ASCOT Statistical Analysis Report

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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)
- oxygen requirement
- 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
- did not require supplemental oxygen
- enrolled in India during the most recent epoch

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

$$\beta_C \overset{iid}{\sim} \text{Normal}(0, 1)$$

$$\beta_A \overset{iid}{\sim} \text{Normal}(0, 1)$$

$$\rho_1 = 0, \rho_r \sim \text{Normal}(0, 1), \quad r = 2, ..., R$$

$$\tau_1 = 0, \tau_t \sim \text{Normal}(\tau_{t-1}, \sigma_\tau^2), \quad t = 2, ..., T$$

$$\sigma_\tau \sim \text{Student-}t(3, 0, 1)$$

$$\xi_{r,s} \sim \text{Normal}(0, \sigma_{\xi_r}^2), \quad s = 1, ..., S_r, \quad r = 1, ..., R$$

$$\sigma_{\xi_r} \sim \text{Student-}t(3, 0, 1), \quad r = 1, ..., R$$

$$\omega_1 \sim \text{Normal}(0, 10^2)$$

$$\omega_2 \sim \text{Normal}(0, 2.5^2)$$

$$\omega_3 \sim \text{Normal}(0, 2.5^2).$$

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

$$\pi(\eta) = \text{logit}^{-1}(\beta_0 + \eta)$$

$$y_i \sim \text{Bernoulli}(\pi(\eta_i))$$

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

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

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

$$
y_i \sim \text{Categorical}(\pi_k(\eta_i))
$$

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

$$
\lambda_m(d, \eta) = \frac{\exp(\alpha_{dm} + \eta_m)}{1 + \sum_{l=1}^{M} \exp(\alpha_{dl} + \eta_l)}, \quad m = 1, 2
$$

$$
y_{id} \sim \text{Multinomial}\left(1, \left(1 - \sum_{l=1}^{2} \lambda_l(d, \eta_i), \lambda_1(d, \eta_i), \lambda_2(d, \eta_i)\right)\right), \quad d \leq d_i,
$$

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.

```
                    ┌──────────────────────────────┐
                    │ Screened for platform eligibility │
                    │            2,254             │
                    └──────────────────────────────┘
```

648 Ineligible for platform:
  179 Did not consent
  174 Not in the patients best interests
   68 No eligible domains
   59 Not committed to active treatment
   43 First positive test - over 14 days ago
   31 No signs or symptoms
   31 First symptoms - over 14 days ago
   28 SARS-CoV-2 not confirmed by test
   18 Receiving acute intensive respiratory support
    6 Did not consent to any domains
    6 Expired platform pending
    4 Previously participated in the trial
    1 Pregnant patients not enrolled at this hospital

Enrolled into platform
1,606

25 Ineligible for anticoagulation domain[†]:
  18 Domain unavailable
  12 Did not consent to domain
   1 Clinician to commence therapeutic anticoagulation
   1 eGFR< 15ml/min/1.73m^2
40 Ineligible for aspirin intervention[†]
  40 Receiving an antiplatelet agent
   1 Hypersensitivity to aspirin

[†]Participants may meet more than one exclusion criteria

Randomised to
anticoagulation domain
1,574

| Low-dose 619 | Intermediate-dose 620 | Low-dose with aspirin 285 | Therapeutic-dose 50 |

23 Excluded:	19 Excluded:	6 Excluded:	0 Excluded:
9 Withdrew follow-up	7 Withdrew follow-up	2 Withdrew follow-up	0 Withdrew follow-up
14 Missing primary outcome	12 Missing primary outcome	4 Missing primary outcome	0 Missing primary outcome

| Included in primary analysis 596 | Included in primary analysis 601 | Included in primary analysis 279 | Included in primary analysis 50 |

Figure 2.1: Combined domain flowchart for anticoagulation.

```
                    ┌─────────────────────────────┐
                    │ Screened for platform eligibility │
                    │            2,254            │
                    └─────────────────────────────┘
                                   │
                                   │      ┌──────────────────────────────────────────────────┐
                                   │      │ 648  Ineligible for platform:                     │
                                   │      │   179 Did not consent                             │
                                   │      │   174 Not in the patients best interests          │
                                   │      │    68 No eligible domains                         │
                                   │      │    59 Not committed to active treatment           │
                                   │─────▶│    43 First positive test - over 14 days ago      │
                                   │      │    31 No signs or symptoms                        │
                                   │      │    31 First symptoms - over 14 days ago           │
                                   │      │    28 SARS-CoV-2 not confirmed by test            │
                                   │      │    18 Receiving acute intensive respiratory support│
                                   │      │     6 Did not consent to any domains              │
                                   │      │     6 Expired platform pending                    │
                                   │      │     4 Previously participated in the trial        │
                                   │      │     1 Pregnant patients cannot be enrolled at this hospital│
                                   │      └──────────────────────────────────────────────────┘
                                   ▼
                    ┌─────────────────────────────┐
                    │    Enrolled into platform    │
                    │            1,606            │
                    └─────────────────────────────┘
```

648 Ineligible for platform:
- 179 Did not consent
- 174 Not in the patients best interests
- 68 No eligible domains
- 59 Not committed to active treatment
- 43 First positive test - over 14 days ago
- 31 No signs or symptoms
- 31 First symptoms - over 14 days ago
- 28 SARS-CoV-2 not confirmed by test
- 18 Receiving acute intensive respiratory support
- 6 Did not consent to any domains
- 6 Expired platform pending
- 4 Previously participated in the trial
- 1 Pregnant patients cannot be enrolled at this hospital

1,448 Ineligible for antiviral domain[†]:
- **1,432** Domain unavailable
- **16** Did not consent to domain

†Participants may meet more than one exclusion criteria

Randomised to antiviral domain
158

Standard of care
73

Nafamostat
85

4 Excluded:
- **0** Withdrew follow-up
- **4** Missing primary outcome

10 Excluded:
- **3** Withdrew follow-up
- **7** Missing primary outcome

Included in primary analysis
69

Included in primary analysis
75

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).
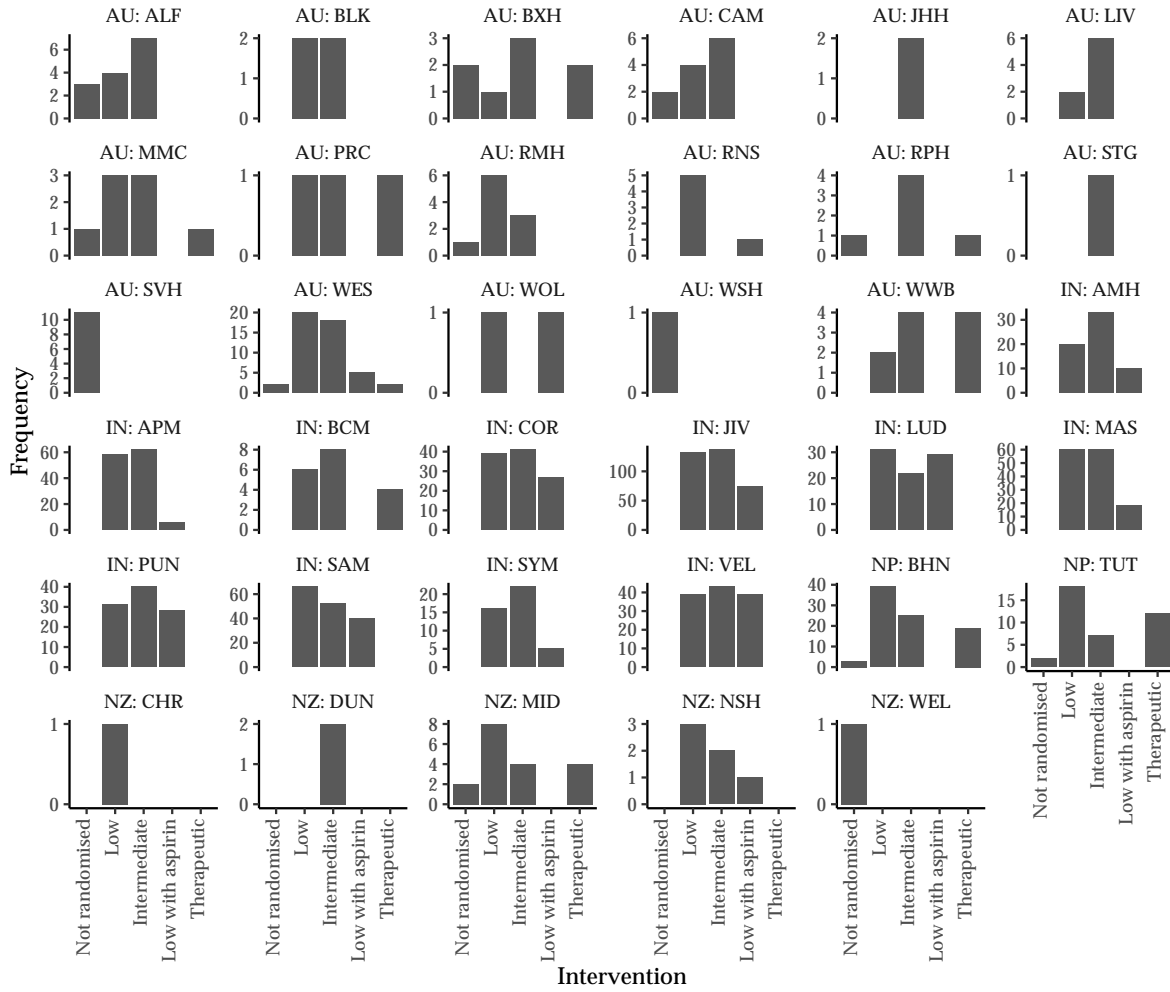
Figure 2.6: Intervention allocations by study site for anticoagulation domain.
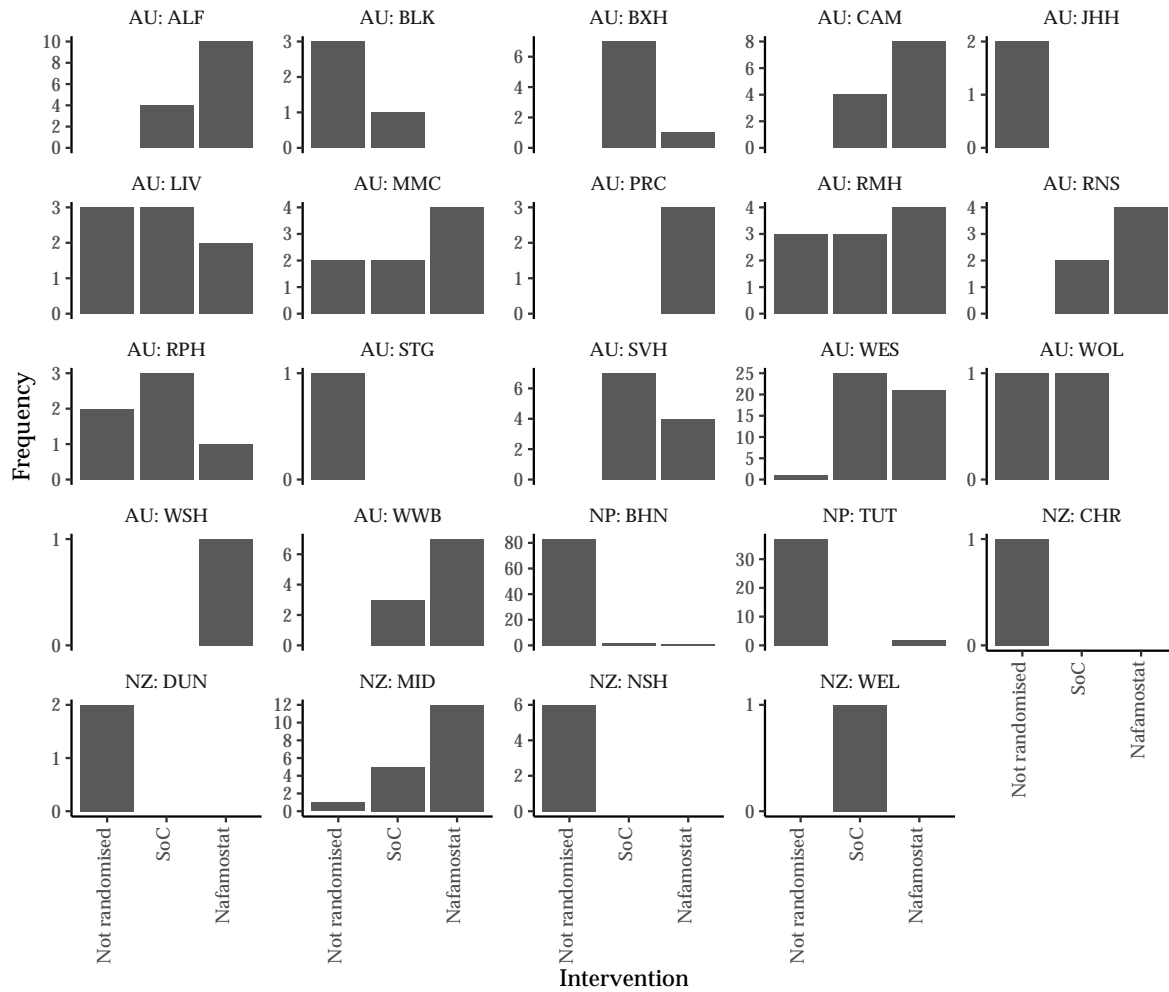
Figure 2.7: Intervention allocations by study site for antiviral domain.

2.1.5 Compliance

There were two participants who received the wrong dosage (according to the antiviral do-main 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.
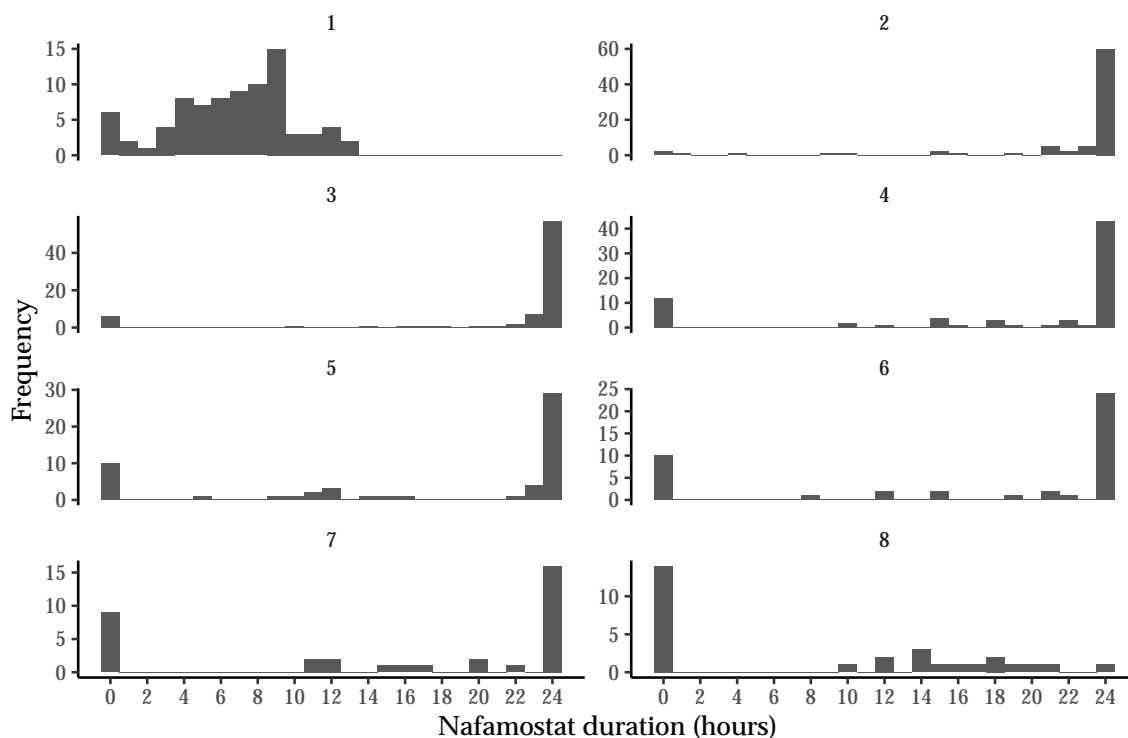
Figure 2.8: Distribution of Nafamostat infusion duration by study day (1 to 8) amongst participants assigned to Nafamostat.

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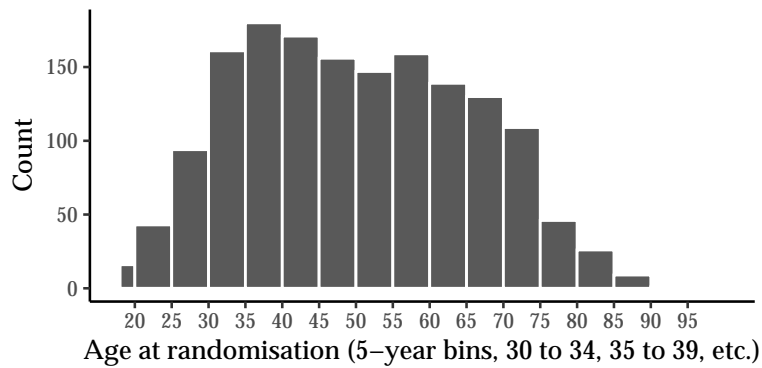
Figure 2.9: Distribution of age amongst participants randomised in the trial.

Baseline demographics stratified by anticoagulation interventions are reported in Table 2.7 and by antiviral interventions in Table 2.8.
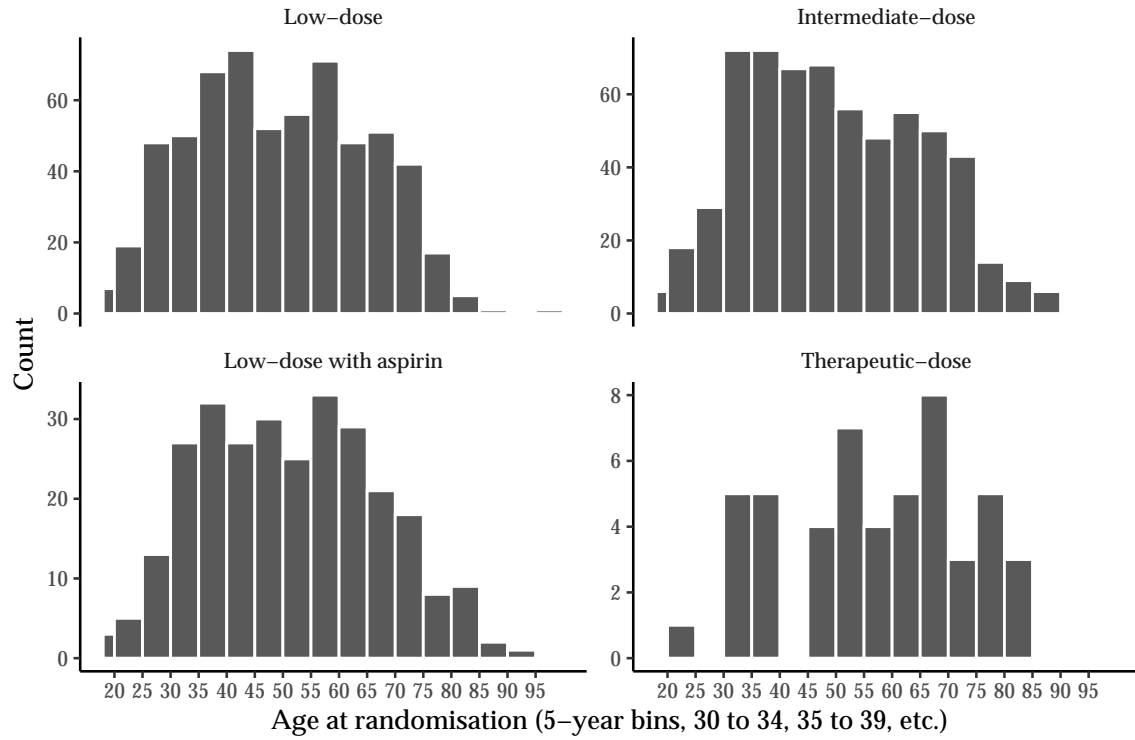
Figure 2.10: Distribution of age amongst participants randomised to the anticoagulation domain.
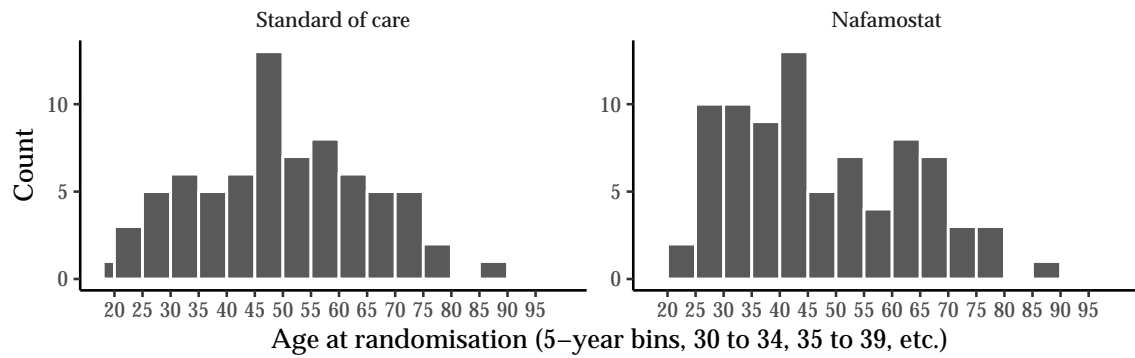
Figure 2.11: Distribution of age amongst participants randomised to the antiviral domain.

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.

| | Anticoagulation | | | | |
Variable	Low dose (n = 610)	Intermediate dose (n = 613)	Low dose with aspirin (n = 283)	Therapeutic dose (n = 50)	Overall (n = 1556)
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.
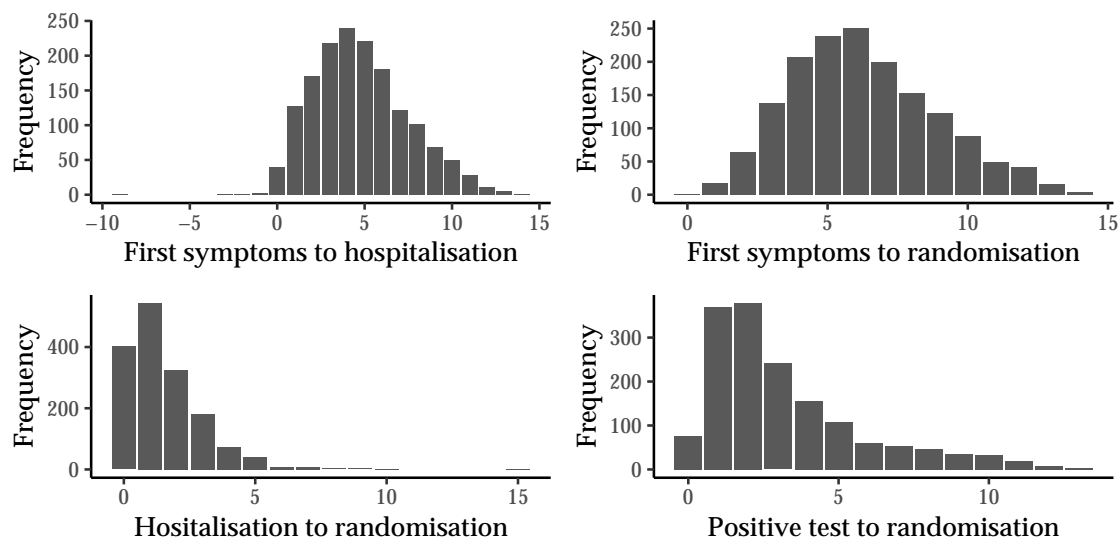

Figure 2.12: Days between events for hospitalisation, randomisation, symptom onset, and first positive test.

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	Not randomised (n = 32)	Low dose (n = 610)	Intermediate dose (n = 613)	Low dose with aspirin (n = 283)	Therapeutic dose (n = 50)	Overall (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)

Anticoaguation

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 ($\geq$ 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, 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 (relative to standard dose) for primary outcome model fit to the FAS-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	0.07	-	-	-
Nafamostat	0.38 (0.10, 1.33)	0.93	0.93	0.09	0.04
Anticoagulation					
Low-dose	1.00	0.07	-	-	-
Intermediate-dose	0.73 (0.41, 1.27)	0.63	0.87	0.22	0.14
Low-dose with aspirin	0.85 (0.45, 1.60)	0.28	0.69	0.42	0.21
Therapeutic-dose	2.44 (0.86, 6.84)	0.01	0.05	0.97	0.04

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	0.38	(0.10, 1.33)	0.46 (0.33)	0.93
Intermediate-dose	0.73	(0.41, 1.27)	0.75 (0.22)	0.87
Low-dose with aspirin	0.85	(0.45, 1.60)	0.90 (0.30)	0.69
Therapeutic-dose	2.44	(0.86, 6.84)	2.79 (1.58)	0.05
Ineligible aspirin	2.36	(0.63, 7.59)	2.81 (1.86)	0.09
Age ≥ 60	1.71	(1.03, 2.77)	1.76 (0.44)	0.02
Oxygen requirement	3.60	(2.17, 6.11)	3.74 (1.01)	0.00
Australia/New Zealand	1.01	(0.24, 3.84)	1.27 (0.98)	0.50
Nepal	1.54	(0.39, 5.24)	1.88 (1.38)	0.26
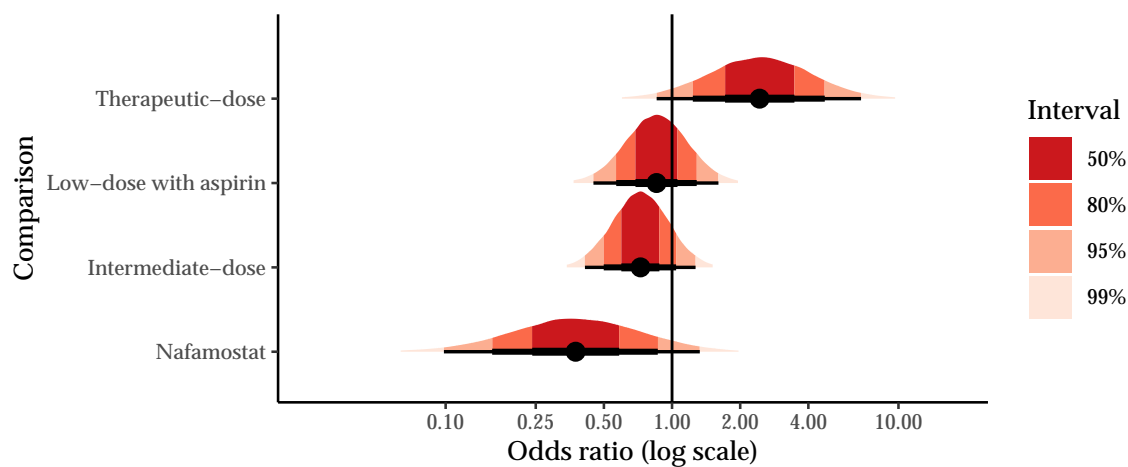
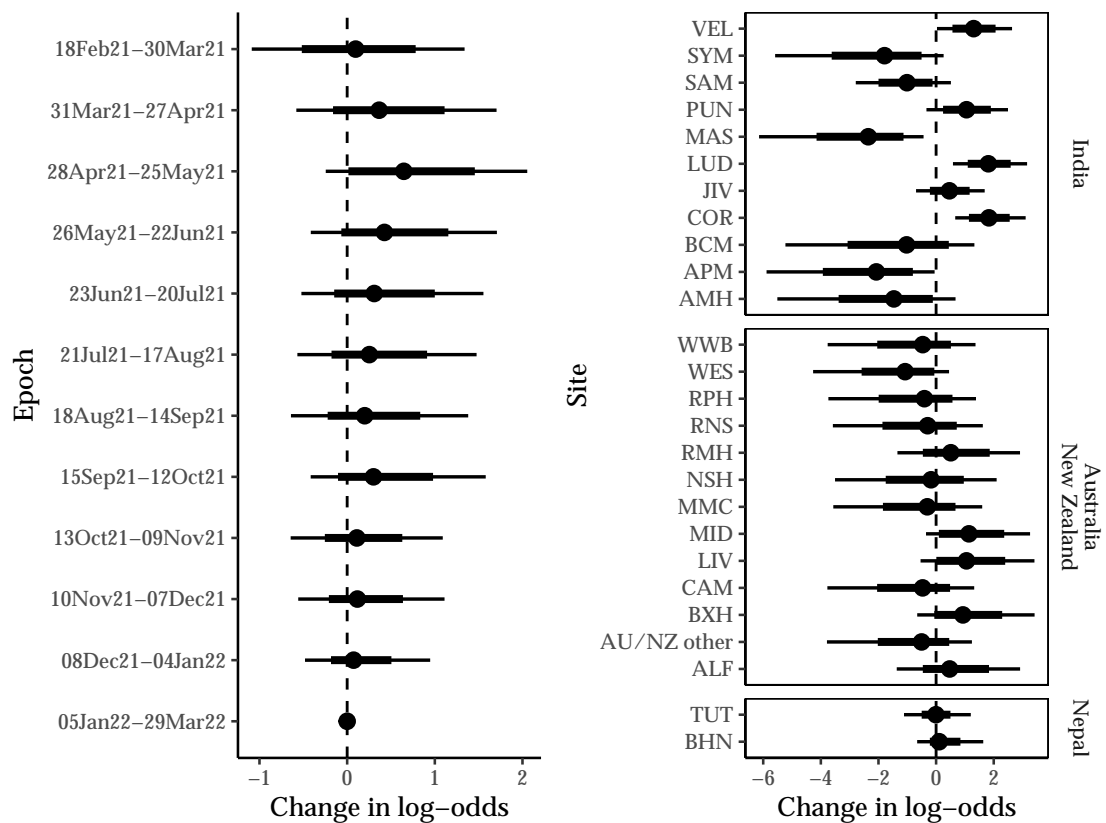Figure 2.13: Posterior densities for the treatment effect odds ratios, FAS-ITT.
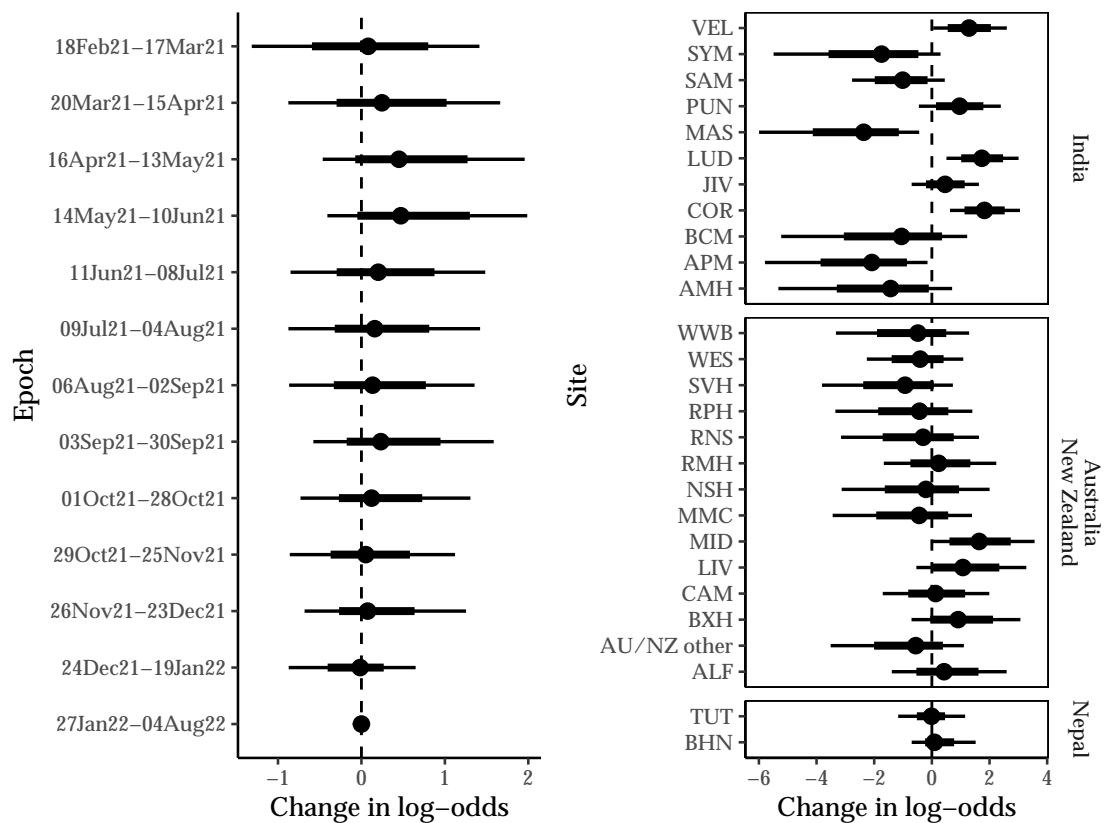
Figure 2.14: Posterior Summaries (point - median, block - 75% CrI, line 0.95% CrI) of odds ratio for epoch and site effects for the primary outcome model fit to the FAS-ITT set.

2.2.2.2 ACS-ITT

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

Table 2.21: 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	0.04	-	-	-
Nafamostat	0.26 (0.05, 1.13)	0.96	0.96	0.05	0.02
Anticoagulation					
Low-dose	1.00	0.07	-	-	-
Intermediate-dose	0.72 (0.41, 1.26)	0.64	0.88	0.20	0.13
Low-dose with aspirin	0.85 (0.45, 1.58)	0.28	0.69	0.42	0.21
Therapeutic-dose	2.43 (0.84, 6.77)	0.01	0.05	0.96	0.04

Table 2.22: 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	0.26	(0.05, 1.13)	0.34 (0.30)	0.96
Intermediate-dose	0.72	(0.41, 1.26)	0.75 (0.22)	0.88
Low-dose with aspirin	0.85	(0.45, 1.58)	0.89 (0.29)	0.69
Therapeutic-dose	2.43	(0.84, 6.77)	2.78 (1.58)	0.05
Ineligible aspirin	2.73	(0.71, 9.13)	3.29 (2.27)	0.07
Age ≥ 60	1.70	(1.03, 2.77)	1.76 (0.45)	0.02
Oxygen requirement	3.71	(2.24, 6.34)	3.86 (1.06)	0.00
Australia/New Zealand	0.83	(0.19, 3.39)	1.07 (0.88)	0.60
Nepal	1.69	(0.41, 5.98)	2.09 (1.57)	0.23
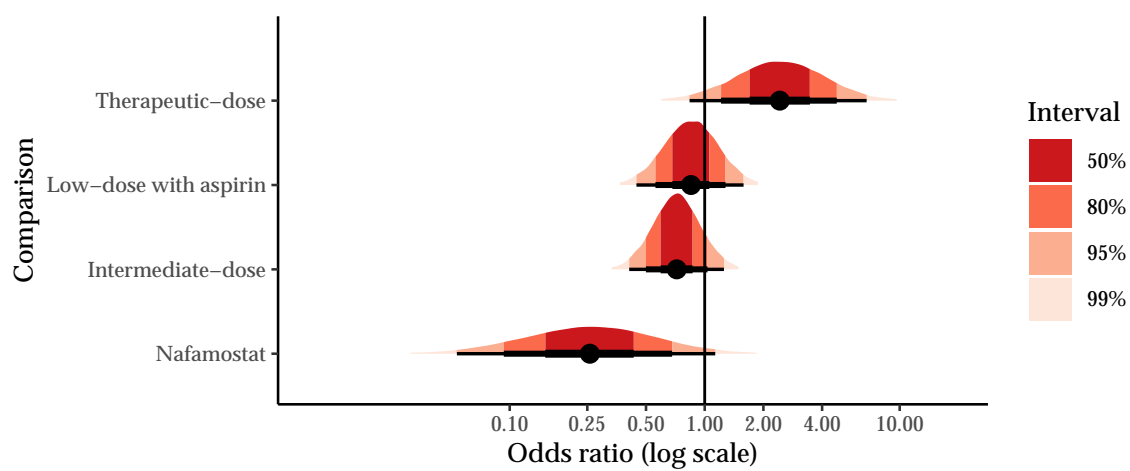
Figure 2.15: Posterior densities for the treatment effect odds ratios, ACS-ITT.

Figure 2.16: 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.

2.2.2.3 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
- **Set**: AVS-ITT

Table 2.23: 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	0.48	(0.15, 1.44)	0.57 (0.35)	0.9
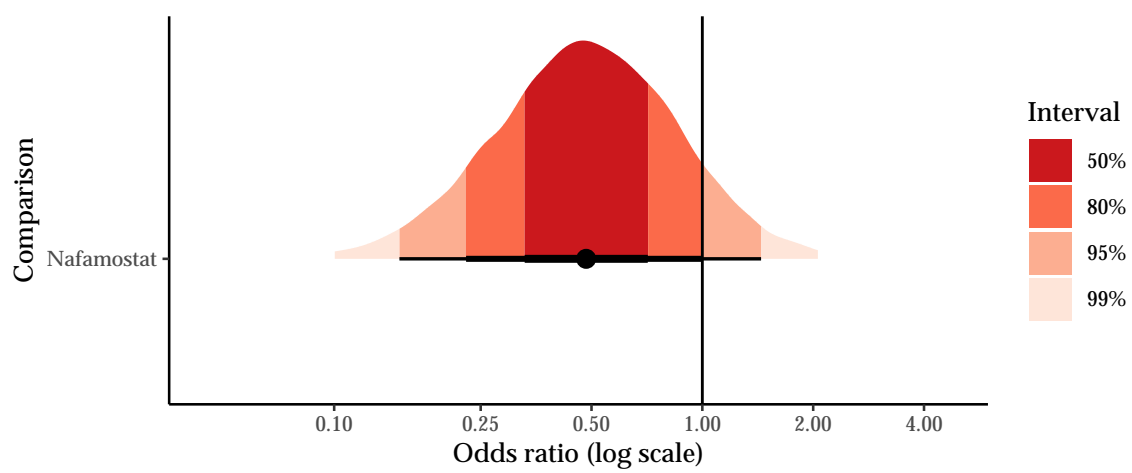
Figure 2.17: Posterior densities for the treatment effect odds ratios, AVS-ITT.

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, region, epoch

- **Set**: FAS-ITT

2.3.1.2 AVS-ITT

- **Model**: multinomial logistic regression
- **Terms**: antiviral intervention
- **Set**: AVS-ITT

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 2.24 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. Similarly for the antiviral arms in Table 2.25. Figure 2.18 and Figure 2.19 report on the distribution of day 28 WHO score.

Table 2.24: 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 2.25: 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)**
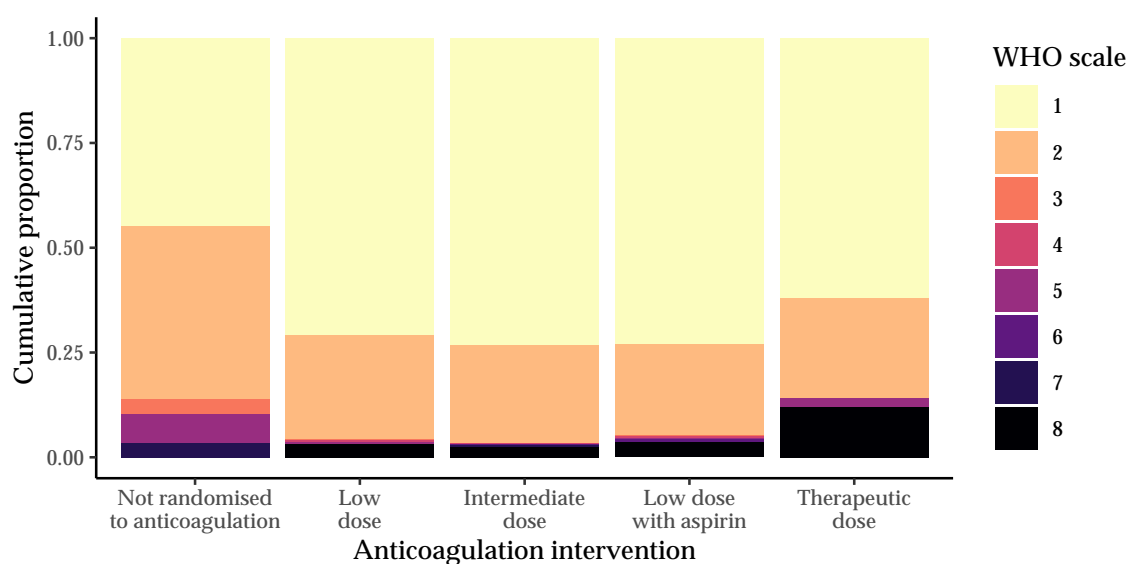
Figure 2.18: Observed distribution of WHO outcome scale at day 28 by anticoagulation treatment group, FAS-ITT.
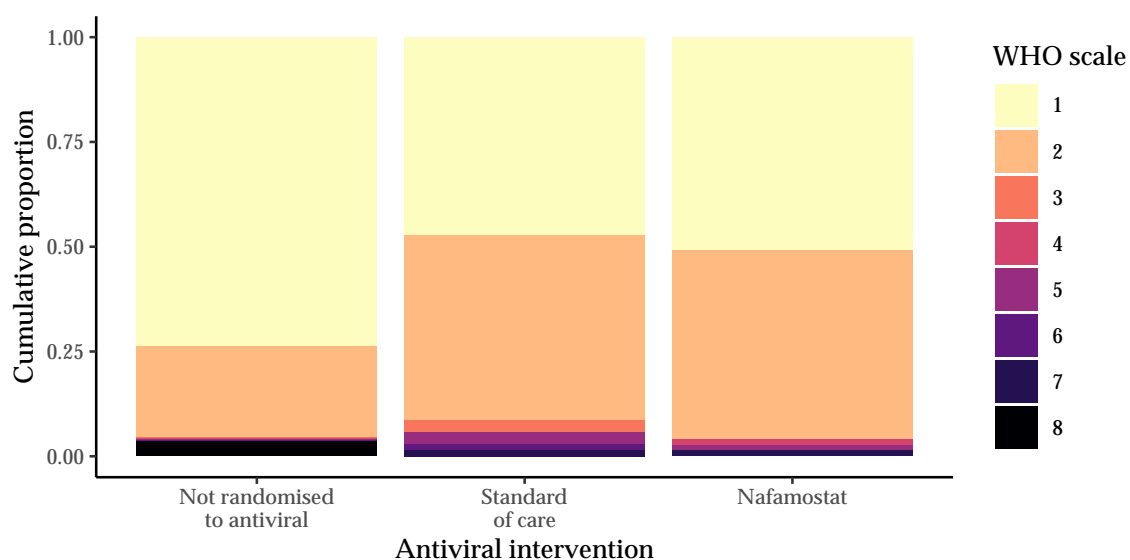
Figure 2.19: Observed distribution of WHO outcome scale at day 28 by antiviral treatment group, FAS-ITT.

2.3.2.1 FAS-ITT

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

The model parameters (odds ratios) are summarised in Table 2.26 for the fixed-effect terms and in Figure 2.21 for the site and epoch specific terms.

Table 2.26: 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	0.69	(0.35, 1.34)	0.73 (0.25)	0.87
Intermediate-dose	0.81	(0.61, 1.08)	0.82 (0.12)	0.93
Low-dose with aspirin	0.73	(0.51, 1.05)	0.75 (0.14)	0.95
Therapeutic-dose	1.70	(0.83, 3.36)	1.80 (0.66)	0.07
Ineligible aspirin	1.62	(0.74, 3.48)	1.75 (0.71)	0.11
Age ≥ 60	2.49	(1.90, 3.27)	2.51 (0.35)	0.00
Oxygen requirement	2.13	(1.60, 2.84)	2.15 (0.32)	0.00
Australia/New Zealand	1.32	(0.42, 4.04)	1.55 (0.96)	0.31
Nepal	0.55	(0.17, 1.94)	0.68 (0.53)	0.84
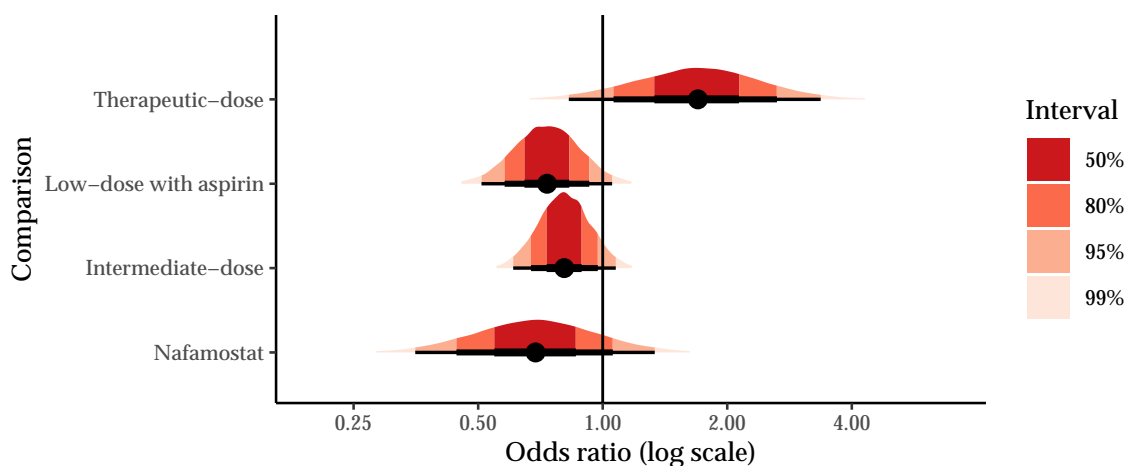
Figure 2.20: Posterior densities for the treatment effect odds ratios, FAS-ITT.
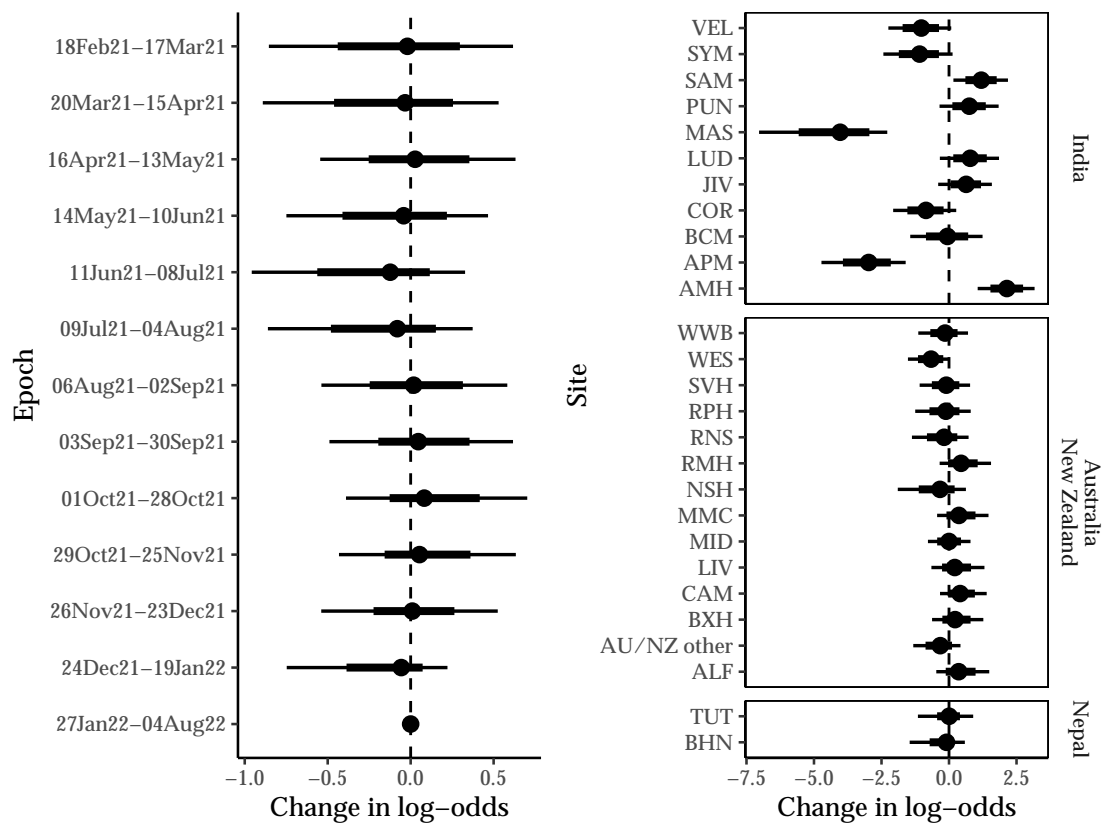
Figure 2.21: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on WHO outcome scale at day 28 for the outcome model fit to the FAS-ITT set.

2.3.2.2 AVS-ITT

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

Table 2.27: 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	0.70	(0.36, 1.36)	0.74 (0.26)	0.85
Intermediate-dose	1.37	(0.62, 3.05)	1.50 (0.64)	0.22
Low-dose with aspirin	0.79	(0.19, 3.09)	1.00 (0.78)	0.63
Therapeutic-dose	1.83	(0.62, 5.41)	2.13 (1.28)	0.14
Age ≥ 60	3.84	(1.79, 8.56)	4.18 (1.76)	0.00
Oxygen requirement	1.20	(0.58, 2.53)	1.30 (0.51)	0.31
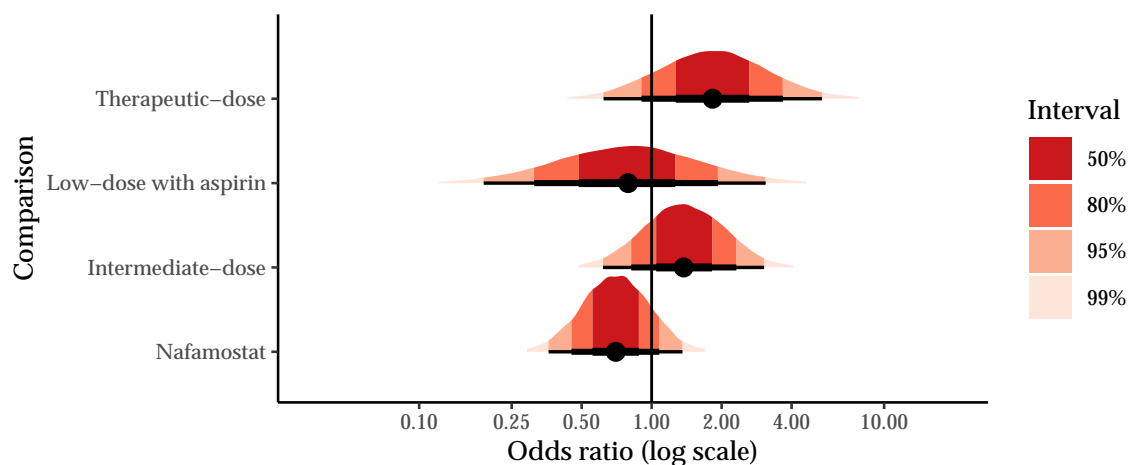
Figure 2.22: Posterior densities for the treatment effect odds ratios, AVS-ITT.

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, oxygen requirement, region, site nested within region, and epoch.
- **Set**: FAS-ITT

2.3.3.2 AVS-ITT

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 2.28 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. Similarly, Table 2.29 for the antiviral domain. The observed distribution of DAFH by domain treatment arm is shown in Figure 2.24, Figure 2.25, Figure 2.26 and Figure 2.27.
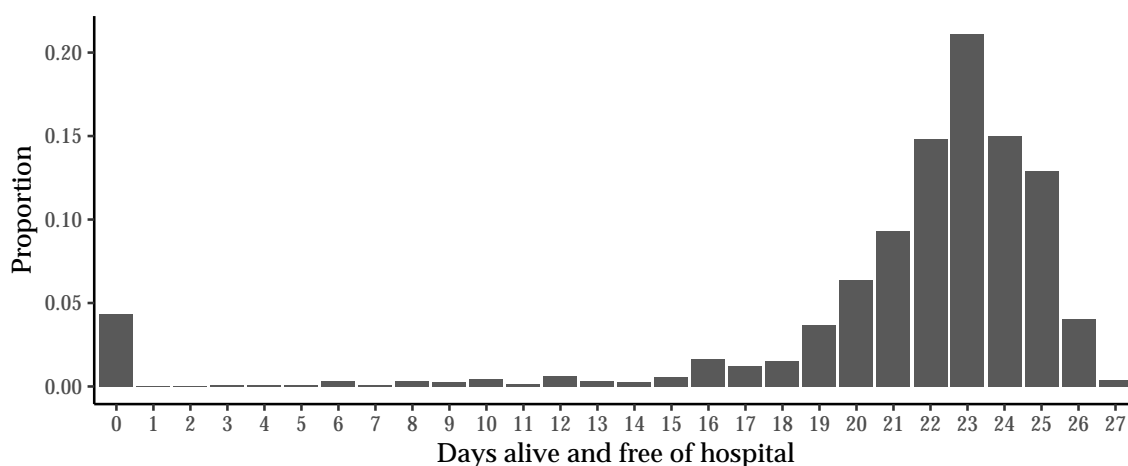
Figure 2.23: Observed overall distribution of days alive and free of hospital at day 28, FAS-ITT.

Table 2.28: Summary of days alive and free of hospital to day 28 by treatment group, ACS-ITT.

Anticoagulation intervention	Patients	Known	Deaths	DAFH, Median (Q1, Q3)
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	**1556**	**1528**	**50 (3%)**	**23 (21, 24)**
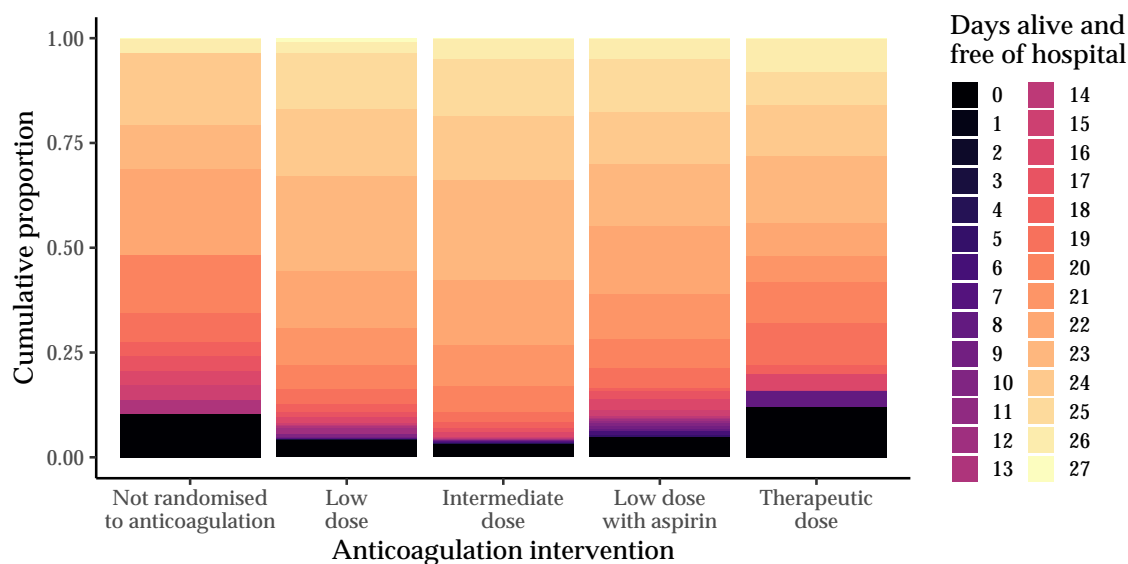
Figure 2.24: Observed distribution of days alive and free of hospital at day 28 by anticoagulation treatment group, ACS-ITT.
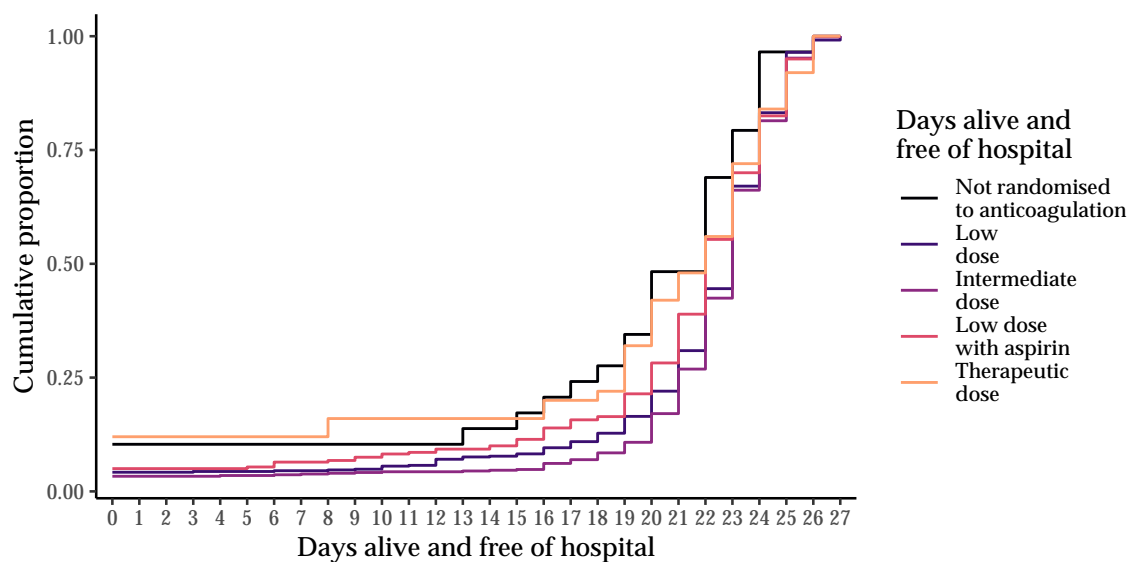
Figure 2.25: Observed cumulative distribution of days alive and free of hospital at day 28 by anticoagulation treatment group, ACS-ITT.

Table 2.29: Summary of days alive and free of hospital to day 28 by treatment group, AVS-ITT.

Antiviral intervention	Patients	Known	Deaths	DAFH, Median (Q1, Q3)
Standard of care	73	70	0 (0%)	22 (20, 24)
Nafamostat	82	75	0 (0%)	22 (19, 24)
Overall	**155**	**145**	**0 (0%)**	**22 (19, 24)**
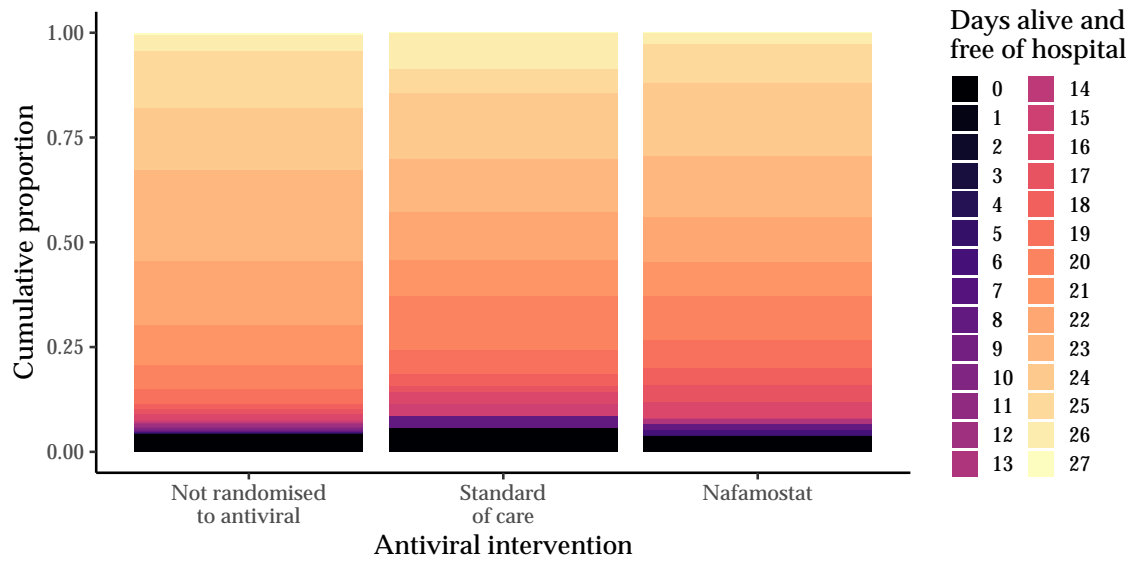
Figure 2.26: Observed distribution of days alive and free of hospital at day 28 by antiviral treatment group, AVS-ITT.
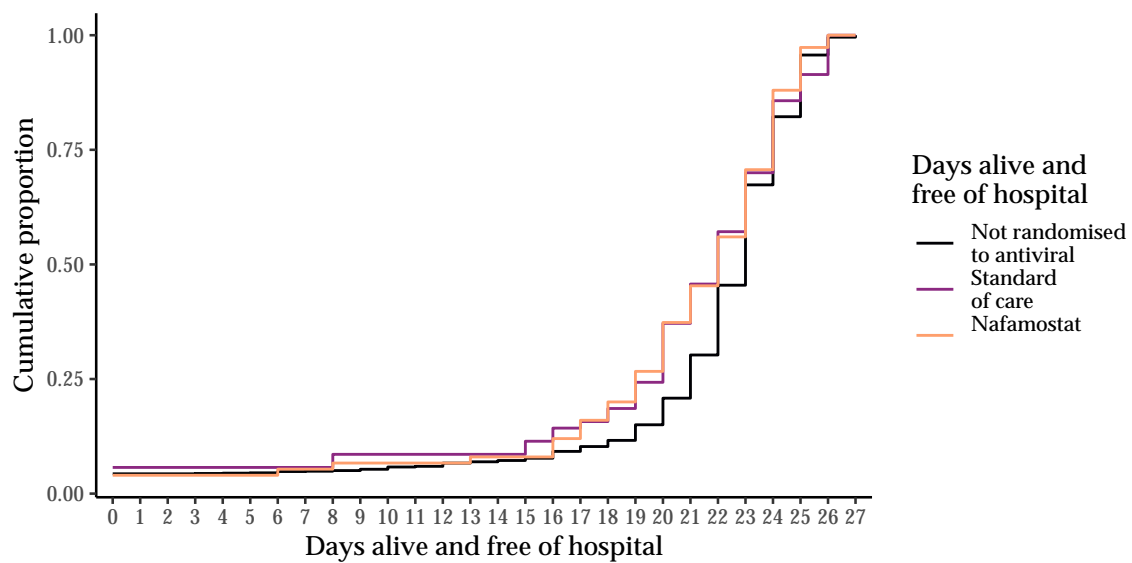
Figure 2.27: Observed cumulative distribution of days alive and free of hospital at day 28 by antiviral treatment group, AVS-ITT.

2.3.4.1 FAS-ITT

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

Table 2.30: 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	1.00	(0.55, 1.85)	1.05 (0.34)	0.50
Intermediate-dose	1.15	(0.94, 1.40)	1.15 (0.12)	0.91
Low-dose with aspirin	1.07	(0.82, 1.41)	1.08 (0.15)	0.69
Therapeutic-dose	0.65	(0.36, 1.19)	0.68 (0.21)	0.08
Ineligible aspirin	1.09	(0.57, 2.07)	1.15 (0.39)	0.61
Age $\geq$ 60	0.62	(0.51, 0.76)	0.62 (0.07)	0.00
Oxygen requirement	0.47	(0.38, 0.58)	0.47 (0.05)	0.00
Australia/New Zealand	0.98	(0.45, 2.20)	1.07 (0.46)	0.48
Nepal	0.87	(0.27, 3.03)	1.06 (0.79)	0.40
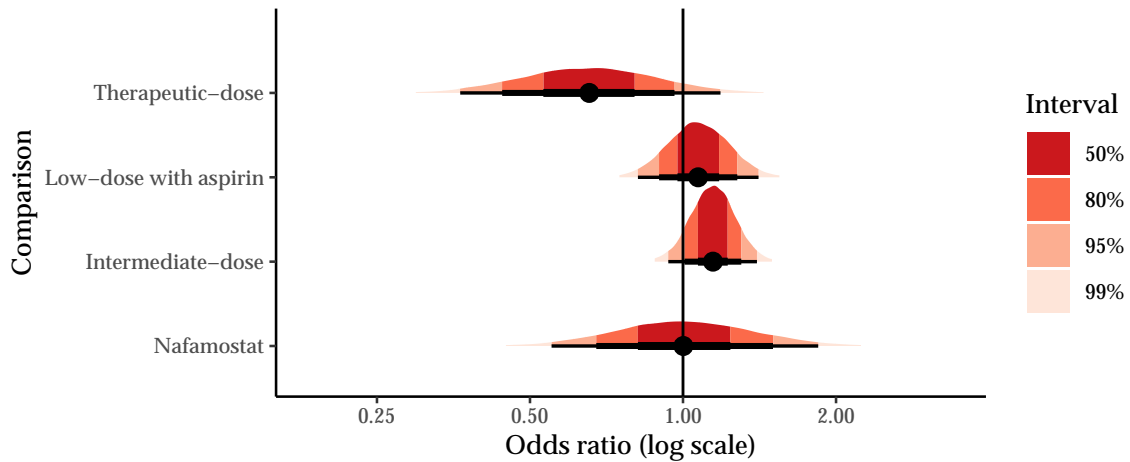
Figure 2.28: Posterior densities for the treatment effect odds ratios, FAS-ITT.
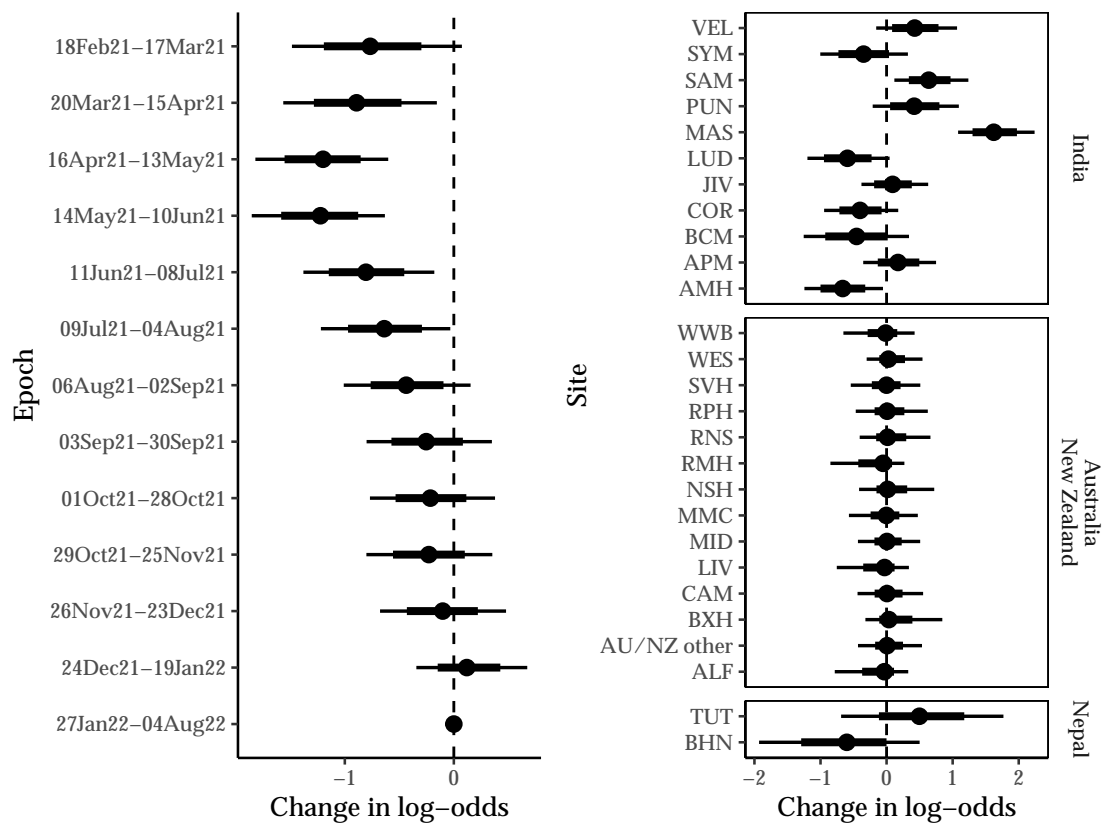
Figure 2.29: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on days alive and free of hospital to day 28 for the outcome model fit to the FAS-ITT set.

2.3.4.2 AVS-ITT

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

Table 2.31: 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	0.89	(0.49, 1.59)	0.93 (0.28)	0.36
Intermediate-dose	2.55	(1.24, 5.32)	2.74 (1.06)	0.99
Low-dose with aspirin	1.93	(0.58, 6.87)	2.38 (1.70)	0.85
Therapeutic-dose	1.52	(0.59, 3.95)	1.72 (0.90)	0.81
Age $\geq$ 60	0.20	(0.10, 0.41)	0.21 (0.08)	0.00
Oxygen requirement	0.74	(0.38, 1.42)	0.78 (0.27)	0.18
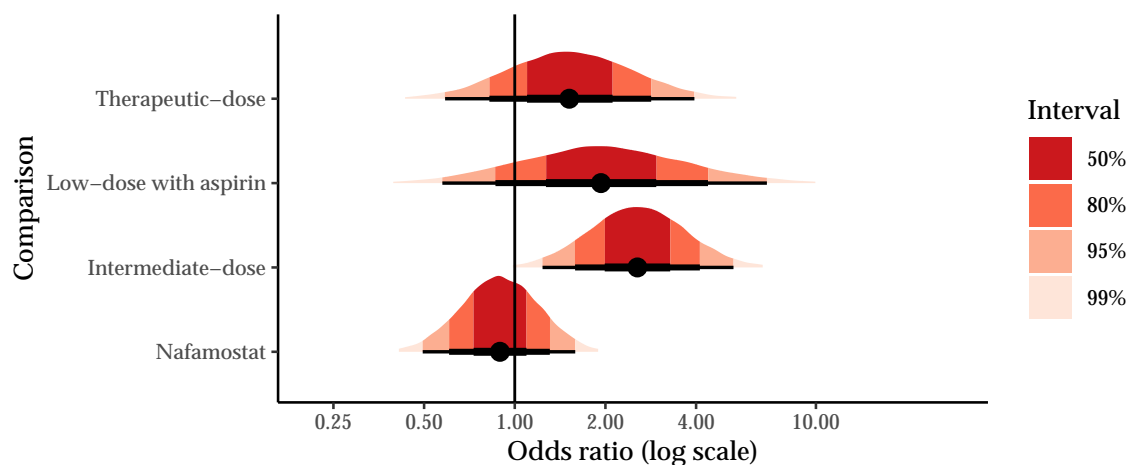
Figure 2.30: Posterior densities for the treatment effect odds ratios, AVS-ITT.

2.3.4.3 ACS-ITT

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

Table 2.32: 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	0.96	(0.48, 1.90)	1.02 (0.37)	0.45
Intermediate-dose	1.14	(0.93, 1.40)	1.15 (0.12)	0.90
Low-dose with aspirin	1.07	(0.82, 1.43)	1.08 (0.16)	0.68
Therapeutic-dose	0.65	(0.35, 1.18)	0.68 (0.21)	0.08
Ineligible aspirin	1.12	(0.59, 2.13)	1.18 (0.40)	0.64
Age ≥ 60	0.62	(0.50, 0.76)	0.62 (0.07)	0.00
Oxygen requirement	0.47	(0.38, 0.58)	0.47 (0.05)	0.00
Australia/New Zealand	1.14	(0.50, 2.71)	1.26 (0.58)	0.62
Nepal	0.83	(0.26, 2.95)	1.03 (0.81)	0.37
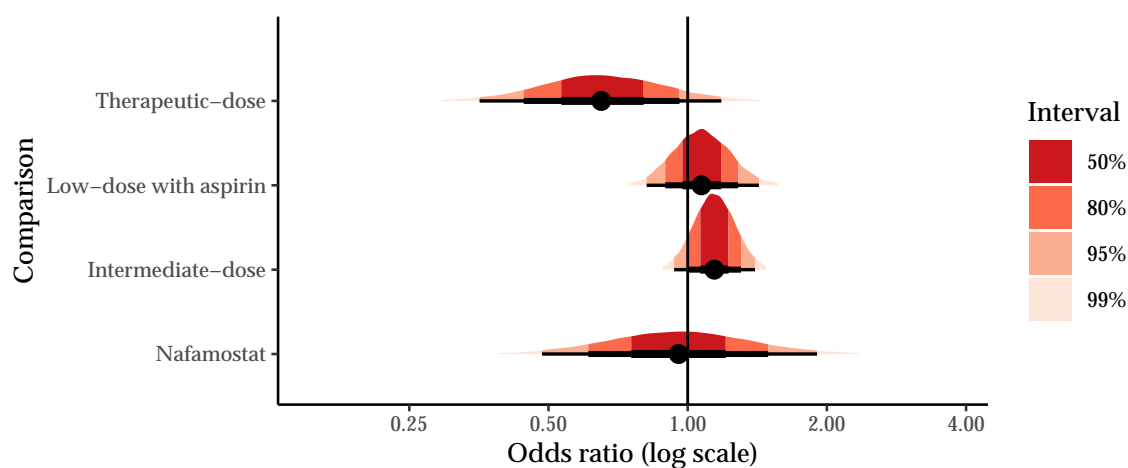
Figure 2.31: Posterior densities for the treatment effect odds ratios, ACS-ITT.

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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 2.33 presents the number of participants where the outcome was observed by the allocated anticoagulation arm. Similarly, Table 2.34 for the antiviral domain. The observed distribution of DAFV by domain treatment arm is shown in Figure 2.33 and Figure 2.34.
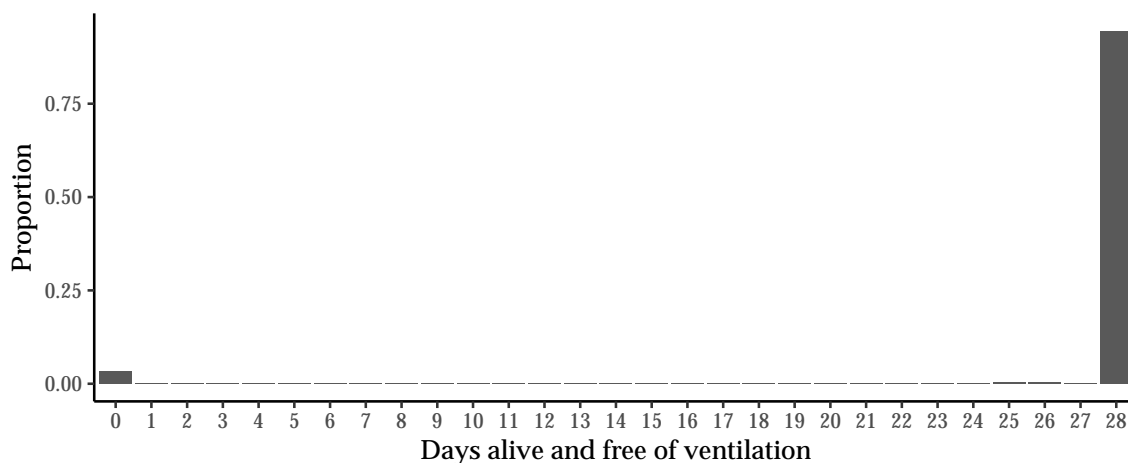
Figure 2.32: Observed overall distribution of days alive and free of hospital at day 28, FAS-ITT.

Table 2.33: 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)
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	**1556**	**1530**	**50 (3%)**	**82 (5%)**	**28 (28, 28)**
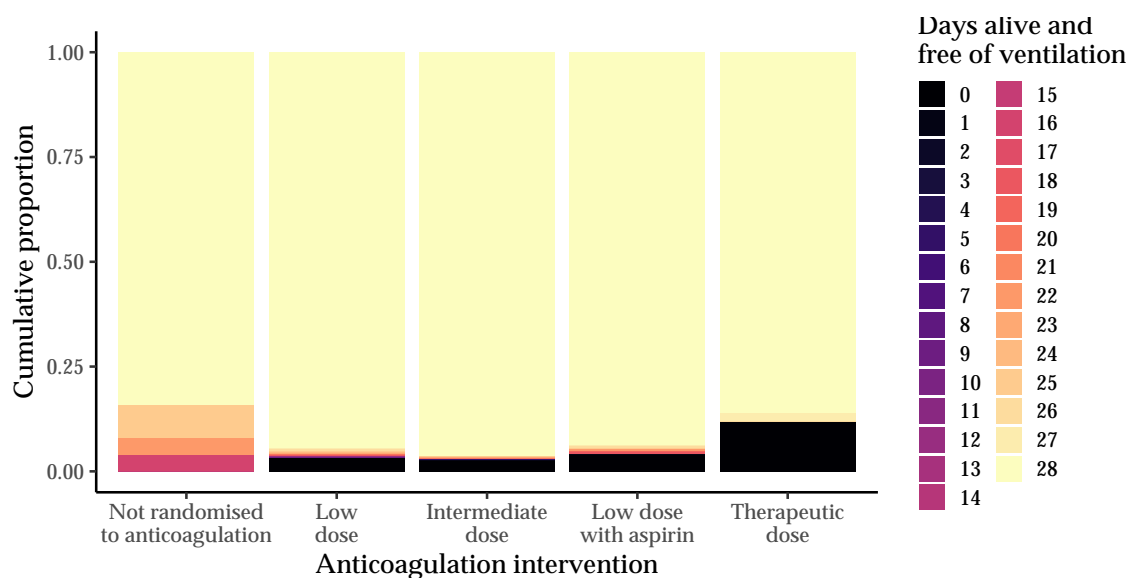
Figure 2.33: Observed distribution of days alive and free of ventilation at day 28 by anticoagulation treatment group, FAS-ITT.

Table 2.34: 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)
Standard of care	73	67	0 (0%)	8 (12%)	28 (28, 28)
Nafamostat	82	74	0 (0%)	4 (5%)	28 (28, 28)
Overall	**155**	**141**	**0 (0%)**	**12 (8%)**	**28 (28, 28)**
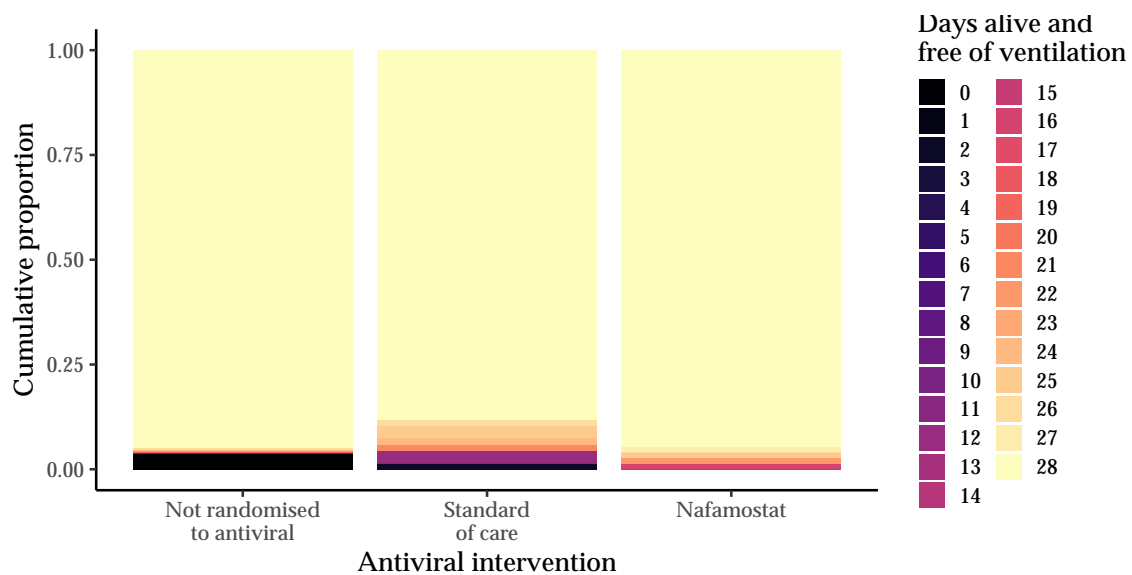
Figure 2.34: Observed distribution of days alive and free of ventilation at day 28 by antiviral treatment group, FAS-ITT.

2.3.5.1 FAS-ITT

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

Table 2.35: 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	2.36	(0.71, 8.24)	2.91 (2.11)	0.92
Intermediate-dose	1.41	(0.81, 2.47)	1.47 (0.43)	0.88
Low-dose with aspirin	1.18	(0.63, 2.24)	1.24 (0.42)	0.69
Therapeutic-dose	0.37	(0.13, 1.05)	0.42 (0.24)	0.03
Ineligible aspirin	0.30	(0.09, 1.10)	0.37 (0.27)	0.03
Age ≥ 60	0.55	(0.34, 0.91)	0.57 (0.15)	0.01
Oxygen requirement	0.28	(0.16, 0.47)	0.29 (0.08)	0.00
Australia/New Zealand	1.16	(0.31, 4.83)	1.50 (1.24)	0.58
Nepal	0.78	(0.22, 3.09)	1.00 (0.83)	0.36
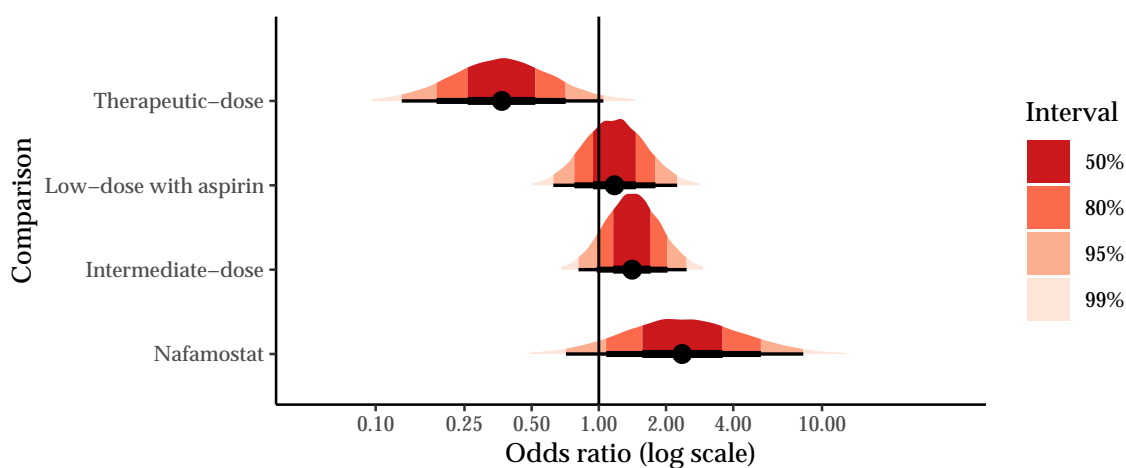
Figure 2.35: Posterior densities for the treatment effect odds ratios, FAS-ITT.
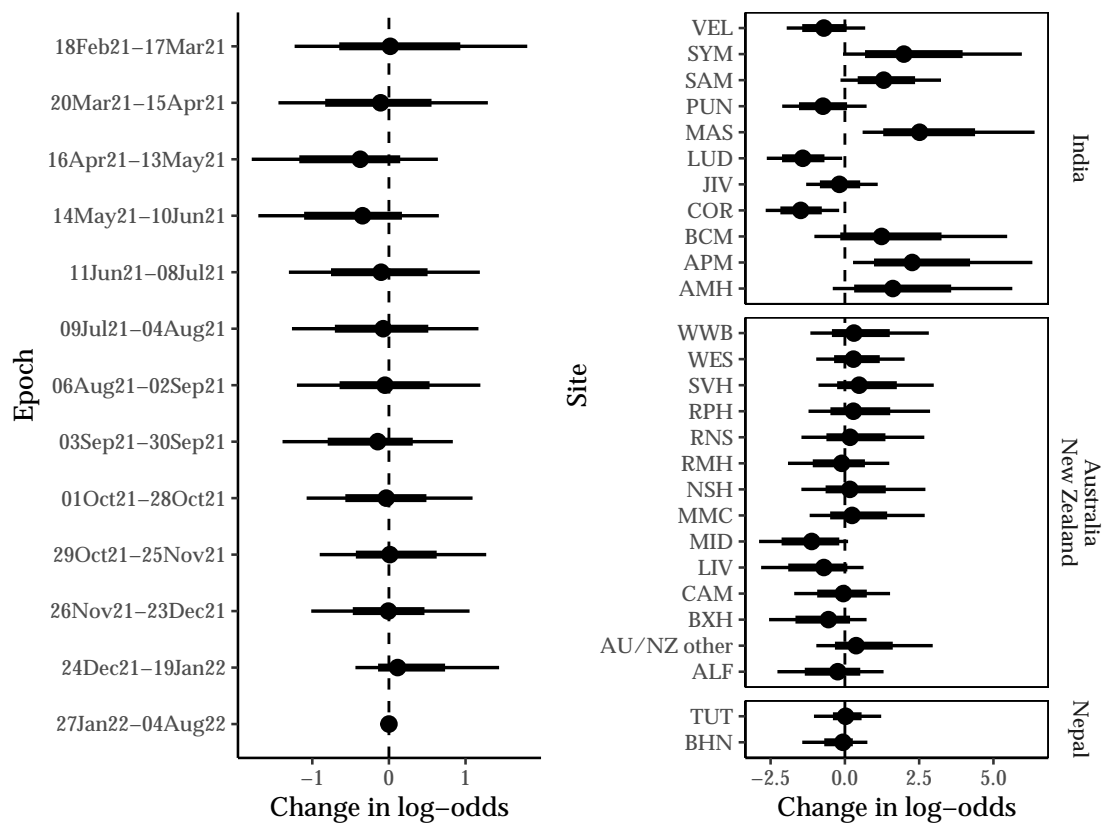
Figure 2.36: Posterior Summaries (point - median, block - 75% CrI, line - 95% CrI) of odds ratio for epoch and site effects on days alive and free of ventilation to day 28 for the primary model fit to the FAS-ITT set.

2.3.5.2 AVS-ITT

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

Table 2.36: 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	2.36	(0.71, 8.27)	2.89 (2.05)	0.92
Intermediate-dose	1.42	(0.81, 2.51)	1.48 (0.43)	0.89
Low-dose with aspirin	1.28	(0.69, 2.44)	1.35 (0.45)	0.78
Therapeutic-dose	0.36	(0.13, 1.02)	0.42 (0.24)	0.03
Age $\geq$ 60	0.53	(0.33, 0.85)	0.54 (0.14)	0.00
Oxygen requirement	0.28	(0.16, 0.47)	0.29 (0.08)	0.00
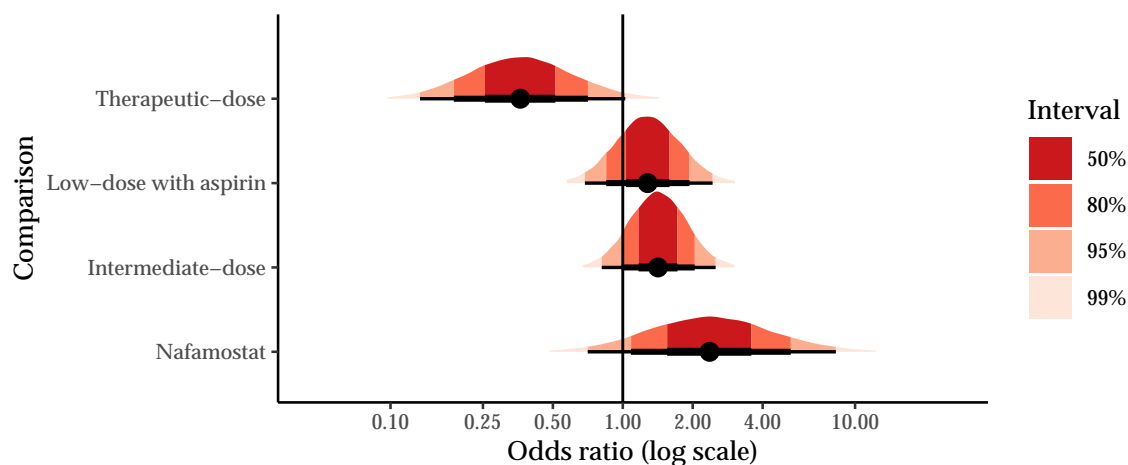
Figure 2.37: Posterior densities for the treatment effect odds ratios, AVS-ITT.

2.3.5.3 ACS-ITT

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

Table 2.37: 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	3.49	(0.84, 16.40)	4.80 (4.57)	0.96
Intermediate-dose	1.41	(0.81, 2.51)	1.48 (0.44)	0.89
Low-dose with aspirin	1.18	(0.63, 2.27)	1.25 (0.42)	0.70
Therapeutic-dose	0.37	(0.13, 1.06)	0.42 (0.25)	0.03
Ineligible aspirin	0.26	(0.08, 0.96)	0.32 (0.24)	0.02
Age $\geq$ 60	0.55	(0.33, 0.93)	0.57 (0.15)	0.01
Oxygen requirement	0.27	(0.16, 0.46)	0.28 (0.08)	0.00
Australia/New Zealand	1.40	(0.36, 6.07)	1.86 (1.67)	0.68
Nepal	0.69	(0.19, 2.86)	0.90 (0.75)	0.29
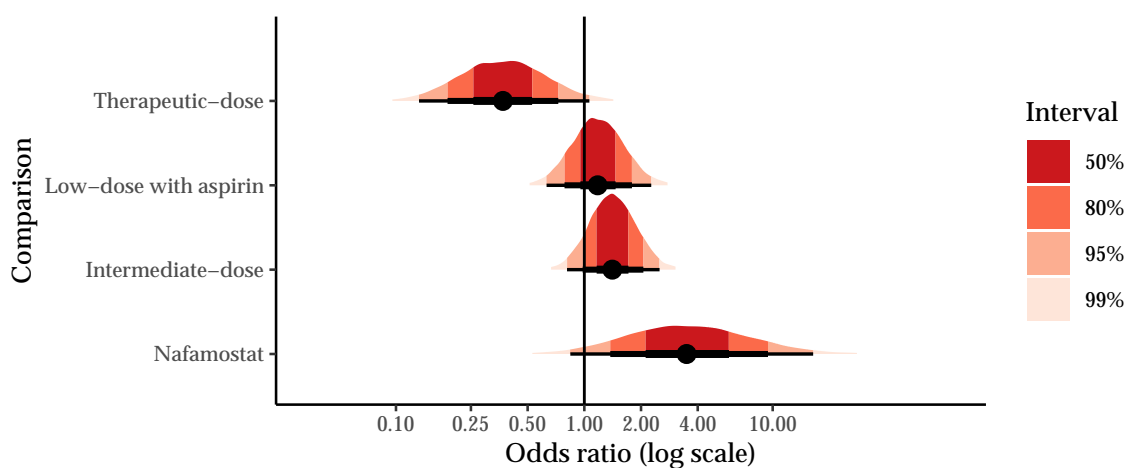
Figure 2.38: Posterior densities for the treatment effect odds ratios, ACS-ITT.

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)
  - elevation of serum potassium
  - decrease of serum sodium
  - 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.

3 Appendix

3.1 Outcomes by Model Covariates (FAS-ITT)

3.1.1 Primary Outcome by Model Covariates (FAS-ITT)
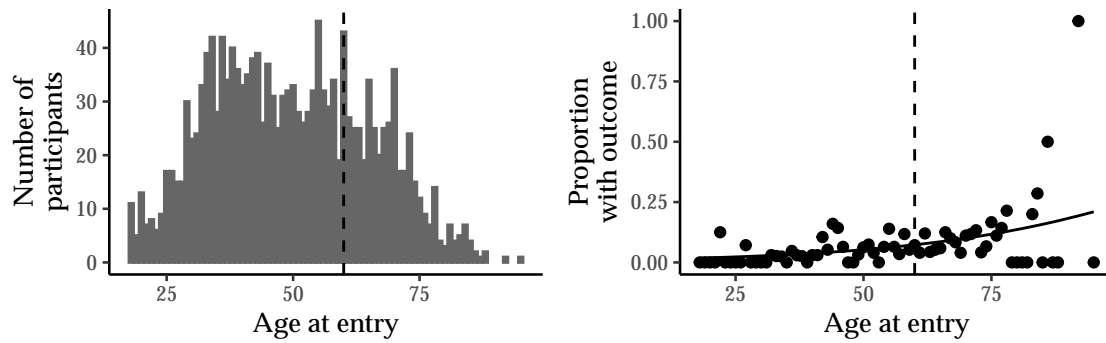
Figure 3.1: Proportion of participants satisfying primary outcome criteria by age at randomisation, FAS-ITT. Vertical dashed line indicates the pre-specified cut-point of 60 years of age.
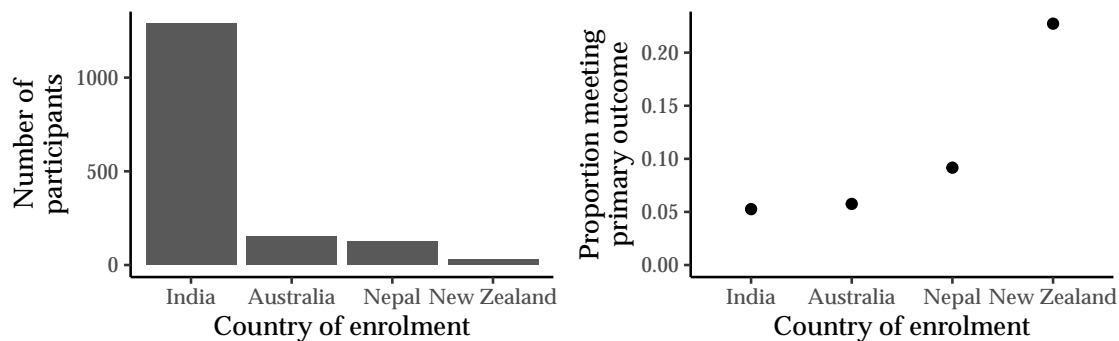
Figure 3.2: Proportion of participants satisfying primary outcome criteria by country of randomisation, FAS-ITT.
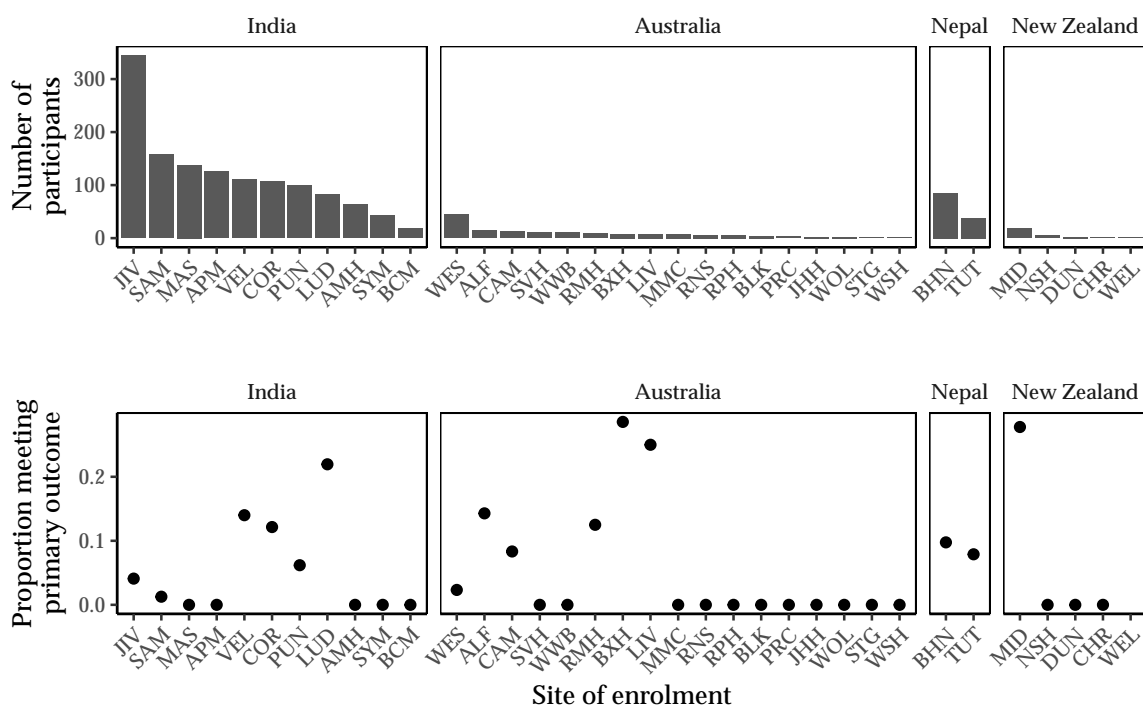
Figure 3.3: Proportion of participants satisfying primary outcome criteria by country and site of randomisation, FAS-ITT.
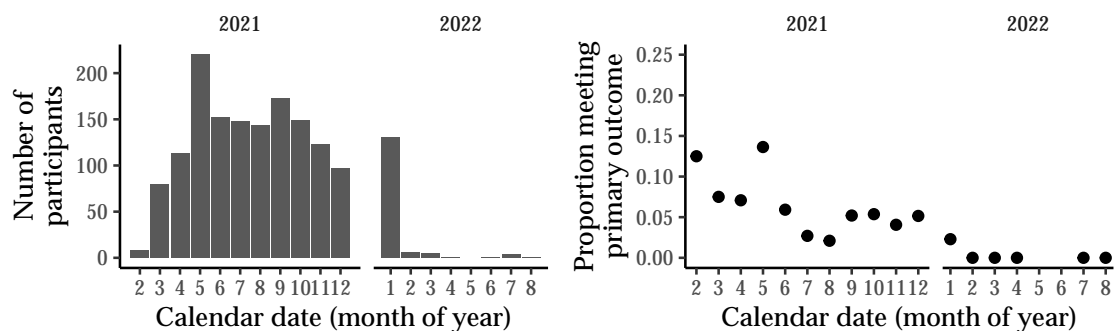
Figure 3.4: Proportion of participants satisfying primary outcome criteria by calendar time (month) of randomisation, FAS-ITT.
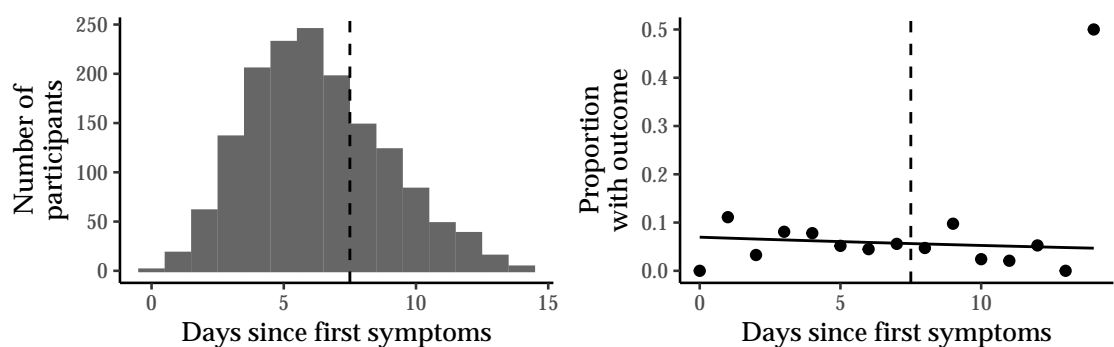
Figure 3.5: Proportion of participants satisfying primary outcome criteria by days since first symptoms at randomisation, FAS-ITT. Vertical dashed line indicates the pre-specified cut-point of 7 days.

3.1.2 Time to recovery to day 28 by model covariates (FAS-ITT)
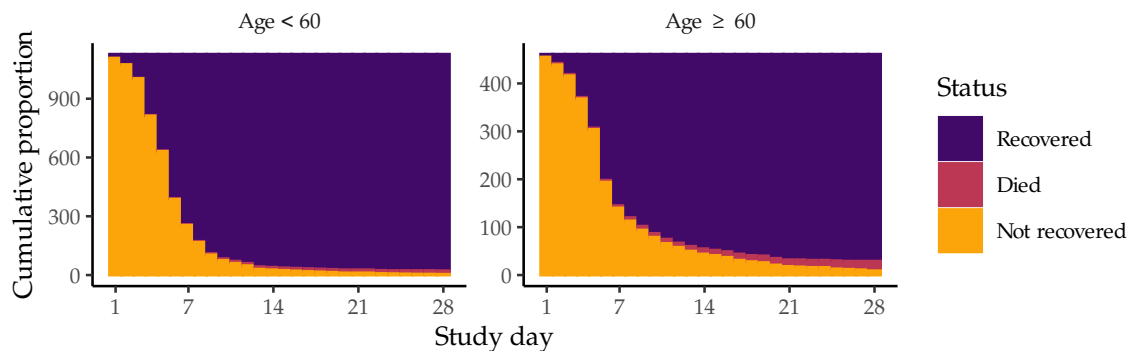
Figure 3.6: Time to clinical recovery to day 28 by age group at randomisation, FAS-ITT.
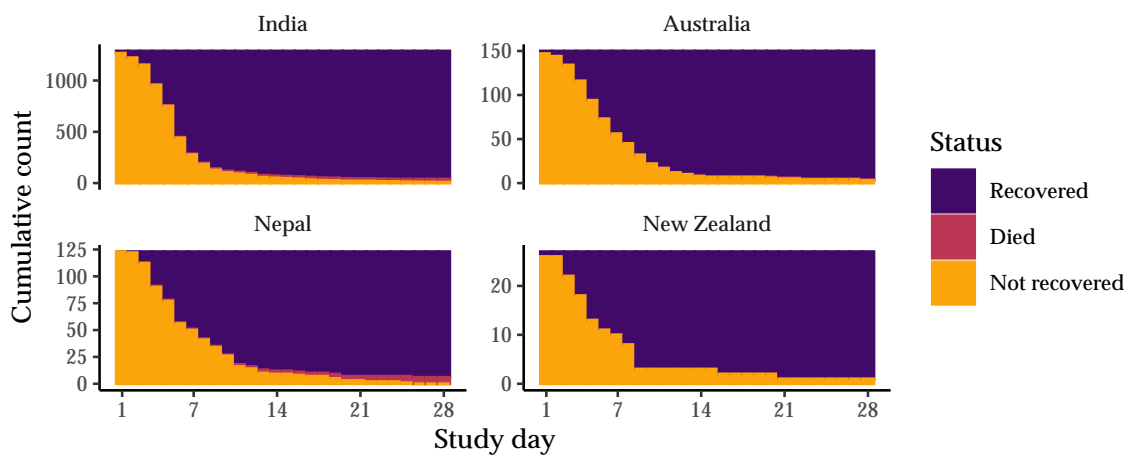
Figure 3.7: Time to clinical recovery to day 28 by country of randomisation, FAS-ITT.
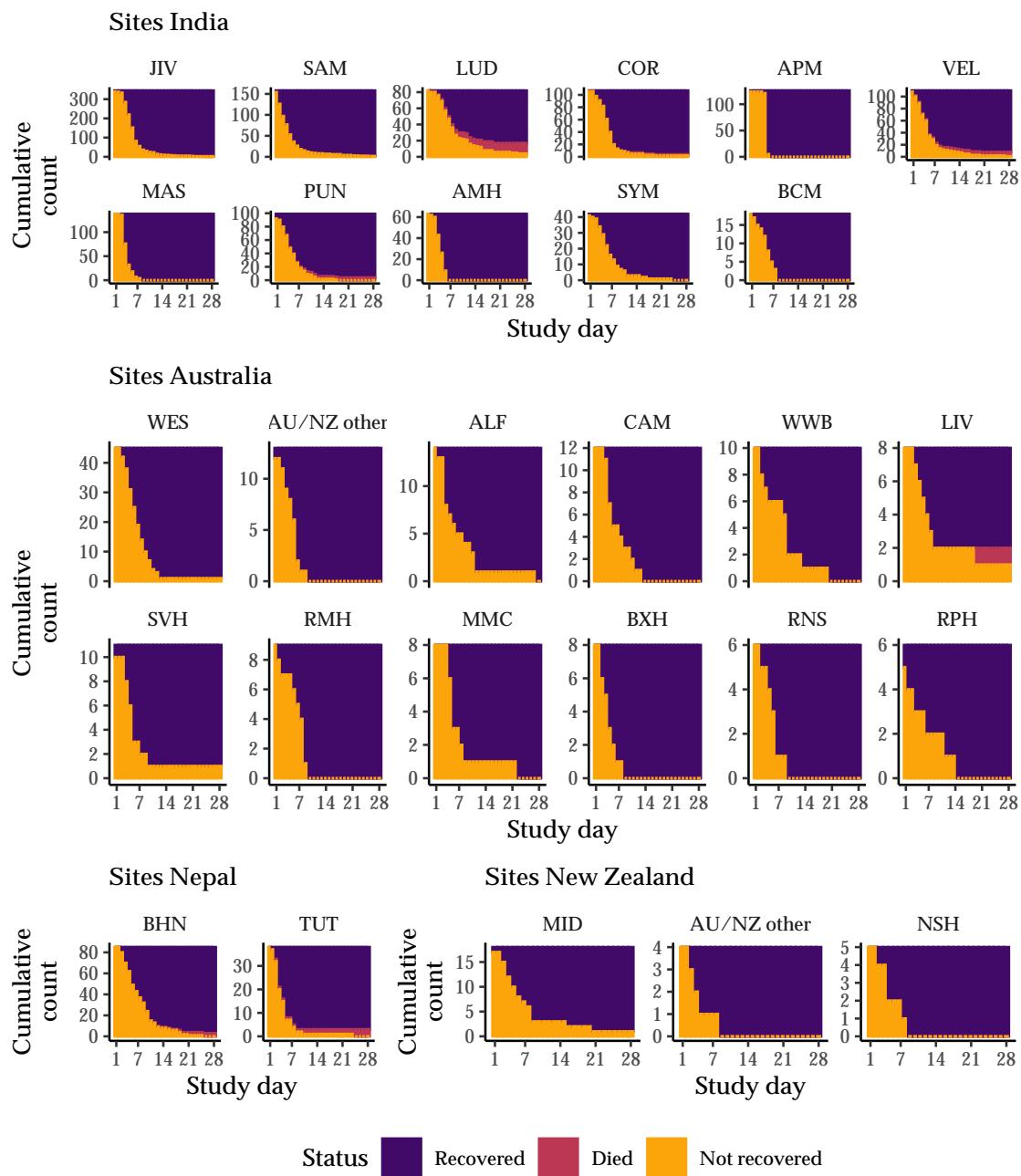
Figure 3.8: Time to clinical recovery to day 28 by country and site of randomisation, FAS-ITT.
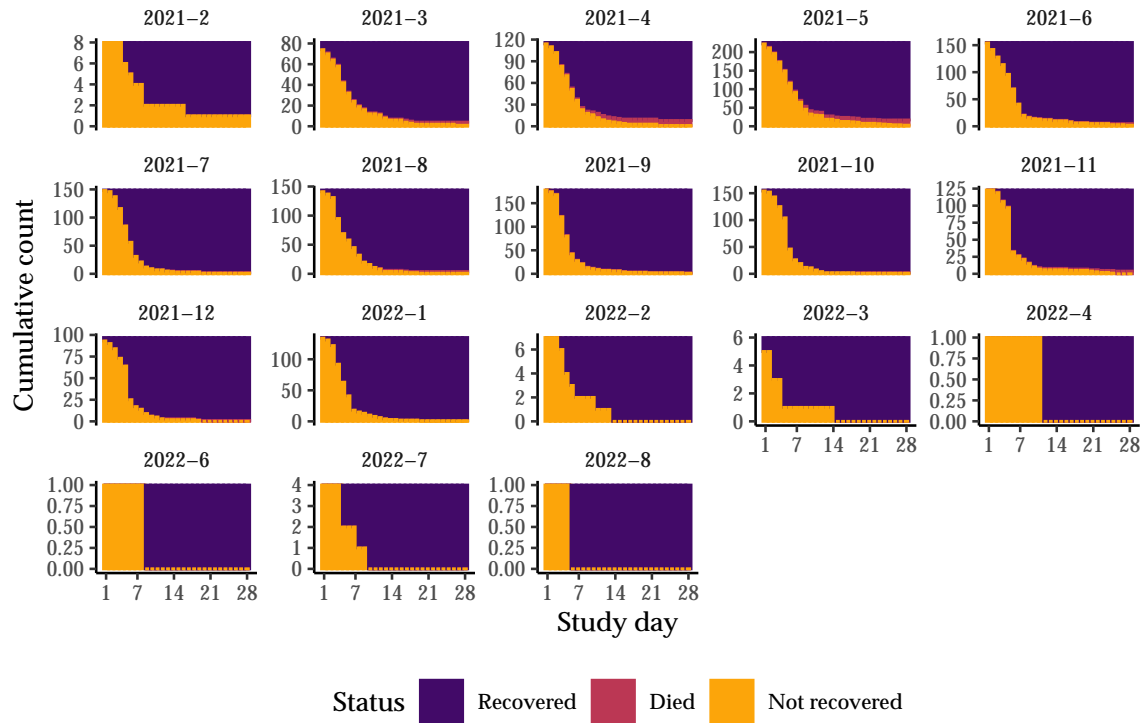
Figure 3.9: Time to clinical recovery to day 28 by calendar time (month) of randomisation, FAS-ITT.

3.1.3 WHO outcome scale at day 28 by model covariates (FAS-ITT)
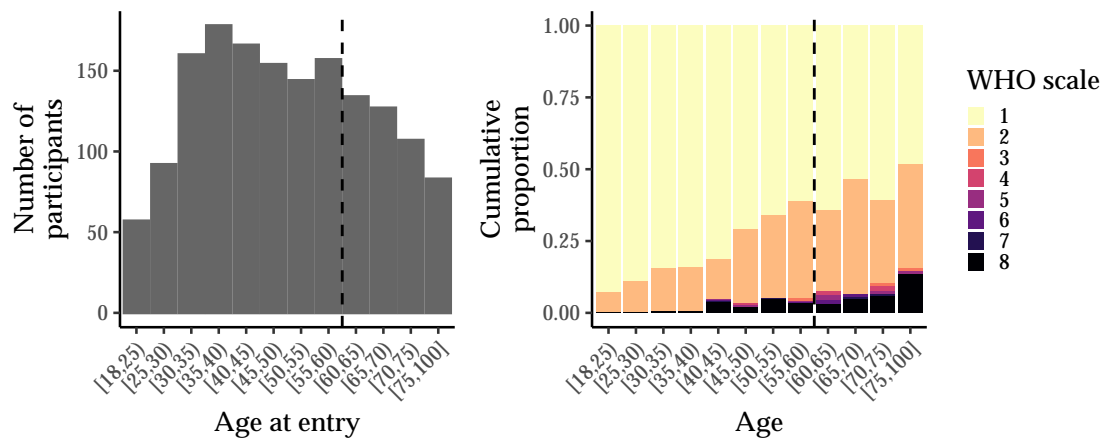
Figure 3.10: Distribution of WHO outcome scale day 28 by age at randomisation, FAS-ITT. Vertical dashed line indicates the pre-specified cut-point of 60 years of age.
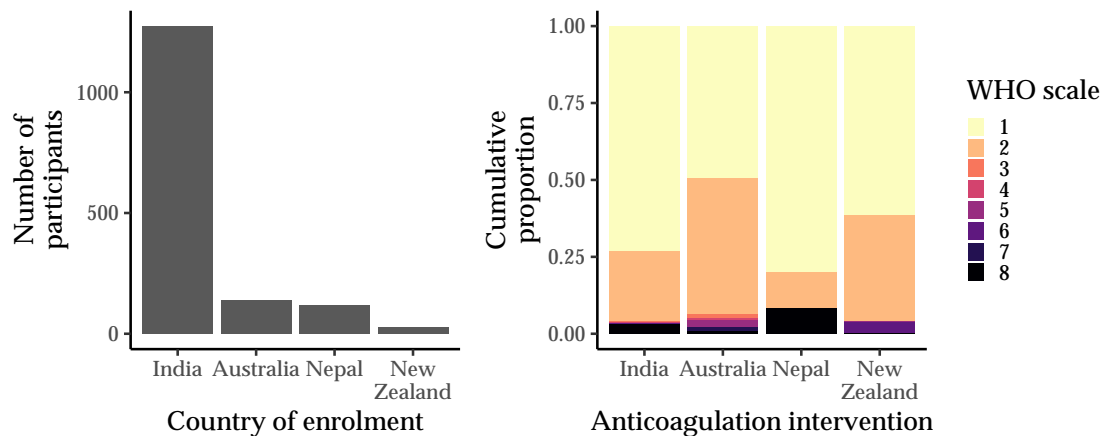
Figure 3.11: Distribution of WHO scale at day 28 by country of randomisation, FAS-ITT.
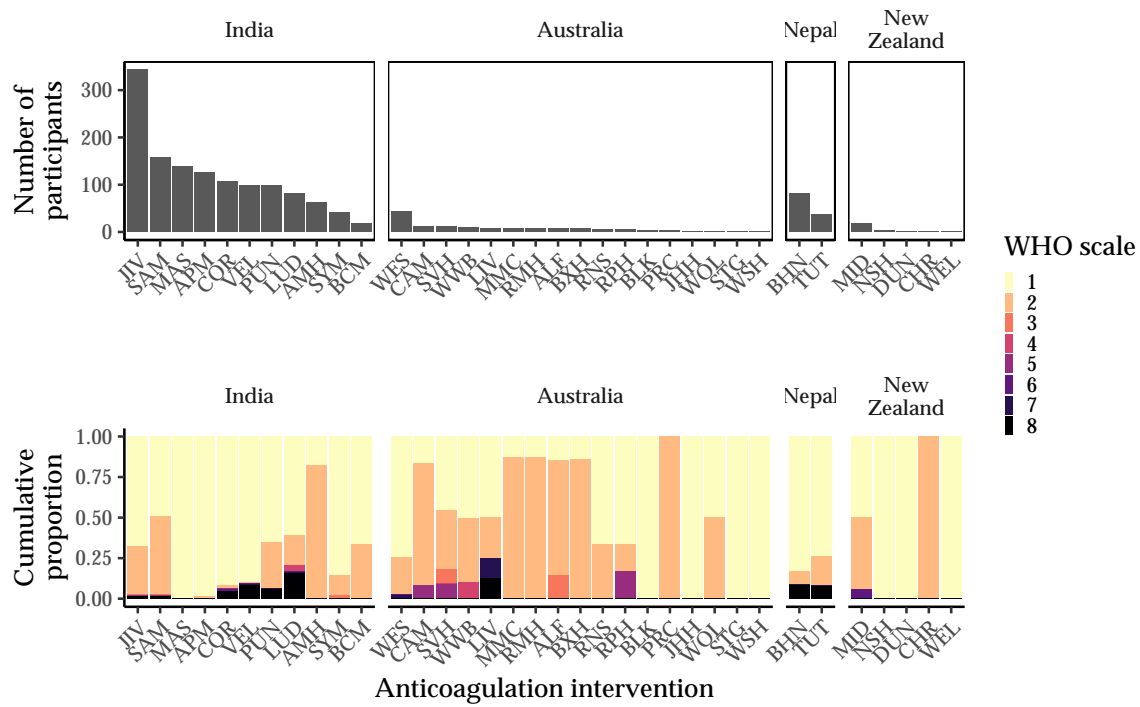
Figure 3.12: Distribution of WHO scale at day 28 by country and site of randomisation, FAS-ITT.
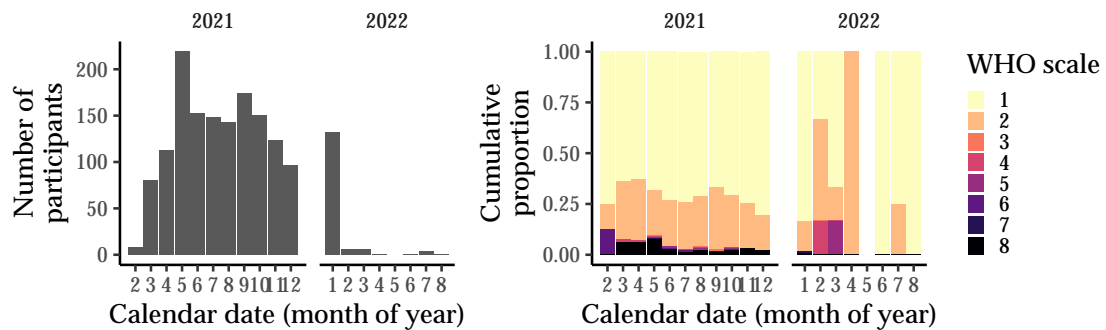
Figure 3.13: Distribution of WHO scale at day 28 by calendar time (month) of randomisation, FAS-ITT.

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

3.1.5 Days alive and free of hospital to day 28 by Model Covariates (FAS-ITT)
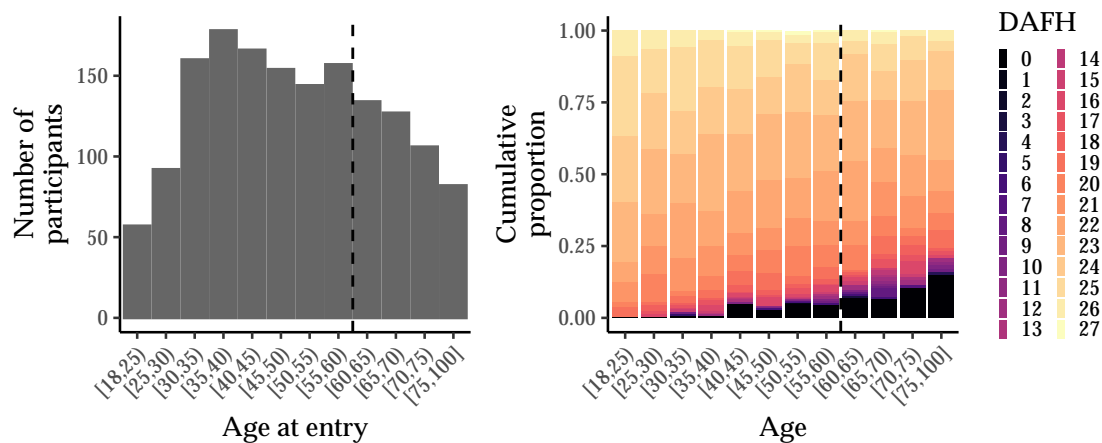
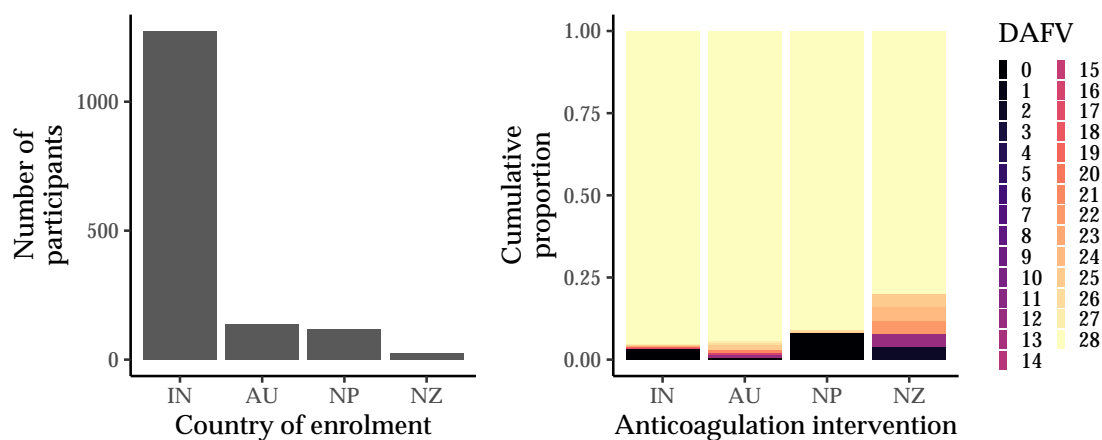Figure 3.14: Distribution of days alive and free of hospital to day 28 by age groups, FAS-ITT.
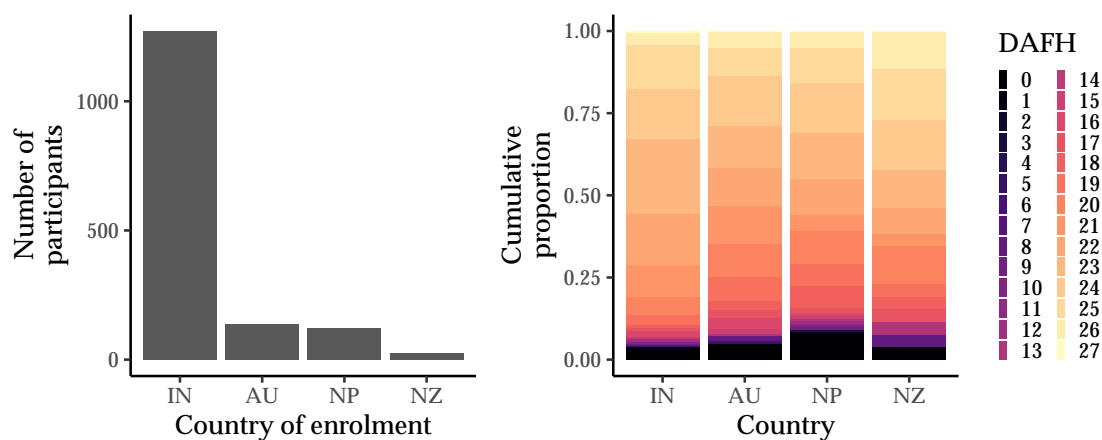
Figure 3.15: Distribution of days alive and free of hospital to day 28 by country of randomisation, FAS-ITT.
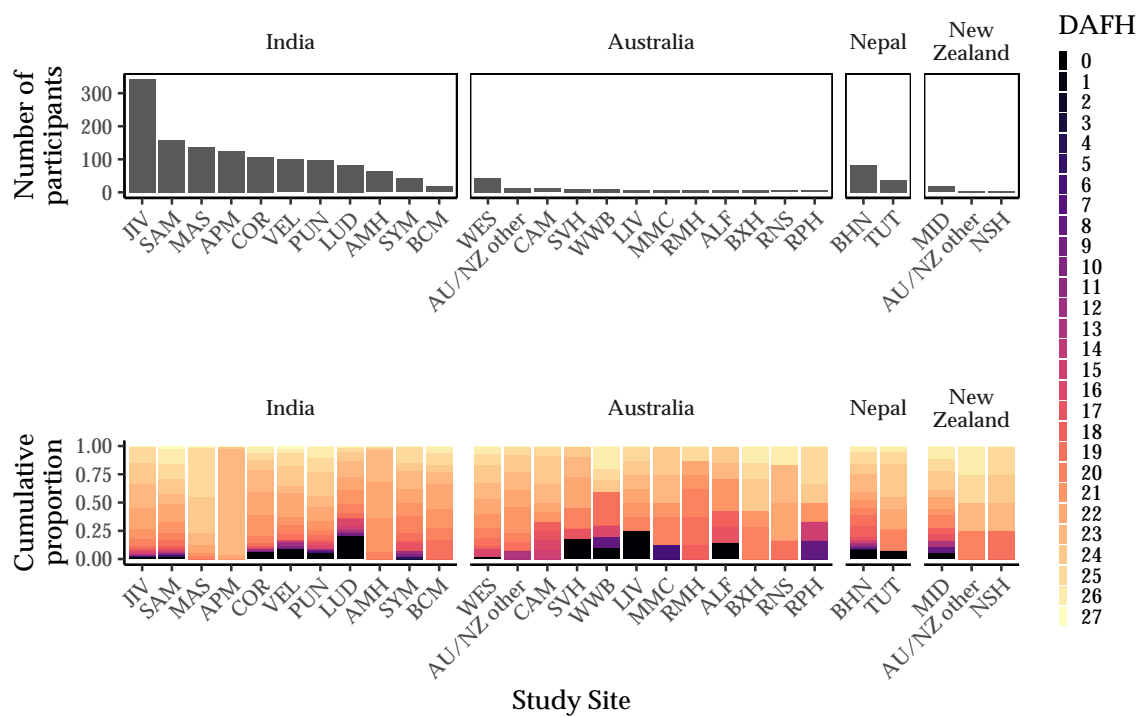
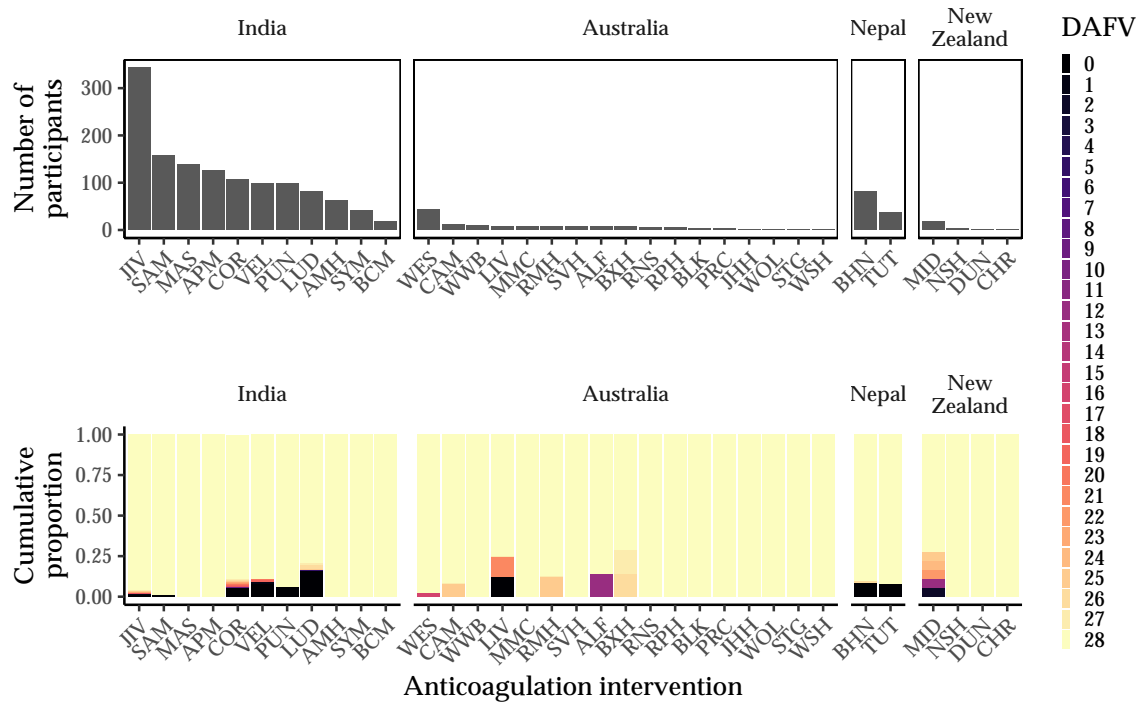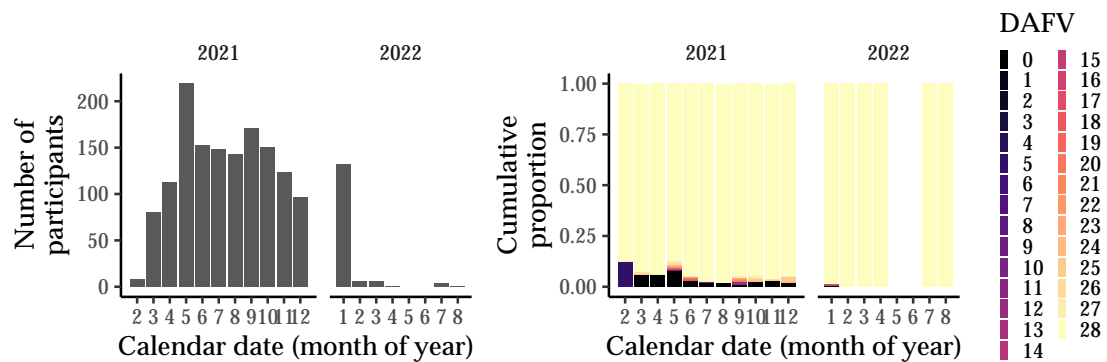Figure 3.16: Distribution of days alive and free of hospital to day 28 by country and site of randomisation, FAS-ITT.
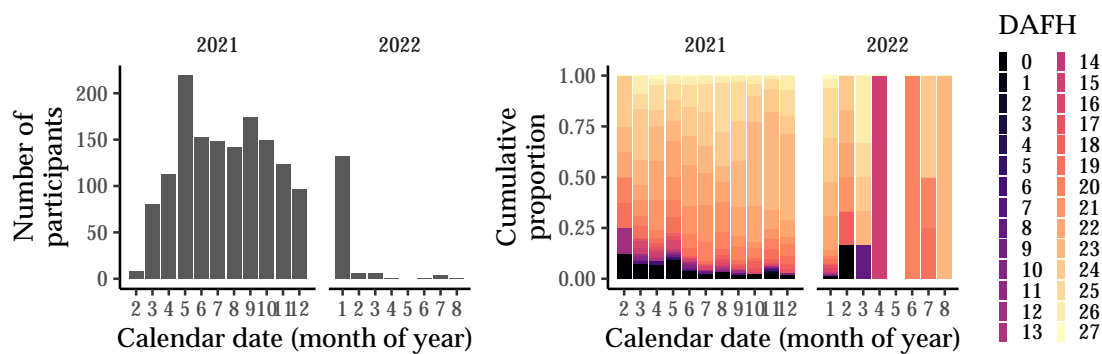
Figure 3.17: Distribution of days alive and free of hospital to day 28 by calendar time (month) of randomisation, FAS-ITT.

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3.1.6 Days alive and free of ventilation to day 28 by Model Covariates (FAS-ITT)
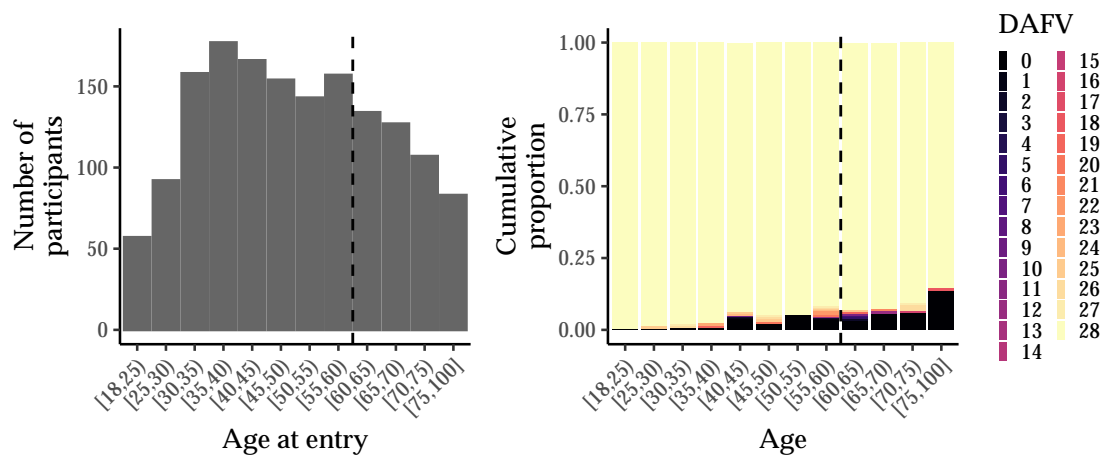
Figure 3.18: Distribution of days alive and free of ventilation to day 28 by age groups, FAS-ITT.

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

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

Figure 3.21: 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)

3.2 Primary Model Posterior Predictive Summaries
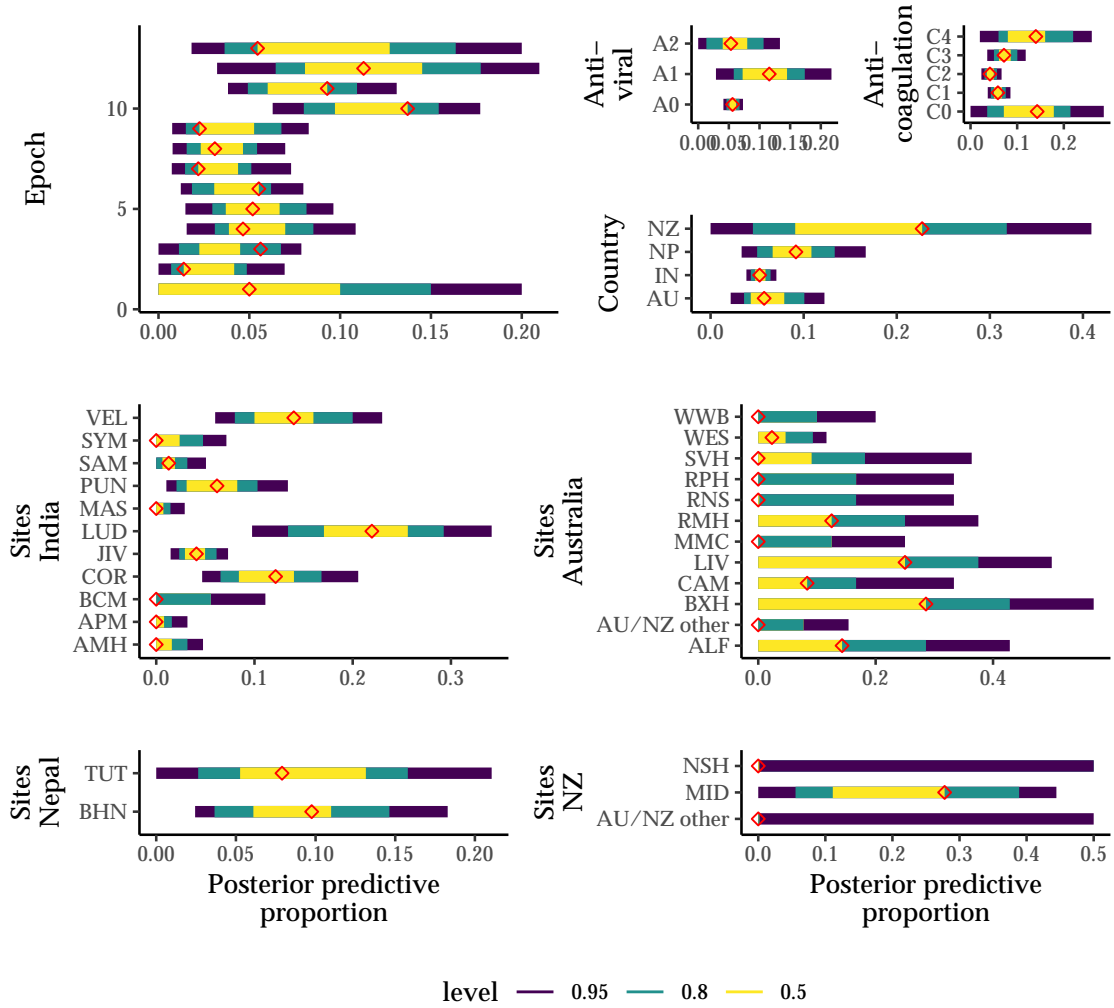
3.2.1 Primary Outcome

Figure 3.22: Posterior predictive distribution for primary outcome by model covariates for primary model using FAS-ITT. Red diamond indicates observed proportions.
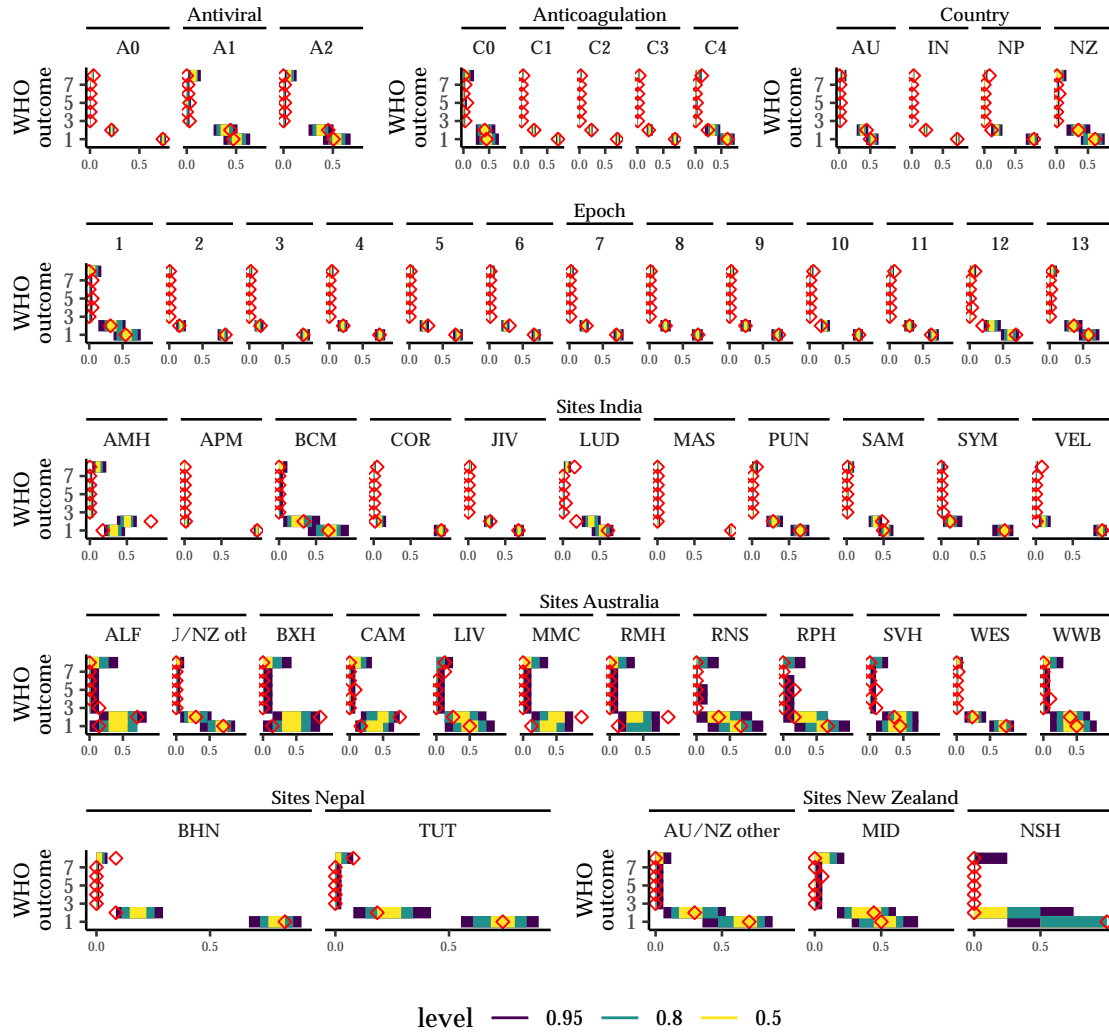
3.2.2 WHO outcome scale at day 28

Figure 3.23: 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
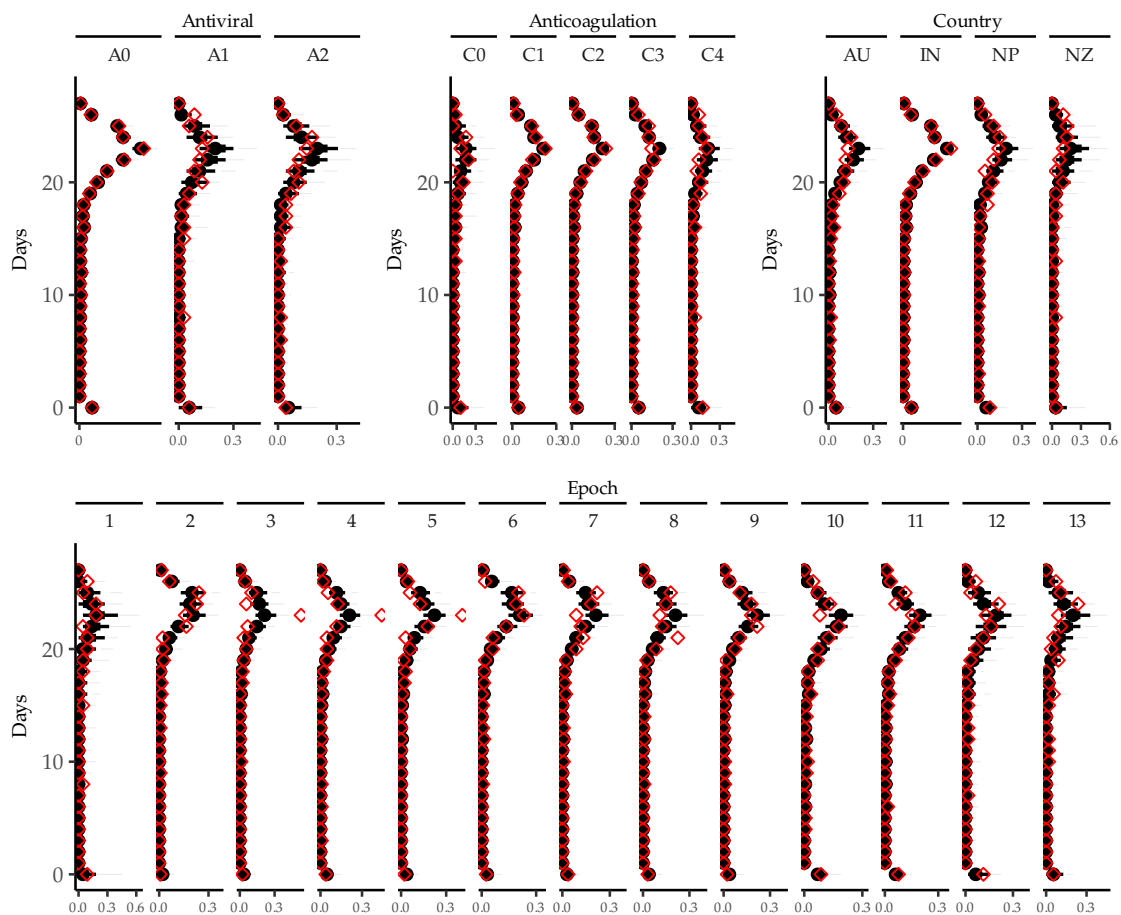
3.2.4 Days alive and free of hospital to day 28

Figure 3.24: 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.
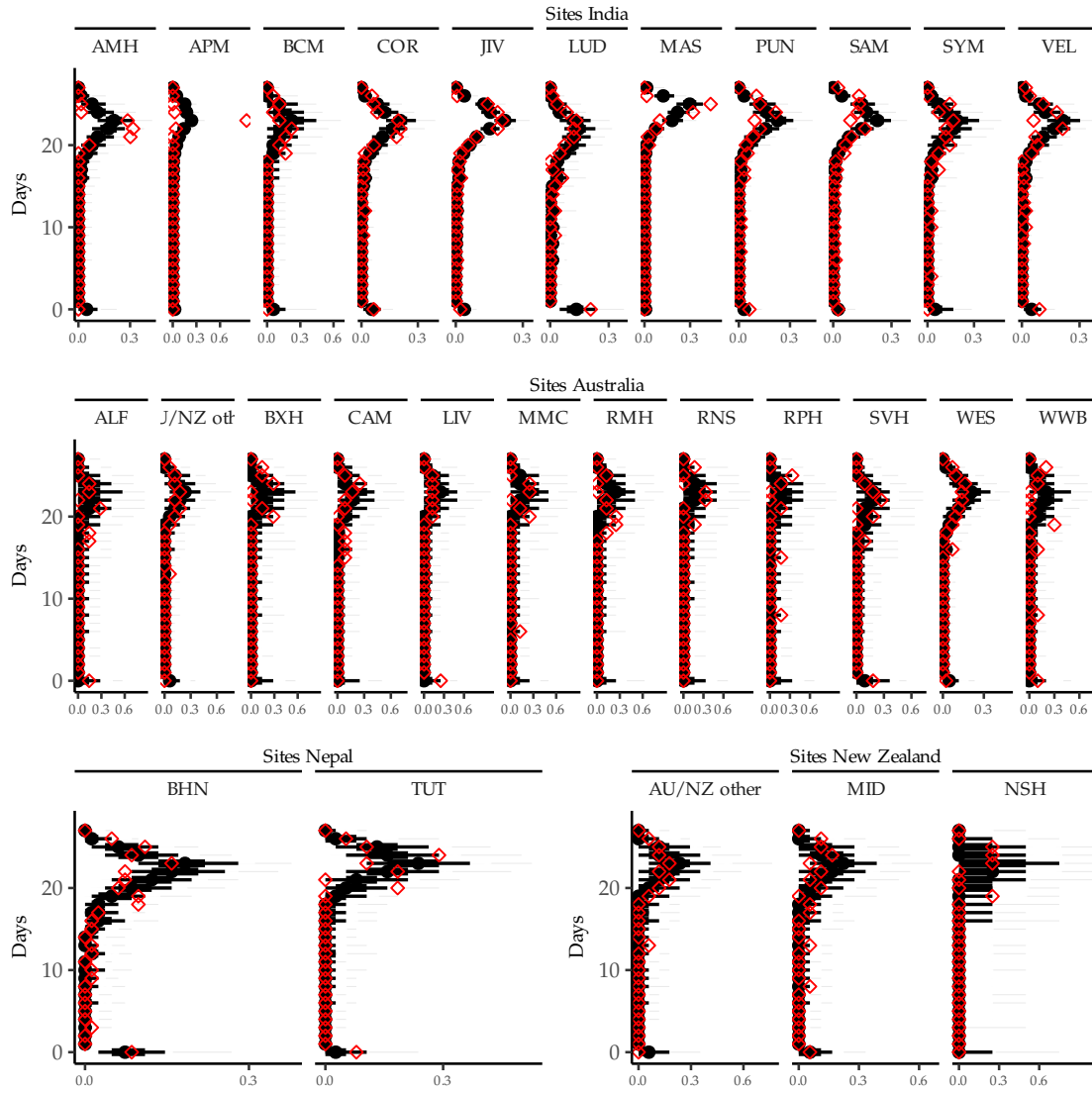
Figure 3.25: Posterior predictive distribution for days alive and free of hospital to day 28 by model covariates (site) for primary model using FAS-ITT. Red diamond indicates observed proportions.

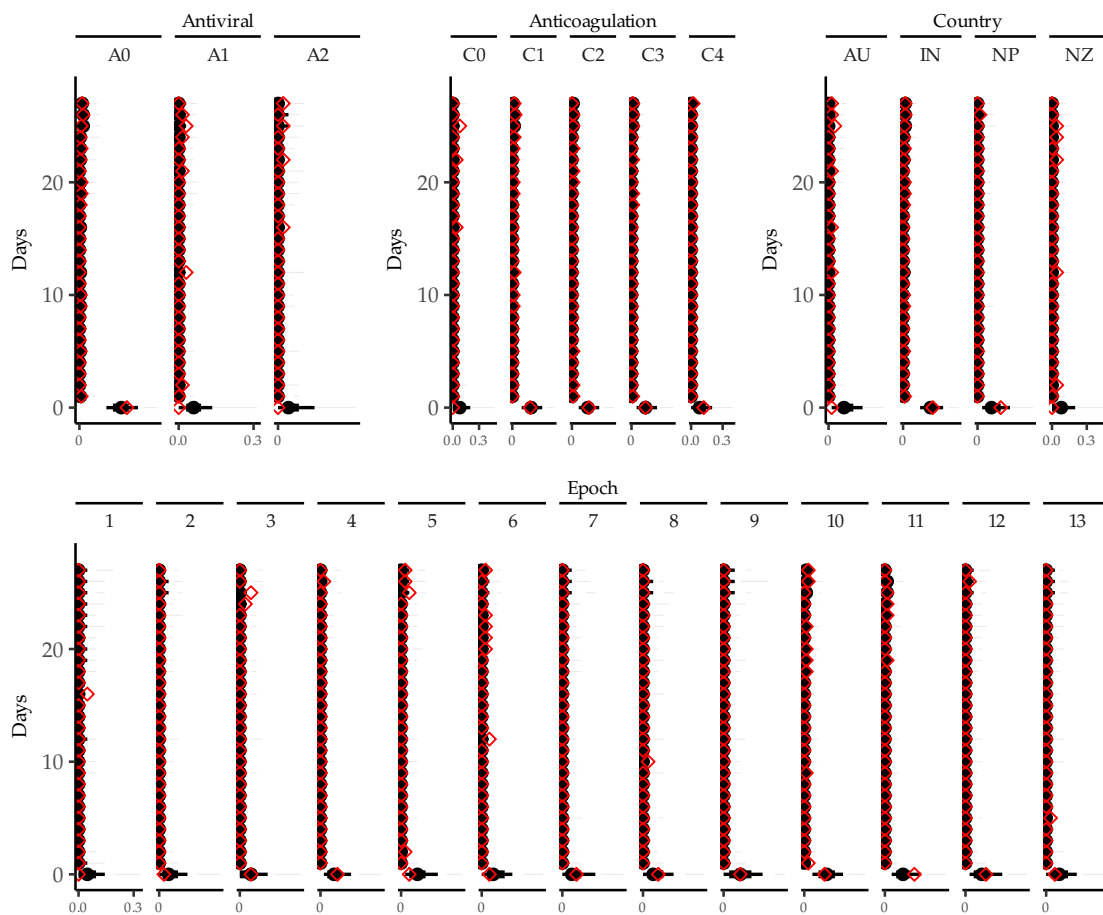### 3.2.5 Days alive and free of ventilation to day 28

Figure 3.26: 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.
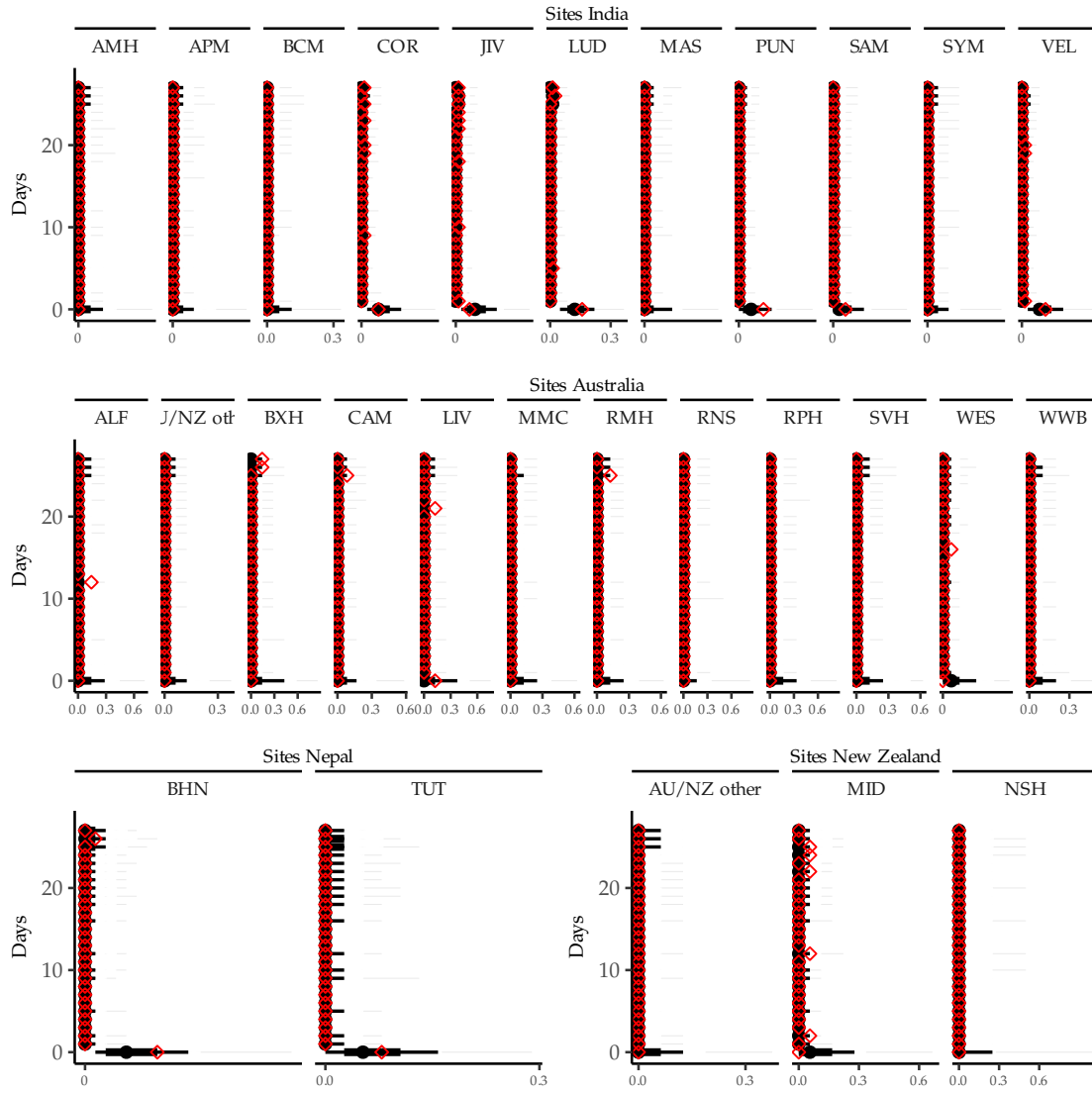
Figure 3.27: Posterior predictive distribution for days alive and free of ventilation to day 28 by model covariates (site) for primary model using FAS-ITT. Red diamond indicates observed proportions.