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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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 simulation approach and results for the operating characteristics for the RSV study. 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.

We provide the data generation assumptions, modelling approaches, scenarios and results that were used to explore the design.

These results are based on simulation `sim01-01` with `10000` simulated trials run per scenario.

2 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. The above values were arbitrary.

Within each region/locality combination we allocated treatment status to intervention vs soc with a 1:1 ratio.

Occurrence of medically attended RSV-LRI in the 6 months after randomisation is simulated as a bernoulli random variable with probability formed 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, we adopt the binary perspective of any occurrence versus none.

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.

3 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)

In practice, the log-odds of RSV-LRI may be differential for locality status within each region, but this has been ignored for now and no interactions are included.

4 Decision procedures

Decision procedures, including thresholds and decision probabilities, follow those that are documented in the SAP.

At each interim, we assess the posterior and if a decision threshold is met then we will stop recruitment for superiority of futility. 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. This approach is based on the current data and are interpreted with reference to the current available evidence. This approach is simple and offers a transparent interpretation but it ignores the possibility that accumulating data may shift the posterior.

5 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.

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.

Table 5.1: 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

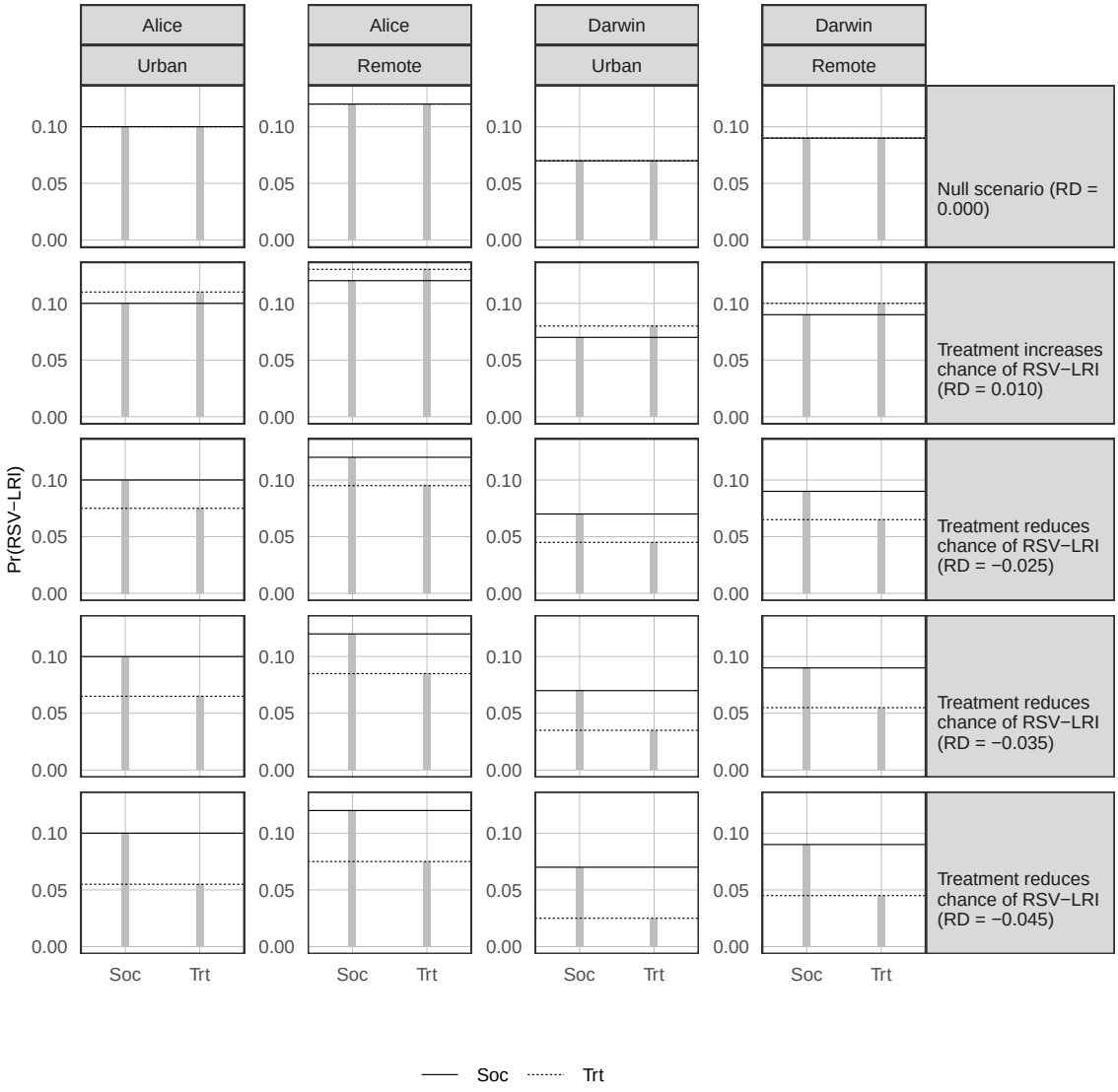

Figure 5.1: Underlying (true) probability of RSV-LRI by strata

6 Results

6.1 Probability of triggering decisions

Table 6.1 provides the cumulative probability of superiority by scenario with the probability of declaring futility in parentheses. Figure 6.1 gives a visual representation of the same data.

Table 6.1: Cumulative probability of decision at each interim

	Enrolments having reached primary endpoint			
Effect size (risk diff)	400	600	800	1000
Null scenario				
0	0.022 (0.419)	0.038 (0.554)	0.05 (0.64)	0.059 (0.699)
Treatment reduces chance of RSV-LRI				
-0.025	0.147 (0.137)	0.244 (0.189)	0.331 (0.216)	0.402 (0.24)
-0.035	0.27 (0.066)	0.432 (0.088)	0.56 (0.101)	0.654 (0.108)
-0.045	0.445 (0.026)	0.647 (0.035)	0.78 (0.038)	0.856 (0.04)
Treatment increases chance of RSV-LRI				
0.01	0.01 (0.561)	0.015 (0.708)	0.018 (0.798)	0.02 (0.852)

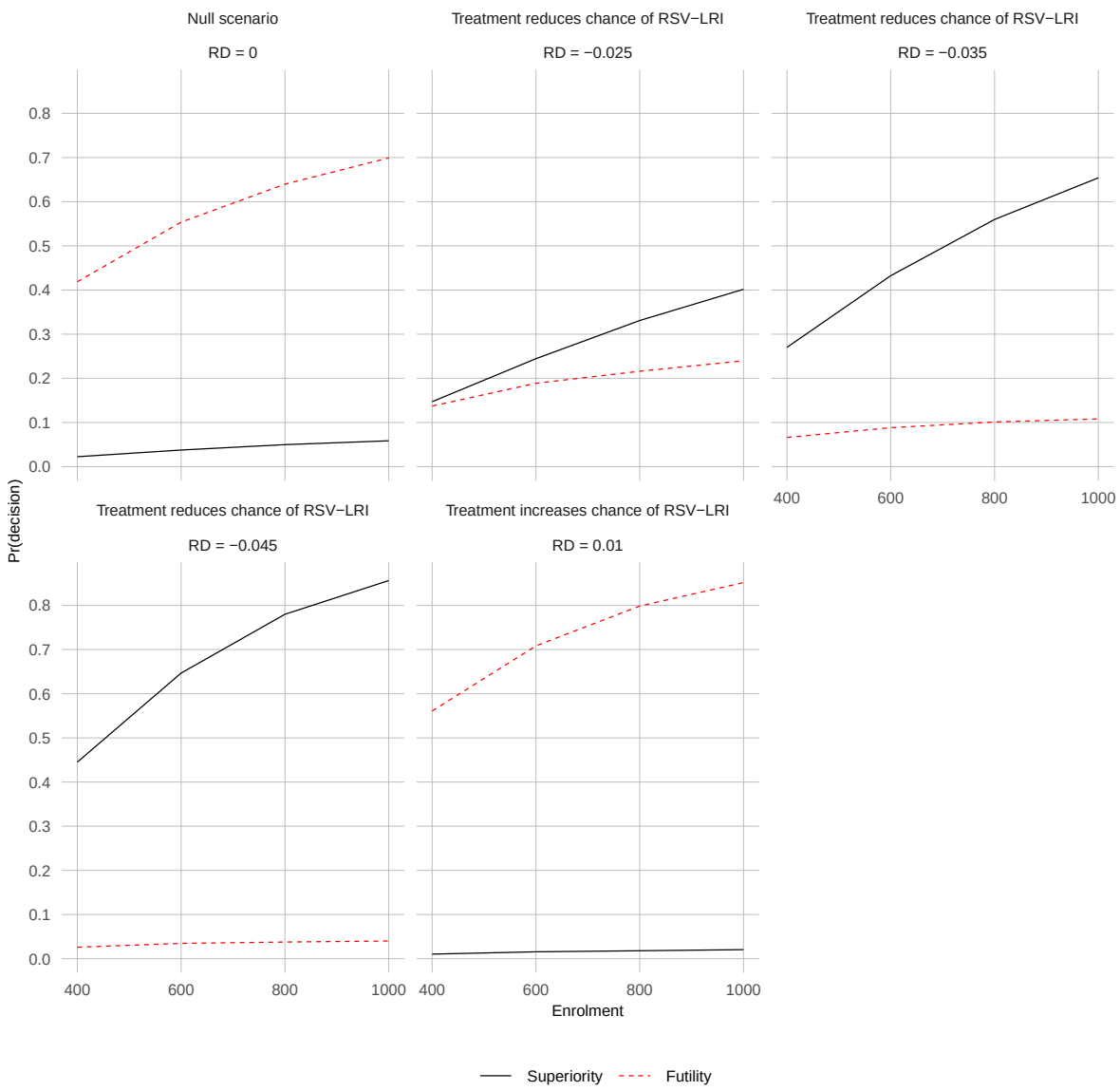

Figure 6.1: Cumulative probability of decision at each interim (enrolment by interim)

6.2 Sample size

6.2.1 Randomised comparisons

Table 6.2 shows the expected number of participants on each treatment for each decision type by scenarios.

Table 6.2: Expected number of participants by treatment group for each scenario

Decision	Proportion of trials	SOC	Trt
Null scenario (RD = 0.000)			
superiority	0.06	314	310
futility	0.7	271	268
no decision	0.24	504	496
Treatment reduces chance of RSV-LRI (RD = -0.025)			
superiority	0.4	322	318
futility	0.24	276	272
no decision	0.36	504	496
Treatment reduces chance of RSV-LRI (RD = -0.035)			
superiority	0.65	309	305
futility	0.11	265	262
no decision	0.24	504	496
Treatment reduces chance of RSV-LRI (RD = -0.045)			
superiority	0.86	283	280
futility	0.04	256	253
no decision	0.1	504	496
Treatment increases chance of RSV-LRI (RD = 0.010)			
superiority	0.02	288	284
futility	0.85	259	256
no decision	0.13	504	496

6.3 Parameter estimation

Table 6.3 and Figure 6.2 show the expected value of the posterior means (and 95% interval) for the treatment effects by scenario.

Table 6.3: 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
Null scenario (RD = 0.000)			
-0.003 (-0.051, 0.046)	0 (-0.051, 0.046)	0.002 (-0.051, 0.046)	0.003 (-0.051, 0.046)
Treatment reduces chance of RSV-LRI (RD = -0.025)			
-0.024 (-0.068, 0.021)	-0.024 (-0.069, 0.021)	-0.025 (-0.069, 0.021)	-0.025 (-0.069, 0.021)
Treatment reduces chance of RSV-LRI (RD = -0.035)			
-0.033 (-0.075, 0.01)	-0.035 (-0.075, 0.011)	-0.036 (-0.075, 0.011)	-0.037 (-0.075, 0.011)
Treatment reduces chance of RSV-LRI (RD = -0.045)			
-0.041 (-0.083, -0.001)	-0.044 (-0.083, 0.001)	-0.045 (-0.083, 0.001)	-0.046 (-0.083, 0.001)
Treatment increases chance of RSV-LRI (RD = 0.010)			
0.007 (-0.042, 0.058)	0.01 (-0.036, 0.058)	0.012 (-0.032, 0.058)	0.013 (-0.029, 0.058)

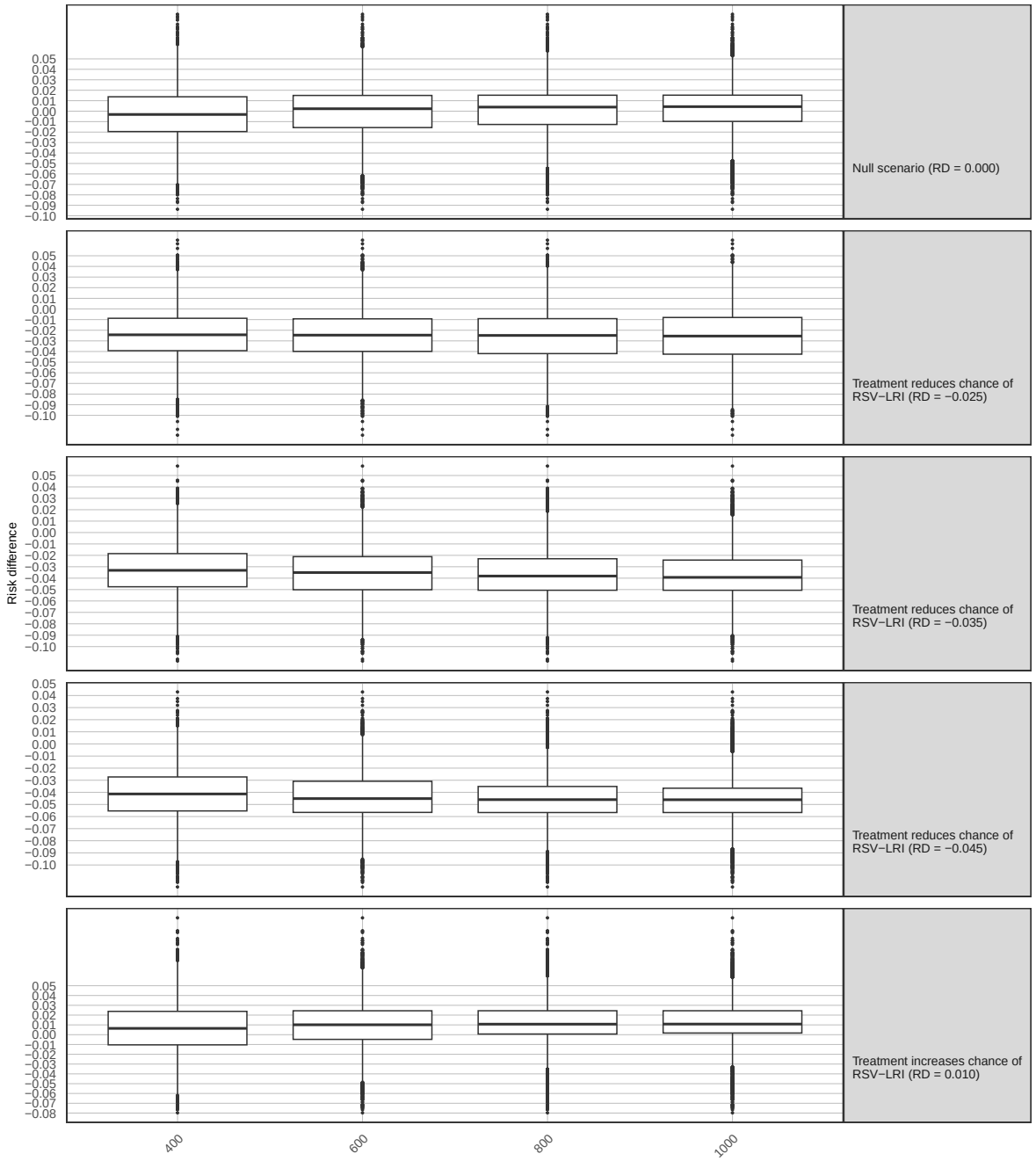

Figure 6.2: Distribution of posterior means for risk difference treatment effects by interim and simulation scenario

6.4 Observed proportion with treatment success

Figure 6.3 shows the observed proportion with treatment success by scenario, strata and treatment arm with the true underlying proportions shown with crosses (also see Figure 5.1).

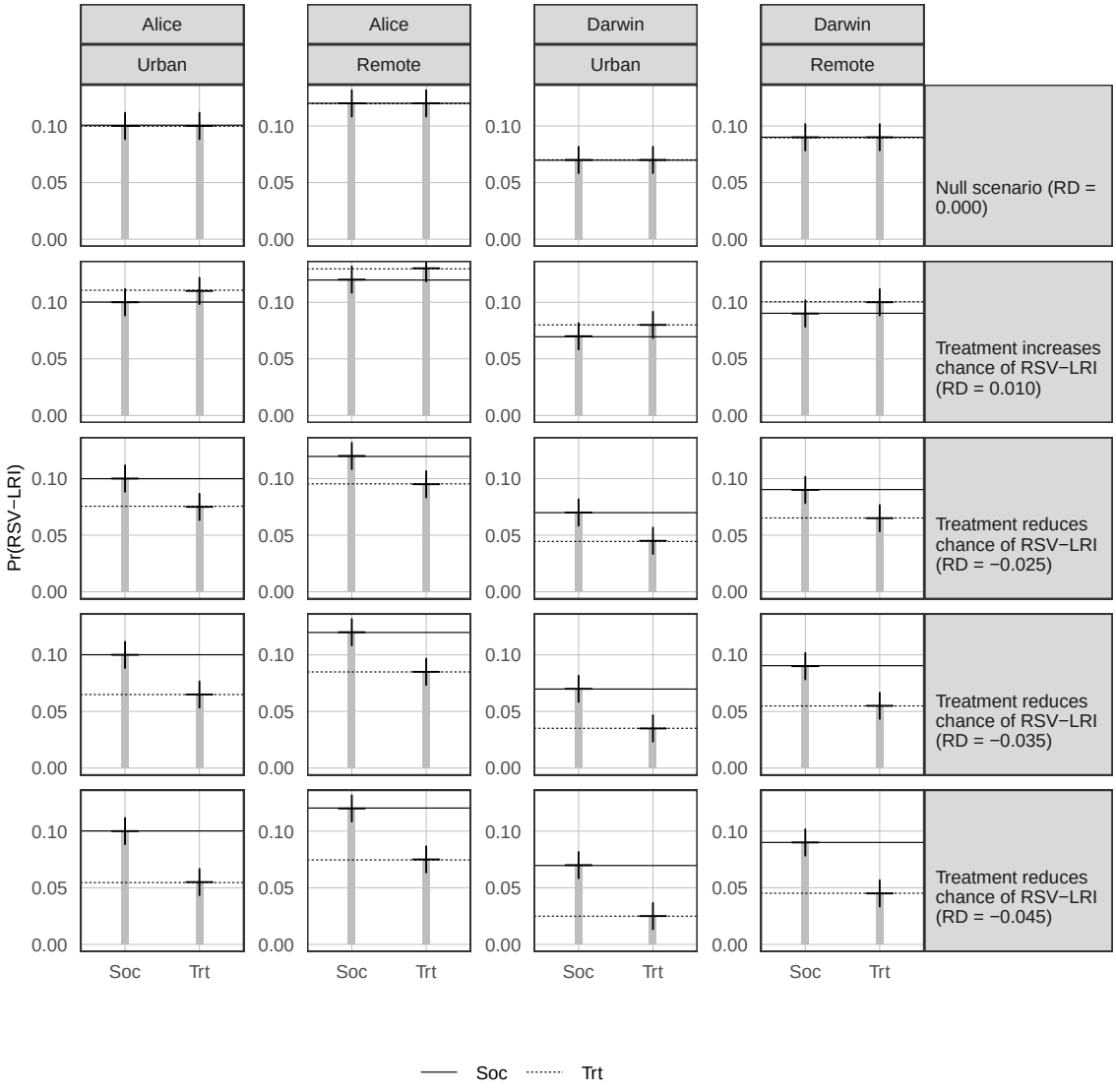

Figure 6.3: Observed proportion with treatment success

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:     [f16b867] 2025-06-27: Minor edits
##
## Branches:        1
## Tags:            0
## Commits:         8
## Contributors:    2
## Stashes:         0
## Ignored files:   7
## Untracked files: 9
## Unstaged files:  0
## Staged files:    0
##
## Latest commits:
## [f16b867] 2025-06-27: Minor edits
## [5f64ec2] 2025-06-27: Narrative edits based on latest results
## [da5ca2f] 2025-06-27: Add parameterised runsim step
## [0609c67] 2025-06-27: Add notes and install template
## [0717602] 2025-06-26: Rough draft
```

6.5 References