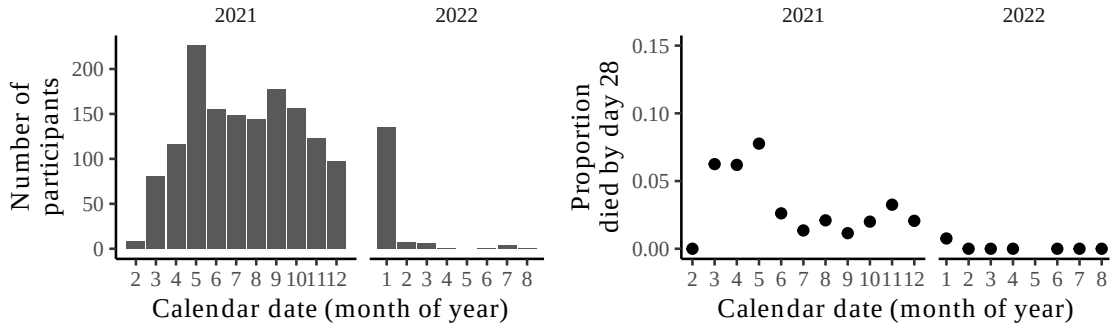

Figure 3.17: Proportion of participants who died by day 28 by calendar time (month) of randomisation, FAS-ITT.

3.1.5 Days alive and free of hospital to day 28 by Model Covariates (FAS-ITT)

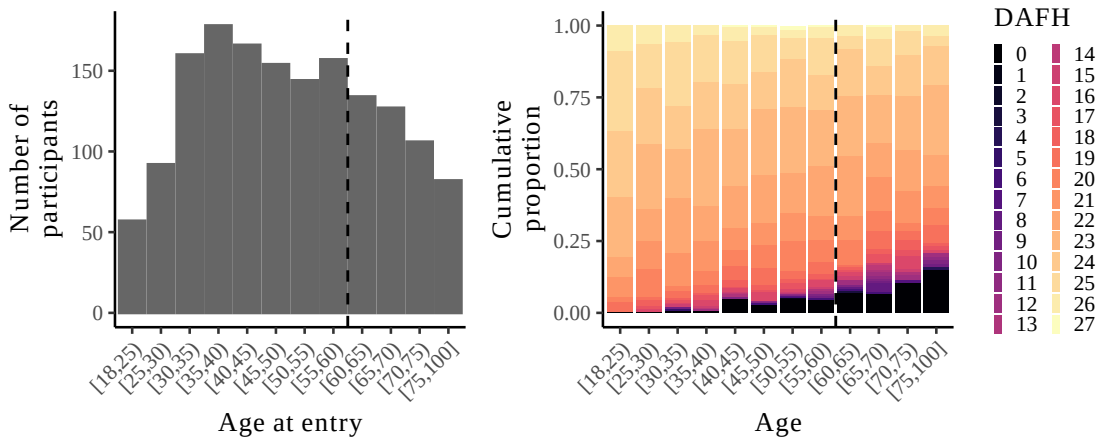

Figure 3.18: Distribution of days alive and free of hospital to day 28 by age groups, FAS-ITT.

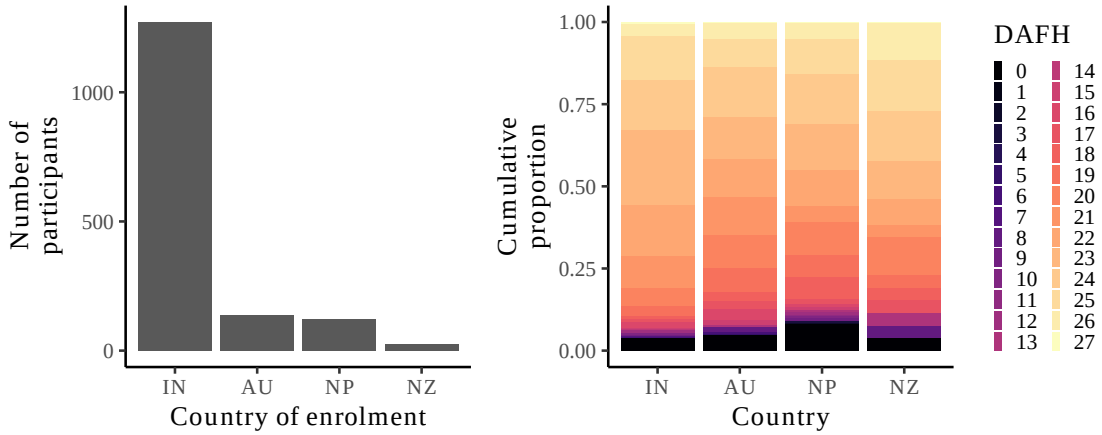

Figure 3.19: Distribution of days alive and free of hospital to day 28 by country of randomisation, FAS-ITT.

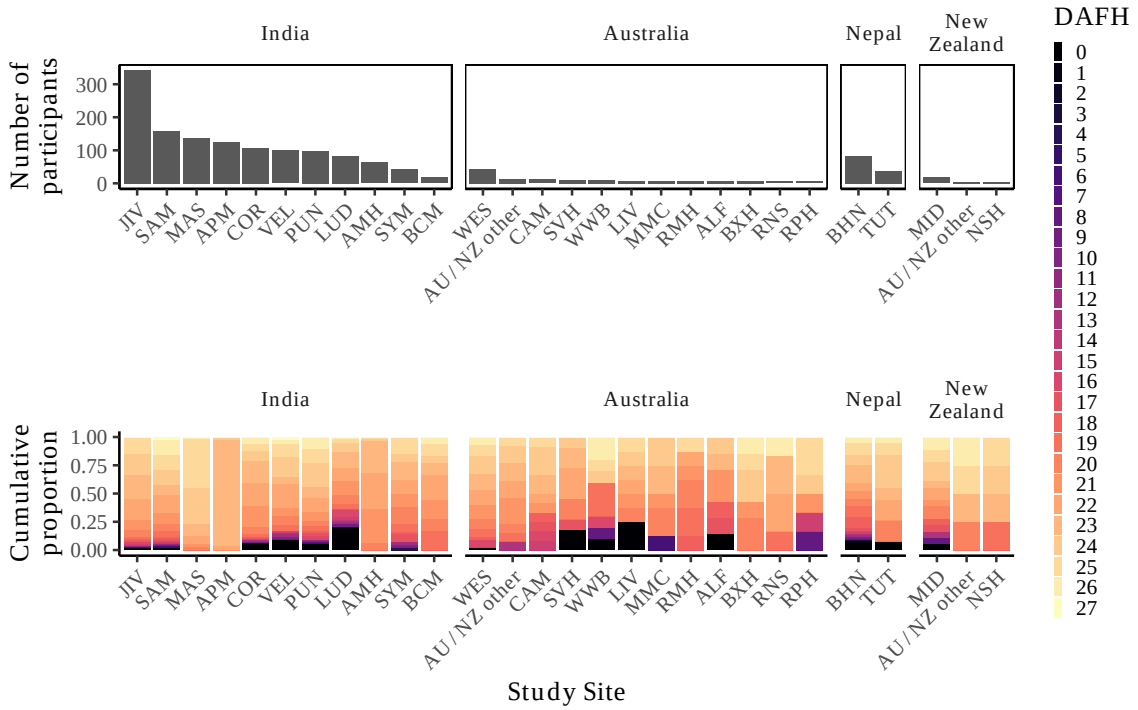

Figure 3.20: Distribution of days alive and free of hospital to day 28 by country and site of randomisation, FAS-ITT.

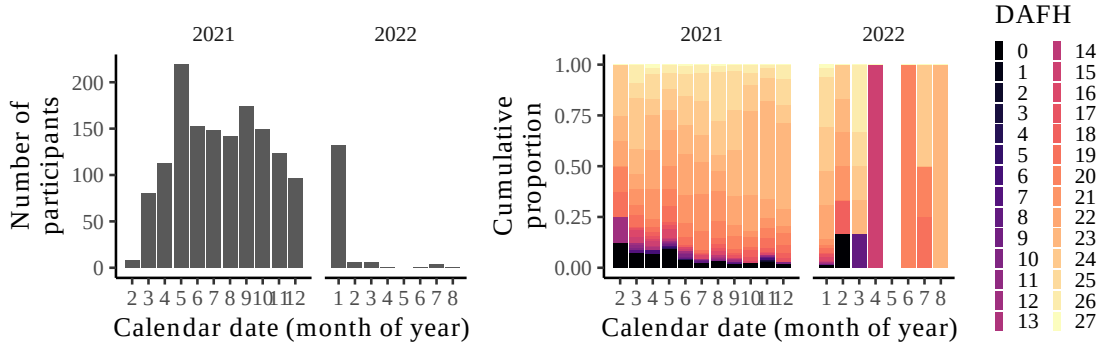

Figure 3.21: Distribution of days alive and free of hospital to day 28 by calendar time (month) of randomisation, FAS-ITT.

3.1.6 Days alive and free of ventilation to day 28 by Model Covariates (FAS-ITT)

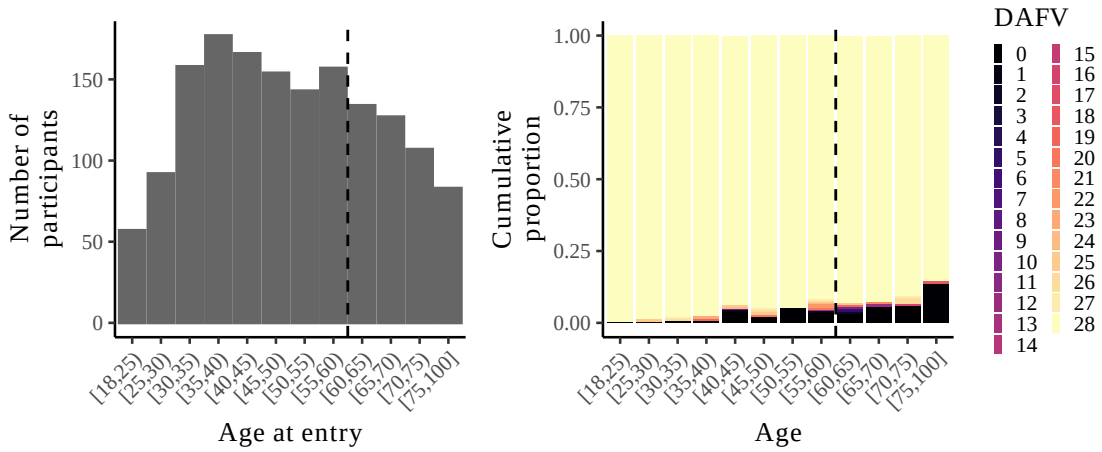

Figure 3.22: Distribution of days alive and free of ventilation to day 28 by age groups, FAS-ITT.

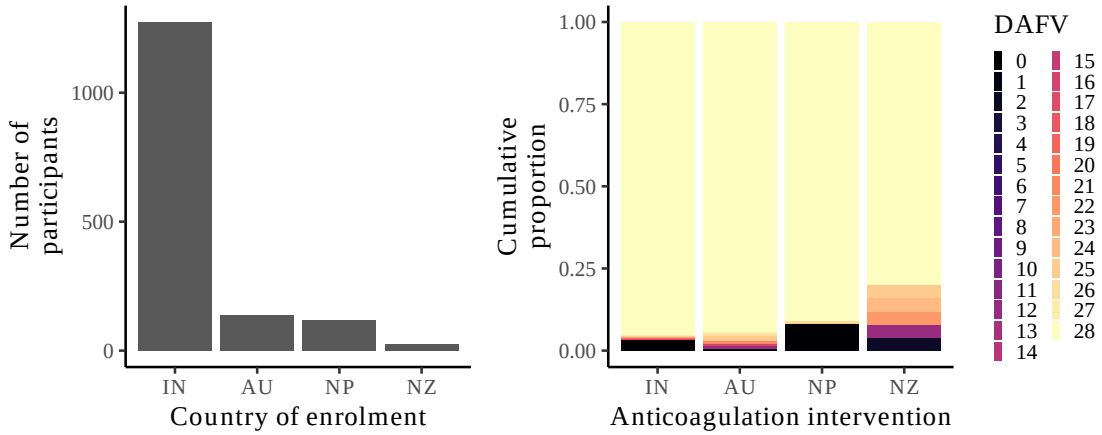

Figure 3.23: Distribution of days alive and free of ventilation to day 28 by country of randomisation, FAS-ITT.

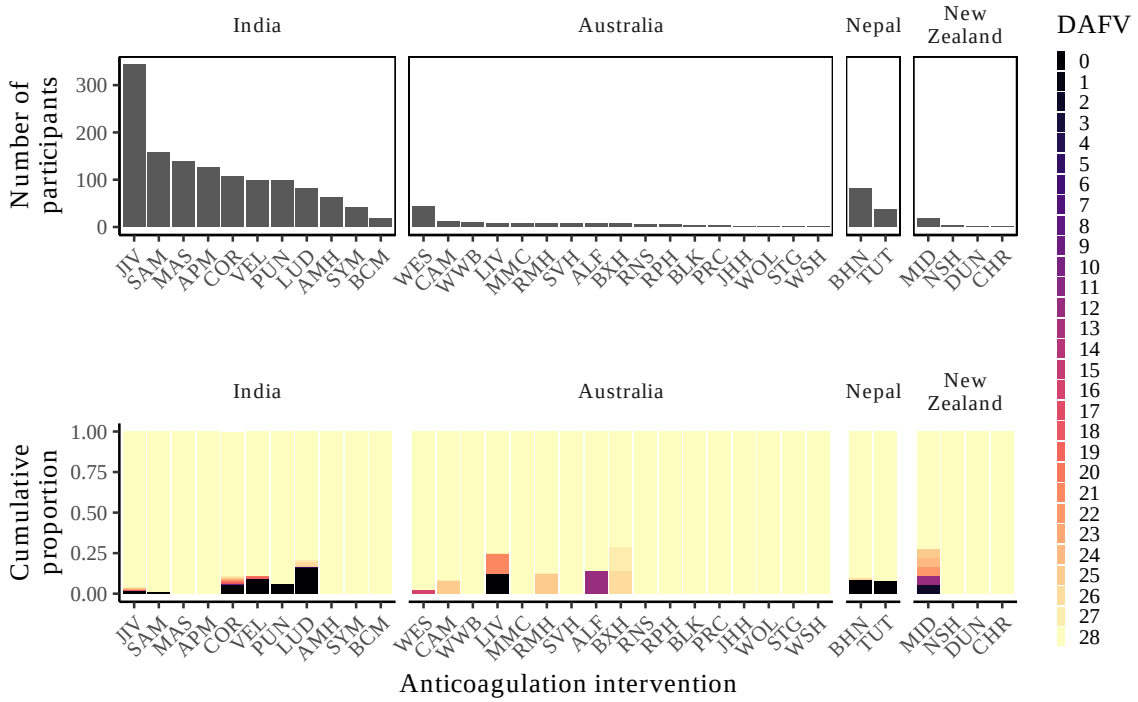

Figure 3.24: Distribution of days alive and free of ventilation to day 28 by country and site of randomisation, FAS-ITT.

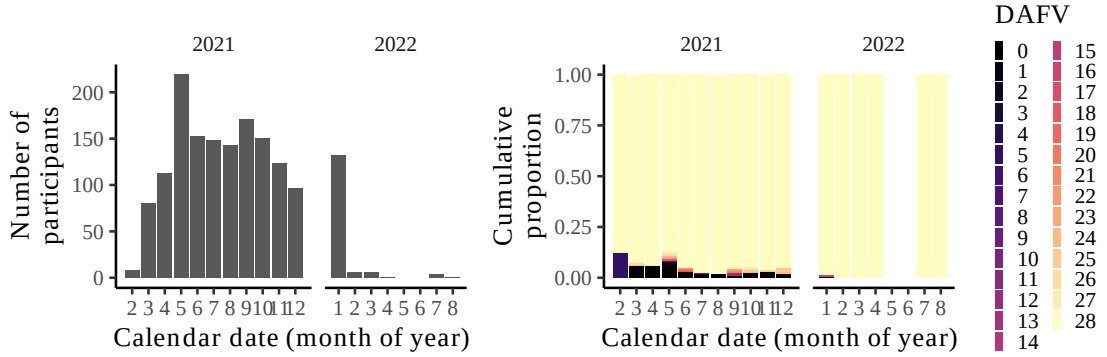

Figure 3.25: Distribution of days alive and free of ventilation to day 28 by calendar time (month) of randomisation, FAS-ITT.

3.1.7 Presence of patient reported shortness of breath at day 28 by model covariates (FAS-ITT)

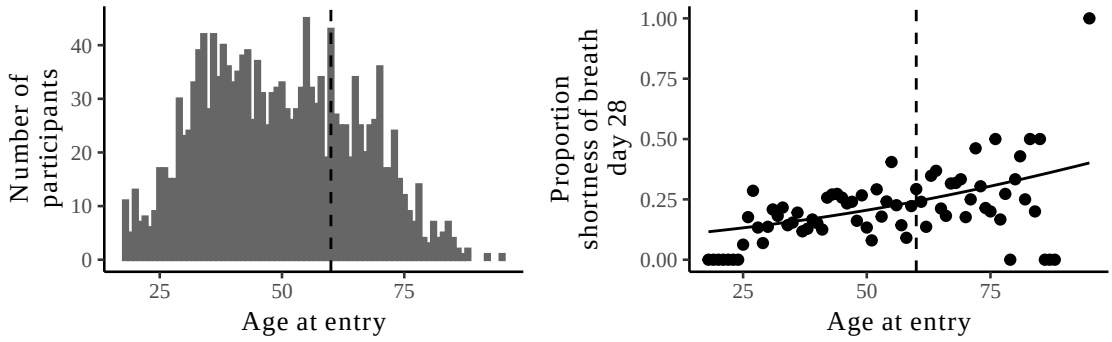

Figure 3.26: Proportion with patient reported shortness of breath at day 28 by age groups.

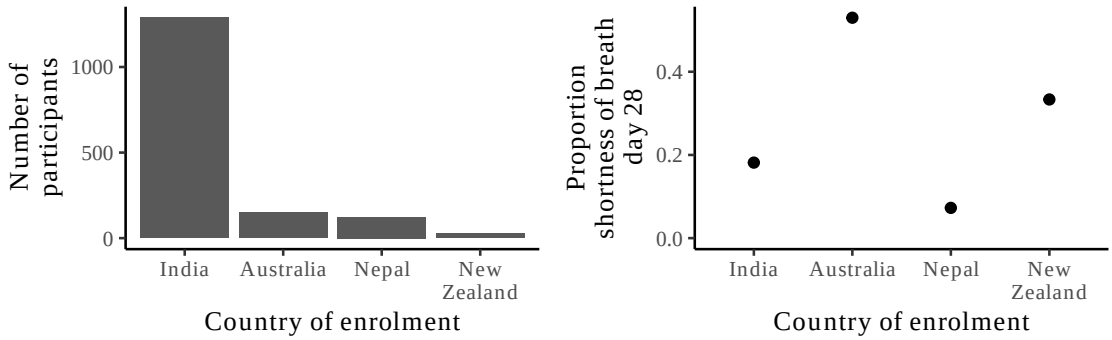

Figure 3.27: Proportion with patient reported shortness of breath at day 28 by country of randomisation.

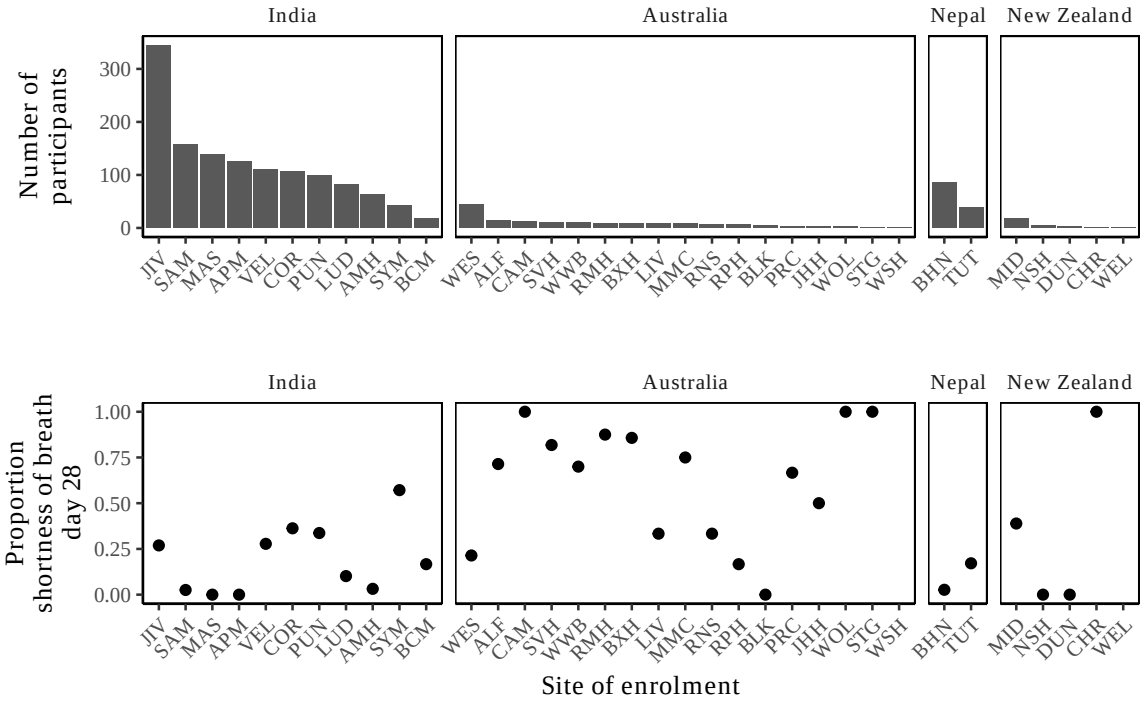

Figure 3.28: Proportion with patient reported shortness of breath at day 28 by country and site of randomisation.

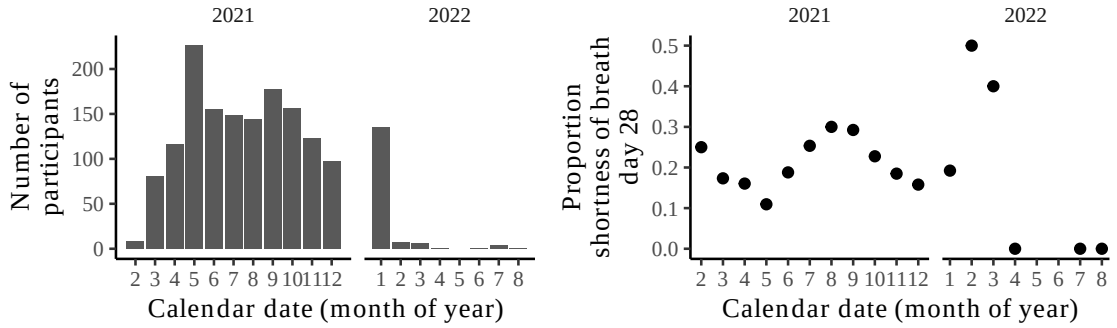

Figure 3.29: Proportion with patient reported shortness of breath at day 28 by calendar time (month) of randomisation.

3.1.8 Modified Medical Research Council (mMRC) breathlessness scale at day 28 (FAS-ITT)

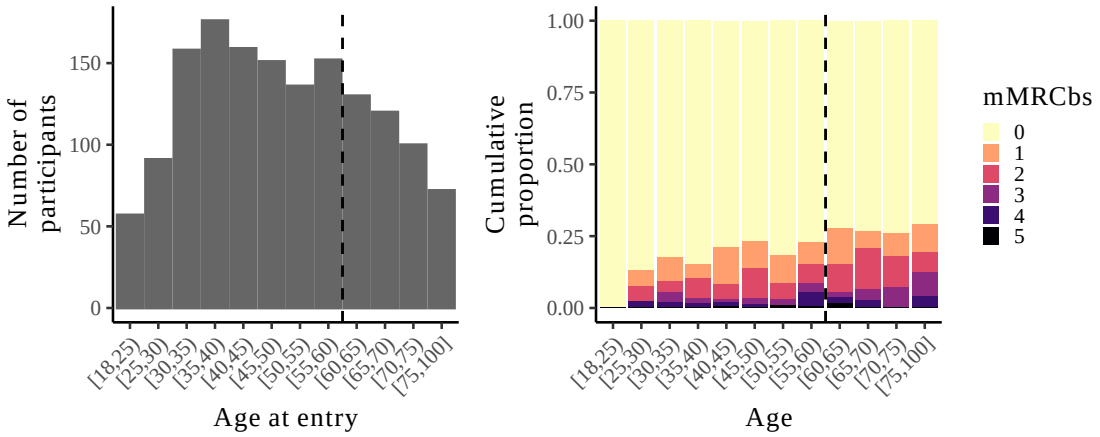

Figure 3.30: Distrubtion of Modified Medical Research Council breathlessness scale (mMRCbs) at day 28 by age groups.

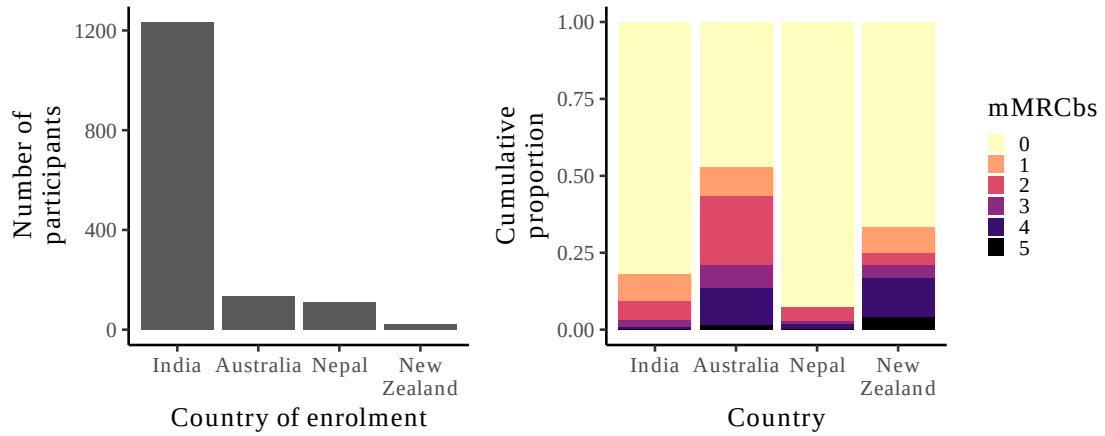

Figure 3.31: Distrubtion of Modified Medical Research Council breathlessness scale (mMRCbs) at day 28 by country of randomisation.

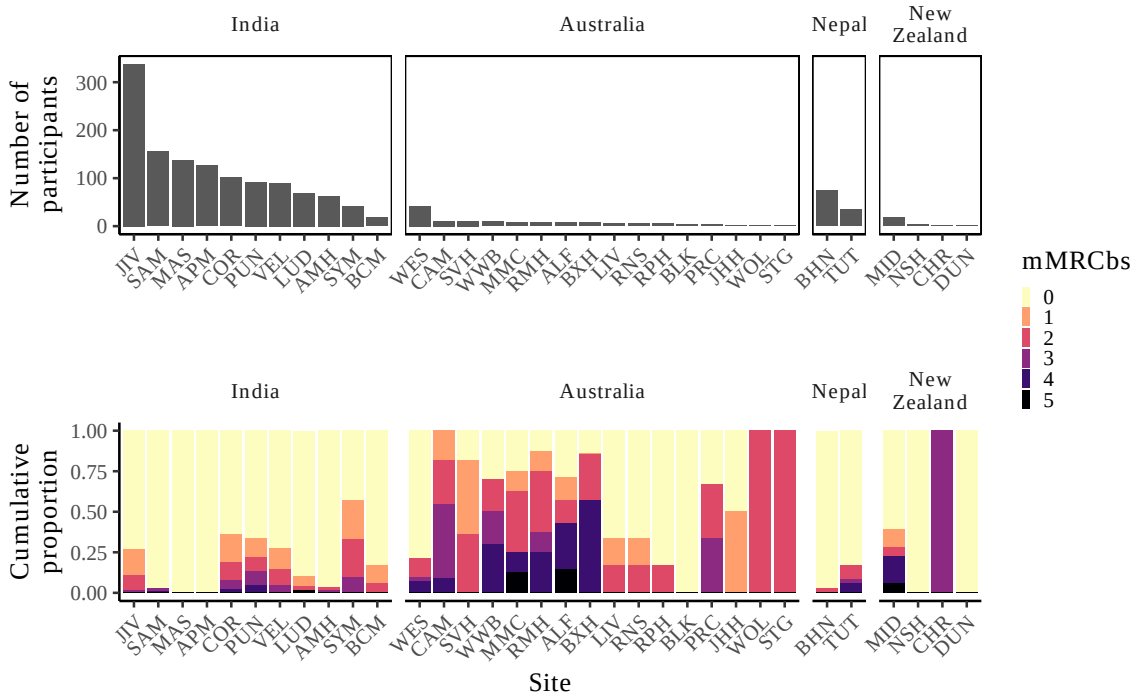

Figure 3.32: Distrubtion of Modified Medical Research Council breathlessness scale (mMRCbs) at day 28 by country and site of randomisation.

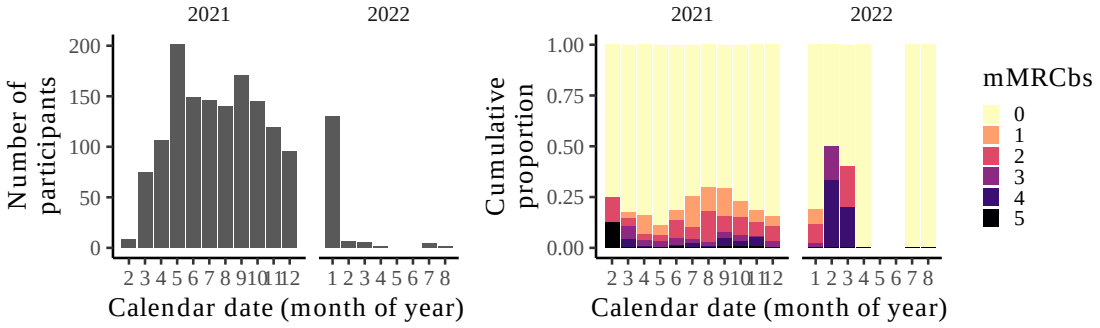

Figure 3.33: Distrubtion of Modified Medical Research Council breathlessness scale (mMRCbs) at day 28 by calendar time (month) of randomisation.

3.2 Primary Model Posterior Predictive Summaries

3.2.1 Primary Outcome

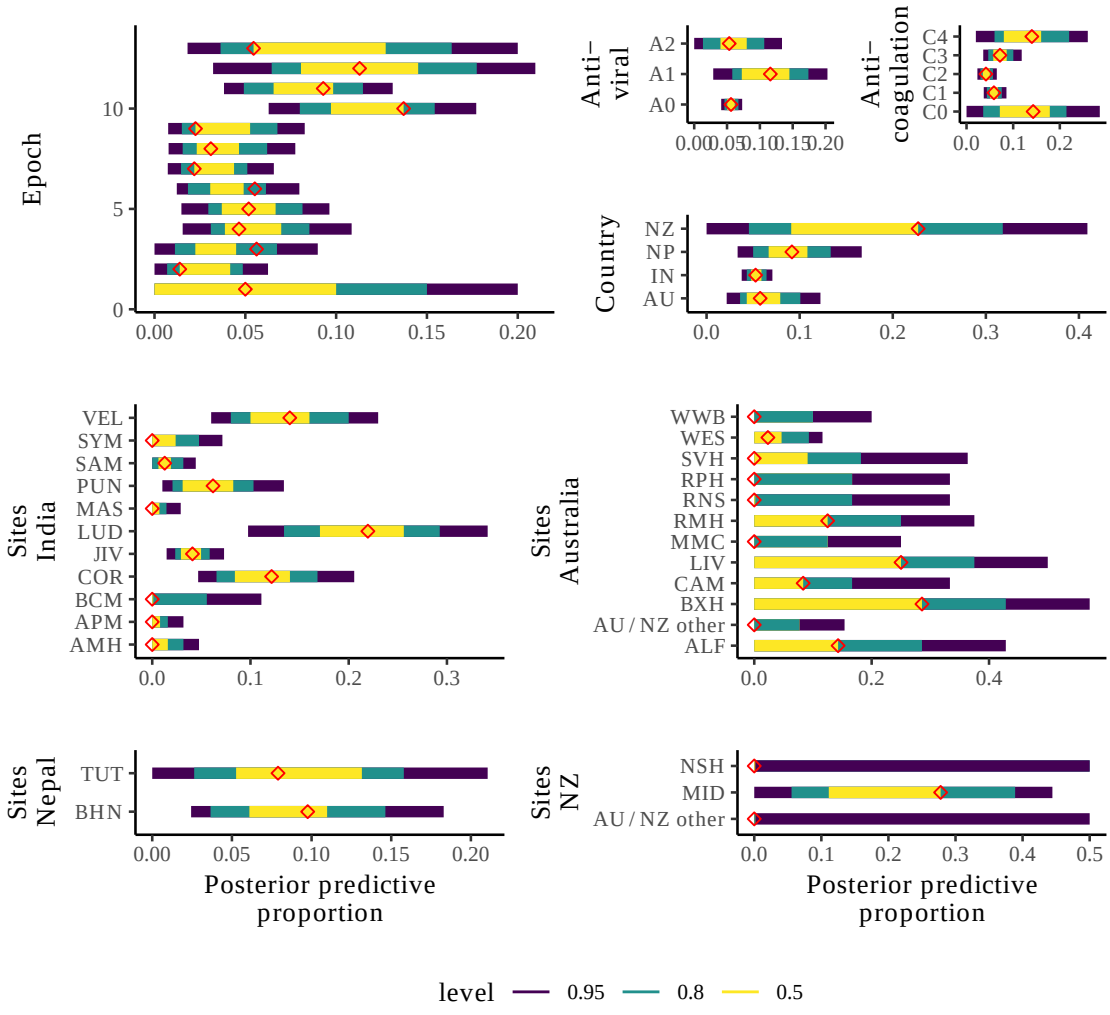

Figure 3.34: Posterior predictive distribution for primary outcome by model covariates for primary model using FAS-ITT. Red diamond indicates observed proportions.

3.2.2 WHO outcome scale at day 28

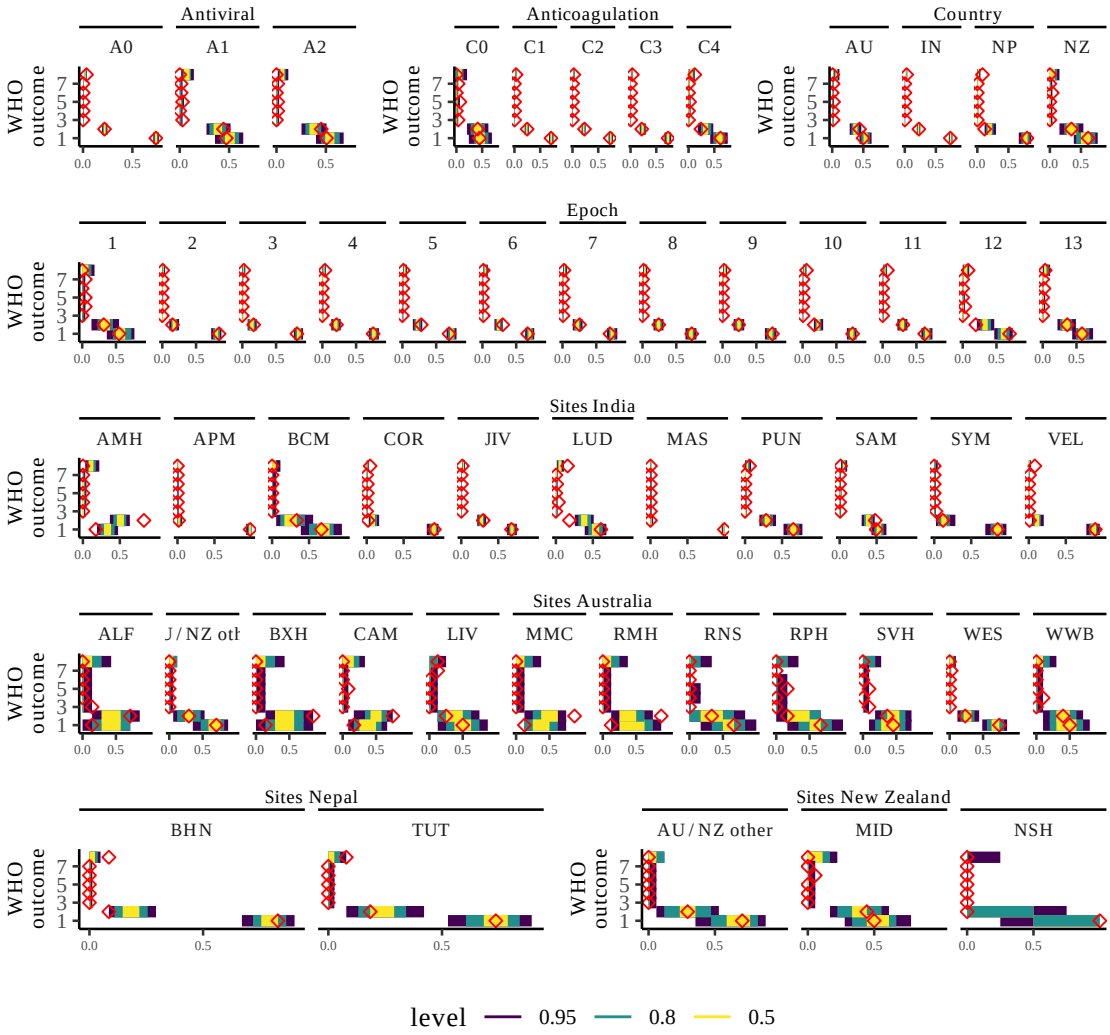

Figure 3.35: Posterior predictive distribution for WHO scale by model covariates for primary model using ACS-ITT. Red diamond indicates observed proportions.

3.2.3 Mortality to day 28

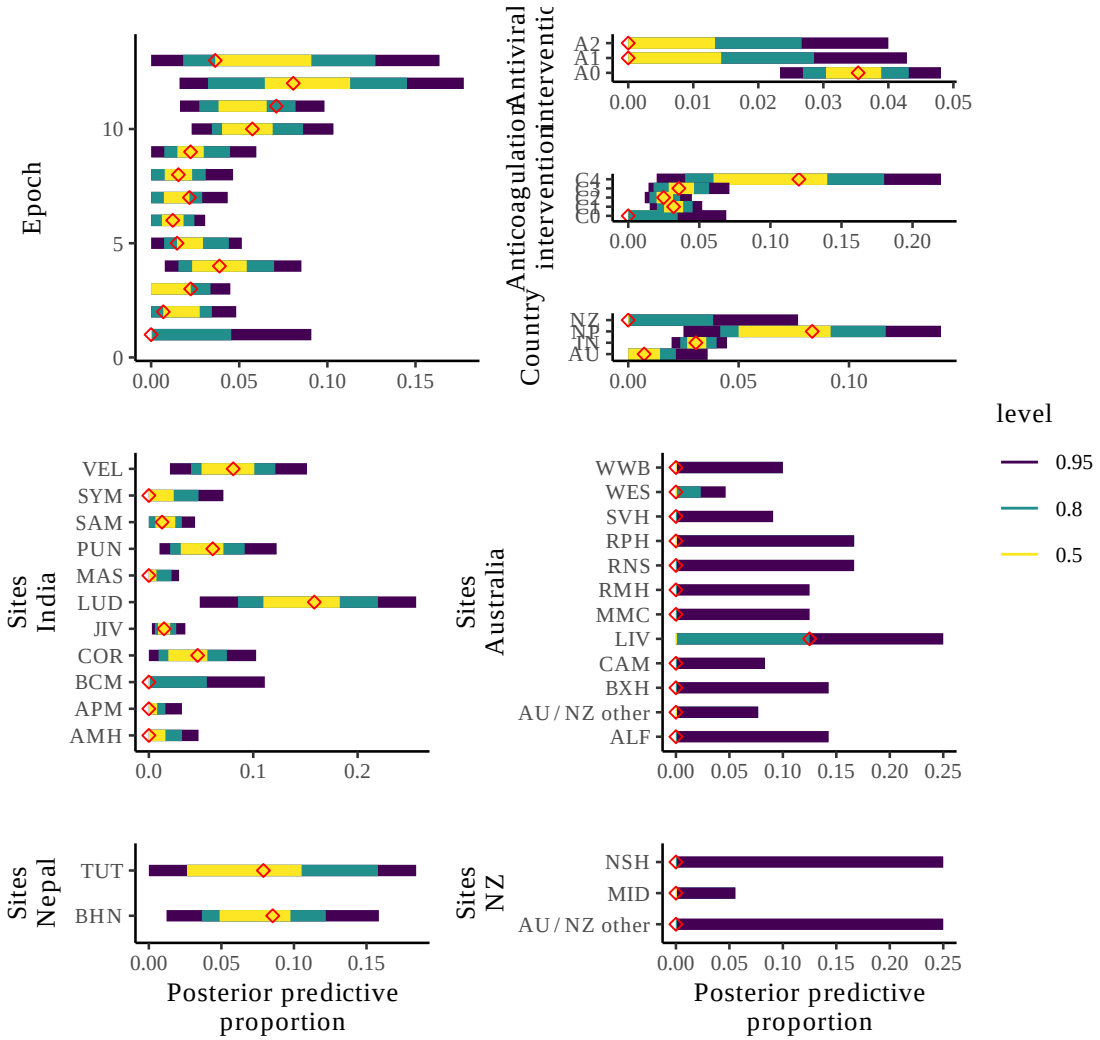

Figure 3.36: Posterior predictive distribution for mortality to day 28 by model covariates for primary model using FAS-ITT. Red diamond indicates observed proportions.

3.2.4 Days alive and free of hospital to day 28

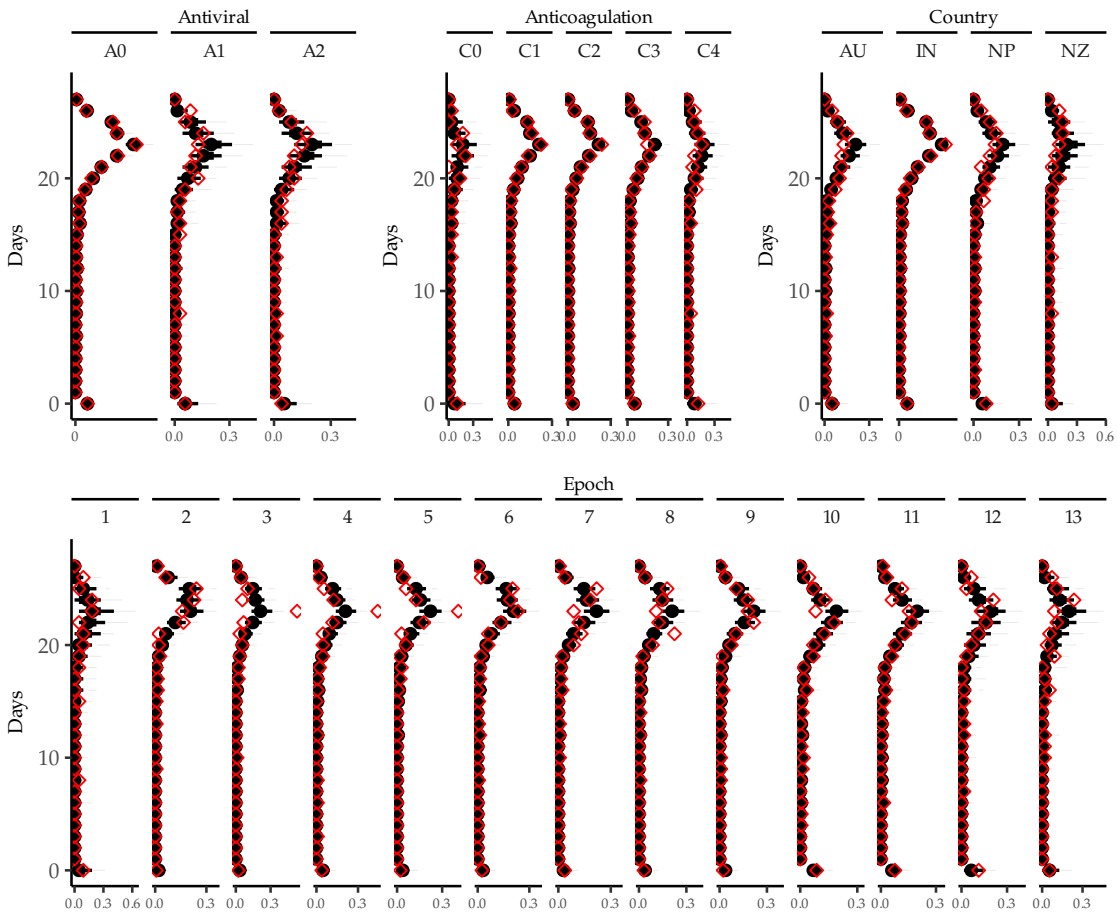

Figure 3.37: Posterior predictive distribution for days alive and free of hospital to day 28 by model covariates (intervention, country, and epoch) for primary model using FAS-ITT. Red diamond indicates observed proportions.

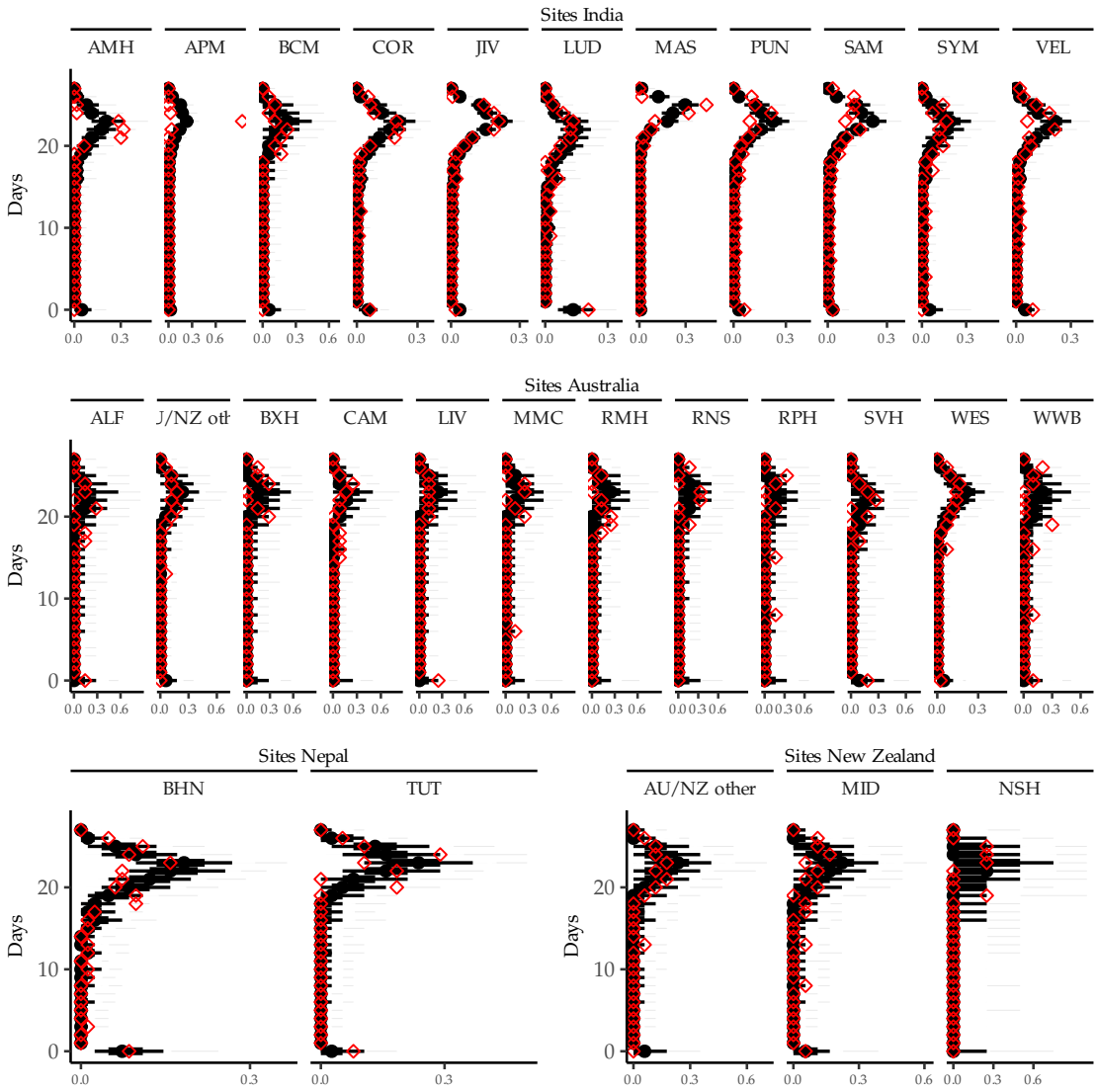

Figure 3.38: Posterior predictive distribution for days alive and free of hospital to day 28 by model covariates (site) for primary model using FAS-ITT. Red diamond indicates observed proportions.

3.2.5 Days alive and free of ventilation to day 28

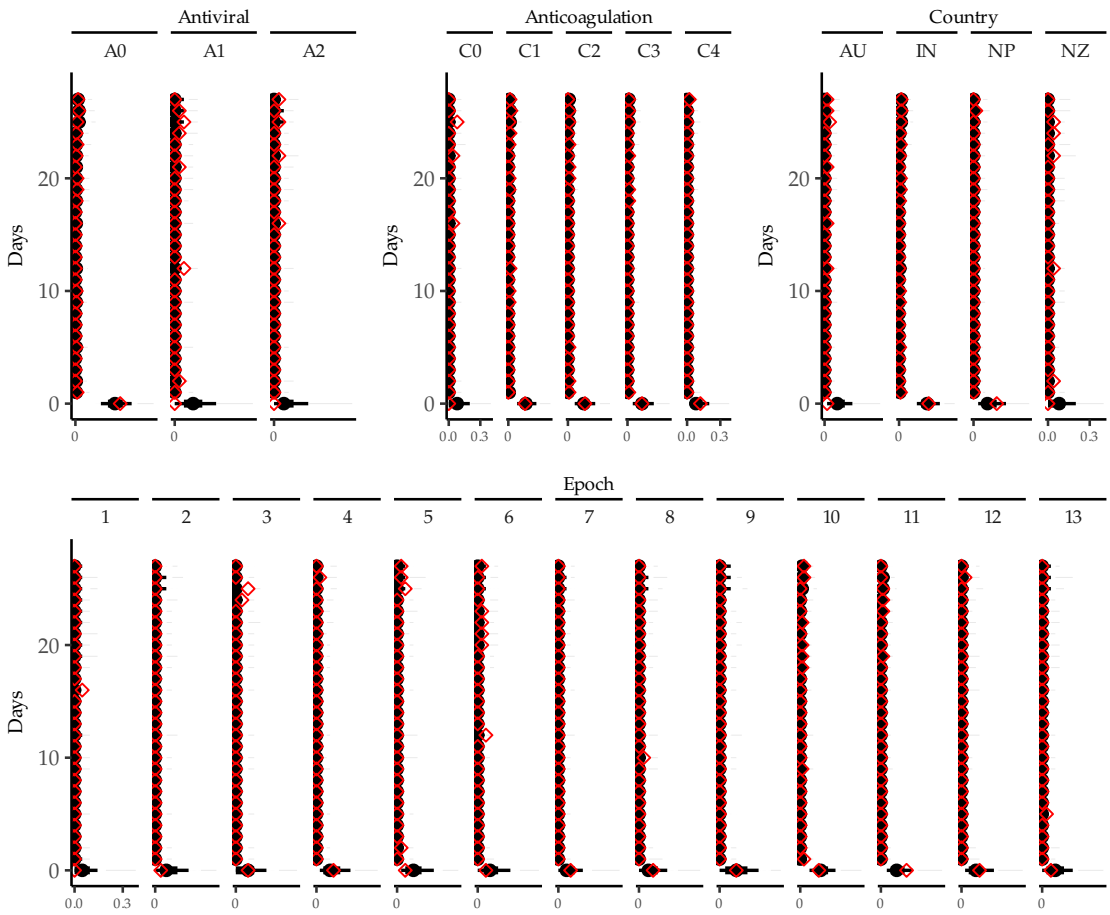

Figure 3.39: Posterior predictive distribution for days alive and free of ventilation to day 28 by model covariates (intervention, country, and epoch) for primary model using FAS-ITT. Red diamond indicates observed proportions.

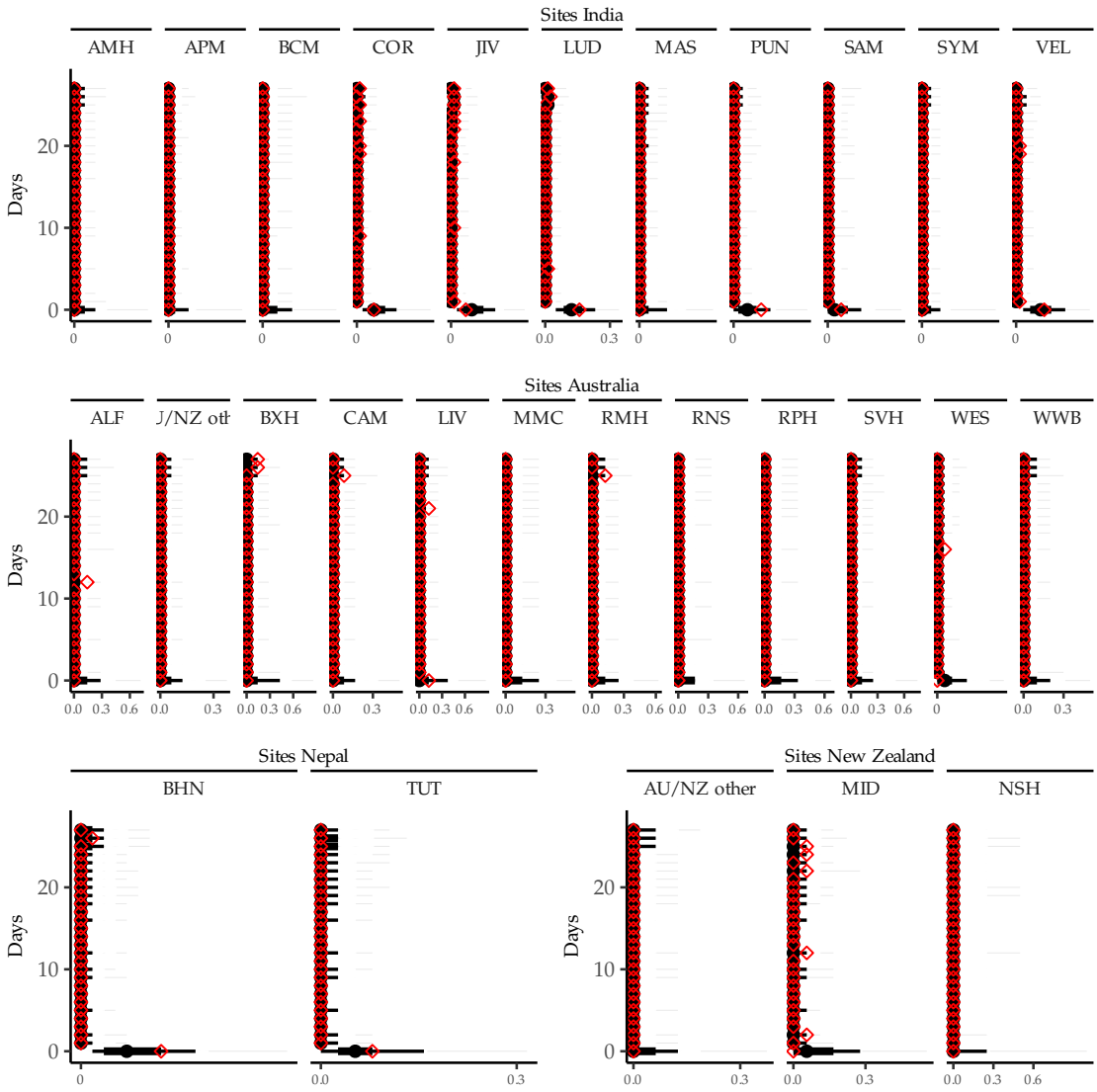

Figure 3.40: Posterior predictive distribution for days alive and free of ventilation to day 28 by model covariates (site) for primary model using FAS-ITT. Red diamond indicates observed proportions.

3.2.6 Presence of patient reported shortness of breath at day 28

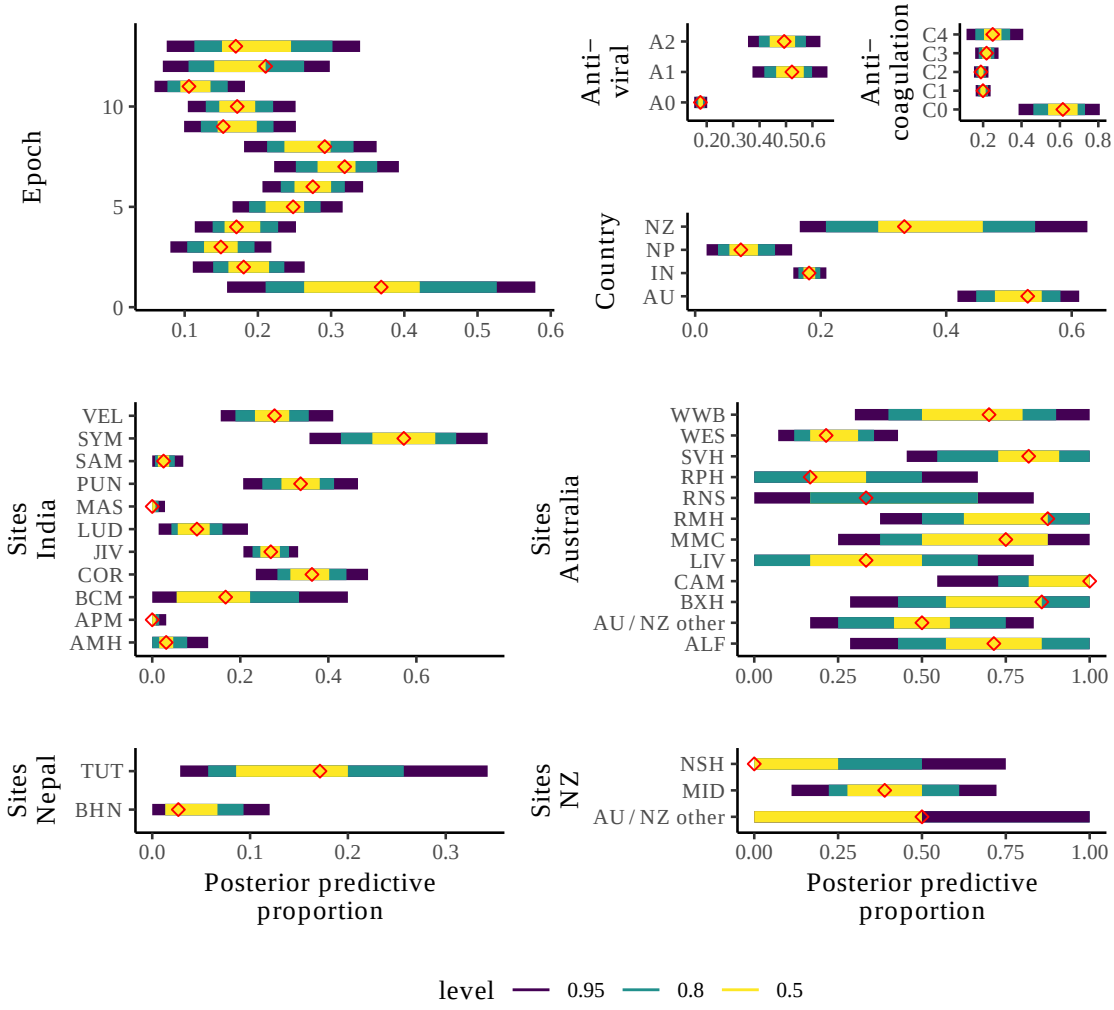

Figure 3.41: Posterior predictive distribution for shortness of breath at day 28 by model covariates for primary model using FAS-ITT. Red diamond indicates observed proportions.

3.2.7 mMRC Breathlessness Scale

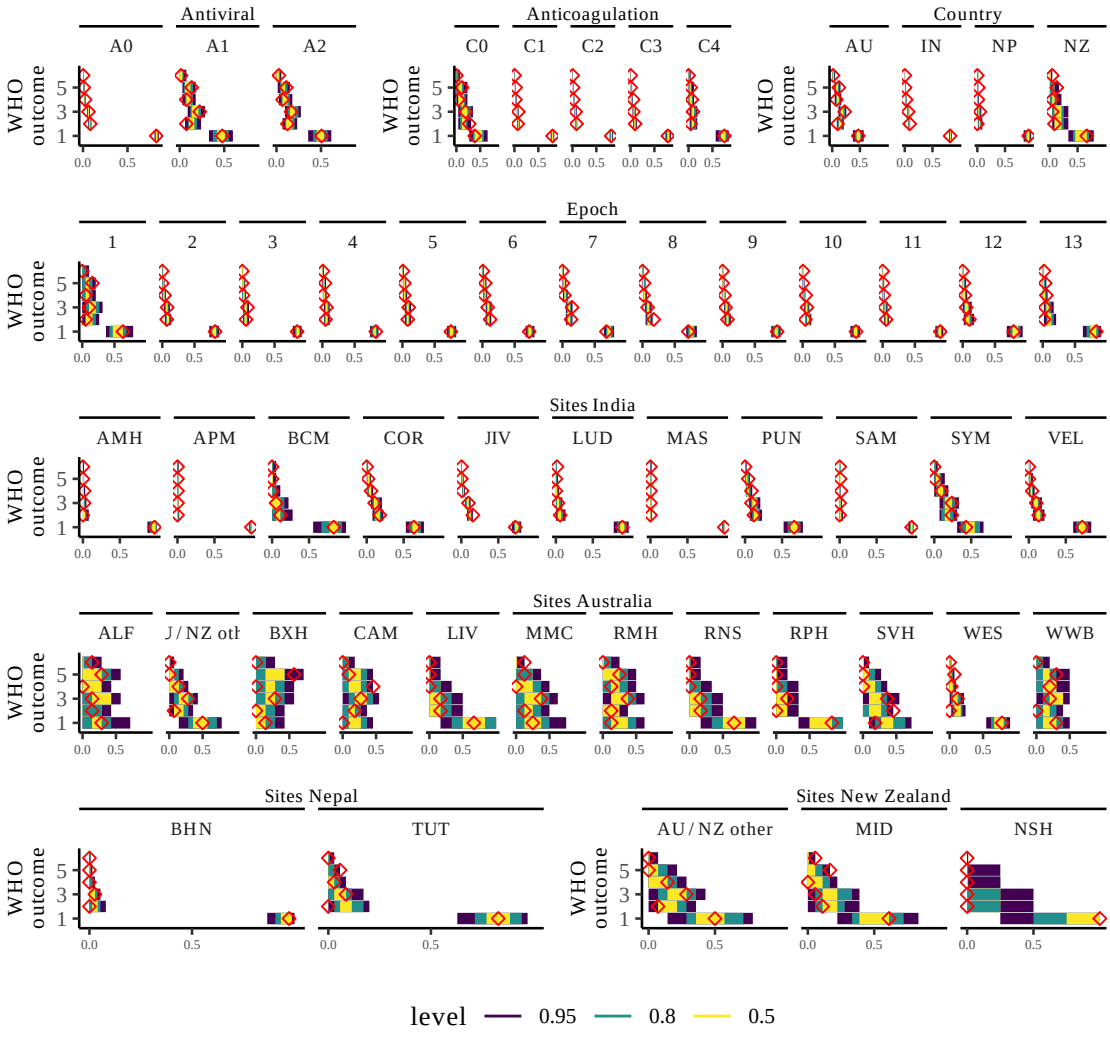

Figure 3.42: Posterior predictive distribution for mMRC scale by model covariates for primary model using FAS-ITT. Red diamond indicates observed proportions.