Bayesian adaptive trial in RSV

Simulation Report

Pragmatic, observer-blinded, randomised controlled clinical trial of a dose of nirsevimab, versus standard care, from six months old to reduce medically attended LRIs among First Nations infants in the NT.

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Table of contents

Study title:	todo
Intervention:	Single IM dose of 50mg in 0.5mL nirsevimab (100mg for infants > 5kg), or standard care.
Outcome:	Any occurrence of medically attended RSV-LRI (RSV-LRI) in the 6 months after randomisation
Study design:	Bayesian adaptive trial with early stopping rules
Sponsor:	todo
Protocol:	todo
Registration:	todo
HREC:	todo
Study date of first consent:	todo
Principal coordinating investigators:	Bianca Middleton

Version history

Version	Date	Change	Reason
0.1	2025-06-27	First version	N/A

1 Introduction

This report documents the methods and results from the simulation study for the RSV trial. The report is an operational document that will be updated, as necessary, over the course of the study. It should be read in conjunction with the relevant version of the statistical analysis plan.

Included are details on the data generation assumptions, modelling, scenarios considered and the results.

The results are based on simulation ID `sim01-01` which had `5000` simulated trials per scenario.

2 Study overview

The study is a pragmatic, observer-blinded, randomised controlled clinical trial of a dose of nirsevimab, versus standard care, from six months old to reduce medically attended LRIs among First Nations infants in the NT.

3 Data generation

Data is generated based on subject matter expertise and while necessarily a simplification of reality, it aims to capture the aspects that are essential to the design. The distributional assumptions of each data component follows.

We simulate design variables for region, locality and treatment assignment.

Regional allocation is based on a multinomial distribution with two levels with the probability of residing in Alice set to 0.6. Conditional on regional allocation, locality (urban or remote) is simulated based on a multinomial distribution with two levels. The probability of remote status given residence in Alice is set to 0.45 and the probability of remote status given residence in Darwin is set to 0.65. These values were selected arbitrarily.

Within each region/locality combination intervention vs soc is allocated 1:1.

Occurrence of medically attended RSV-LRI in the 6 months after randomisation is simulated as a bernoulli random variable for each participant with probability computed from a linear risk model. While it is possible that participants will have one or more occurrences of medically attended RSV-LRI in the 6 months after randomisation, the outcome variable simply reflects any occurrence versus none.

No interactions are considered in any aspect of the data generating process. For example, in practice, there may be different distributions for the probability of RSV-LRI based on locality status within each region, i.e. the shift in the probability of RSV-LRI associated with remote vs urban may be different for Alice and Darwin, but this has been ignored for now and no interactions are included in the data generation nor model.

The participant characteristics and their outcome variables are generated at the start of each interim analysis so that the data accrues sequentially for the analyses. As the trial progresses, decisions may be made which lead to early stopping of treatment arms. Given the study has only two arms, early stopping of an arm would lead to the termination of the trial.

To speed up parameter estimation, we aggregate the number of successes and number of trials by covariate group and this gives the analogous binomial random variable representation.

4 Modelling

While the data are simulated using a linear risk model, the simulation model is specified as a multivariable logistic regression model from which we subsequently transform the parameters back to the risk scale via the inverse link and a g-computation step. The model form is:

$$y \sim \text{Binomial}(\pi, n)$$
$$\text{logit}(\pi) = \alpha + \beta_{[\text{reg}]} + \gamma_{[\text{loc}]} + \delta_{[\text{trt}]}$$

where y is a binomial variable for the number of events out of n trials for a distinct covariate pattern occurring with probability π calculated from the linear predictor as follows:

- α reference level log-odds of a successful outcome
- β_j effect of region (alice, darwin)
- γ_k effect of locality (urban, remote)
- δ_l effect of treatment (soc, intervention)

No interactions are considered.

The model uses priors:

- $\alpha \sim \text{Logistic}(-1.8, 0.5)$
- $\beta_j \sim \text{Normal}(0, 1)$
- $\gamma_k \sim \text{Normal}(0, 1)$
- $\delta_l \sim \text{Normal}(0, 1)$

all of which are on the log-odds or log-odds ratio scale.

Transformed to the probability scale, the intercept prior is shown in Figure 4.1 and reflects the prior probability of medically attended RSV-LRI in the 6 months after randomisation in the reference covariate groups. The prior has 90% of the density between 0.04 and 0.42.

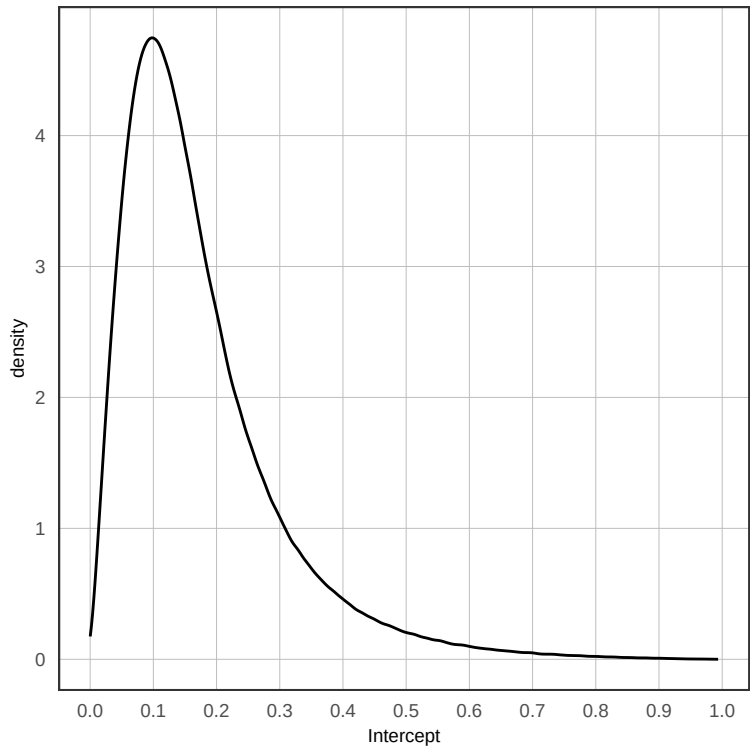

Figure 4.1: Prior on intercept

In addition to the target adaptive design, results are provided under a fixed design that adopts a beta-binomial model, independent uniform priors on the proportion of failures in each group and a single analysis at the maximum sample size. The reference design uses the same rules, decision thresholds and evidential values as the adaptive design.

5 Decision procedures

The decision processes are based on the data accumulated up to the current time and are thus interpreted with reference to the current available evidence. The approach is simple and offers a transparent interpretation, but it ignores the possibility that subsequent data may shift the posterior.

If the treatment strategy is successful, then the probability of medically attended RSV-LRI in the 6 months after randomisation will be lower in the treatment arm than it will under standard of care and this would lead to negative risk difference values.

In the current design, we implement superiority and futility rules for early stopping. Superiority is framed as a high probability that the risk difference is negative, whereas futility is framed as a low probability that the risk difference is below some small negative reference value. If a decision threshold is met, then we will stop recruitment into the relevant arm. This approach is adopted for each interim and the final analysis.

The decisions are constructed as a static rule of the form $\Pr(RD < \epsilon|y) > \zeta$ where ϵ and ζ are pre-specified values corresponding to a clinical meaningful difference and an evidentiary requirement in terms of probability. The decision thresholds and evidential thresholds are shown in Table 5.1.

Table 5.1: Decision threshold parameters

Decision type	Reference value (ϵ)	Threshold (ζ)	Formula
Superiority	0.00	0.975	$\Pr(RD < \epsilon) > \zeta$
Inferiority	-0.02	0.200	$\Pr(RD < \epsilon) < \zeta$

6 Scenarios

Each scenario adopts a maximum sample size of 1000 with interim analyses run after 400 enrolments have reached their primary endpoint and every 200 thereafter. Given the use of a linear risk model in the data generation process, the treatment effects were specified as risk differences.

Table 6.1: Simulation scenarios

ID	Scenario	Effect size (risk difference)
1	Null scenario	0.000
2	Treatment reduces chance of RSV-LRI	-0.025
3	Treatment reduces chance of RSV-LRI	-0.035
4	Treatment reduces chance of RSV-LRI	-0.045
5	Treatment increases chance of RSV-LRI	0.010

Table 6.1 shows the scenarios evaluated within these simulations and Figure 6.1 provides a visual summary of the probability of medically attended RSV-LRI in the 6 months after randomisation in each strata for the simulations. All scenarios used fixed covariate distributions and effects over the duration of the study. Additionally, all simulations used the same reference values and decision thresholds.

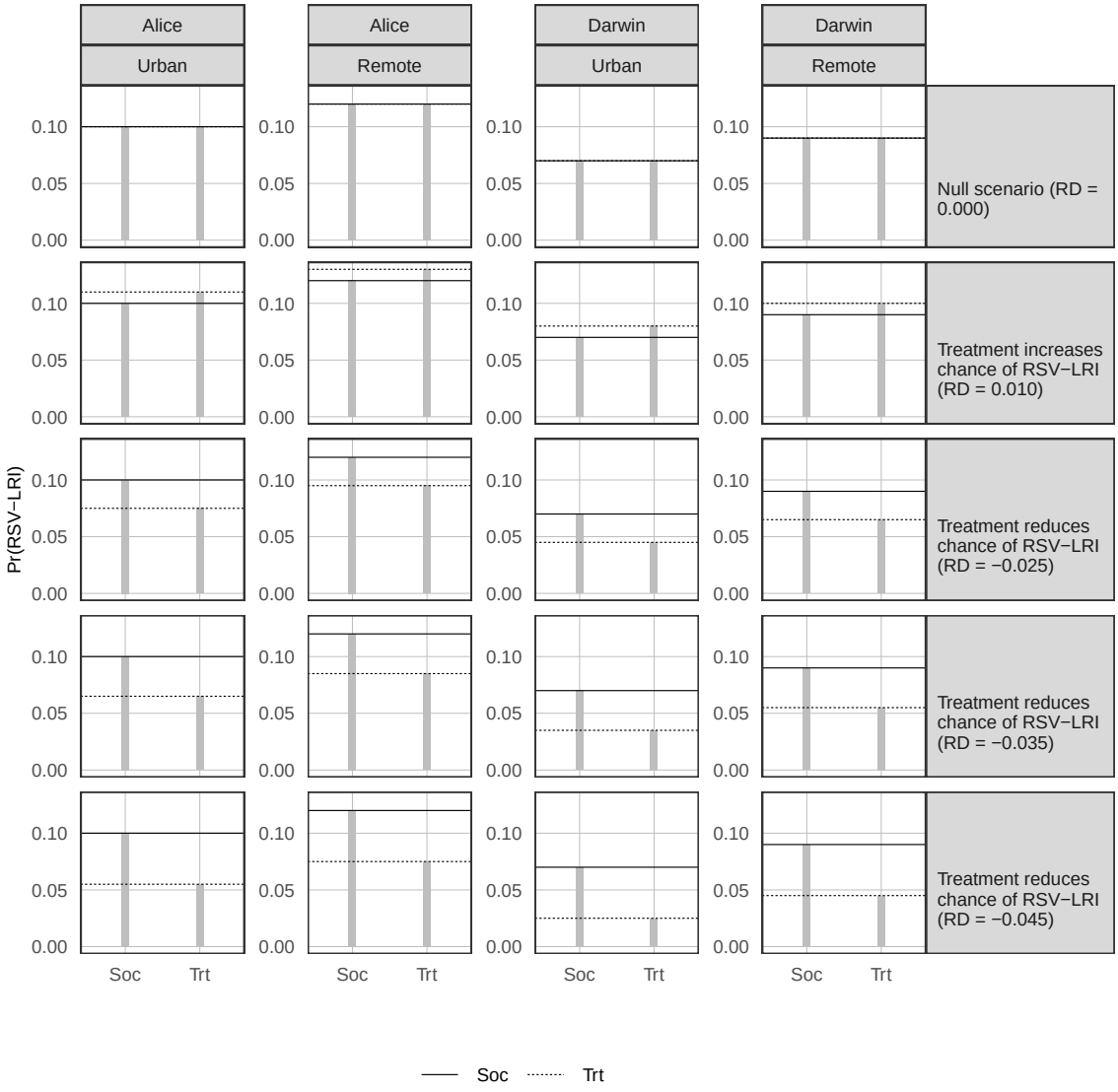

Figure 6.1: Underlying (true) probability of RSV-LRI by strata

7 Results

7.1 Probability of triggering decisions

Table 7.1 provides the cumulative probability of superiority by scenario with the probability of declaring futility in parentheses. The final column in the table provides the probability of superiority (futility) under a fixed design with a single analysis at the maximum sample size. Figure 7.1 gives a visual representation of the same data.

Table 7.1: Cumulative probability of superiority (futility) at each interim

	Enrolments having reached primary endpoint				
Effect size (risk diff)	400	600	800	1000	Fixed design
Null scenario					
0	0.027 (0.417)	0.045 (0.546)	0.053 (0.627)	0.062 (0.694)	0.023 (0.602)
Treatment reduces chance of RSV-LRI					
-0.025	0.162 (0.136)	0.259 (0.184)	0.347 (0.217)	0.417 (0.24)	0.303 (0.125)
-0.035	0.277 (0.061)	0.432 (0.082)	0.548 (0.093)	0.643 (0.1)	0.56 (0.039)
-0.045	0.438 (0.025)	0.644 (0.034)	0.777 (0.038)	0.857 (0.039)	0.799 (0.01)
Treatment increases chance of RSV-LRI					
0.01	0.013 (0.541)	0.02 (0.689)	0.023 (0.777)	0.026 (0.839)	0.007 (0.771)

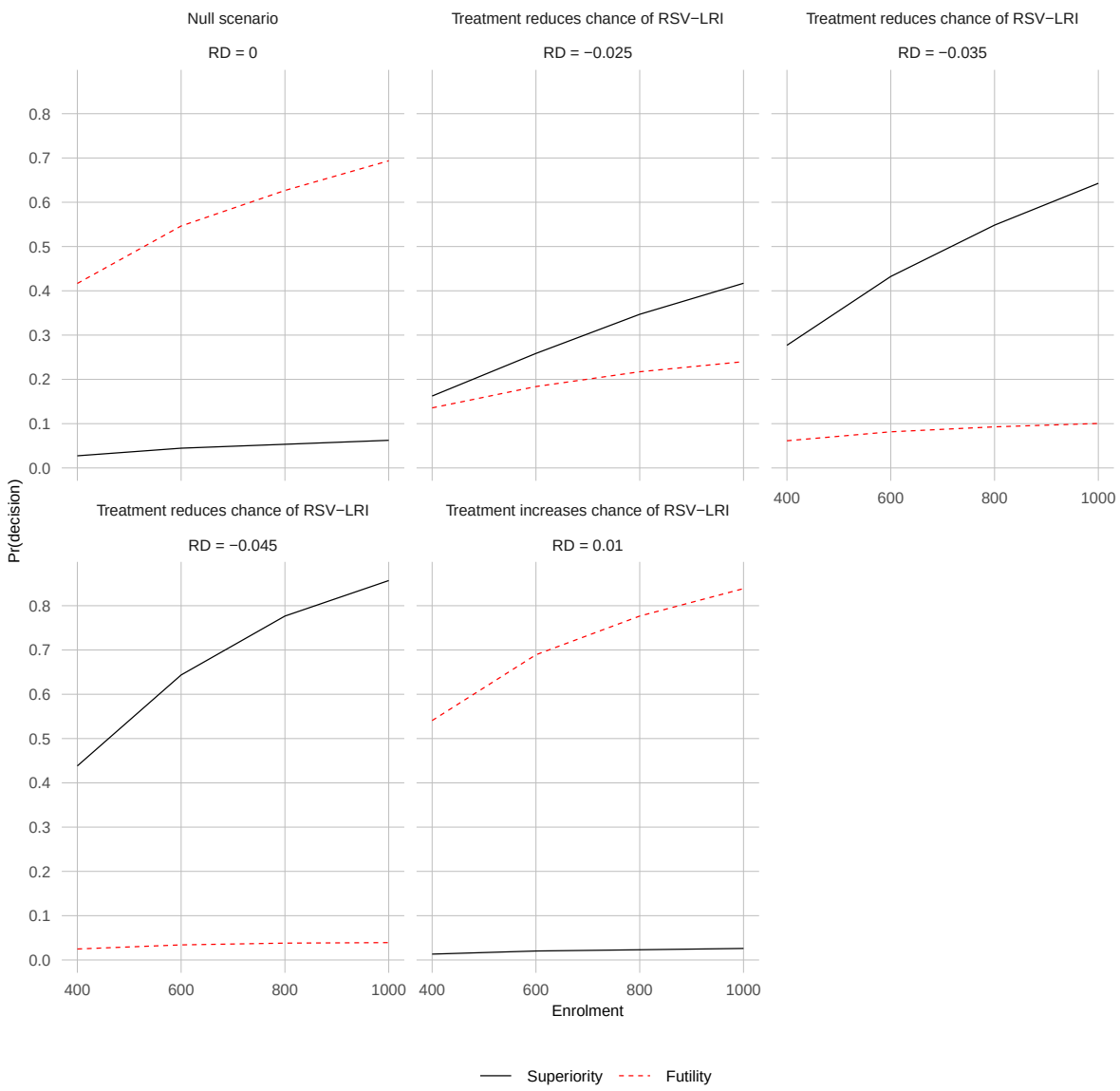

Figure 7.1: Cumulative probability of superiority (futility) at each interim

7.2 Sample size

7.2.1 Randomised comparisons

Table 7.2 shows the expected number of participants on each treatment for each decision type by scenarios.

Table 7.2: Expected number of participants by treatment group for each scenario

Decision	Proportion of trials	SOC	Trt
Null scenario (RD = 0.000)			
superiority	0.06	301	297
futility	0.69	273	269
no decision	0.24	504	496
Treatment reduces chance of RSV-LRI (RD = -0.025)			
superiority	0.42	318	314
futility	0.24	278	275
no decision	0.34	504	496
Treatment reduces chance of RSV-LRI (RD = -0.035)			
superiority	0.64	306	302
futility	0.1	267	264
no decision	0.26	504	496
Treatment reduces chance of RSV-LRI (RD = -0.045)			
superiority	0.86	285	281
futility	0.04	255	252
no decision	0.1	504	496
Treatment increases chance of RSV-LRI (RD = 0.010)			
superiority	0.03	285	281
futility	0.84	262	259
no decision	0.14	504	496

7.3 Parameter estimation

Table 7.3 and Figure 7.2 show the expected value of the posterior means (and the 2.5 and 97.5 percentiles for the distribution of posterior means) for the treatment effects by scenario.

Table 7.3: Parameter estimation - risk difference (expectation of posterior means and 95% interval)

Risk difference (expectation of posterior means and 95 pct interval)				
400	600	800	1000	Fixed design
Null scenario (RD = 0.000)				
-0.003 (-0.053, 0.045)	0 (-0.053, 0.045)	0.001 (-0.054, 0.045)	0.002 (-0.054, 0.045)	0 (-0.035, 0.036)
Treatment reduces chance of RSV-LRI (RD = -0.025)				
-0.025 (-0.072, 0.021)	-0.025 (-0.072, 0.022)	-0.026 (-0.072, 0.022)	-0.026 (-0.072, 0.022)	-0.025 (-0.058, 0.008)
Treatment reduces chance of RSV-LRI (RD = -0.035)				
-0.034 (-0.076, 0.009)	-0.035 (-0.076, 0.009)	-0.036 (-0.076, 0.009)	-0.037 (-0.076, 0.009)	-0.035 (-0.067, -0.002)
Treatment reduces chance of RSV-LRI (RD = -0.045)				
-0.042 (-0.085, -0.001)	-0.045 (-0.085, 0)	-0.046 (-0.085, 0)	-0.047 (-0.085, 0)	-0.045 (-0.077, -0.013)
Treatment increases chance of RSV-LRI (RD = 0.010)				
0.006 (-0.045, 0.055)	0.009 (-0.039, 0.055)	0.011 (-0.036, 0.055)	0.012 (-0.035, 0.055)	0.01 (-0.027, 0.045)

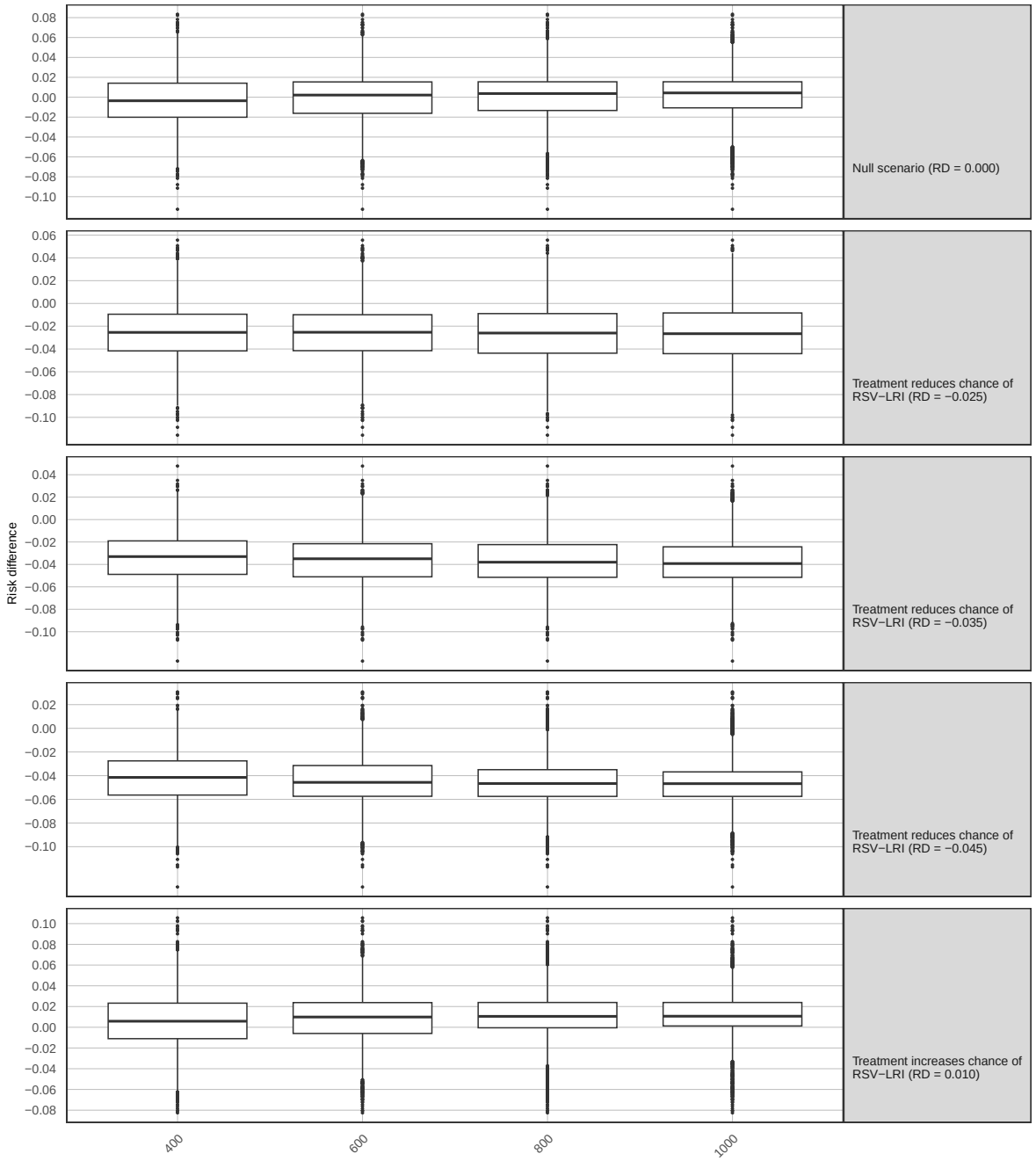

Figure 7.2: Distribution of posterior means for risk difference treatment effects by interim and simulation scenario

7.4 Observed proportion with treatment success

Table 7.4 shows the observed proportion with treatment success by scenario, strata and treatment arm.

Table 7.4: Observed proportion of failures and differences by scenario, treatment and strata

		Proportion with treatment failure		Difference in proportions
Region	Locality	SoC	Treatment	RD
Null scenario (RD = 0.000)				
Alice	Urban	0.101	0.100	-0.001
Alice	Remote	0.120	0.120	0.000
Darwin	Urban	0.070	0.070	0.000
Darwin	Remote	0.090	0.090	0.000
Treatment reduces chance of RSV-LRI (RD = -0.025)				
Alice	Urban	0.100	0.075	-0.025
Alice	Remote	0.119	0.095	-0.025
Darwin	Urban	0.071	0.045	-0.026
Darwin	Remote	0.091	0.065	-0.026
Treatment reduces chance of RSV-LRI (RD = -0.035)				
Alice	Urban	0.101	0.065	-0.036
Alice	Remote	0.120	0.086	-0.035
Darwin	Urban	0.070	0.035	-0.034
Darwin	Remote	0.090	0.055	-0.035
Treatment reduces chance of RSV-LRI (RD = -0.045)				
Alice	Urban	0.100	0.055	-0.045
Alice	Remote	0.120	0.076	-0.044
Darwin	Urban	0.071	0.025	-0.046
Darwin	Remote	0.090	0.045	-0.045
Treatment increases chance of RSV-LRI (RD = 0.010)				
Alice	Urban	0.100	0.110	0.010
Alice	Remote	0.120	0.130	0.009
Darwin	Urban	0.070	0.079	0.009
Darwin	Remote	0.090	0.100	0.011

Repository status

```
## Local:    main /Users/mark/Documents/project/penta-pipeline-rsv/src/rsv-sim
## Remote:   main @ origin (https://github.com/maj-biostat/rsv-sim.git)
## Head:     [d14b3c4] 2025-07-23: Minor edit
##
## Branches:          1
## Tags:              0
## Commits:          17
## Contributors:      2
## Stashes:           0
## Ignored files:     6
## Untracked files: 10
## Unstaged files:    1
## Staged files:      0
##
## Latest commits:
## [d14b3c4] 2025-07-23: Minor edit
## [580b5e9] 2025-07-22: Update sims to 5000 iterations
## [a0c60d0] 2025-07-22: Add fixed design. Fix stan model variable naming
## [30d1969] 2025-07-22: revise priors
## [70fc8a4] 2025-07-22: todo
```

7.5 References