CLARITY 2.0 Trial Simulations

Version 1.0

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Contents

1 Background

1.1 Aim

The aim of CLARITY 2.0 is to evaluate the safety and efficacy of dual treatment with repagermanium and candesartan compared to placebo for patients hospitalised for management of COVID-19.

1.2 Objectives

The primary objective is to evaluate the safety and efficacy of dual treatment with repagermanium and candesartan in patients hospitalised with COVID-19 disease, assessed by clinical Health Score at day 14.

The clinical health score is a 8 point ordinal scale (1) best and (8) worst.

1.3 Interventions

Participants will be randomised into three treatment arms:

1. Placebo [candesartan] + placebo [repagermanium] (P+P) (Control Arm #2)
2. Candesartan + placebo [repagermanium] (C+P), (Control Arm #1)
3. Candesartan + repagermanium (C+R), (Investigational Arm)

1.4 Randomisation

Initially, treatment allocation will be with a 1:1:1 block randomisation between the three arms, stratified by centre.

1.5 Sample Size

- Stage 1: 80 participants (1:1 to arms 2 and 3) in India only, following which, a safety analysis will be undertaken
- Stage 2: 520 participants (1:1:1 to all arms), following which, an analysis will be undertaken to decide whether to proceed to Stage 3, and whether one control group could potentially be dropped
- Stage 3: up to 1,500 additional participants between either 3 (1:1:1) or 2 (1:1) arms. Total sample size may therefore be up to 2,100 participants.

1.6 Statistical Analysis

A cumulative logistic regression model will be used to assess the effectiveness of the investigational arm compared to each control arm (or the single control arm). The investigational arm will be compared to each control arm, and effectiveness assessed in terms of the common odds ratio of being in a better clinical health status at day 14.

2 Simulations

2.1 Model Specification

Let $Y_i \in \{1, \ldots, 8\}$ be the day 14 clinical health status for participant i where 1 is best and 8 is worst (death). Let $\tau_i \in \{1, 2, 3\}$ denote treatment arm and x_i the corresponding design encoding such that $\eta_\tau = x_\tau^\mathsf{T}\beta$ is the shift in the log-odds of each outcome for participant receiving treatment τ. Our interest is in the comparisons $\eta_3 - \eta_1$ and $\eta_3 - \eta_2$. For the (reduced) primary model we specify:

$$P(Y_i \leq k|\alpha, \beta, x_i) = \text{logit}^{-1}(\alpha_k + x_i^T\beta) \quad i = 1, 2, ..., k = 1, ..., 8,$$

where $\{\alpha_k\}$ is increasing in k. These simulations assume an orthonormal design coding such that α governs the distribution of outcome levels averaged across all treatment groups.

The average (equally weighted across treatment groups) distribution of outcomes is governed by

$$\pi_k = \begin{cases} 1 - \text{logit}^{-1}(\alpha_1) & k = 1 \\ \text{logit}^{-1}(\alpha_{k-1}) - \text{logit}^{-1}(\alpha_k) & k \in \{2, ..., 7\} \\ \text{logit}^{-1}(\alpha_7) & k = 8 \end{cases}$$

If an outcome level had zero observations at an interim analysis, then that level was dropped from the outcome, and the prior mass applied across the remaining levels.

2.1.1 Priors

The prior on π was intended to be uninformative. The specification used in simulations was $\kappa_k = 1/4$ for $k = 1, ..., 8$.

$$\pi \sim \text{Dirichlet}(\kappa).$$

The prior on β was intended to be slightly regularising and was specified as

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

2.2 Decision Rules

In terms of the above model, we consider two possible decision processes in the simulations.

2.2.1 Effectiveness

Effectiveness of the intervention against each control group is assessed by (conditional on data from n participants)

$$\mathbb{P}(\eta_3 - \eta_1 > \delta | \texttt{data}_n) \quad \text{(C+R > P+P)} \tag{1}$$

$$\mathbb{P}(\eta_3 - \eta_2 > \delta | \texttt{data}_n) \quad \text{(C+R > C+P)} \tag{2}$$

$$\mathbb{P}(\eta_3 - \eta_1 > \delta, \eta_3 - \eta_2 > \delta | \texttt{data}_n) \quad \text{(C+R > P+P and C+P).} \tag{3}$$

If both probabilities (1) and (2) exceed some threshold, ϵ_{eff}, at an analysis then a decision of effectiveness relative to each control is recommended. Alternatively, if only one of (1) or (2) exceeds the threshold, then the corresponding control arm is dropped from the trial and the remaining arms are continued with 1:1 allocation. The simulations specify $\delta = 0$.

2.2.2 Trial Futility

Futility of the trial itself may be monitored according to the predicted probability of an effectiveness decision at the maximum sample size conditional on data from n participants assuming an additional m participants will be recruited

$$\text{PPoS}_{\text{P+P}}(\texttt{data}_n, m) = \mathbb{E}[\mathbb{P}(\eta_3 - \eta_2 > \delta | \texttt{data}_{n+m}) > \epsilon_{\text{eff}} | \texttt{data}_n] \tag{4}$$

$$\text{PPoS}_{\text{C+P}}(\texttt{data}_n, m) = \mathbb{E}[\mathbb{P}(\eta_3 - \eta_1 > \delta | \texttt{data}_{n+m}) > \epsilon_{\text{eff}} | \texttt{data}_n] \tag{5}$$

$$\text{PPoS}_{\text{P+P,C+P}}(\texttt{data}_n, m) = \mathbb{E}[\mathbb{P}(\eta_3 - \eta_1 > \delta, \eta_3 > 0 - \eta_2 > \delta) > \epsilon_{\text{eff}} | \texttt{data}_{n+m}) | \texttt{data}_n] \tag{6}$$

If either probability (4) or (5) fall below some threshold, ϵ_{fut}, at an analysis then a decision of trial futility with respect to at least one of the controls is recommended. It may still be likely for the trial to be successful for one of the control groups, but it may be futile with respect to one of them.

In practice, calculation of these predictive quantities requires assumptions about the future distribution of covariates included in the model. In the simulations, the only covariate is assigned treatment which is assumed to be assigned 1:1 up to the maximum sample size amongst still active arms. The future outcome data is generated from the posterior predictive distribution for the model.

2.3 Scenarios

The simulations were setup to reflect the planned recruitment, with:

- first 80 1:1 allocation to arms 2 and 3
- next 520 1:1:1 between all 3 arms

We then consider the following parameters:

- **interim analyses:** every 300, 450, or 600 participants, with a first analysis at 600 participants

- **effectiveness:** a fixed threshold of 0.95, 0.96, 0.97, 0.98 applied at each interim
- **futility:** a fixed futility threshold of 0.00, 0.02, 0.05, 0.10, 0.15, 0.2.
- **odds ratios:** odds ratios of 1, 1.1, 1.2, 1.3, and 1.5 whilst the other intervention is held at 1, and an odds ratio of 1.3 while the other intervention has an odds ratio of 1.1.

The simulations ignore the delay in outcome.

2.4 Computational Details

At each interim analysis, posterior draws are generated using HMC via Stan using `rstan::sampling`. To calculate PPoS, a sub-sample is used to generate 500 posterior predictive draws as imputed future data, the posteriors approximated via Laplace's method using `rstan::optimizing`, and the required quantities are then derived.

For each scenario, 1,000 trial replications are simulated.

3 Operating Characteristics

3.1 Stage 2

At the end of stage 2 there will be 600 participants randomised between the three arms with approximately: 173 assigned to control arm 1, and 213/214 assigned to each of control arm 2 and the investigational arm.

After 600 participants enrolled, ~40% of trials had the effectiveness when the investigational arm had odds 1.5 times both the control groups.

Table 1: Proportion of trials reaching conclusion for effectiveness, $\epsilon_{\text{eff}} = 0.95$.

OR: ctrl. 2, inv. arm (relative to ctrl. 1)	Investigational vs control 1	Investigational vs control 2	Both effective
1.00, 0.91	0.02	0.03	0.00
1.00, 1.00	0.05	0.04	0.01
1.00, 1.10	0.10	0.11	0.04
1.00, 1.20	0.20	0.20	0.09
1.00, 1.30	0.34	0.36	0.20
1.00, 1.50	0.57	0.61	0.42
1.10, 1.30	0.34	0.20	0.11

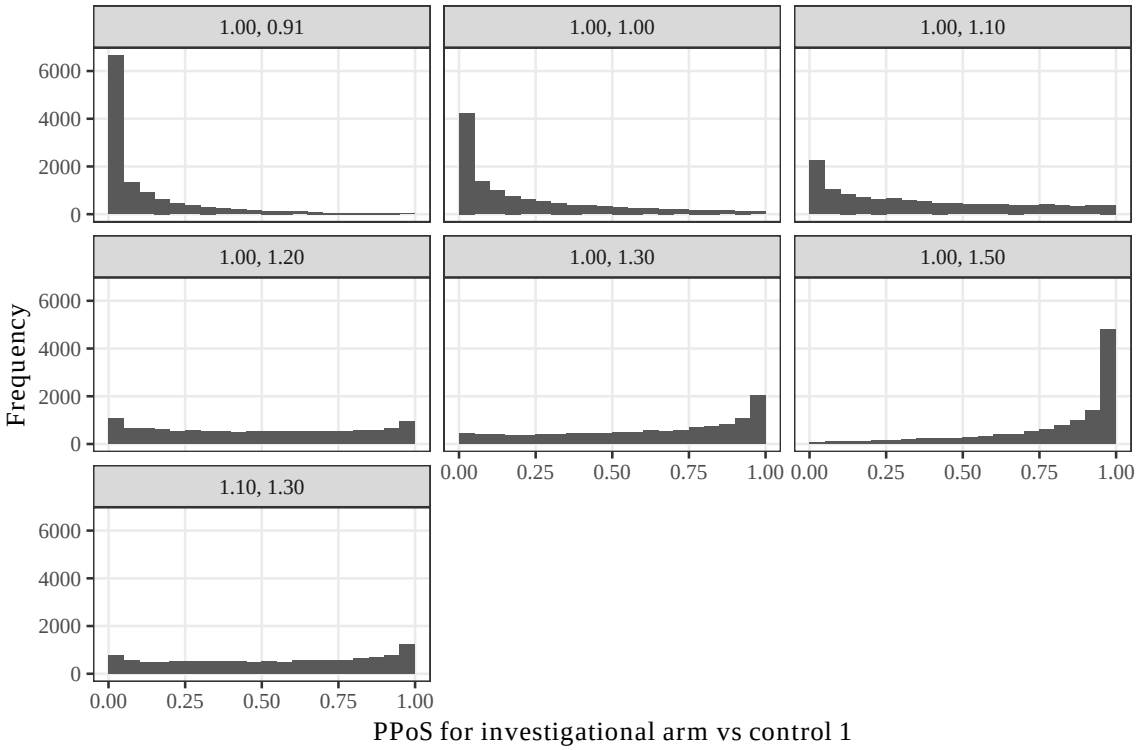

Figure 1: Distribution of PPoS for investigational arm vs control 1 at end of stage 2, n = 600.

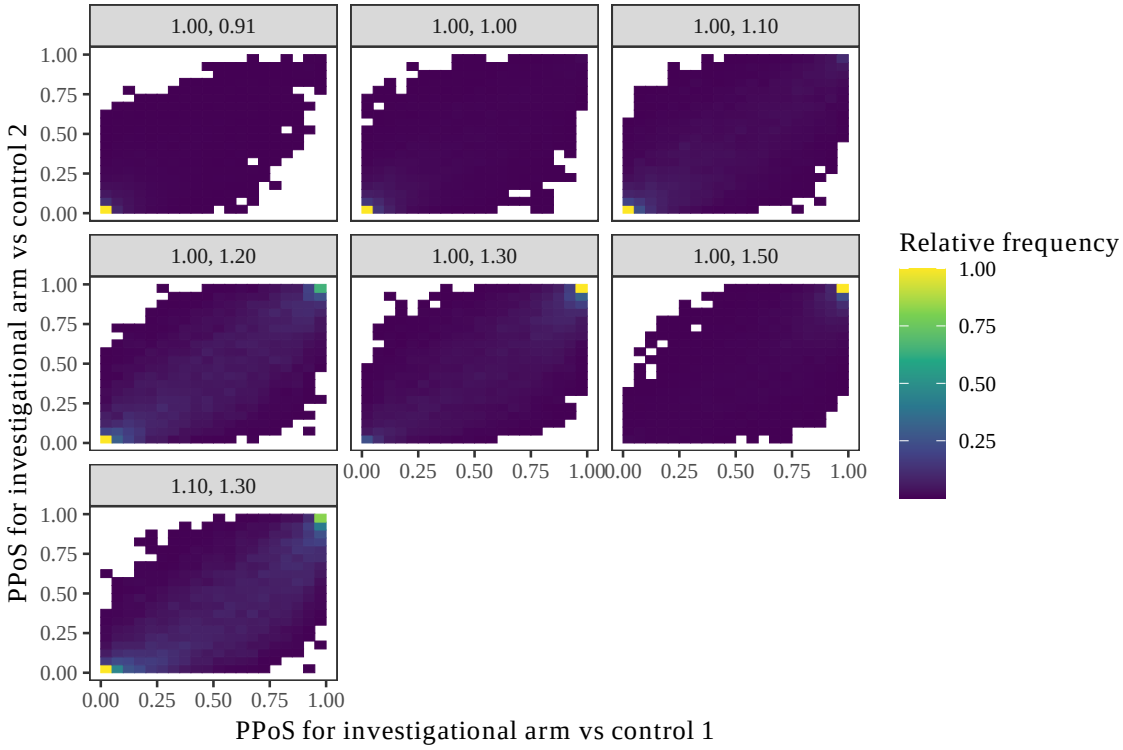

Figure 2: Distribution of PPoS for investigational arm vs control 1 and control 2 at end of stage 2, n = 600 across 10,000 trials.

Table 2: Probability of satisfying futility condition at end of stage 2, $\epsilon_{\text{eff}} = 0.95$

	ϵ_{fut}							
OR	0.01	0.02	0.025	0.05	0.1	0.15	0.2	0.25
1.00, 0.91	0.34	0.42	0.45	0.55	0.68	0.75	0.81	0.85
1.00, 1.00	0.19	0.27	0.31	0.41	0.53	0.59	0.66	0.72
1.00, 1.10	0.08	0.12	0.14	0.20	0.30	0.39	0.45	0.51
1.00, 1.20	0.04	0.07	0.07	0.12	0.20	0.26	0.31	0.37
1.00, 1.30	0.01	0.02	0.02	0.04	0.08	0.12	0.16	0.20
1.00, 1.50	0.00	0.01	0.01	0.01	0.03	0.04	0.05	0.07
1.10, 1.30	0.03	0.05	0.06	0.10	0.20	0.25	0.31	0.36

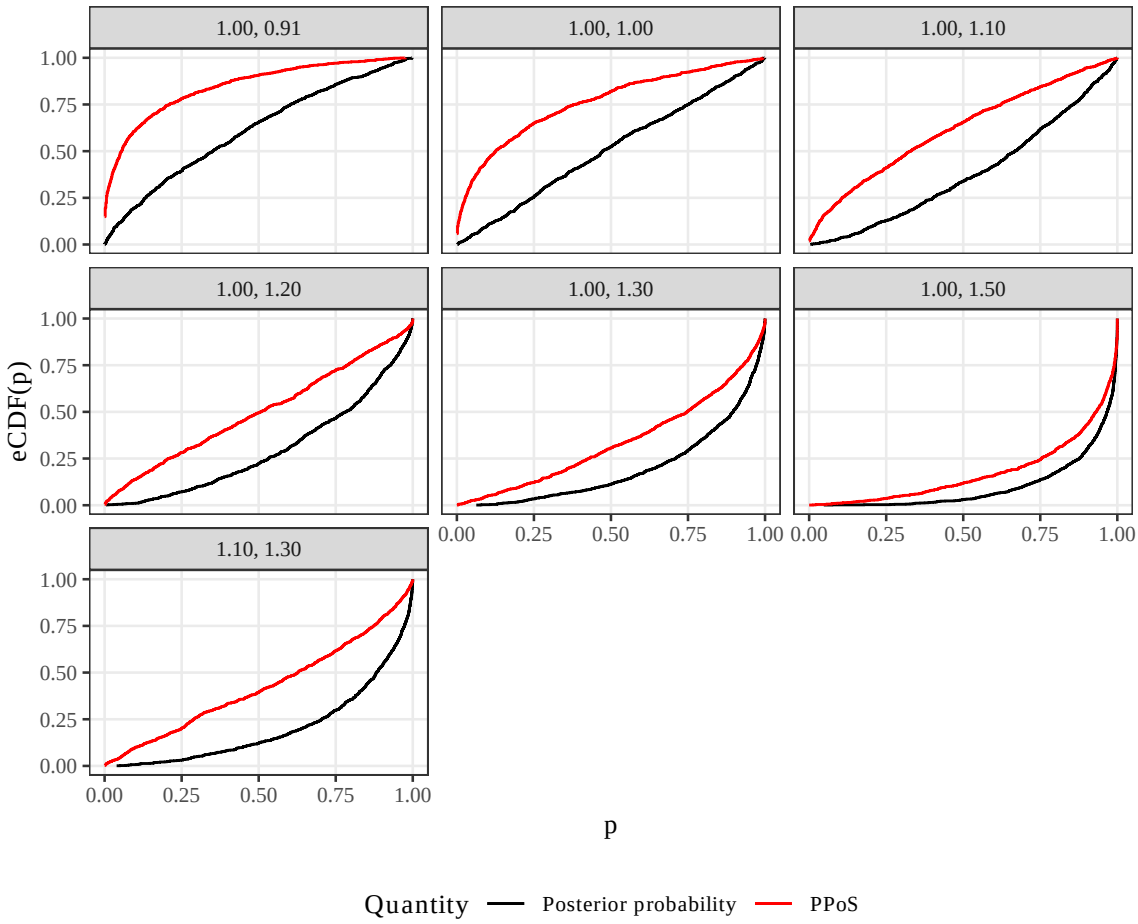

Figure 3: Distribution of posterior probabilities of effectiveness and predictive probabilities for effectiveness ($\epsilon_{\text{eff}} = 0.95$), for investigational arm versus control 1, after n = 600 enrolments.

3.2 Stage 3

3.2.1 Overview

Given the trial is only considered to have reached a conclusion for effectiveness if the investigational arm is superior to *both* control groups, the effectiveness threshold results in a probability of stopping for effectiveness as less than 0.05 under the null scenario. However, the probability of declaring the investigiational arm as effective relative to *one* of the arms at some point throughout the trials duration is much higher than that given the multiple analyses.

Table 3: Proportion of trials reaching given conclusion when no stopping for futility, $\epsilon_{\text{eff}} = 0.95$.

	Effective			No result		
OR (control 1, inv. arm)	K = 4	K = 5	K = 6	K = 4	K = 5	K = 6
1.00, 0.91	0.01	0.01	0.00	0.99	0.99	1.00
1.00, 1.00	0.03	0.04	0.04	0.97	0.96	0.96
1.00, 1.10	0.18	0.21	0.19	0.82	0.79	0.81
1.00, 1.20	0.41	0.46	0.52	0.59	0.54	0.48
1.00, 1.30	0.76	0.75	0.77	0.24	0.25	0.23
1.00, 1.50	0.98	0.98	0.98	0.02	0.01	0.01
1.10, 1.30	0.52	0.56	0.55	0.48	0.44	0.45

Table 4: Proportion of trials where effectiveness was declared (at any analysis) for each comparison (no futility stopping), $\epsilon_{\text{eff}} = 0.95$.

	Control 1			Control 2			Control 1 and 2 (sep)			Control 1 and 2 (joint)		
OR	K=4	K=5	K=6	K=4	K=5	K=6	K=4	K=5	K=6	K=4	K=5	K=6
1.00, 0.91	0.03	0.04	0.03	0.04	0.02	0.03	0.01	0.01	0.00	0.00	0.00	0.00
1.00, 1.00	0.10	0.13	0.14	0.10	0.11	0.12	0.03	0.04	0.04	0.02	0.02	0.02
1.00, 1.10	0.31	0.35	0.36	0.31	0.38	0.33	0.18	0.21	0.19	0.11	0.13	0.13
1.00, 1.20	0.58	0.61	0.67	0.57	0.60	0.65	0.41	0.46	0.52	0.29	0.34	0.36
1.00, 1.30	0.84	0.83	0.84	0.84	0.84	0.86	0.76	0.75	0.77	0.62	0.58	0.61
1.00, 1.50	0.99	0.99	0.99	0.99	0.99	0.99	0.98	0.98	0.98	0.90	0.90	0.87
1.10, 1.30	0.83	0.83	0.81	0.56	0.61	0.59	0.52	0.56	0.55	0.41	0.43	0.40

Table 5: Proportion of trials reaching given conclusion when no stopping for futility, $\epsilon_{\text{eff}} = 0.97$.

	Effective			No result		
OR (control 1, inv. arm)	K = 4	K = 5	K = 6	K = 4	K = 5	K = 6
1.00, 0.91	0.00	0.00	NA	1.00	1.00	1.00
1.00, 1.00	0.01	0.01	0.02	0.99	0.98	0.98
1.00, 1.10	0.08	0.09	0.09	0.92	0.91	0.91
1.00, 1.20	0.25	0.28	0.28	0.75	0.71	0.72
1.00, 1.30	0.59	0.56	0.60	0.41	0.44	0.40
1.00, 1.50	0.94	0.93	0.94	0.06	0.07	0.06
1.10, 1.30	0.33	0.36	0.33	0.67	0.64	0.67

Table 6: Proportion of trials where effectiveness was declared (at any analysis) for each comparison (no futility stopping), $\epsilon_{\text{eff}} = 0.98$.

	Control 1			Control 2			Control 1 and 2 (sep)			Control 1 and 2 (joint)		
OR	K=4	K=5	K=6	K=4	K=5	K=6	K=4	K=5	K=6	K=4	K=5	K=6
1.00, 0.91	0.01	0.01	0.01	0.02	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00
1.00, 1.00	0.06	0.07	0.07	0.04	0.04	0.06	0.01	0.01	0.02	0.01	0.01	0.01
1.00, 1.10	0.20	0.19	0.20	0.19	0.20	0.20	0.08	0.09	0.09	0.05	0.06	0.05
1.00, 1.20	0.41	0.43	0.42	0.42	0.44	0.44	0.25	0.28	0.28	0.18	0.22	0.19
1.00, 1.30	0.69	0.67	0.71	0.71	0.72	0.70	0.59	0.56	0.60	0.50	0.43	0.45
1.00, 1.50	0.96	0.96	0.96	0.97	0.95	0.97	0.94	0.93	0.94	0.84	0.81	0.80
1.10, 1.30	0.69	0.69	0.64	0.36	0.40	0.39	0.33	0.36	0.33	0.26	0.28	0.25

Table 7: Proportion of trials reaching given conclusion when futility threshold is 0.025.

	Effective			Futile			No result		
OR (control 1, inv. arm)	K = 4	K = 5	K = 6	K = 4	K = 5	K = 6	K = 4	K = 5	K = 6
1.00, 0.91	0.01	0.01	0.00	0.96	0.98	0.97	0.03	0.01	0.02
1.00, 1.00	0.03	0.04	0.04	0.84	0.89	0.87	0.12	0.07	0.09
1.00, 1.10	0.17	0.21	0.18	0.58	0.63	0.58	0.25	0.17	0.24
1.00, 1.20	0.40	0.45	0.50	0.32	0.37	0.31	0.29	0.18	0.19
1.00, 1.30	0.74	0.74	0.76	0.10	0.13	0.12	0.15	0.12	0.12
1.00, 1.50	0.97	0.98	0.98	0.01	0.01	0.01	0.02	0.01	0.01
1.10, 1.30	0.51	0.55	0.54	0.28	0.31	0.29	0.21	0.14	0.17

Table 8: Proportion of trials reaching given conclusion when $\epsilon_{\text{eff}} = 0.95$ and futility threshold is 0.05.

	Effective			Futile			No result		
OR (control 1, inv. arm)	K = 4	K = 5	K = 6	K = 4	K = 5	K = 6	K = 4	K = 5	K = 6
1.00, 0.91	0.01	0.01	0.00	0.97	0.99	0.99	0.02	0.01	0.01
1.00, 1.00	0.03	0.04	0.04	0.90	0.92	0.91	0.07	0.04	0.05
1.00, 1.10	0.16	0.19	0.17	0.70	0.71	0.71	0.14	0.10	0.12
1.00, 1.20	0.38	0.42	0.47	0.43	0.47	0.42	0.18	0.11	0.11
1.00, 1.30	0.71	0.71	0.72	0.19	0.20	0.20	0.10	0.08	0.08
1.00, 1.50	0.96	0.95	0.96	0.03	0.04	0.04	0.01	0.01	0.01
1.10, 1.30	0.46	0.51	0.50	0.43	0.41	0.43	0.11	0.08	0.07

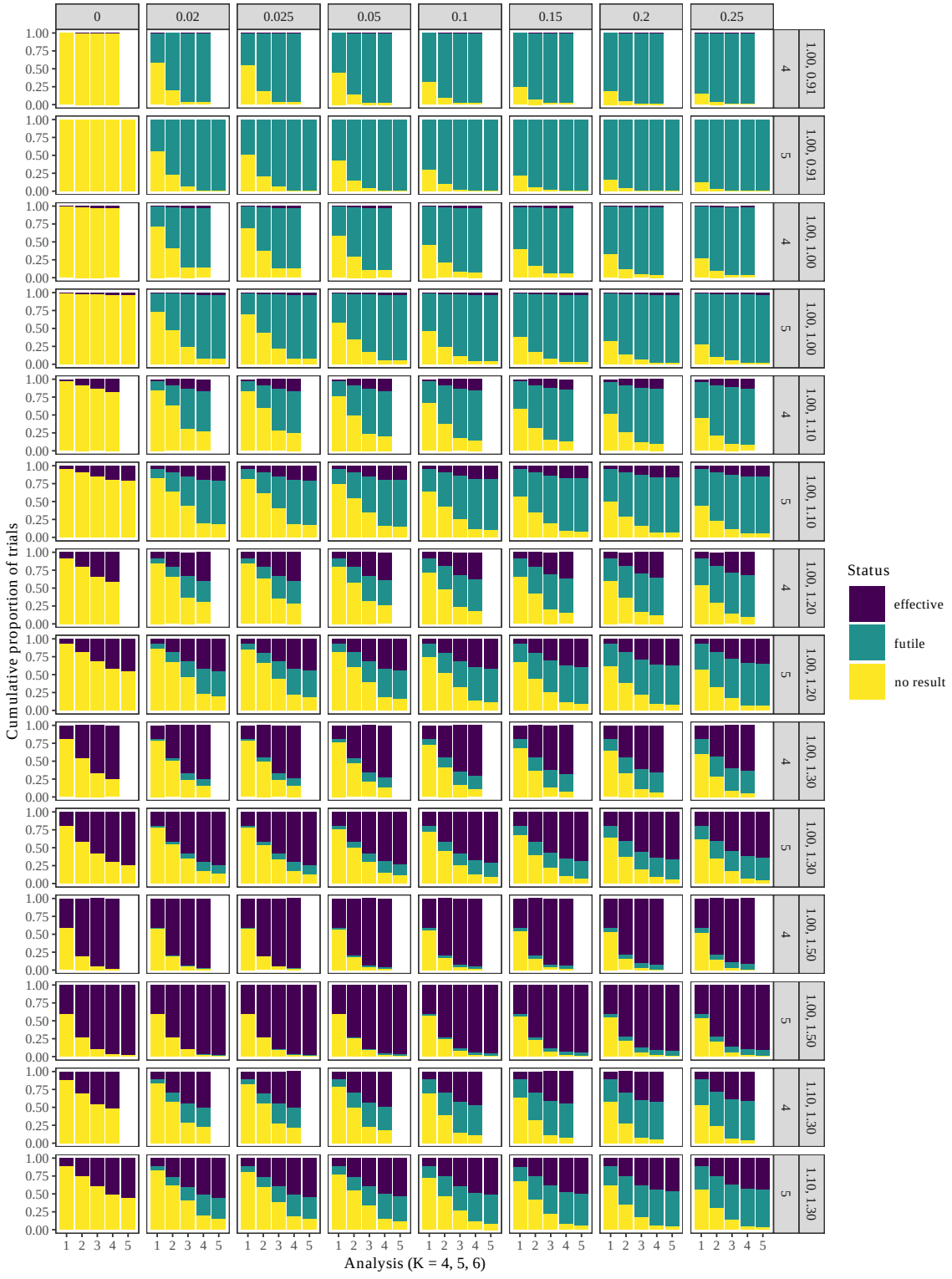

Figure 4: Cumulative proportion of trials meeting decision criteria by futility threshold (columns), number of interims (rows = 4, 5, 6), and odds ratios (rows), for effectiveness threshold of $\epsilon = 0.95$.

4 Appendix - Other Figures

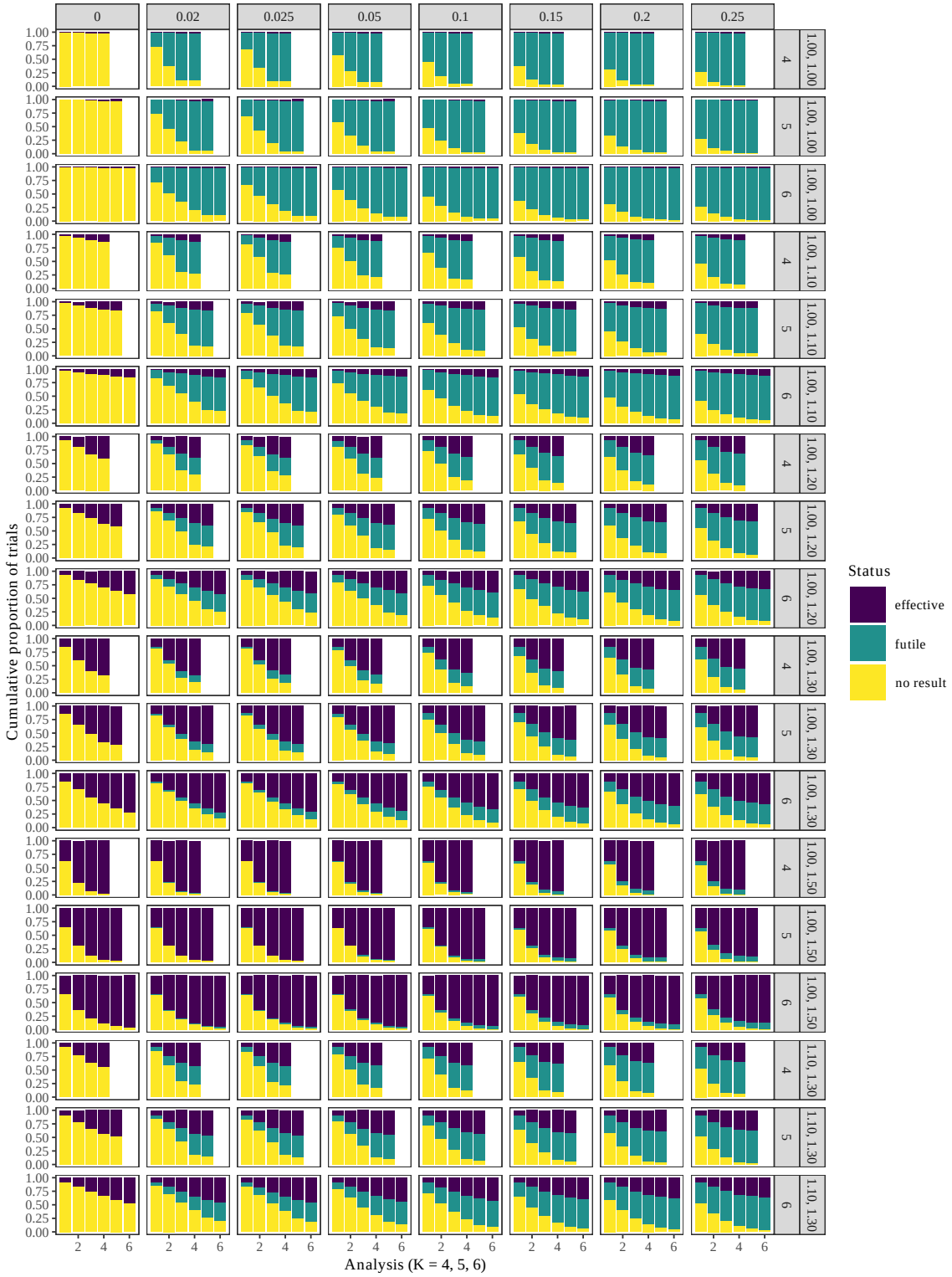

Figure 5: Cumulative proportion of trials meeting decision criteria by futility threshold (columns), number of interims (rows = 4, 5, 6), and odds ratios (rows), for effectiveness threshold of $\epsilon = 0.96$.

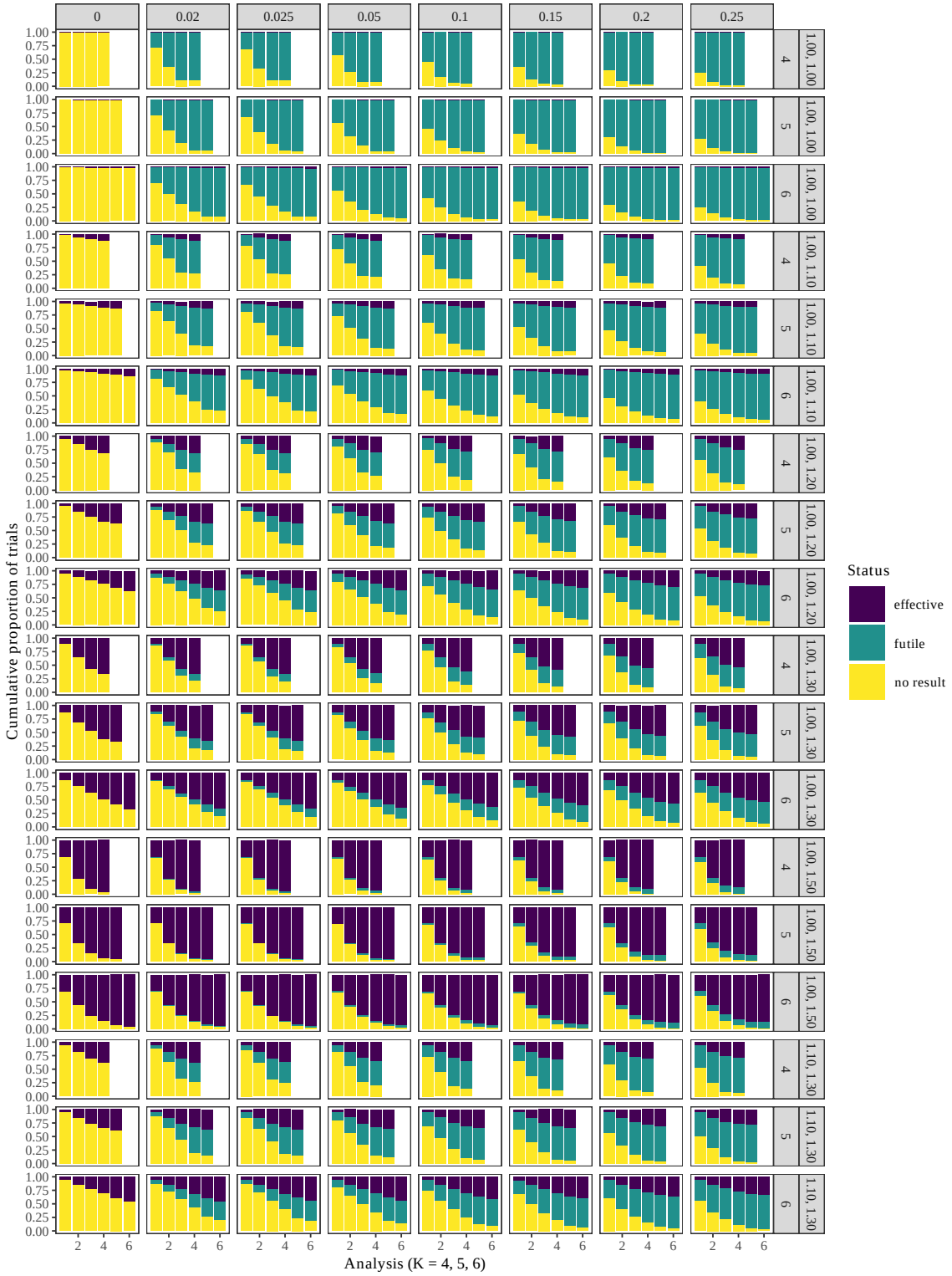

Figure 6: Cumulative proportion of trials meeting decision criteria by futility threshold (columns), number of interims (rows = 4, 5, 6), and odds ratios (rows), for effectiveness threshold of $\epsilon = 0.97$.

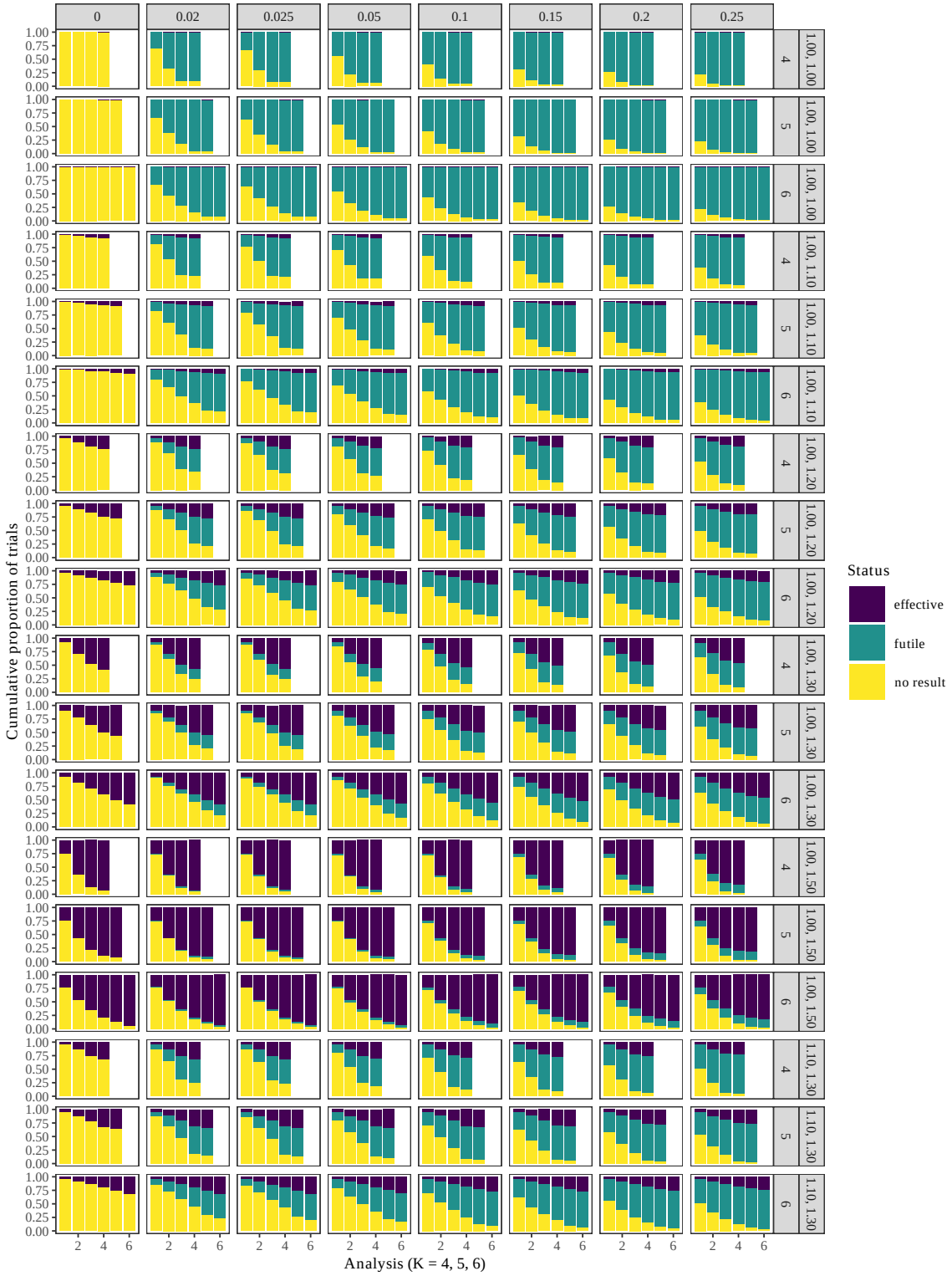

Figure 7: Cumulative proportion of trials meeting decision criteria by futility threshold (columns), number of interims (rows = 4, 5, 6), and odds ratios (rows), for effectiveness threshold of $\epsilon = 0.98$.

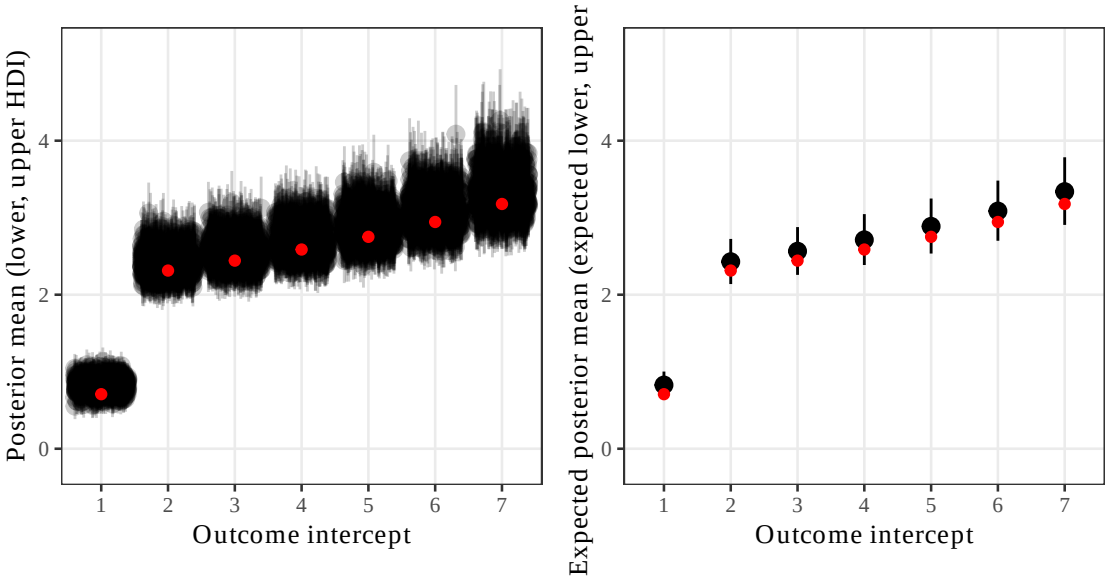

Figure 8: Estimates for model parameters, α.

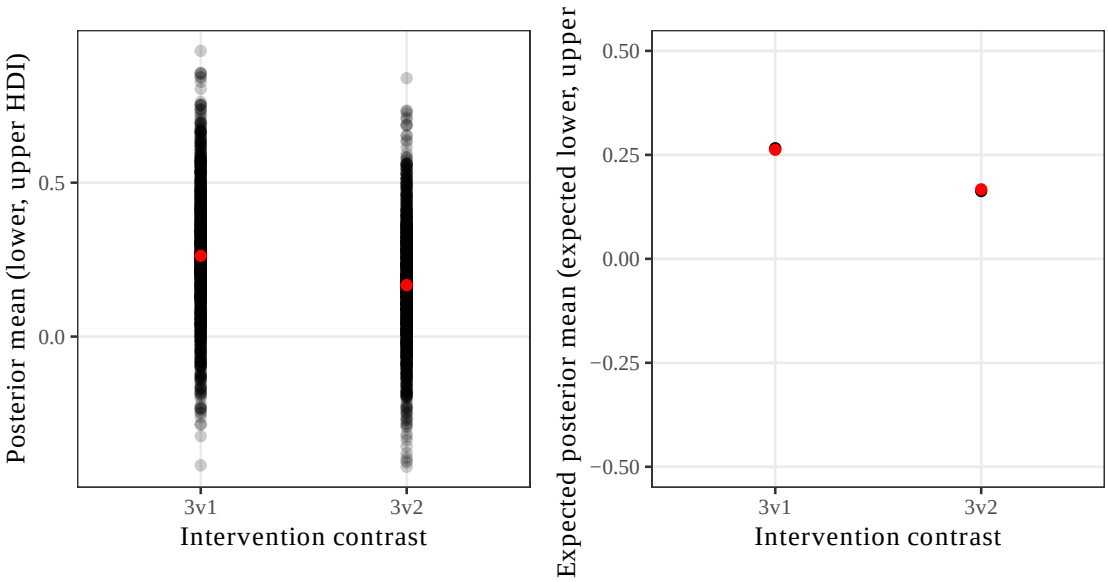

Figure 9: Estimates for model contrasts.

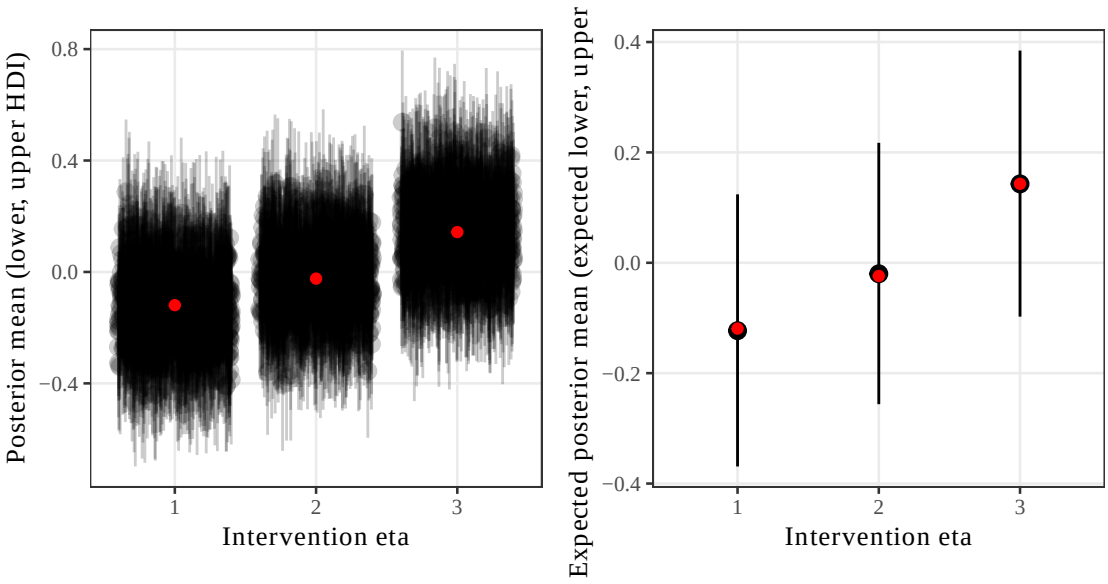

Figure 10: Estimates for model linear predictors, η.