Asthma Trial Simulations

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Background

Aim

We want to explore the use of oscillometry used as part of a pre-emptive strategy in a sub group of kids with poorly controlled asthma, i.e. kids requiring hospitalistion.

Interventions

1. standard therapy control: do daily oscillometery but this isn't used to guide therapy
2. maximum therapy control: daily oscillometry but remain on maximum therapy (full dose steroids)
3. investigational arm: daily oscillometry with trigger for escalation of therapy.

Randomisation

Target treatment allocation will be 1:1:1 to three arms.

Primary Outcome

Symptoms as quantified by the number of days in which any symptoms are reported (out of 100 days). Symptoms reported daily via smart phone.

Interest lies in the difference in the expected number of days in which any symptoms are reported under each intervention.

Sample Size

A proposed feasibile sample size is 200 participants. The following will assess power and trial operating characteristics assuming a sample size of 200 participants.

Analyses

In the trial we will randomly assign up to $n = 200$ participants to one of 3 arms. For participant $i = 1, ..., n$ we denote their number of days with symptoms (DWS) as $Y_i \in \{0, 1, 2, ..., 100\}$. We denote by $X \in \{1, 2, 3\}$ the possible interventions (standard, maximum, investigational respectively). Our interest is in $\mathbb{E}[Y|X]$ and we aim to decide that the investigational arm is:

- Effective: $\mathbb{E}[Y|X = 3] < \mathbb{E}[Y|X = 1]$ (investigational arm has lower expected symptom days than standard therapy);
- Non-inferior: $\mathbb{E}[Y|X = 3] < \mathbb{E}[Y|X = 2] - 10$ (investigational arm has expected symptom days no more than 10 days higher compared to maximum therapy).

The decision criteria are:

- if $\Pr(\mathbb{E}[Y|X = 3] < \mathbb{E}[Y|X = 1]) > 0.98$ then the investigational aim satisfies effectiveness relative to standard therapy.
- if $\Pr(\mathbb{E}[Y|X = 3] - 10 < \mathbb{E}[Y|X = 2]) > 0.98$ then the investiational aim satisfies non-inferiority relative to maximal therapy.

Modelling

An ordinal cumulative logistic regression model is used to analyse the data. The model assumes that the distribution of DWS in the population is smooth (e.g. the examples below) and assumes a proportional effect of treatment on the log cumulative odds ratio.

That is, for $Y^\star = Y + 1$,

$$\mathbb{P}[Y^\star \leq k] = \text{logit}^{-1}(\alpha_k - x^\mathsf{T}\beta), \quad k = 1, ..., 100.$$

for non-decreasing α, where

$$\alpha_k = f(k) = \alpha^\star + \sum_{i=1}^{m} \theta_i I_i(k; d, t)$$

for an I-spline basis function of degree d with knot locations t with coefficients $\theta_i > 0$. For the simulations $d = 3$ and inner knot locations were set to $\{10, 20, ..., 80, 90\}$ with boundary knots at $\{1, 100\}$.

Priors were,

$$\begin{aligned} \beta_j - \beta_l &\sim \text{Normal}(0, \sqrt{2.5}), \text{ for } j \neq l, \text{ subject to } \bar{\beta} = 0 \\ \alpha^\star &\sim \text{Normal}(0, 100) \\ \theta_i &\sim \text{Normal}^+(0, 100) \end{aligned}$$

Examples

Example 1

The following provides an example simulated trial under an assumed population. These populations are representative of the kinds of distributions which have been assumed for the trial simulations used to assess operating characteristics. Suppose that days with symptoms is distributed as in Figure 1.

The first 100 participants are randomly assigned to one of three interventions. Sample data is shown in Figure 2.

An ordinal regression model for DWS is inferred from the data which assumes a proportional effect on the conditional odds of having a lower/higher DWS. The modelled distribution for DWS for each intervention group are in Figure 3. The posterior mean difference in DWS is in Figure 4. In this example trial, the investigational arm is found to be effective to standard therapy and non-inferior to maximum therapy. This trial would have ceased recruitment after 100 participants.

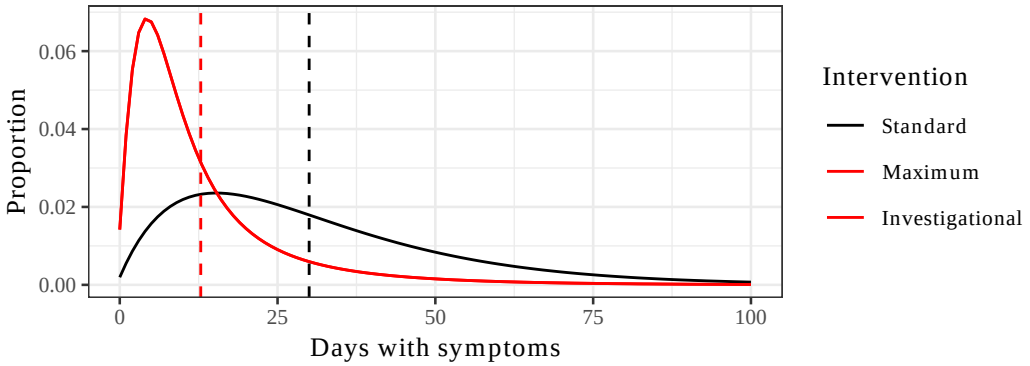

Figure 1: Example distribution of days with any symptoms for standard care group and investigational group.

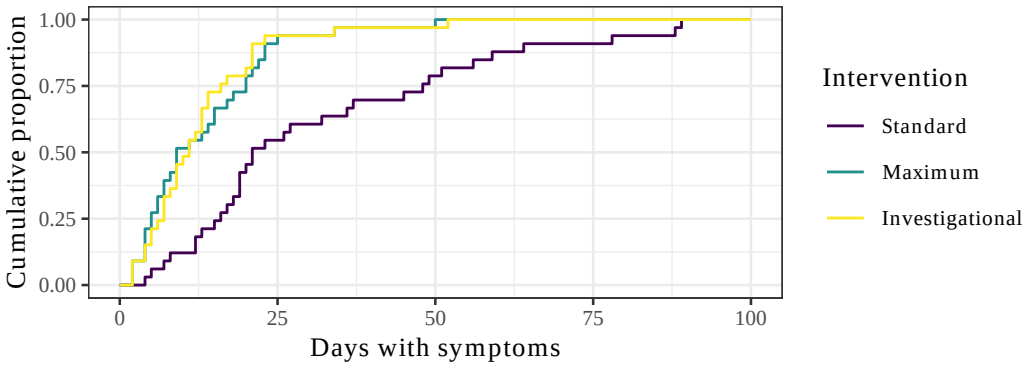

Figure 2: Sample distributions of days with symptoms by treatment group.

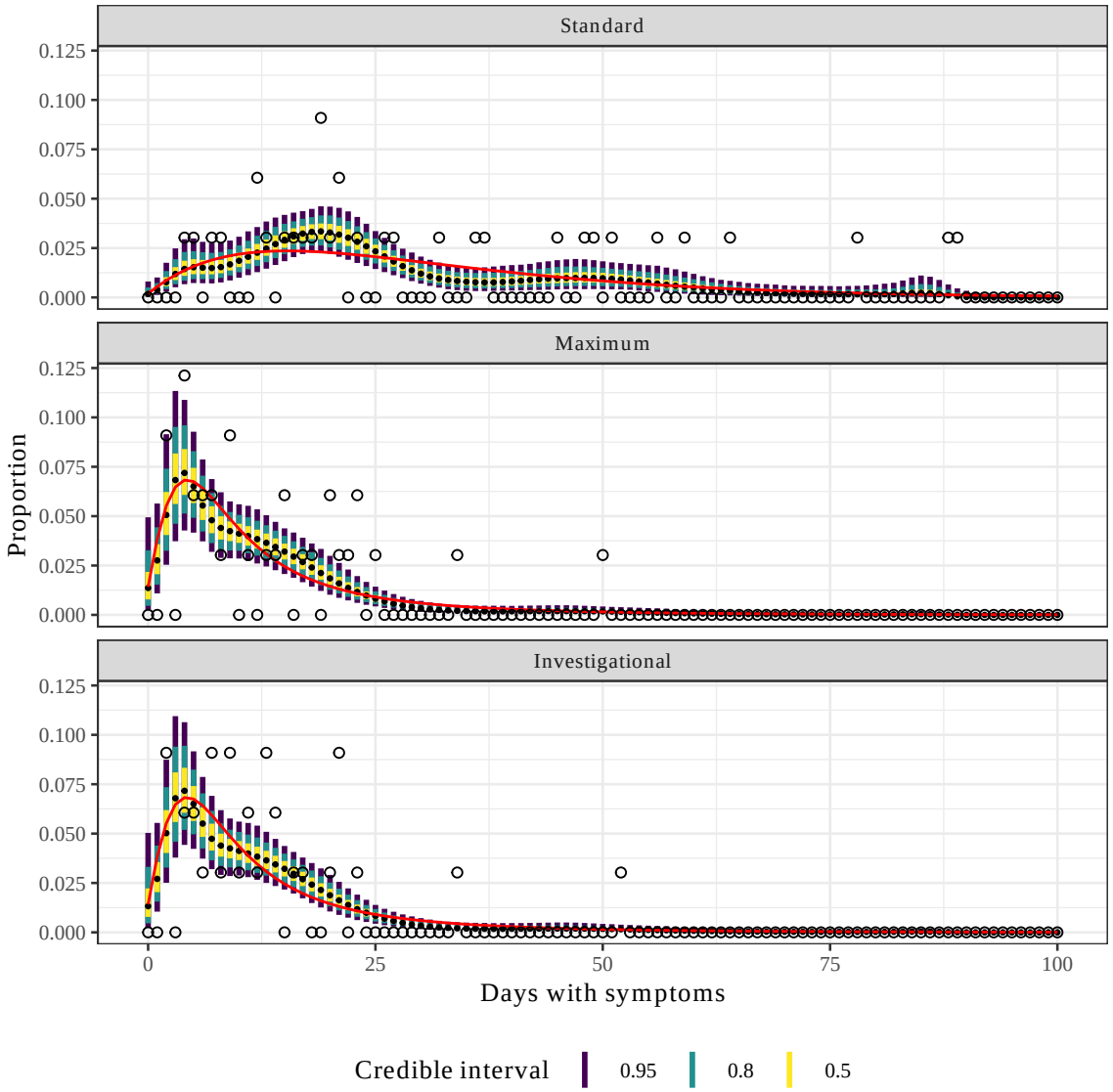

Figure 3: Model estimated distribution of days with symptoms by intervention group. Black points indicate posterior median, and coloured rectanges posterior credible intervals of increasing width. Red line indicates true underlying population distribution. Open points indicate observed sample proportions in each outcome level.

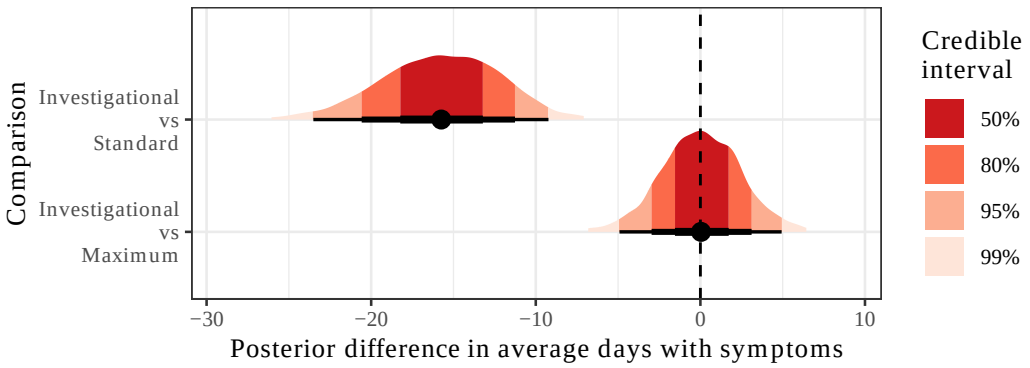

Figure 4: Posterior difference in average number of days with symptoms for investigational arm vs standard and maximum.

Example 2

Suppose that days with symptoms is distributed as in Figure 5. In the standard therapy group (black lines) the average number of days with symptoms is 50 and in the maximal group (red lines), the average number of days with symptoms is 30. The investigational intervention group is in between these two, and is both effective and non-inferior under this setting.

The first 100 participants are randomly assigned to one of three interventions. Sample data is shown in Figure 6.

The modelled distribution for DWS for each intervention group are in Figure 7. The posterior mean difference in DWS is in Figure 8.

In this example trial, the investigational arm is found to be effective to standard therapy and non-inferior to maximum therapy. This trial would have ceased recruitment after 100 participants.

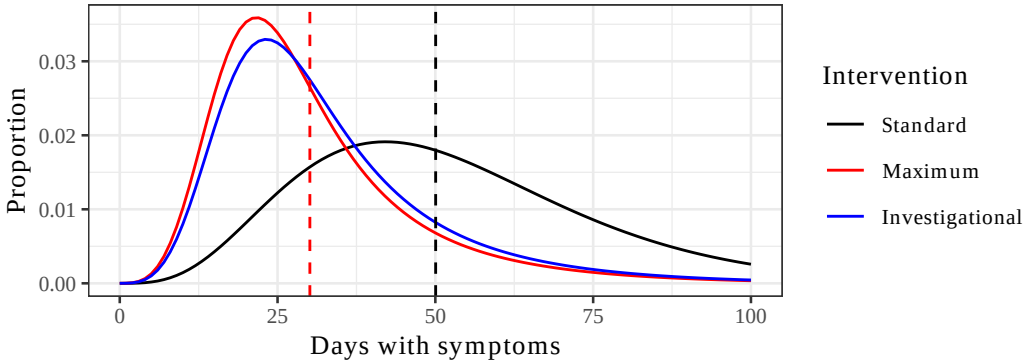

Figure 5: Example distribution of days with any symptoms for standard care group and investigational group.

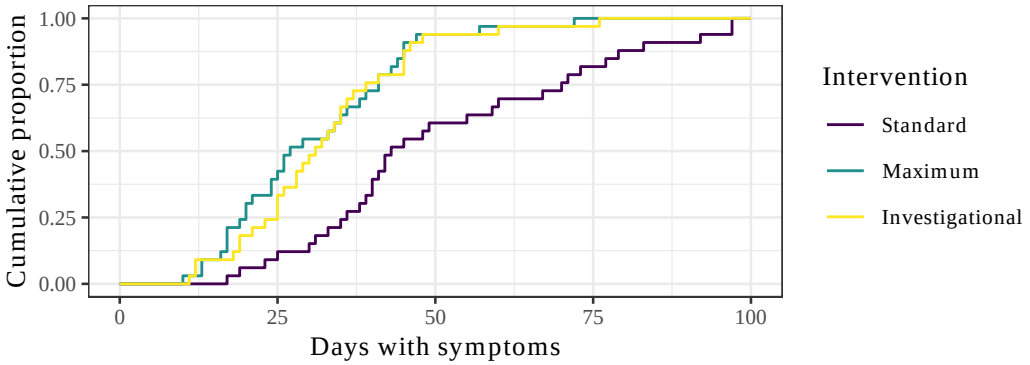

Figure 6: Sample distributions of days with symptoms by treatment group.

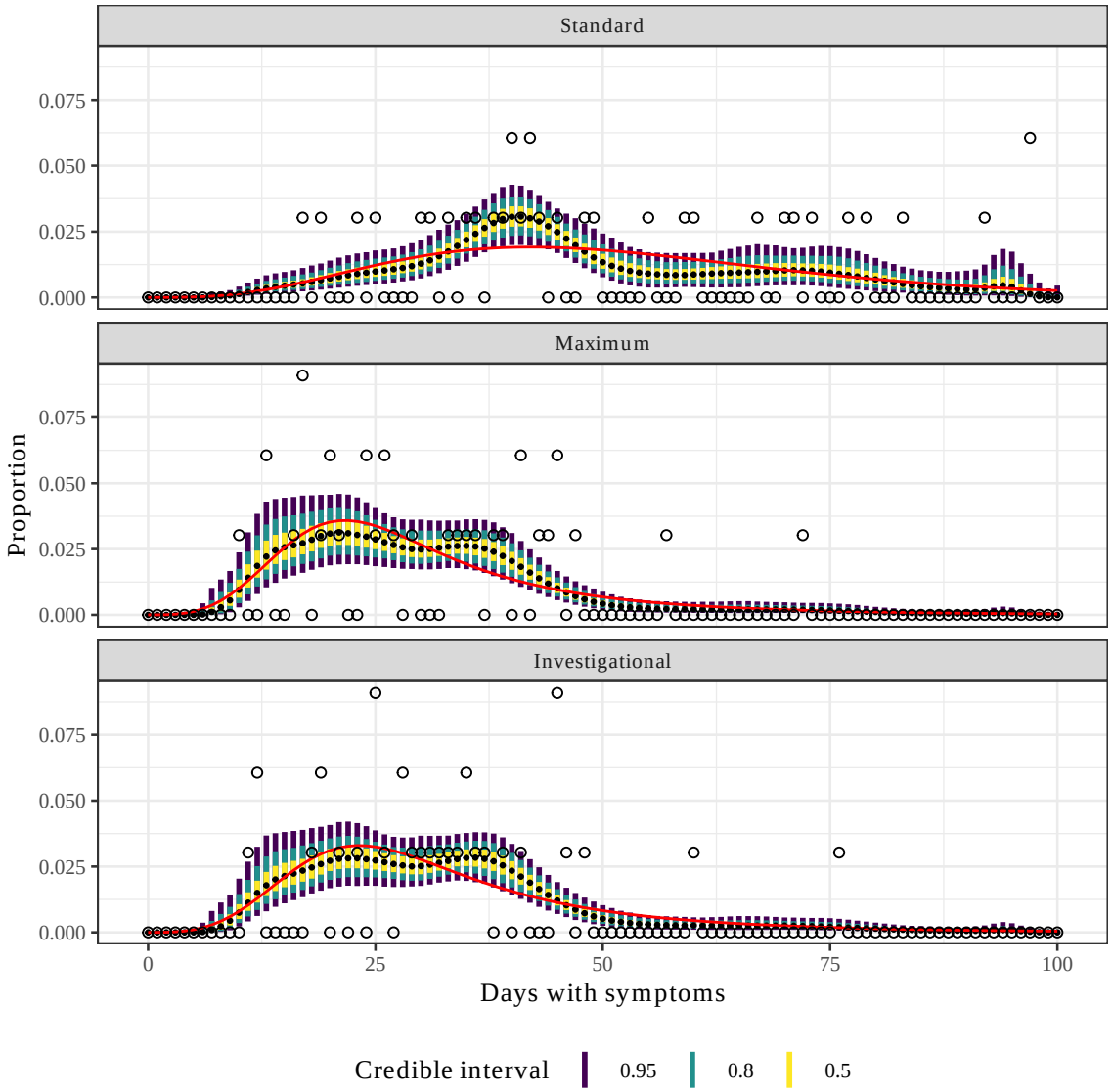

Figure 7: Model estimated distribution of days with symptoms by intervention group. Black points indicate posterior median, and coloured rectanges posterior credible intervals of increasing width. Red line indicates true underlying population distribution. Open points indicate observed sample proportions in each outcome level.

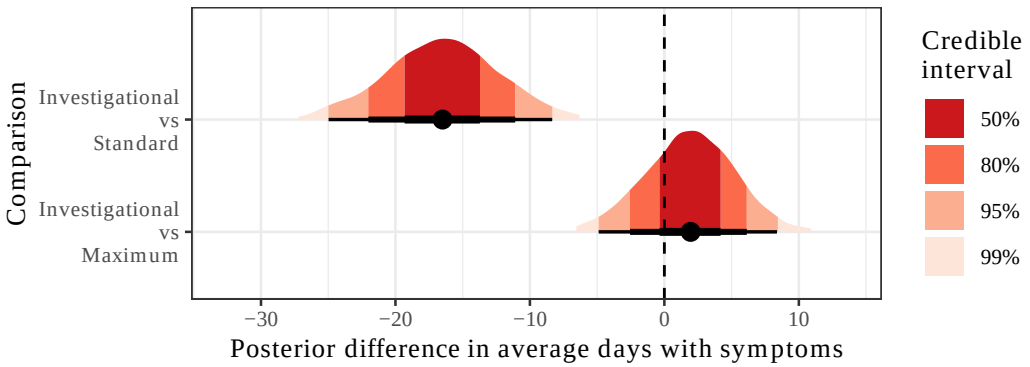

Figure 8: Posterior difference in average number of days with symptoms for investigational arm vs standard and maximum.

Operating Characteristics

Simulations were undertaken to assess trial operating characteristics (type I error and power) under a number of assumed populations.

In general:

- operating characteristics under each scenario are based on 500 trial simulations.
- assume that 3 analyses occur at sample sizes of: 100, 150, and 200.
- enrolment rate has been ignored; given that the primary outcome requires at least 100 days of follow-up to be determined, it's conceivable that many more participants have been enrolled into the study by the time 100 participants have completed follow-up. This is not accounted for in the simulations.

The scenarios (in terms of averae days with symptoms) considered are given in Table 1. For data generation it is also necessary to assume a shape of the distribution in addition to the mean. These are reported for each scenario.

Table 1: Scenarios investigated, numbers are average days with symptoms in each intervention group.

Scenario	Standard	Maximum	Investigational
1	30	10	10, 15, 20, 25, 30
2	50	20	20, 30, 40, 50
3	70	30	30, 40, 50, 60, 70

Scenario 1

In this scenario, days with symptoms in the population under each intervention were assumed to be as in Figure 9 with differences as in Table 2.

A summary of the trial power is in Table 3. In the no effect scenario, the decision criteria for effectiveness is satisfied in 5% of trials.

Summaries of posterior means and probabilities across trials are shown in Figure 14, Figure 15, and Figure 16.

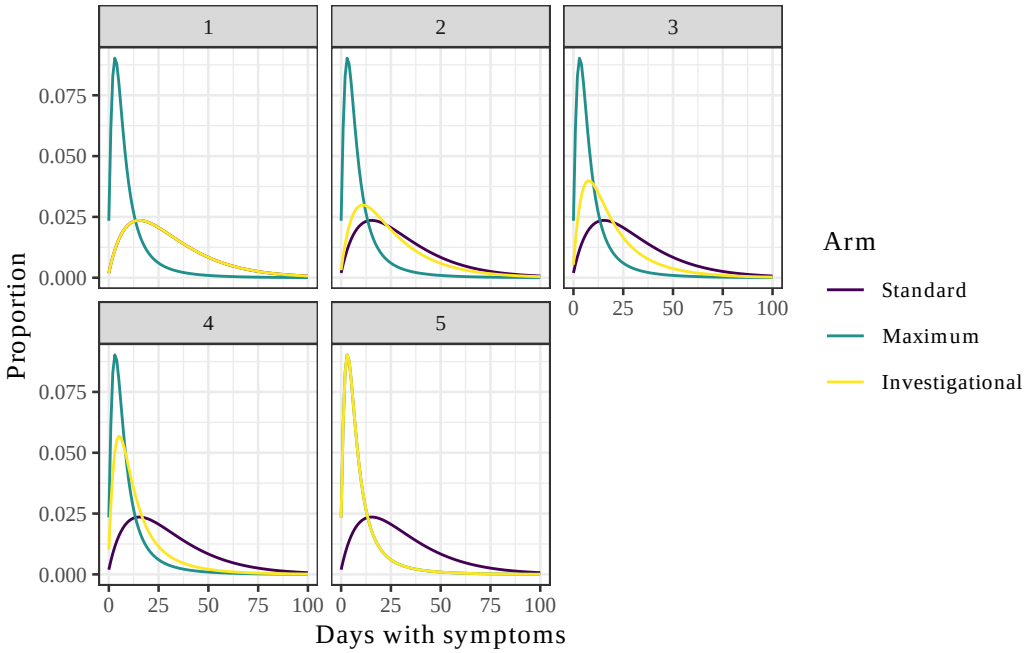

Figure 9: Assumed distribution of days with symptoms for each arm across scenario configurations.

Table 2: Differences in mean days with symptoms for each configuration. Positive numbers more days with symptoms and negative numbers fewer days with symptoms.

configuration	Investigational vs maximum	Investigational vs standard	Maximum vs standard
1	20	0	-20
2	15	-5	-20
3	10	-10	-20
4	5	-15	-20
5	0	-20	-20

Table 3: Summary of power for decision criteria using a posterior probability threshold of 0.98.

				Marginal power			Cumulative power		
Configuration	Comparison	Difference in E[DWS]	Event	1	2	3	1	2	3
1	Investigational vs standard	0	Difference < 0	0.02	0.02	0.02	0.02	0.04	0.04
1	Investigational vs maximum	20	Difference < 10	0.00	0.00	0.00	0.00	0.00	0.00
2	Investigational vs standard	-5	Difference < 0	0.21	0.27	0.37	0.21	0.33	0.43
2	Investigational vs maximum	15	Difference < 10	0.00	0.00	0.00	0.00	0.00	0.00
3	Investigational vs standard	-10	Difference < 0	0.67	0.83	0.92	0.67	0.85	0.94
3	Investigational vs maximum	10	Difference < 10	0.02	0.03	0.03	0.02	0.04	0.05
4	Investigational vs standard	-15	Difference < 0	0.98	1.00	1.00	0.98	1.00	1.00
4	Investigational vs maximum	5	Difference < 10	0.54	0.64	0.76	0.54	0.69	0.82
5	Investigational vs standard	-20	Difference < 0	1.00	1.00	1.00	1.00	1.00	1.00
5	Investigational vs maximum	0	Difference < 10	1.00	1.00	1.00	1.00	1.00	1.00

Table 4: Summary of power for meeting both effectiveness and non-inferiority at a threshold of 0.98 by sequential analysis (1 - 100, 2 - 150, 3 - 200 participants).

configuration	1	2	3
1	0.00	0.00	0.00
2	0.00	0.00	0.00
3	0.02	0.04	0.05
4	0.54	0.69	0.82
5	1.00	1.00	1.00

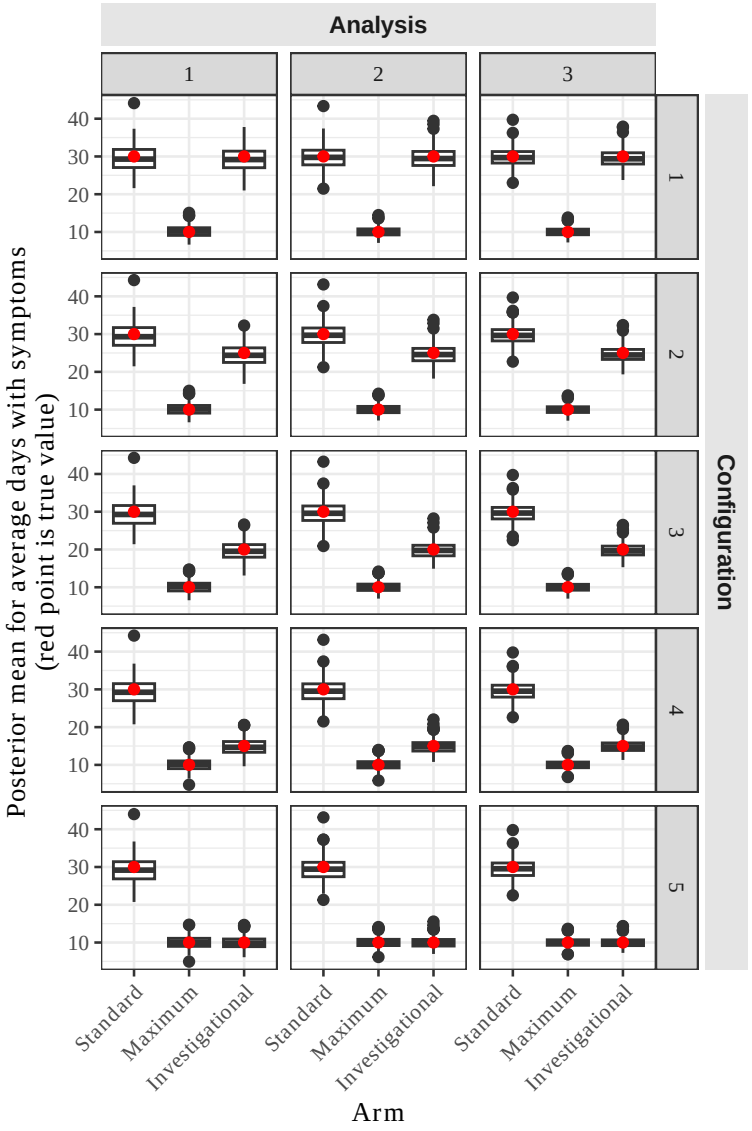

Figure 10: Distribution of posterior mean for average days with symptoms across trials by configuration (rows) and analysis (columns).

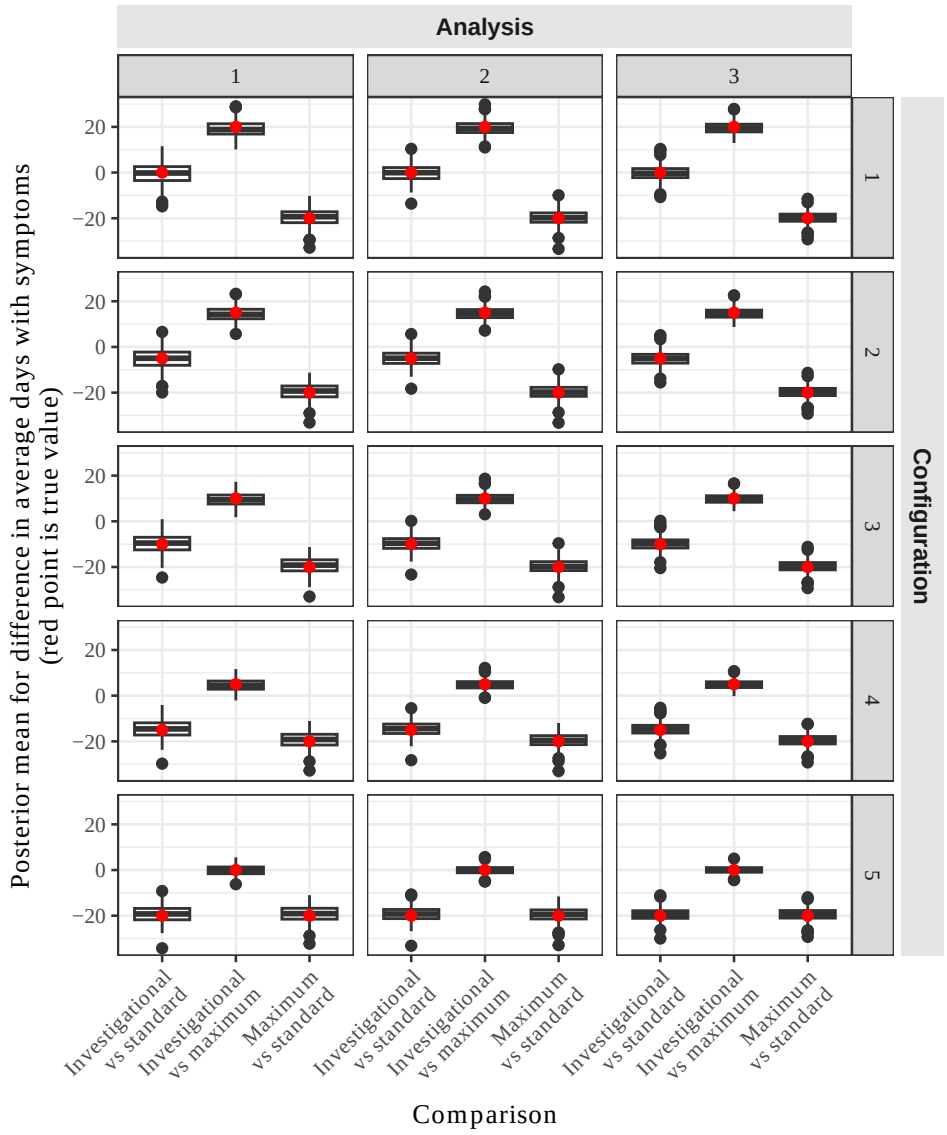

Figure 11: Distribution of posterior mean for difference in average days with symptoms across trials by configuration (rows) and analysis (columns).

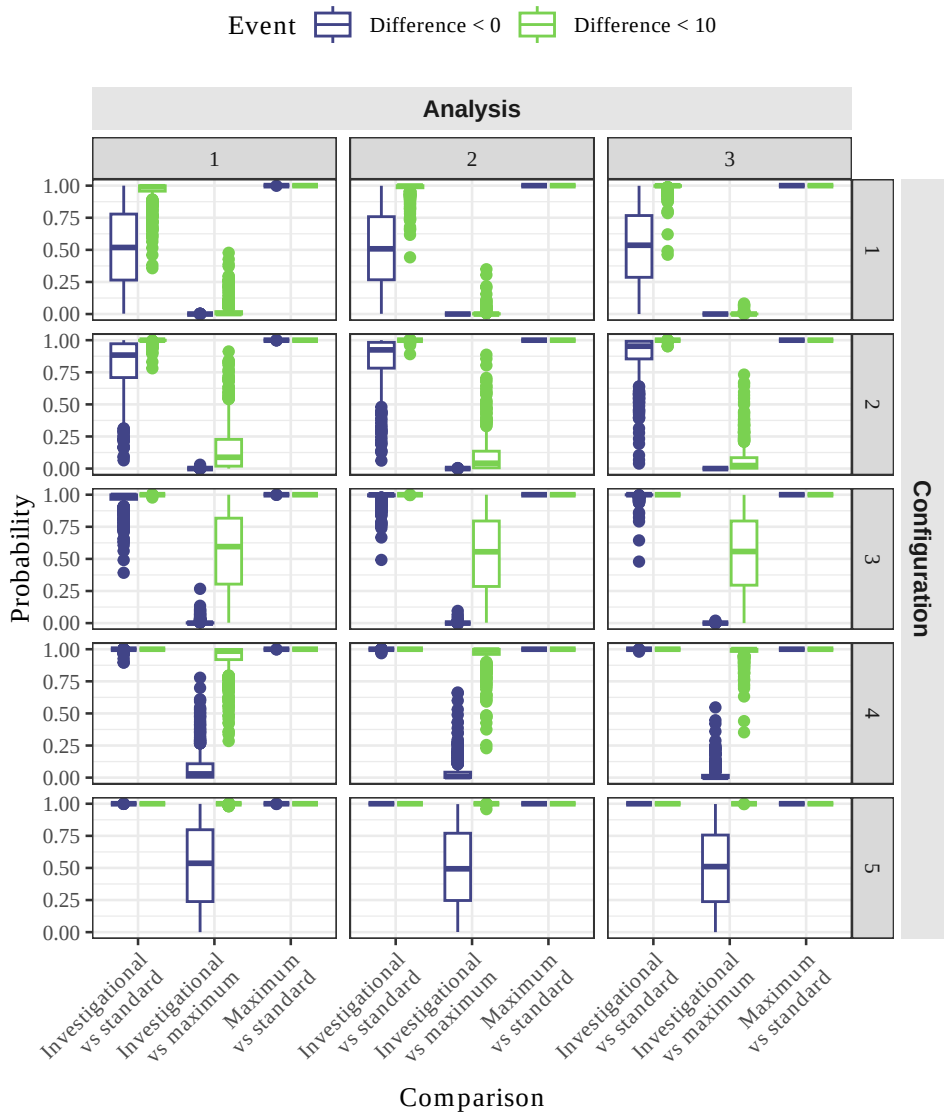

Figure 12: Distribution of event probabilities by comparison, configuration (rows) and analysis (columns).

Scenario 2

In this scenario, days with symptoms in the population under each intervention were assumed to be as in Figure 13. In all configurations, the average days with symptoms in the standard intervention group was 50 and in the maximum group was 20. The average DWS in the investigational group varied between 50, 40, 30, and 20.

A summary of the trial power is in Table 6. In the no effect scenario, the decision criteria for effectiveness is satisfied in 5% of trials.

Summaries of posterior means and probabilities across trials are shown in Figure 14, Figure 15, and Figure 16.

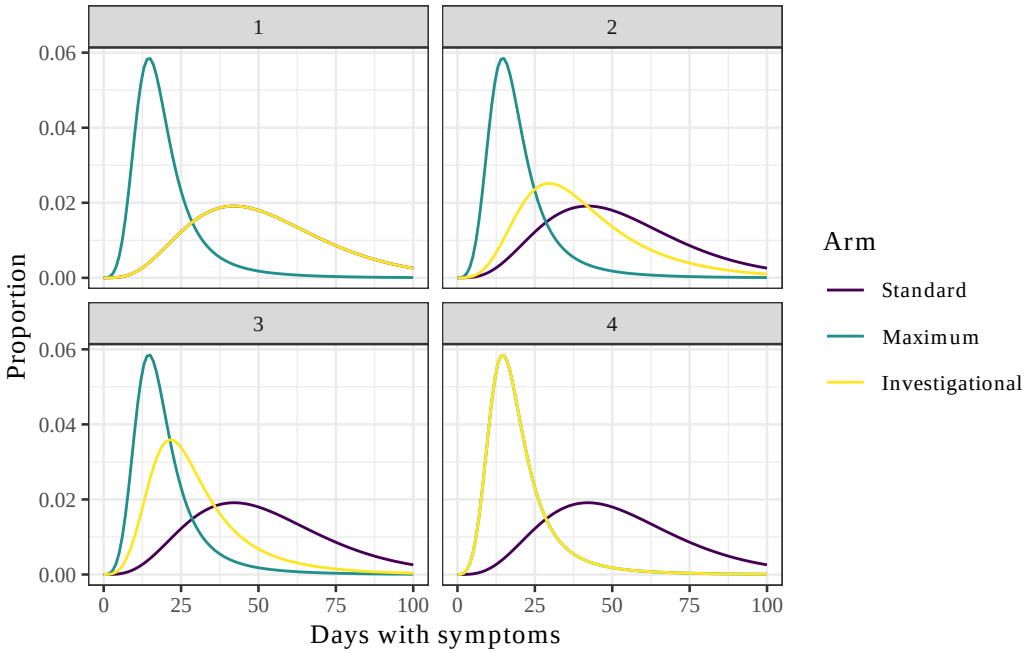

Figure 13: Assumed distribution of days with symptoms for each arm across scenario configurations.

Table 5: Differences in mean days with symptoms for each configuration. Positive numbers more days with symptoms and negative numbers fewer days with symptoms.

configuration	Investigational vs maximum	Investigational vs standard	Maximum vs standard
1	30	0	-30
2	20	-10	-30
3	10	-20	-30
4	0	-30	-30

Table 6: Summary of power for decision criteria using a posterior probability threshold of 0.98.

			Marginal power			Cumulative power		
Configuration	Comparison	Event	1	2	3	1	2	3
1	Investigational vs standard	Difference < 0	0.02	0.03	0.03	0.02	0.04	0.05
1	Investigational vs maximum	Difference < 10	0.00	0.00	0.00	0.00	0.00	0.00
2	Investigational vs standard	Difference < 0	0.59	0.76	0.87	0.59	0.79	0.91
2	Investigational vs maximum	Difference < 10	0.00	0.00	0.00	0.00	0.00	0.00
3	Investigational vs standard	Difference < 0	1.00	1.00	1.00	1.00	1.00	1.00
3	Investigational vs maximum	Difference < 10	0.02	0.03	0.02	0.02	0.04	0.04
4	Investigational vs standard	Difference < 0	1.00	1.00	1.00	1.00	1.00	1.00
4	Investigational vs maximum	Difference < 10	0.97	1.00	1.00	0.97	1.00	1.00

Table 7: Summary of power for meeting both effectiveness and non-inferiority at a threshold of 0.98 by sequential analysis (1 - 100, 2 - 150, 3 -200 participants).

configuration	1	2	3
1	0.00	0.00	0.00
2	0.00	0.00	0.00
3	0.02	0.04	0.04
4	0.97	1.00	1.00

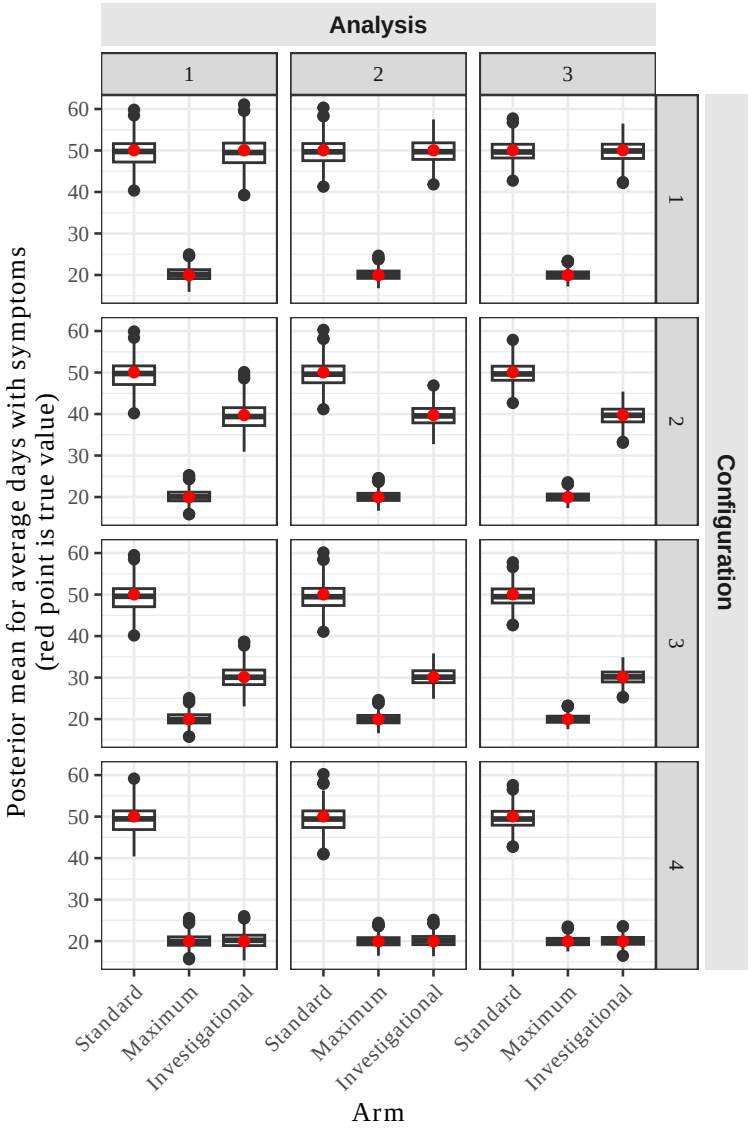

Figure 14: Distribution of posterior mean for average days with symptoms across trials by configuration (rows) and analysis (columns).

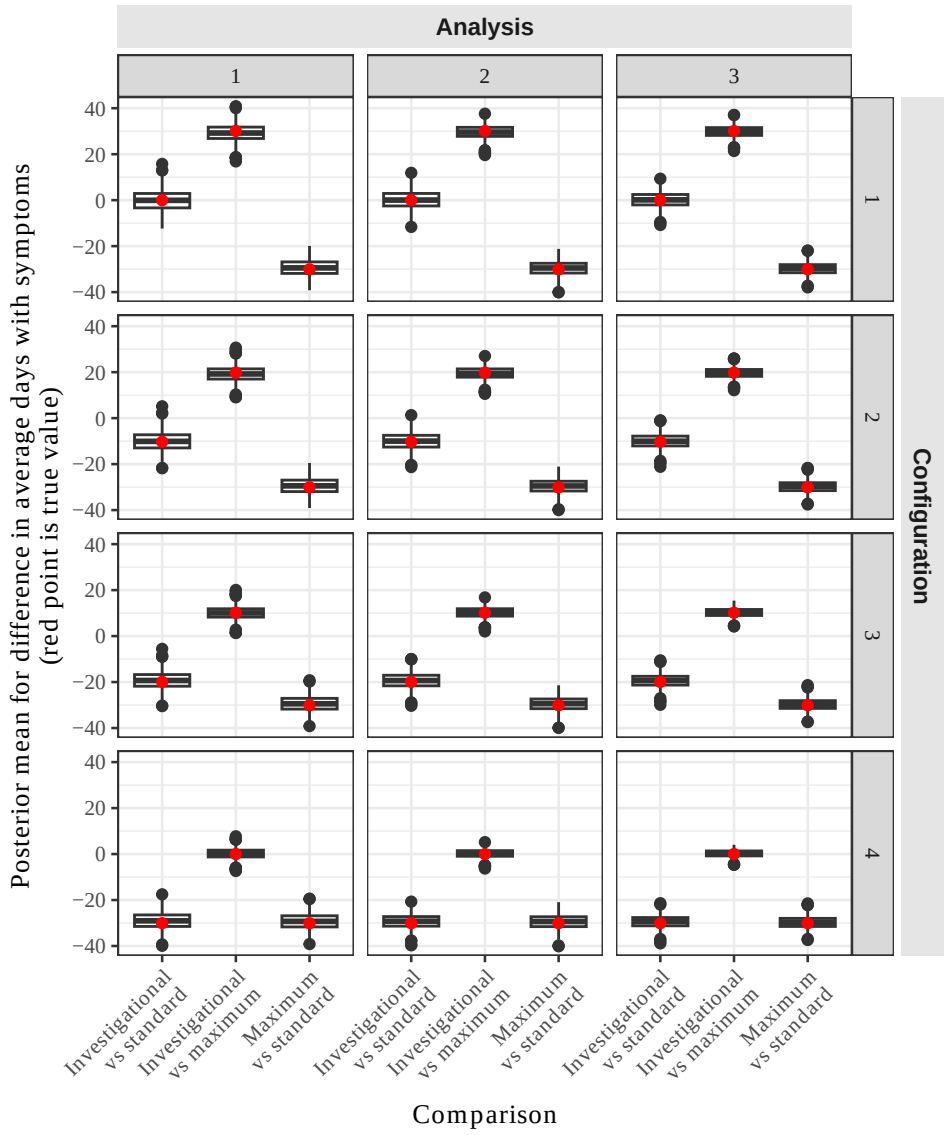

Figure 15: Distribution of posterior mean for difference in average days with symptoms across trials by configuration (rows) and analysis (columns).

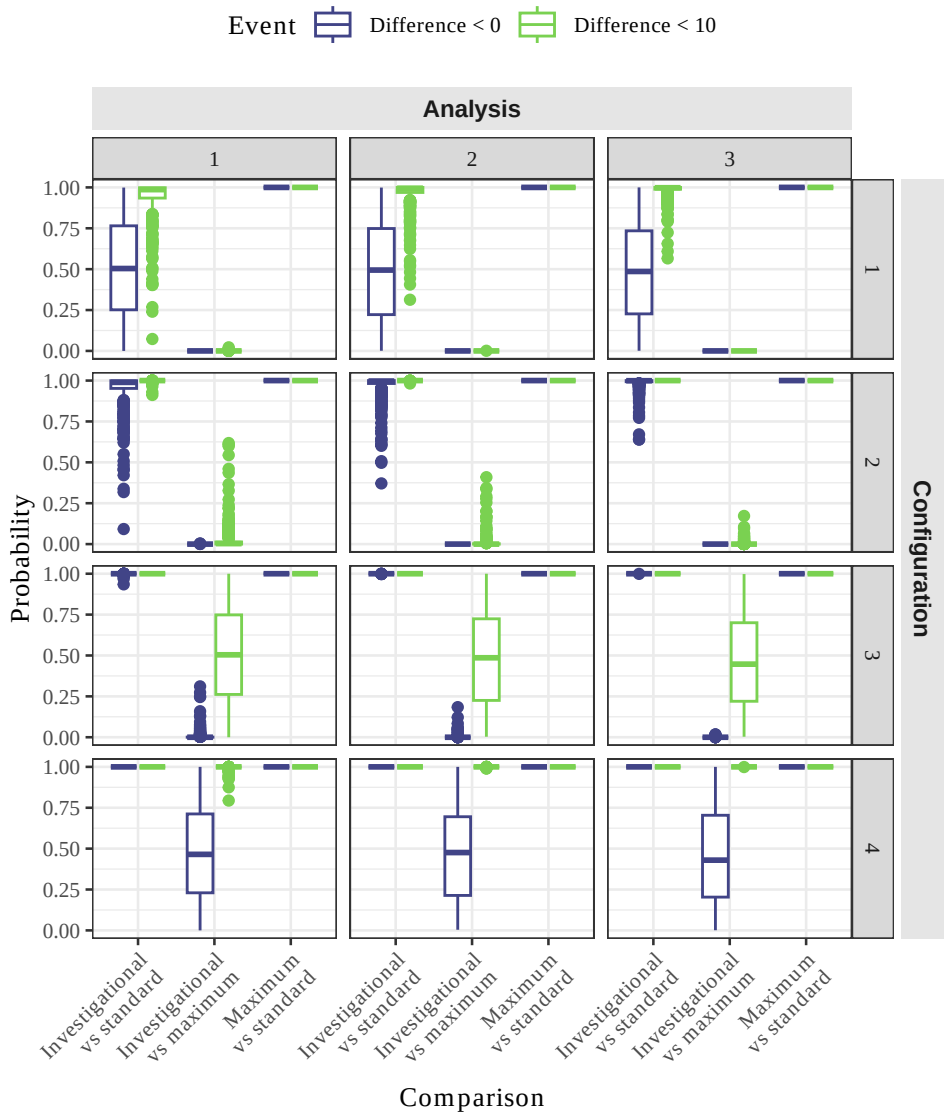

Figure 16: Distribution of event probabilities by comparison, configuration (rows) and analysis (columns).

Scenario 3

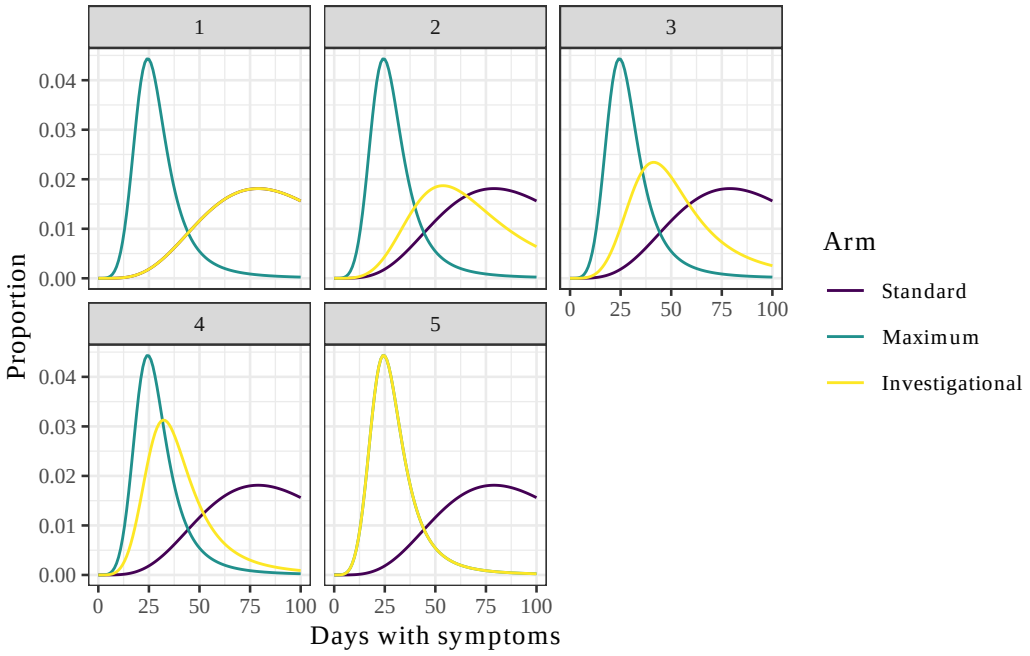

Figure 17: Assumed distribution of days with symptoms for each arm across scenario configurations.

Table 8: Differences in mean days with symptoms for each configuration. Positive numbers more days with symptoms and negative numbers fewer days with symptoms.

configuration	Investigational vs maximum	Investigational vs standard	Maximum vs standard
1	40	0	-40
2	30	-10	-40
3	20	-20	-40
4	10	-30	-40
5	0	-40	-40

Table 9: Summary of power for decision criteria using a posterior probability threshold of 0.98.

			Marginal power			Cumulative power		
Configuration	Comparison	Event	1	2	3	1	2	3
1	Investigational vs standard	Difference < 0	0.02	0.03	0.03	0.02	0.04	0.05
1	Investigational vs maximum	Difference < 10	0.00	0.00	0.00	0.00	0.00	0.00
2	Investigational vs standard	Difference < 0	0.55	0.72	0.83	0.55	0.75	0.86
2	Investigational vs maximum	Difference < 10	0.00	0.00	0.00	0.00	0.00	0.00
3	Investigational vs standard	Difference < 0	0.99	1.00	1.00	0.99	1.00	1.00
3	Investigational vs maximum	Difference < 10	0.00	0.00	0.00	0.00	0.00	0.00
4	Investigational vs standard	Difference < 0	1.00	1.00	1.00	1.00	1.00	1.00
4	Investigational vs maximum	Difference < 10	0.03	0.03	0.02	0.03	0.04	0.06
5	Investigational vs standard	Difference < 0	1.00	1.00	1.00	1.00	1.00	1.00
5	Investigational vs maximum	Difference < 10	0.92	0.98	1.00	0.92	0.99	1.00

Table 10: Summary of power for meeting both effectiveness and non-inferiority at a threshold of 0.98 by sequential analysis (1 - 100, 2 - 150, 3 - 200 participants).

configuration	1	2	3
1	0.00	0.00	0.00
2	0.00	0.00	0.00
3	0.00	0.00	0.00
4	0.03	0.04	0.06
5	0.92	0.99	1.00

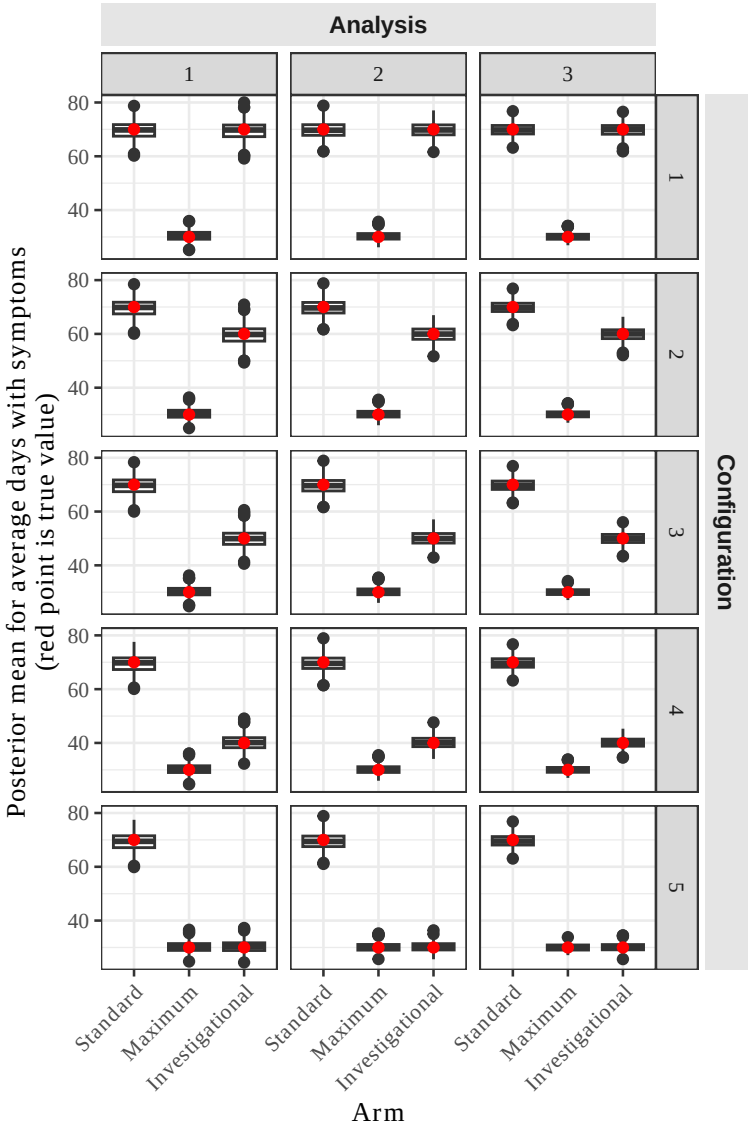

Figure 18: Distribution of posterior mean for average days with symptoms across trials by configuration (rows) and analysis (columns).

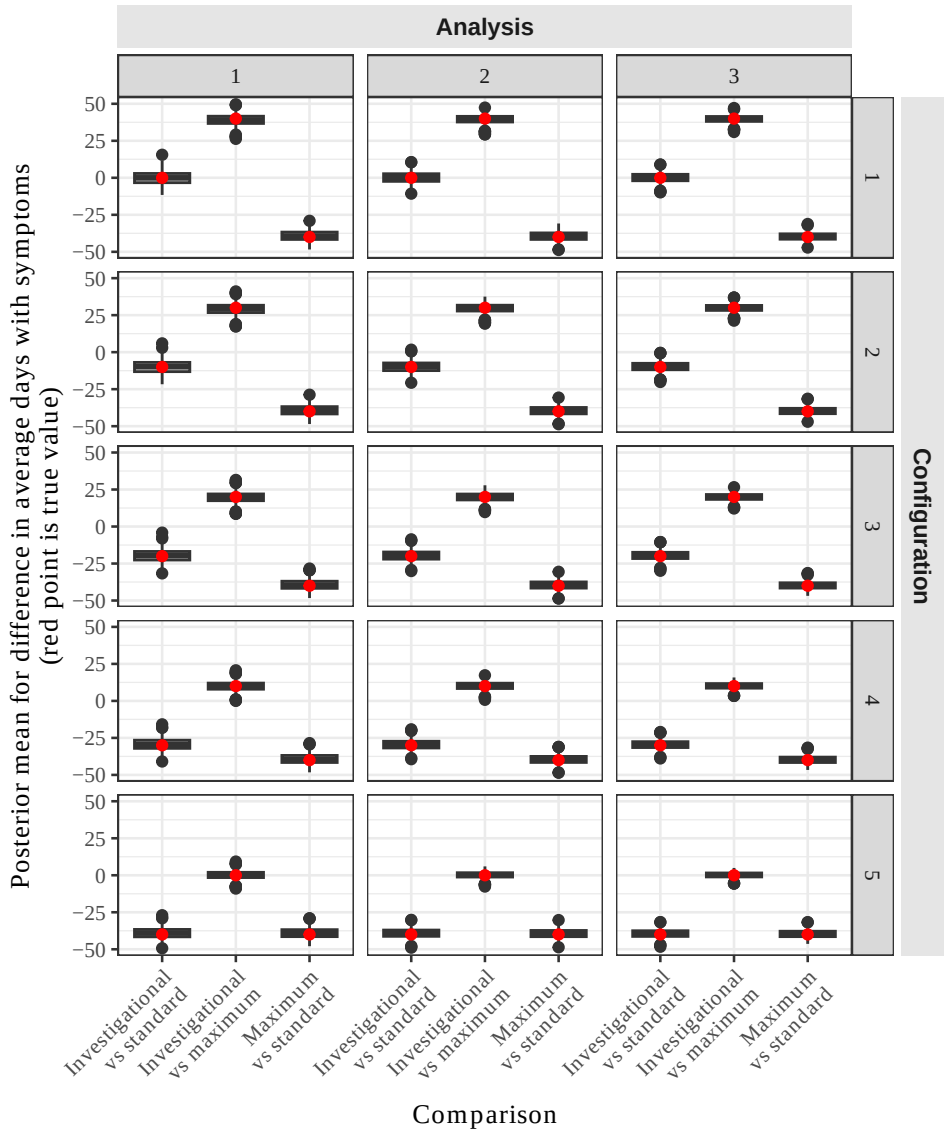

Figure 19: Distribution of posterior mean for difference in average days with symptoms across trials by configuration (rows) and analysis (columns).

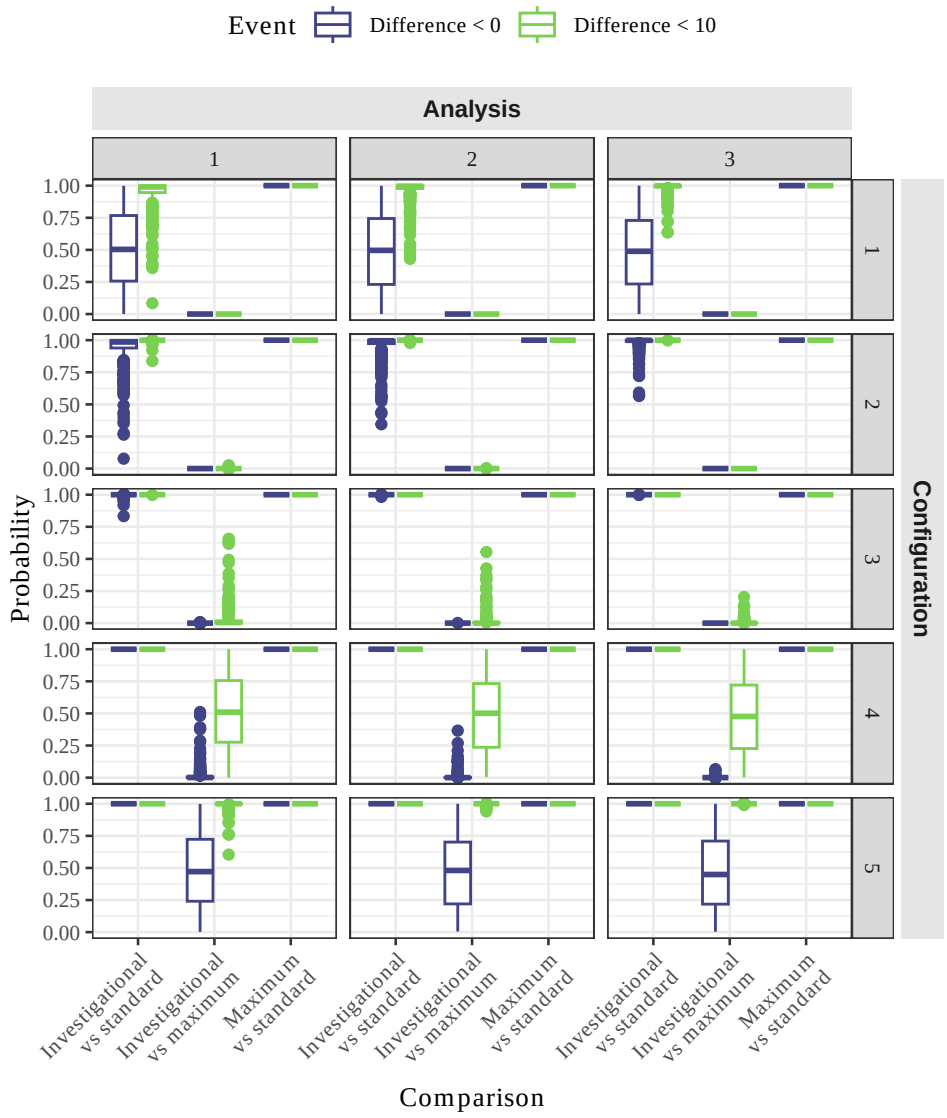

Figure 20: Distribution of event probabilities by comparison, configuration (rows) and analysis (columns).