



ASCOT ADAPT Trial Simulation Report

Version 0.1
July 2020

Contents

Version History	1
1 Introduction	2
2 Simulation Design	3
2.1 Model	3
2.2 Decisions and Adaptations	5
2.3 Simulation Assumptions	6
2.4 Scenarios	6
3 Operating Characteristics	8
3.1 Domain A (6 treatments with one combination)	8
3.2 Domain B (4 treatments)	20
3.3 Domain C (2 treatments)	29

Version History

Version	Date	Author	Description
0.1	July 2020	JT	Draft outline

1 Introduction

This document is an appendix to the ASCOT ADAPT trial core protocol. It details the technical details of the clinical trial simulations and results used in planning the ASCOT ADAPT trial decision thresholds. The simulations are used to understand the operating characteristics of the platform trial under various design configurations. For full details of the analysis plan refer to the Statistical Analysis appendix.

2 Simulation Design

2.1 Model

The primary endpoint in the trial is death from any cause or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation. This endpoint is binary and in these simulations a participants response is coded as 1 if they died or required new intensive respiratory support or vasopressor/inotropic support ventilation-free to 28 days and is 0 if they did not. Therefore, a beneficial treatment is one which reduces the probability of response. The outcome is modelled by logistic regression and treatment effects are expressed in terms of their reduction in the log-odds of the outcome.

2.1.1 Domains

For the purposes of this simulation document, 3 domains have been considered. To make the document generalisable, these domains and the comprising treatments are not explicitly denoted, but are treated as generic.

The generic domains considered are labelled:

- Domain A , consisting of 6 treatment combinations $A_0, A_1, A_2, A_3, A_4, A_5 = A_1 + A_2$. Treatment A_0 is the absence of any treatment from domain A (standard of care) and treatment A_5 is the combination of treatments A_1 and A_2 within the domain.
- Domain B , consisting of 4 treatments B_0, B_1, B_2, B_3 . Treatment B_0 is the absence of any domain B treatment.
- Domain C , consisting of 2 treatments C_0, C_1 .

A regimen is a combination of one treatment option from each domain. Every participant receives one regimen. The number of unique regimens in these simulations, assuming all combinations are viable, is $6 \times 4 \times 2 = 48$.

The model used in these simulations are, for a given participant i

$$\begin{aligned}\eta_i &= \beta_0 + x_{A(i)}^T \beta_A + x_{B(i)}^T \beta_B + x_{C(i)}^T \beta_C, \quad i = 1, 2, 3, \dots \\ \pi_i &= \text{logit}^{-1}(\eta_i)\end{aligned}$$

where η_i is there participants linear predictor as given by the combination of treatments they receive and π_i is the participants probability of ventilation-free survival by 28 days after enrolment.

The vectors, e.g. $x_{A(i)}$, select the relevant parameters from β_A , for example if participant i receives treatment A_5 then $x_{A(i)}^T = (0 \ 1 \ 1 \ 0 \ 0 \ 1)$ where β_{A1} is the effect of treatment A_1 alone, β_{A2} is the effect of A_2 alone, and β_{A5} is the interaction effect between A_1 and A_2 when given in combination. This complete set of treatment option within a domain is expressed by the design matrix. For example, domain A has design

$$X_A = \begin{matrix} & \beta_{A0} & \beta_{A1} & \beta_{A2} & \beta_{A3} & \beta_{A4} & \beta_{A5} \\ \begin{matrix} A_0 \\ A_1 \\ A_2 \\ A_3 \\ A_4 \\ A_5 \end{matrix} & \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 1 & 1 & 0 & 0 & 1 \end{pmatrix} \end{matrix}$$

and the notation $A(i)$ indicates which row of the design matrix X_A applies for participant i .

The current model does not allow for interactions between separate domains, all treatment effects within domains are therefore assumed to be additive in combination.

2.1.2 Prior

The prior distributions for the parameters are

$$\begin{aligned}\beta_0 &\sim N(0, 10^2) \\ \beta_{A0}, \beta_{B0}, \beta_{C0} &= 0 \\ \beta_{A1}, \dots, \beta_{A5}, \beta_{B1}, \dots, \beta_{B3}, \beta_{C1} &\sim N(0, 1).\end{aligned}$$

For identifiability, the effect of receiving A_0, B_0 and C_0 are set to zero implying that β_0 is the log-odds of response when no treatments are received in any domain (standard of care).

2.1.3 Model Quantities

For the purpose of decision making, expected response under each regimen is of primary interest. Define

$$\begin{aligned}\eta_j &= \beta_0 + x_{A(j)}^\top \beta_A + x_{B(j)}^\top \beta_B + x_{C(j)}^\top \beta_C, \quad j = 1, \dots, 48 \\ \pi_j &= \text{logit}^{-1}(\eta_j)\end{aligned}$$

to be the log-odds and probability of response under regimen j . As before, the notation $A(j) \in \{0, 1, 2, 3, 4, 5\}$ indicates which combination of domain A treatments forms regimen j .

The parameters of primary interest are the treatment effects relative to no treatment (or another treatment within the domain) and the best treatment within each domain.

In what follows, all probabilities are implicitly conditional on the model and available data at the time of the analysis.

Best Regimen

Define $j^* = \text{argmin}_j \eta_j$ to be the regimen which minimises the log-odds of response. The probability that regimen j is the best regimen (in terms of minimising the log-odds of response) is

$$\mathbb{P}[\text{regimen } j \text{ is best}] = \mathbb{P}[j^* = j] = \mathbb{P}[\eta_j < \eta_l, l \neq j], \quad j = 1, \dots, 48.$$

Best Treatment

Define the probability that a treatment combination within each domain A , B , and C is in the best regimen by

$$\begin{aligned}\mathbb{P}[\text{treatment } A_k \text{ is in best}] &= \mathbb{P}[A(j^*) = k], \quad k = 0, 1, 2, 3, 4, 5 \\ \mathbb{P}[\text{treatment } B_k \text{ is in best}] &= \mathbb{P}[B(j^*) = k], \quad k = 0, 1, 2, 3 \\ \mathbb{P}[\text{treatment } C_k \text{ is in best}] &= \mathbb{P}[C(j^*) = k], \quad k = 0, 1\end{aligned}$$

Treatment Comparisons

Define the probability that a treatment combination has a lower log-odds of the outcome than another treatment combination by

$$\begin{aligned}\mathbb{P}[\text{treatment } A_k \text{ better than treatment } A_l] &= \mathbb{P}[x_{A(k)}^\top \beta_A < x_{A(l)}^\top \beta_A], \quad k, l \in \{0, 1, 2, 3, 4, 5\} \\ \mathbb{P}[\text{treatment } B_k \text{ better than treatment } B_l] &= \mathbb{P}[x_{B(k)}^\top \beta_B < x_{B(l)}^\top \beta_B], \quad k, l \in \{0, 1, 2, 3\} \\ \mathbb{P}[\text{treatment } C_k \text{ better than treatment } C_l] &= \mathbb{P}[x_{C(k)}^\top \beta_C < x_{C(l)}^\top \beta_C], \quad k, l \in \{0, 1\}\end{aligned}$$

For example, the probability that treatment A_5 reduces the log-odds of response compared to A_0 is

$$\mathbb{P}[\text{treatment } A_5 \text{ better than treatment } A_0] = \mathbb{P}[\beta_{A1} + \beta_{A2} + \beta_{A5} < 0]$$

and the probability that treatment A_5 reduces the log-odds of the response compared to A_1 is

$$\mathbb{P}[\text{treatment } A_5 \text{ better than treatment } A_1] = \mathbb{P}[\beta_{A2} + \beta_{A5} < 0].$$

2.2 Decisions and Adaptations

A variety of trial decisions and adaptations may be possible as the trial progresses, for example, dropping the no treatment option within a domain if at least one treatment is found effective (reduces the log-odds of response compared to no treatment), or dropping all other treatment options if one treatment is found superior to all others (results in the lowest log-odds of response amongst all treatments).

Example decisions and their definitions are provided in Table 1. These example decisions are presented for a single treatment, A_5 . Not all decisions will be defined or of interest for all treatment combinations and these examples are indicative only. Some of the treatments overlap and some definitions are redundant in that they can be defined in terms of other decisions (e.g. harm is contained in futility and inferiority is the complement of superiority).

Table 1: Example trial decisions and definitions.

Decision	Comparison	Quantity	Threshold	Action
A_5 is effective	A_5 vs A_0	$\mathbb{P}[\beta_{A1} + \beta_{A2} + \beta_{A5} < 0]$	0.99	Drop A_0
A_5 is harmful	A_5 vs A_0	$\mathbb{P}[\beta_{A1} + \beta_{A2} + \beta_{A5} > 0]$	0.99	Drop A_5
A_5 is futile	A_5 vs A_0	$\mathbb{P}[\beta_{A1} + \beta_{A2} + \beta_{A5} > -\Delta]$	0.95	Drop A_5
A_5 is equivalent	A_5 vs A_0	$\mathbb{P}[\beta_{A1} + \beta_{A2} + \beta_{A5} < \Delta]$	0.90	Drop A_5
A_5 is futile	A_5 vs A_1	$\mathbb{P}[\beta_{A2} + \beta_{A5} > -\Delta]$	0.95	Drop A_5
A_5 is futile	A_5 vs A_2	$\mathbb{P}[\beta_{A1} + \beta_{A5} > -\Delta]$	0.95	Drop A_5
A_5 is superior	A_5 vs all A	$\mathbb{P}[A(j^*) = 5]$	0.99	Drop all A except A_5
A_5 is inferior	A_5 vs all A	$\mathbb{P}[A(j^*) \neq 5]$	0.99	Drop A_5

For completeness, the actual decisions and thresholds used in the trial simulations for domain A are given in Table 2. The decisions for domains B and C are similar except for the absence of the extra futility check for a combination treatment.

Table 2: Simulation trial decisions and thresholds ($\Delta = \ln(1.1)$)

Decision	Comparison	Quantity	Threshold	Action
A_1 is effective	A_1 vs A_0	$\mathbb{P}[\beta_{A1} < 0]$	> 0.99	Drop A_0
A_2 is effective	A_2 vs A_0	$\mathbb{P}[\beta_{A2} < 0]$	> 0.99	Drop A_0
A_3 is effective	A_3 vs A_0	$\mathbb{P}[\beta_{A3} < 0]$	> 0.99	Drop A_0
A_4 is effective	A_4 vs A_0	$\mathbb{P}[\beta_{A4} < 0]$	> 0.99	Drop A_0
A_5 is effective	A_5 vs A_0	$\mathbb{P}[\beta_{A1} + \beta_{A2} + \beta_{A5} < 0]$	> 0.99	Drop A_0
A_1 is futile	A_1 vs A_0	$\mathbb{P}[\beta_{A1} > -\Delta]$	> 0.95	Drop A_1
A_2 is futile	A_2 vs A_0	$\mathbb{P}[\beta_{A2} > -\Delta]$	> 0.95	Drop A_2
A_3 is futile	A_3 vs A_0	$\mathbb{P}[\beta_{A3} > -\Delta]$	> 0.95	Drop A_3
A_4 is futile	A_4 vs A_0	$\mathbb{P}[\beta_{A4} > -\Delta]$	> 0.95	Drop A_4
A_5 is futile	A_5 vs A_0	$\mathbb{P}[\beta_{A1} + \beta_{A2} + \beta_{A5} > -\Delta]$	> 0.95	Drop A_5
A_5 is futile	A_5 vs A_1	$\mathbb{P}[\beta_{A2} + \beta_{A5} > -\Delta]$	> 0.95	Drop A_5
A_5 is futile	A_5 vs A_2	$\mathbb{P}[\beta_{A1} + \beta_{A5} > -\Delta]$	> 0.95	Drop A_5
A_1 is superior	A_1 vs all A	$\mathbb{P}[A(j^*) = 1]$	> 0.99	Drop all but A_1
A_2 is superior	A_2 vs all A	$\mathbb{P}[A(j^*) = 2]$	> 0.99	Drop all but A_2
A_3 is superior	A_3 vs all A	$\mathbb{P}[A(j^*) = 3]$	> 0.99	Drop all but A_3
A_4 is superior	A_4 vs all A	$\mathbb{P}[A(j^*) = 4]$	> 0.99	Drop all but A_4
A_5 is superior	A_5 vs all A	$\mathbb{P}[A(j^*) = 5]$	> 0.99	Drop all but A_5
A_1 is inferior	A_1 vs all A	$\mathbb{P}[A(j^*) = 1]$	$< 0.01/5$	Drop A_1
A_2 is inferior	A_2 vs all A	$\mathbb{P}[A(j^*) = 2]$	$< 0.01/5$	Drop A_2
A_3 is inferior	A_3 vs all A	$\mathbb{P}[A(j^*) = 3]$	$< 0.01/5$	Drop A_3
A_4 is inferior	A_4 vs all A	$\mathbb{P}[A(j^*) = 4]$	$< 0.01/5$	Drop A_4
A_5 is inferior	A_5 vs all A	$\mathbb{P}[A(j^*) = 5]$	$< 0.01/5$	Drop A_5

2.3 Simulation Assumptions

The following assumptions are made for the purpose of simulation:

- all combinations of treatment are allowed and all participants are eligible for all treatment combinations.
- there are no interactions between treatment effects.
- additional covariates to be included in the full model separate from the effect of treatment have not been included (e.g. adjustment for region, site, and time of enrolment).
- no drop-outs occur, there is no missing data, and at the time of each interim analysis full information is available on all enrolled participants.
- the trial is perpetual (there is no criteria to completely stop enrolment to the trial).
- for computational purposes, mean-field variational Bayes is used to approximate posterior densities and posterior quantities are calculated on the basis of 20,000 Monte Carlo draws from this posterior.
- Summaries of trial operating characteristics are based on 10,000 simulations under each scenario.

2.4 Scenarios

In all scenarios, the simulations assume that the first interim occurs when 400 participants have completed follow-up and subsequent interim analyses occur every additional 200 participants. For the purposes of simulation, results up to a total trial sample size of 5,000 participants are presented. In all scenarios the baseline probability of response was 0.2 and the reference value for futility was $\ln(1.1)$.

The scenarios considered are summarised in Table 3.

Table 3: Trial simulation scenarios.

Scenario	Description	Effect size (OR)
Global null	All interventions in all domains have no effect	1.00
One effective	One intervention in a domain increases odds	1.10
One effective	One intervention in a domain reduces odds	1/1.10
One effective	One intervention in a domain reduces odds	1/1.25
One effective	One intervention in a domain reduces odds	1/1.50
One effective	One intervention in a domain reduces odds	1/2.00
Two effective	Two interventions in a domain increase odds	1.10
Two effective	Two interventions in a domain reduce odds	1/1.10
Two effective	Two interventions in a domain reduce odds	1/1.25
Two effective	Two interventions in a domain reduce odds	1/1.50
Two effective	Two interventions in a domain reduce odds	1/2.00

3 Operating Characteristics

For each scenario we present various operating characteristics. The focus is on the probability of triggering each decision as the trial progresses, the changing probability of allocation to each treatment, and the probability of response.

3.1 Domain A (6 treatments with one combination)

3.1.1 Global Null Scenario

The global null scenario for domain A shows a probability of less than 0.2 of dropping the no treatment option (either due to inferiority or a treatment declared effective) by 5,000 participants enrolled. Each intervention option in the domain has less than 0.05 probability of having been declared effective by 5,000 participants enrolled (approx 0.04). The global probability of dropping the standard care arm by 5,000 participants is approximately 0.2.

There is moderate probability of deciding ineffective arms as futile by 5,000 participants enrolled (at least 0.4 for each ineffective arm). As the trial progresses, the expected probability of receiving the no treatment option increases due to the probability of dropping active treatments for futility. Due to the changing allocation probabilities, the no treatment option has the highest median number assigned. The extra futility check of A_5 compared to A_1 and A_2 results in a high probability of futility for this intervention compared to the others.

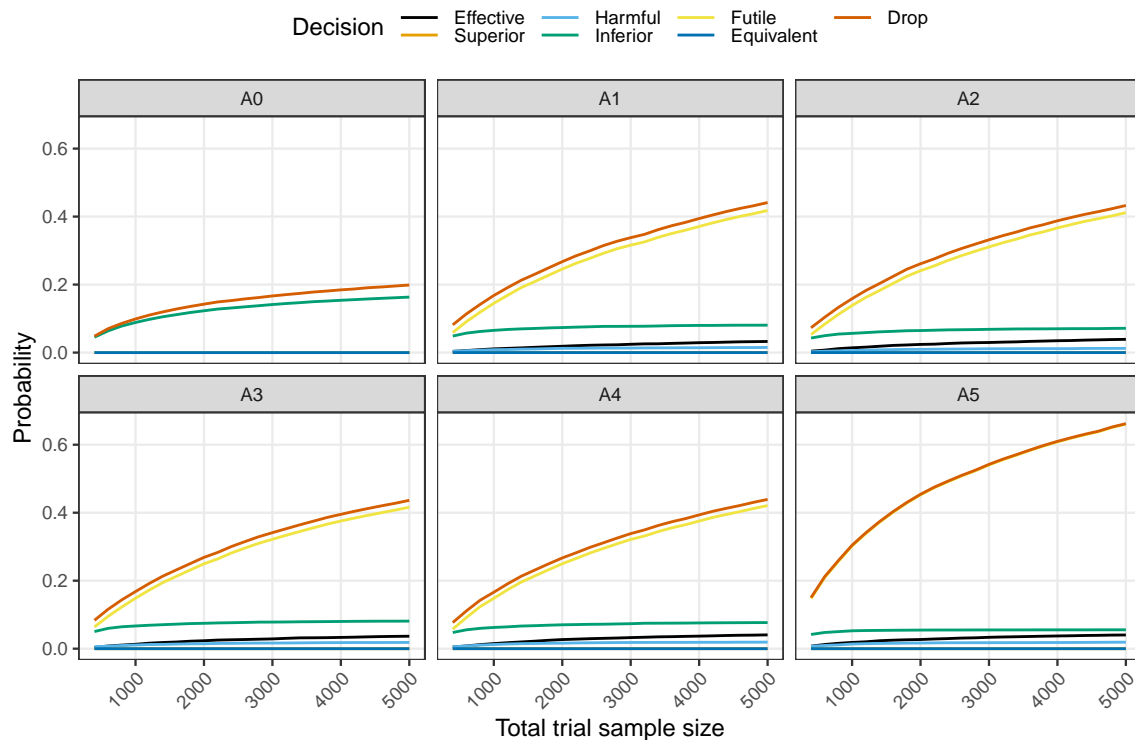


Figure 1: Probability of decision for domain A treatments as trial progresses.

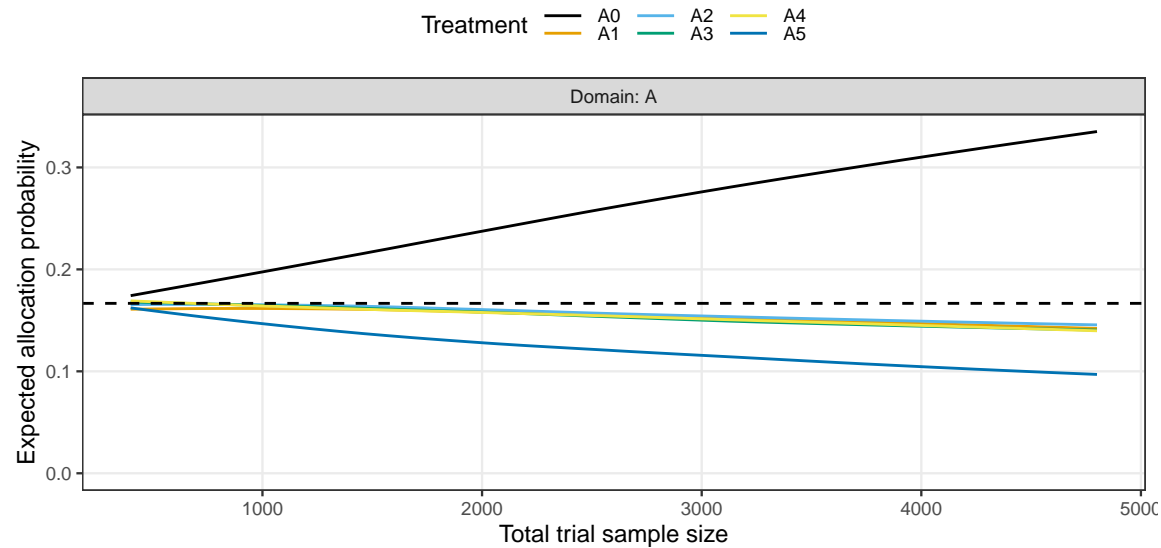


Figure 2: Expected allocation probability in domain A treatments as trial progresses.

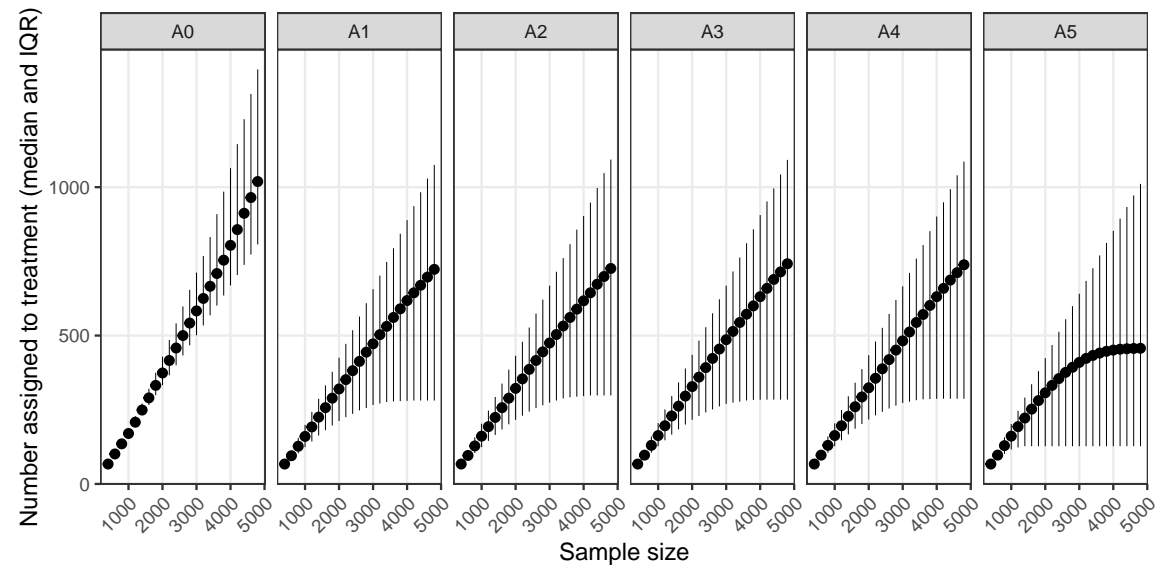


Figure 3: Number assigned to each treatment.

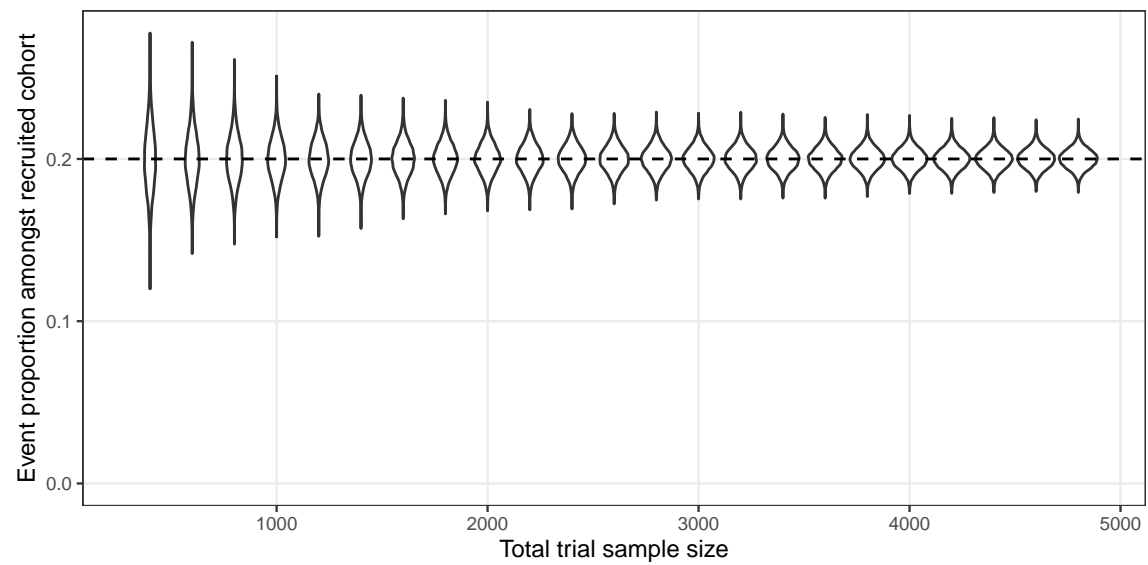


Figure 4: Probability of response as trial progresses.

3.1.2 One treatment effective

In the following, one treatment in domain A (A_3) is effective (or harmful). The probability of deciding effectiveness exceeds 0.9 by 4,000 participants enrolled when A_3 changes the odds of the outcome by a factor of $2/3$ and exceeds 0.9 by 1,600 participants enrolled when A_3 changes the odds of the outcome by a factor of 0.5.

When A_3 reduces the odds of the outcome by a factor 0.5, the probability of declaring superiority by 5,000 participants is 0.9.

Figures 6 and 7 show the expected allocation probabilities and expected outcome probabilities respectively under the varying effect size.

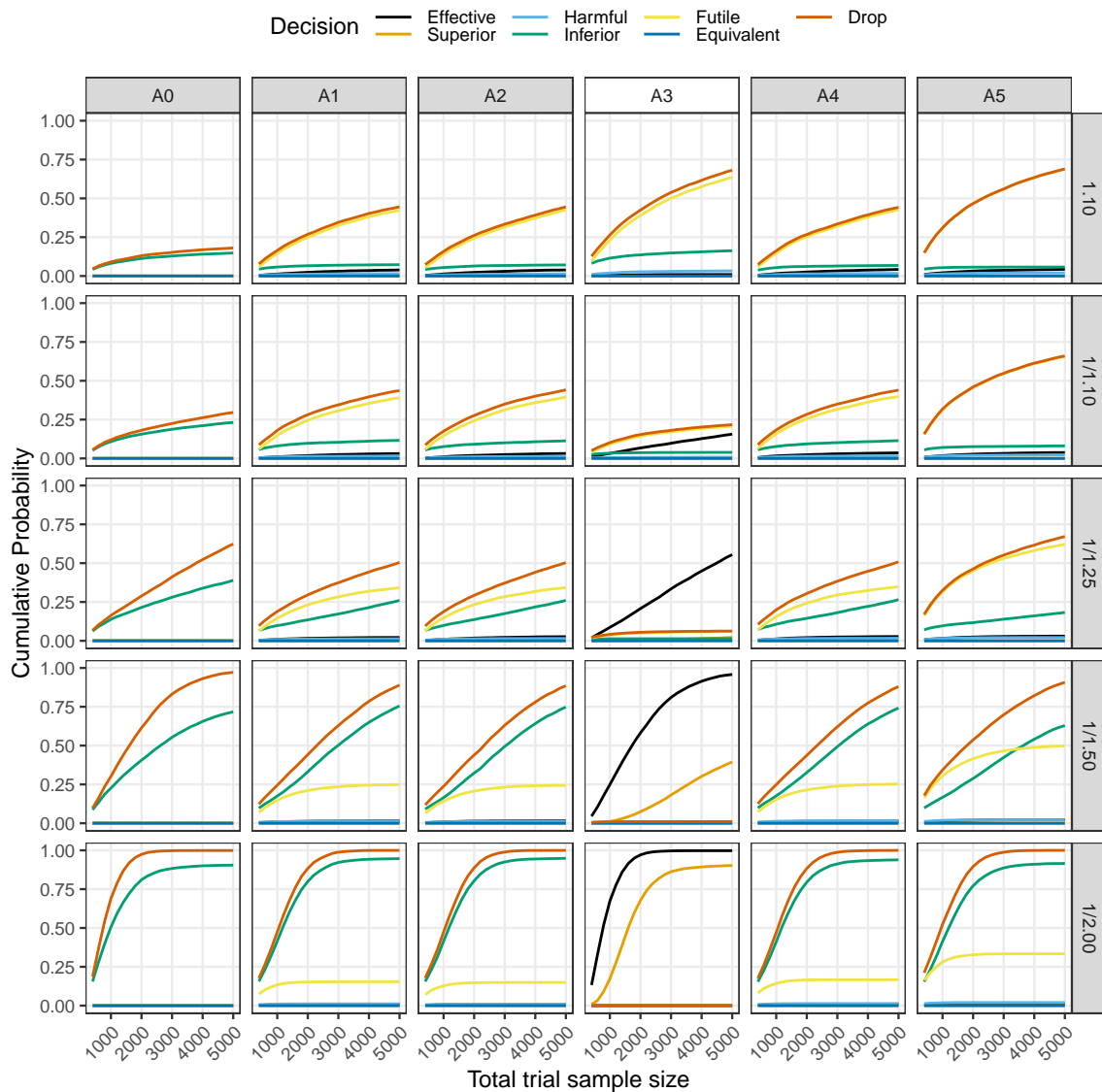


Figure 5: Probability of decision for domain A treatments as trial progresses (white facets are the affected treatments).

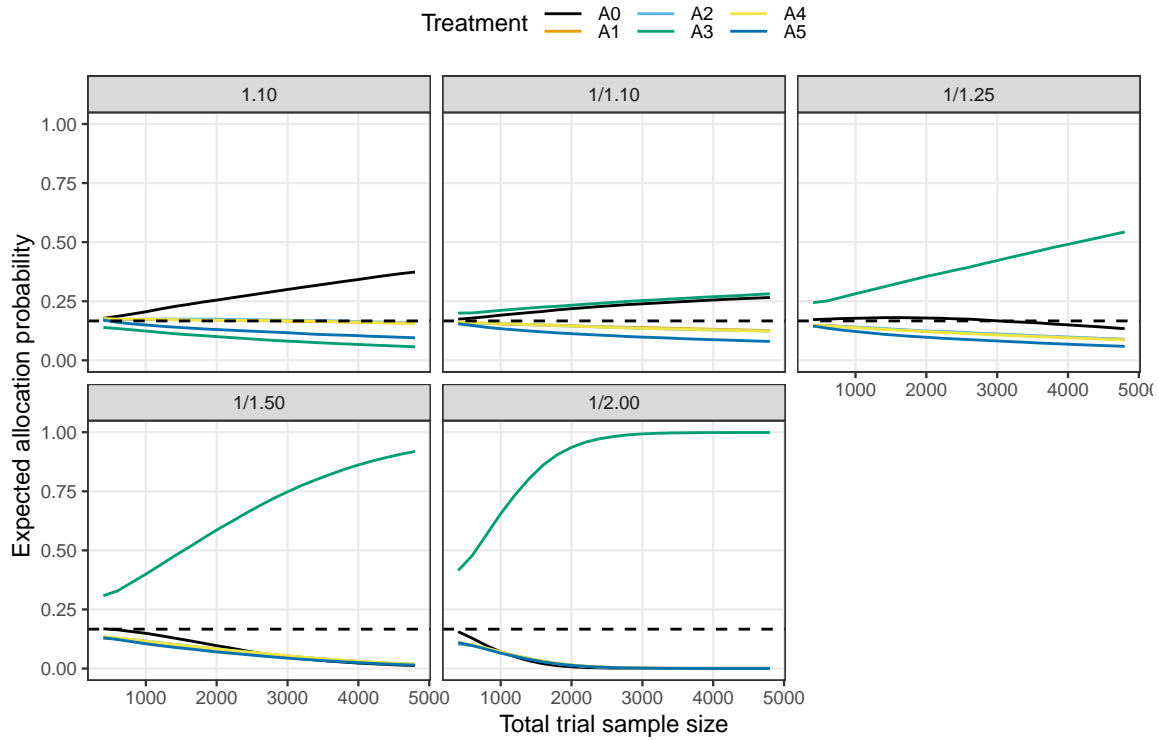


Figure 6: Expected allocation probability in domain A treatments as trial progresses. Affected treatments are A_3 .

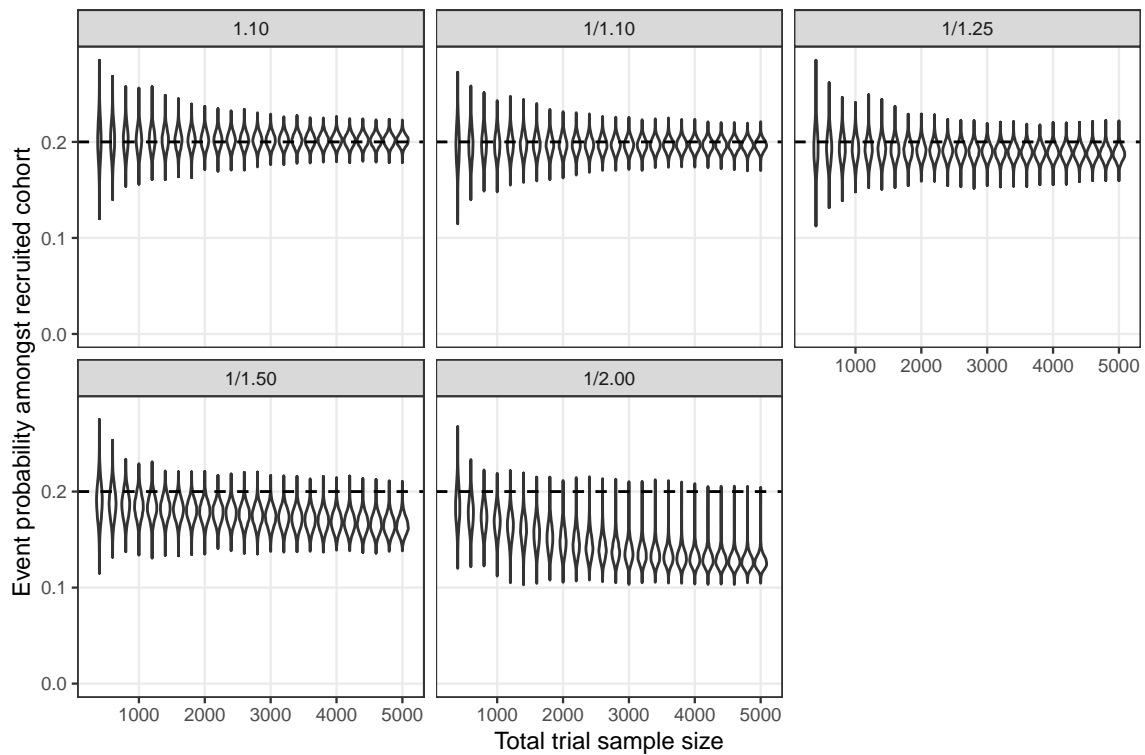


Figure 7: Probability of response as trial progresses.

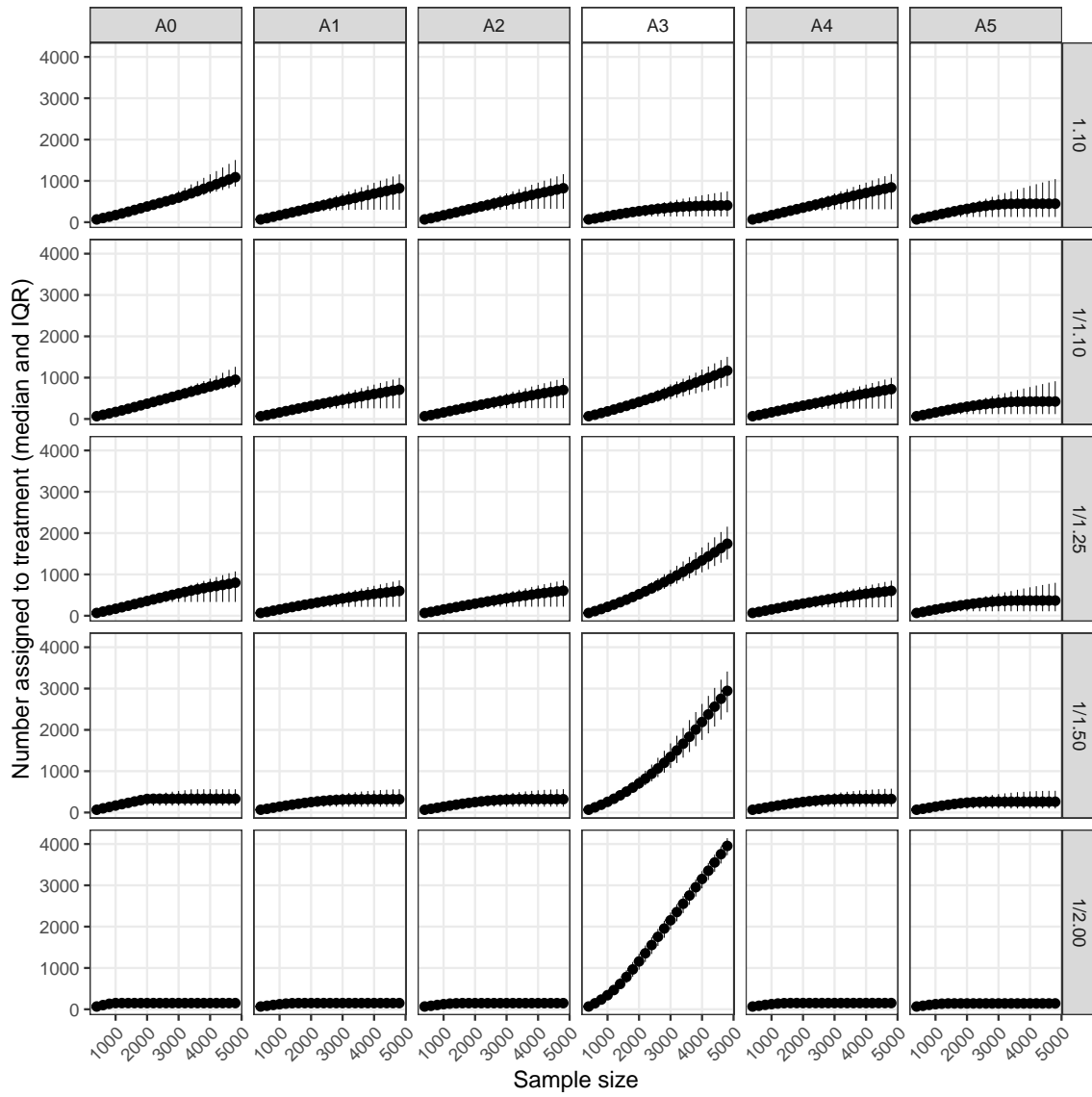


Figure 8: Number assigned to each treatment.

3.1.3 Two treatments effective

In the following, two treatments in domain A (A_3, A_4) are effective (or harmful).

When the effect size is $1/1.50$ the probability of declaring at least one of A_3 or A_4 effective exceeds 0.8 by 2,600 participants enrolled and 0.9 by 3,400 participants. The probability of dropping at least one of A_3 or A_4 is 0.08 by 5,000 participants.

When the effect size is $1/2.00$ the probability of declaring at least one effective exceeds 0.9 by 1,400 participants enrolled. The probability of dropping at least one of A_3 or A_4 is 0.07 by 5,000 participants.

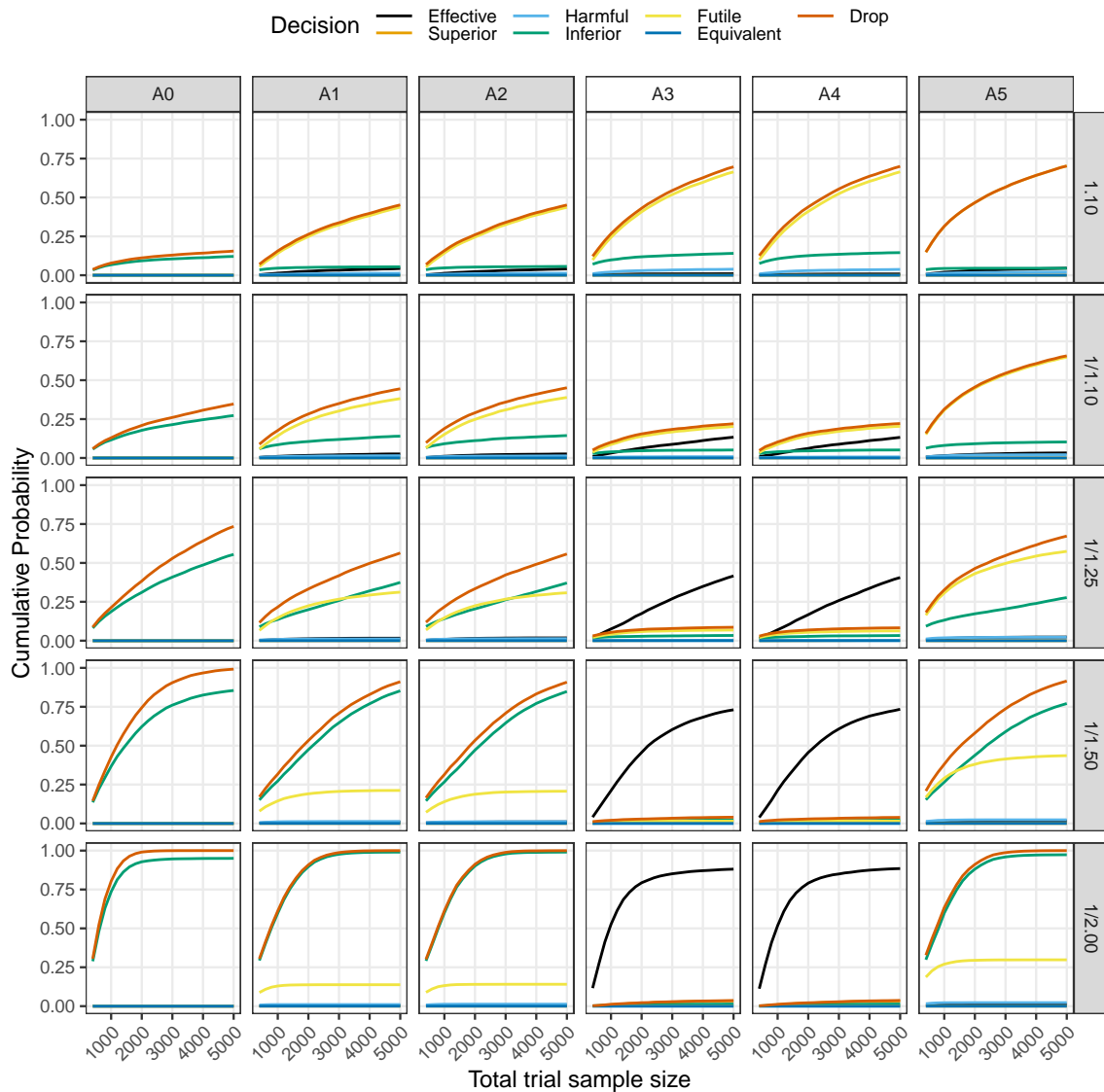


Figure 9: Probability of decision for domain A treatments as trial progresses (white facets are the affected treatments).

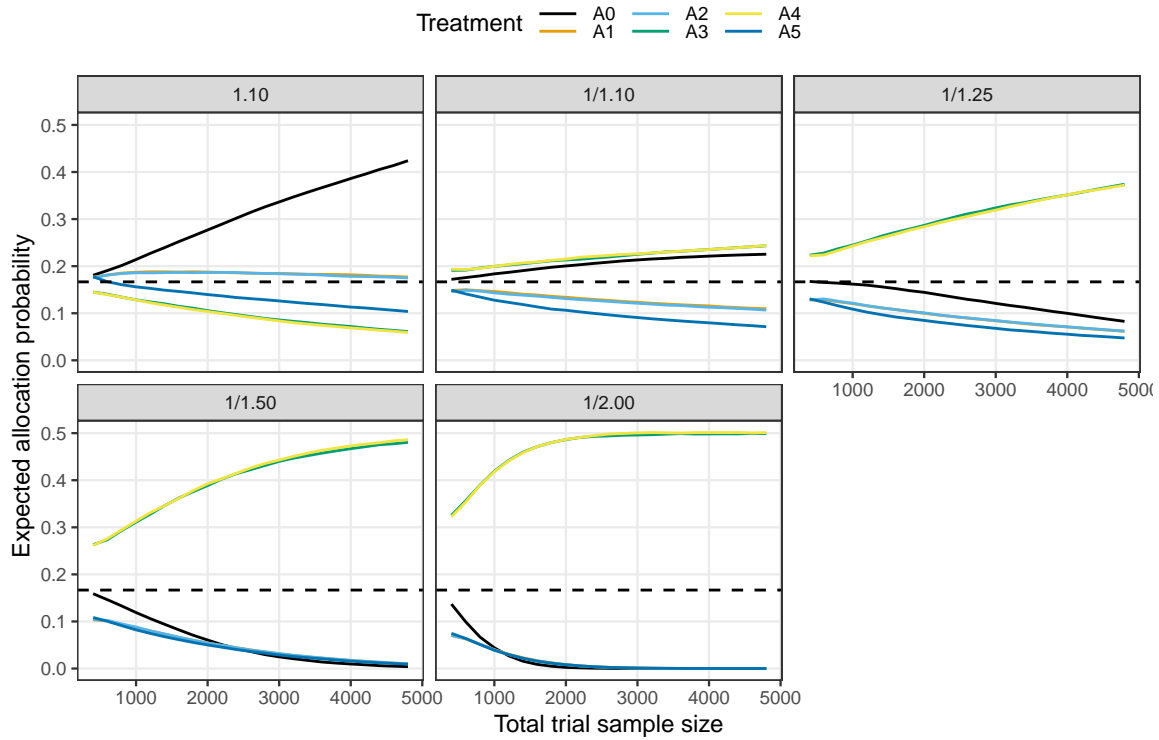


Figure 10: Expected allocation probability in domain A treatments as trial progresses. Affected treatments are A_3, A_4 .

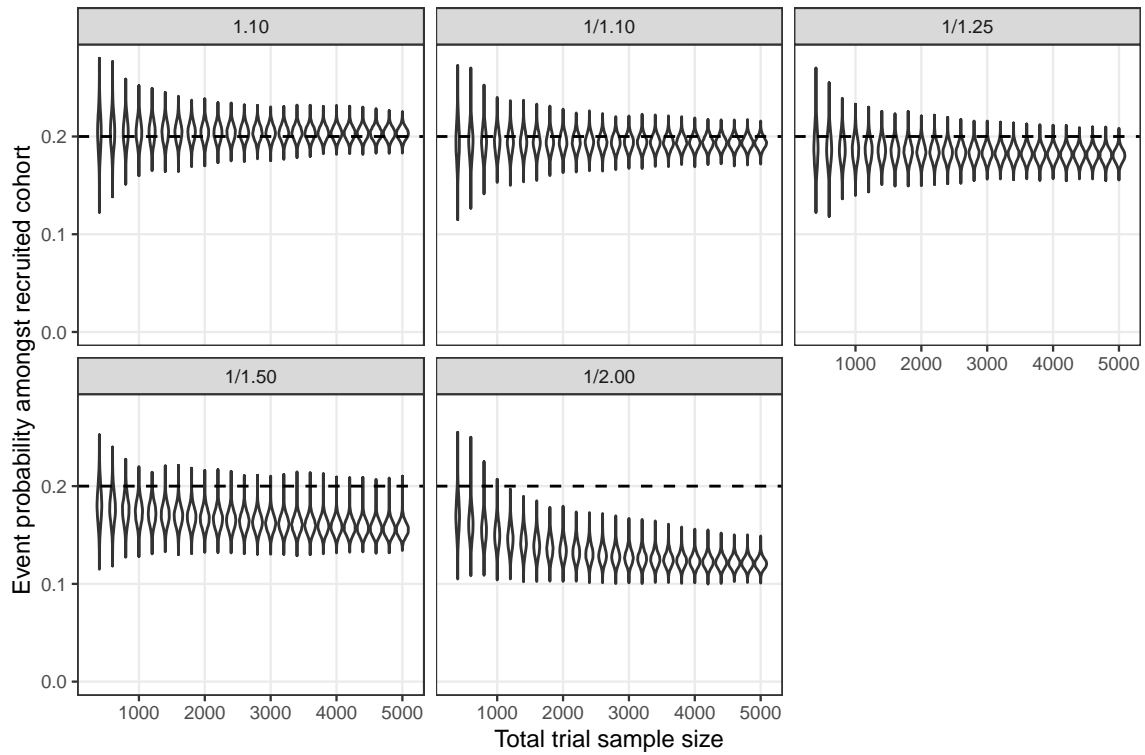


Figure 11: Probability of response as trial progresses. Reference line is response under SoC.

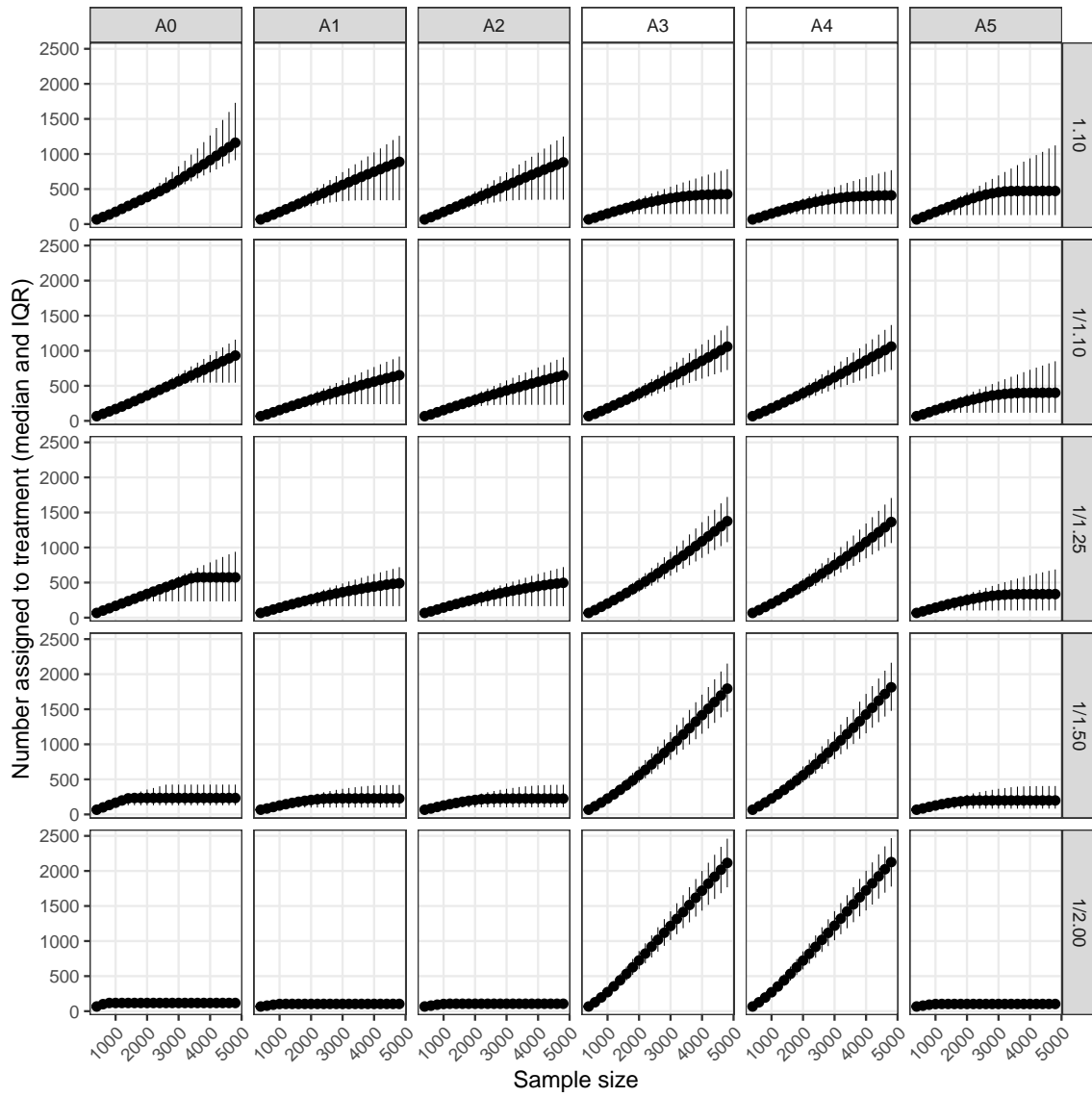


Figure 12: Number assigned to each treatment.

3.1.4 One element of a combination treatment effective

In this configuration, treatment A_1 is effective and there is no interaction between A_1 and A_2 so that the combination treatment $A_5 = A_1 + A_2$ is equally effective to A_1 but involves the additional ineffective treatment A_2 . In such a situation, preference would be the selection of A_1 over A_5 .

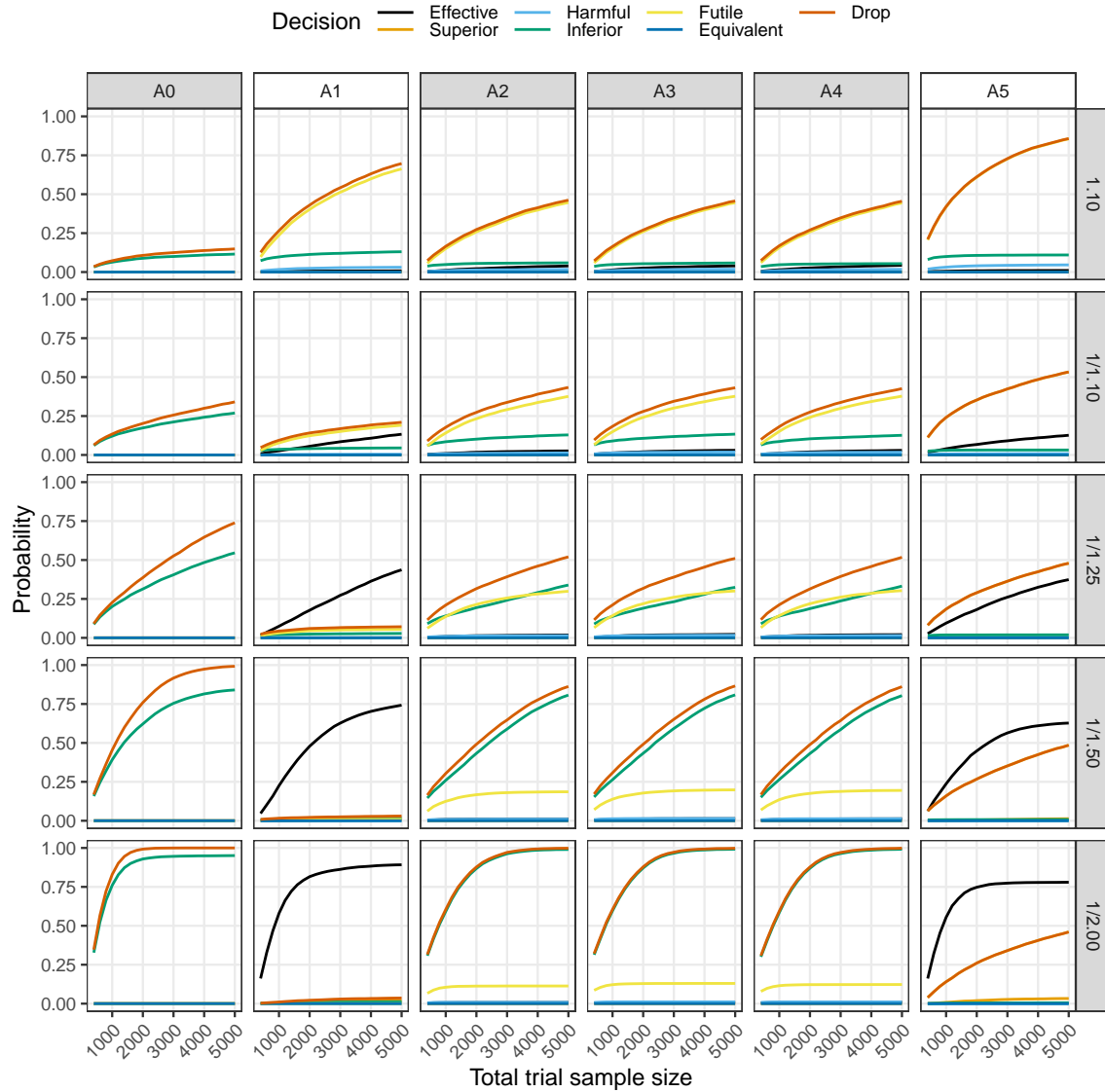


Figure 13: Probability of decision for domain A treatments as trial progresses (white facets are the affected treatments).

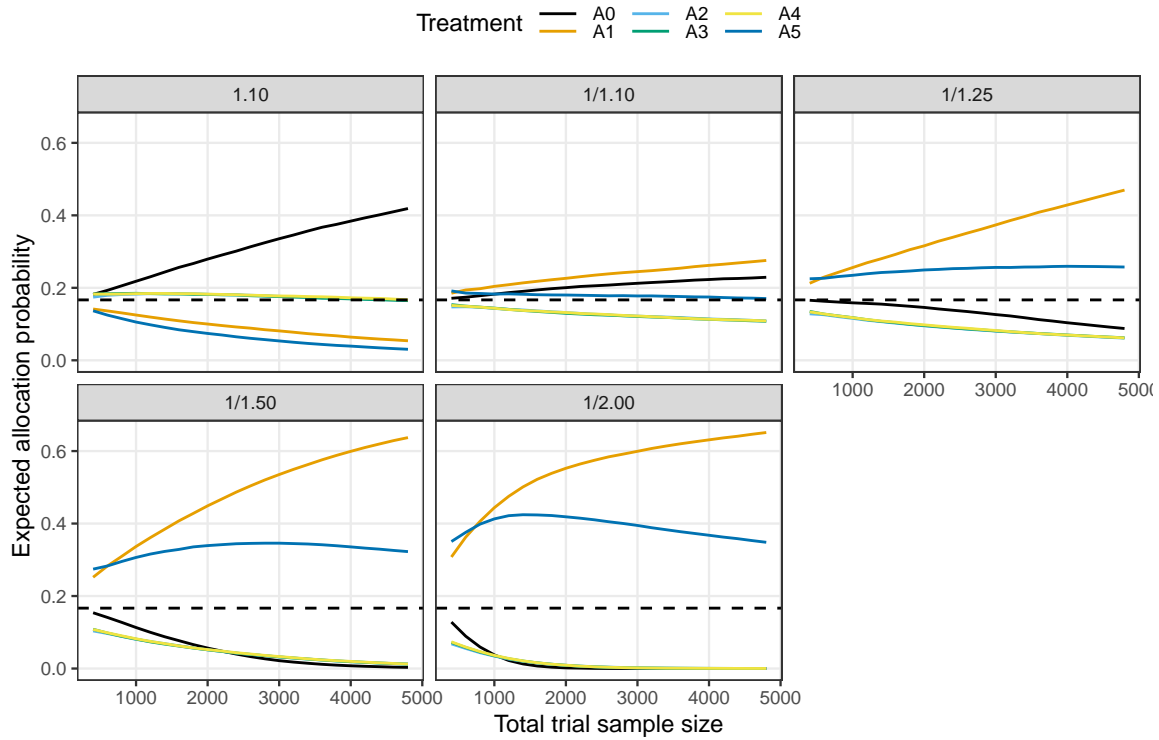


Figure 14: Expected allocation probability in domain A treatments as trial progresses. Treatments A_1 and A_5 are equally effective.

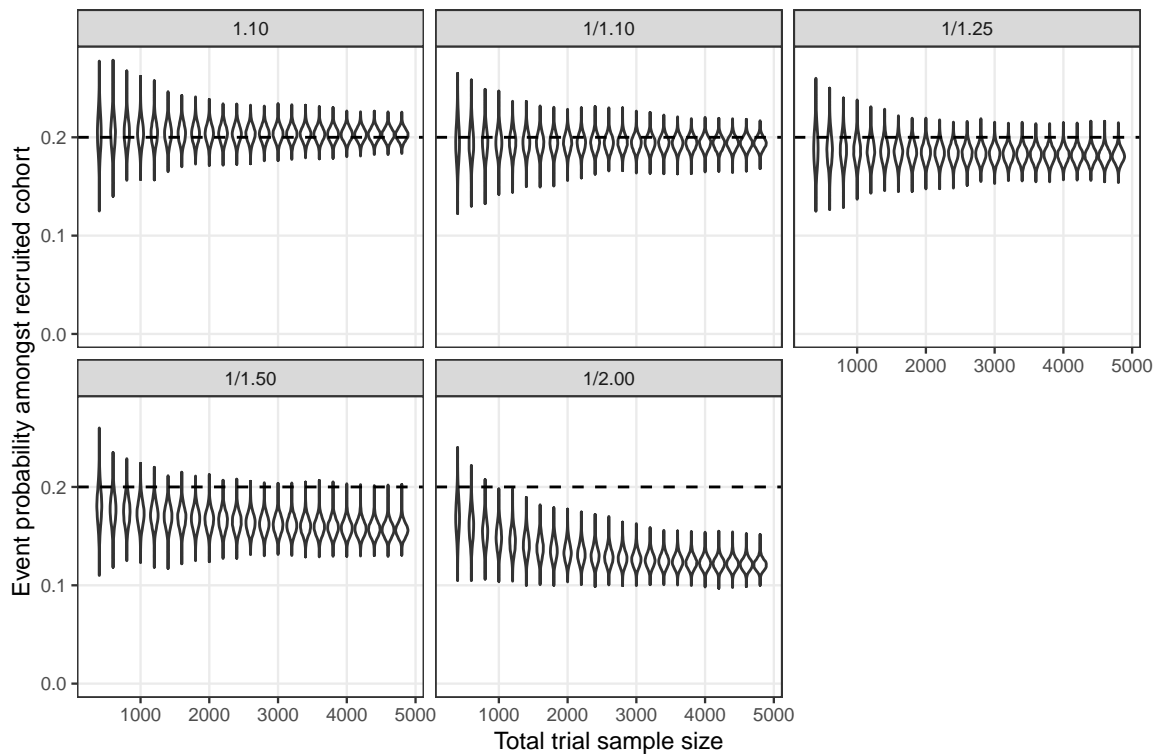


Figure 15: Probability of response as trial progresses.

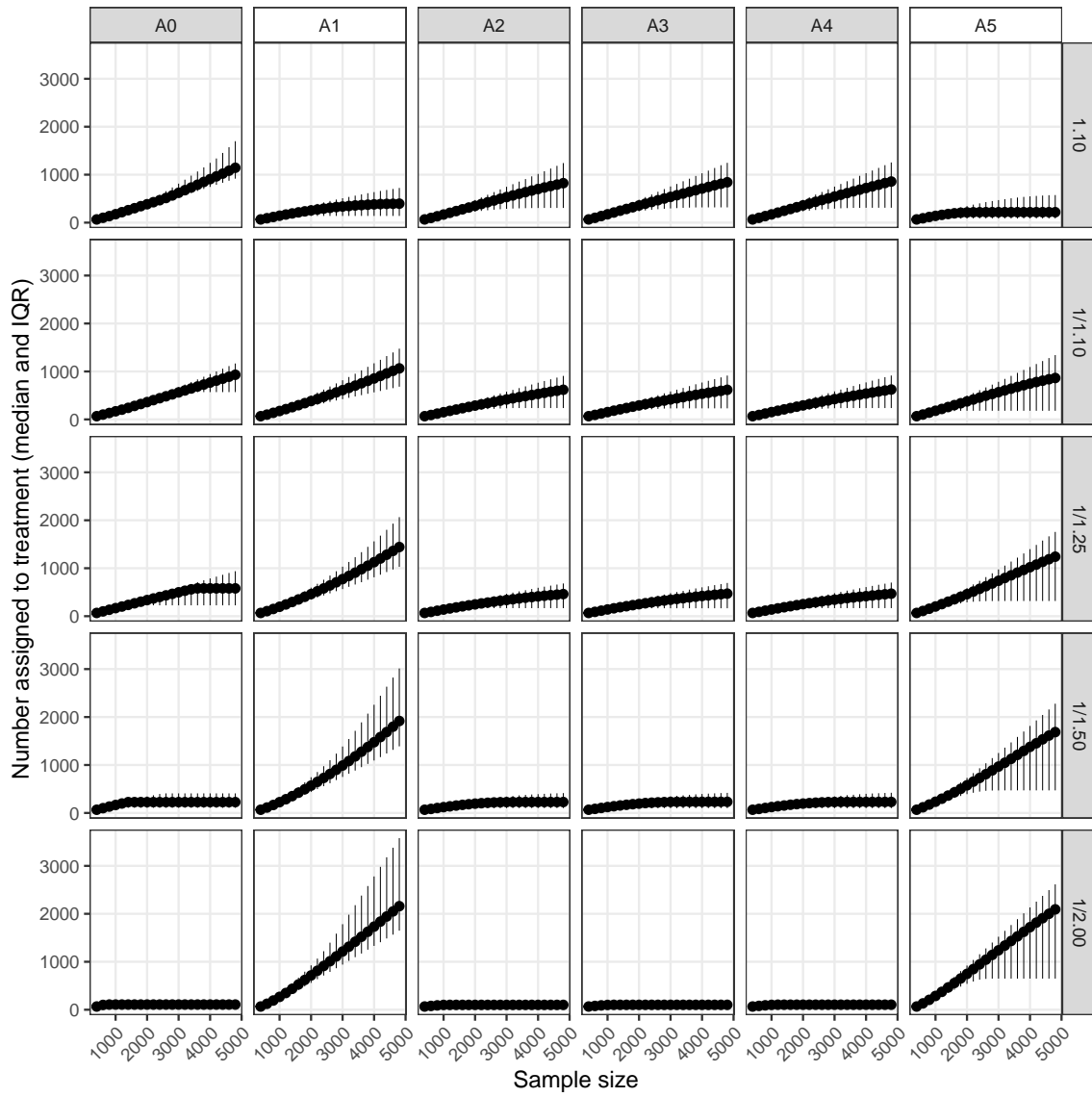


Figure 16: Number assigned to each treatment.

3.2 Domain B (4 treatments)

In this scenario a domain of four treatments under the following design is assumed

$$X_B = \begin{matrix} & \beta_{B0} & \beta_{B1} & \beta_{B2} & \beta_{B3} \\ \begin{matrix} B_0 \\ B_1 \\ B_2 \\ B_3 \end{matrix} & \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \end{matrix}$$

3.2.1 Global Null Scenario

The global null scenario for domain A shows a probability of less than 0.15 of dropping the no treatment option (either due to inferiority or a treatment declared effective) by 5,000 participants enrolled. Each intervention option in the domain has less than 0.05 probability of having been declared effective by 5,000 participants enrolled (approx 0.04). There is moderate probability of deciding ineffective arms as futile by 5,000 participants enrolled (approximately 0.5 for each ineffective arm). As the trial progresses, the expected probability of receiving the no treatment option increases due to the probability of dropping active treatments for futility. Due to the changing allocation probabilities, the no treatment option has the highest median number assigned.

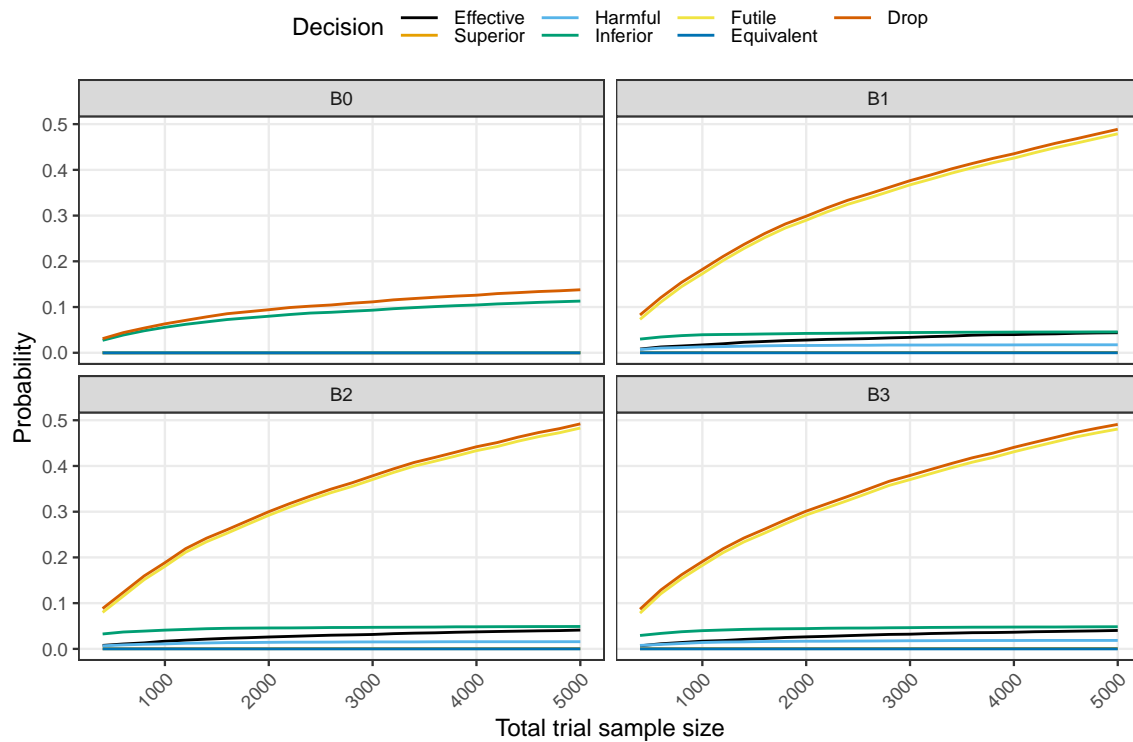


Figure 17: Probability of decision for domain B treatments as trial progresses.

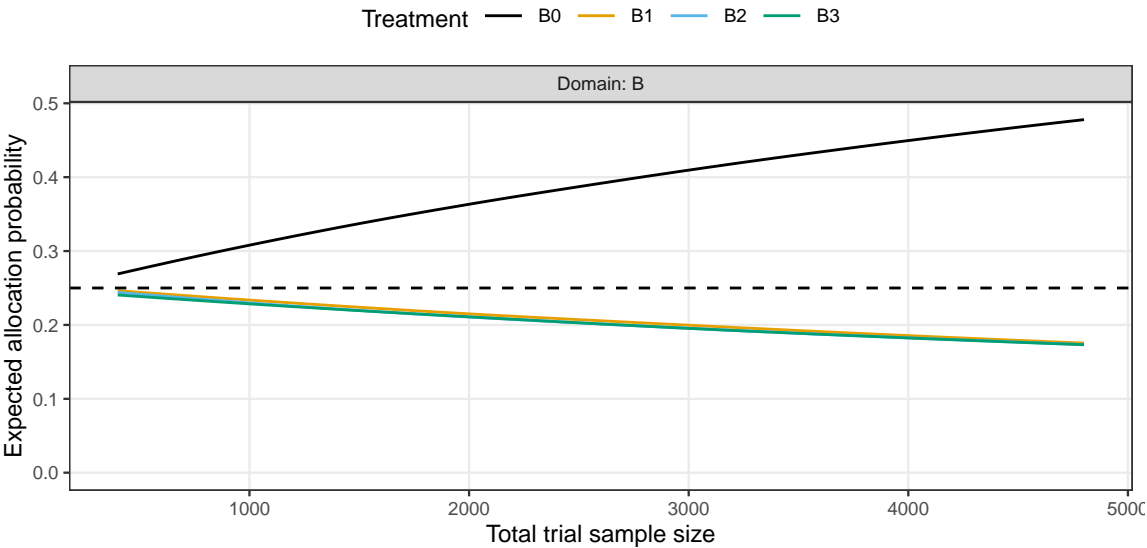


Figure 18: Expected allocation probability in domain B treatments as trial progresses.

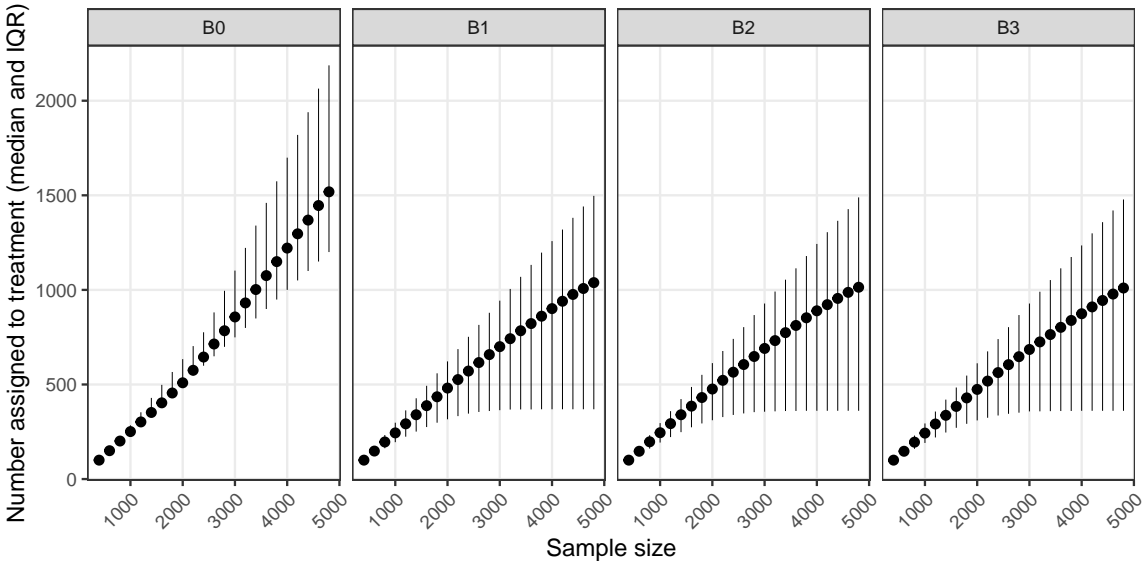


Figure 19: Number assigned to each treatment.

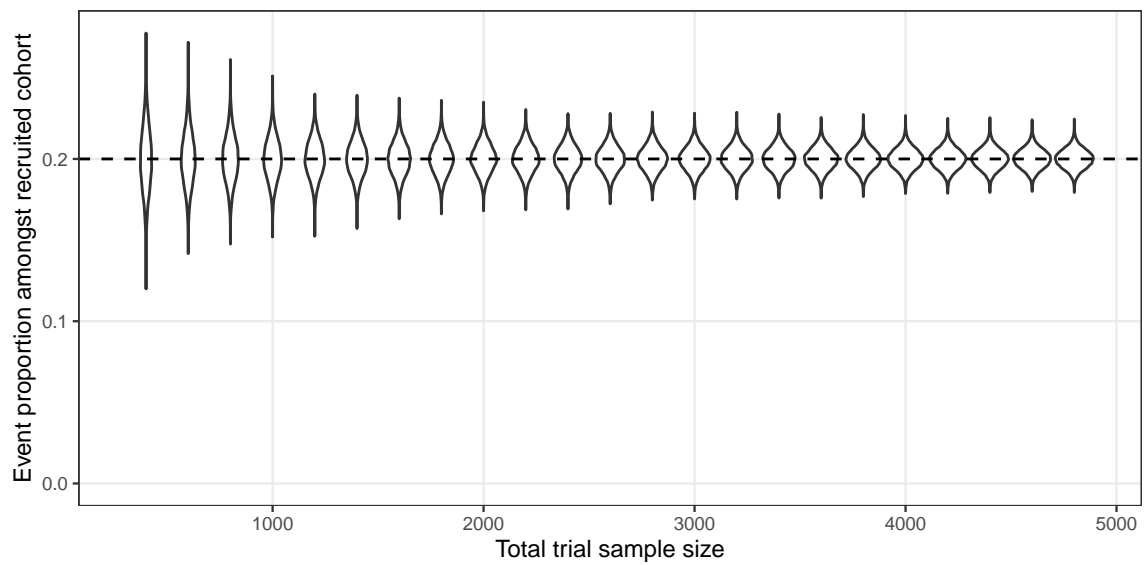


Figure 20: Probability of response as trial progresses.

3.2.2 One Treatment Effective

In the following, one treatment in domain B (B_1) is effective (or harmful).

The probability of deciding effectiveness exceeds 0.9 by 3,000 participants enrolled when B_1 changes the odds of the outcome by a factor of $2/3$ and exceeds 0.9 by 1,400 participants enrolled when B_1 changes the odds of the outcome by a factor of 0.5. When B_1 reduces the odds of the outcome by $1/1.25$, the probability of dropping B_1 remains below 0.06 by 5,000 participants enrolled.

When B_1 reduces the odds of the outcome by a factor 0.5, the probability of declaring superiority is 0.9 by 2,200 participants enrolled.

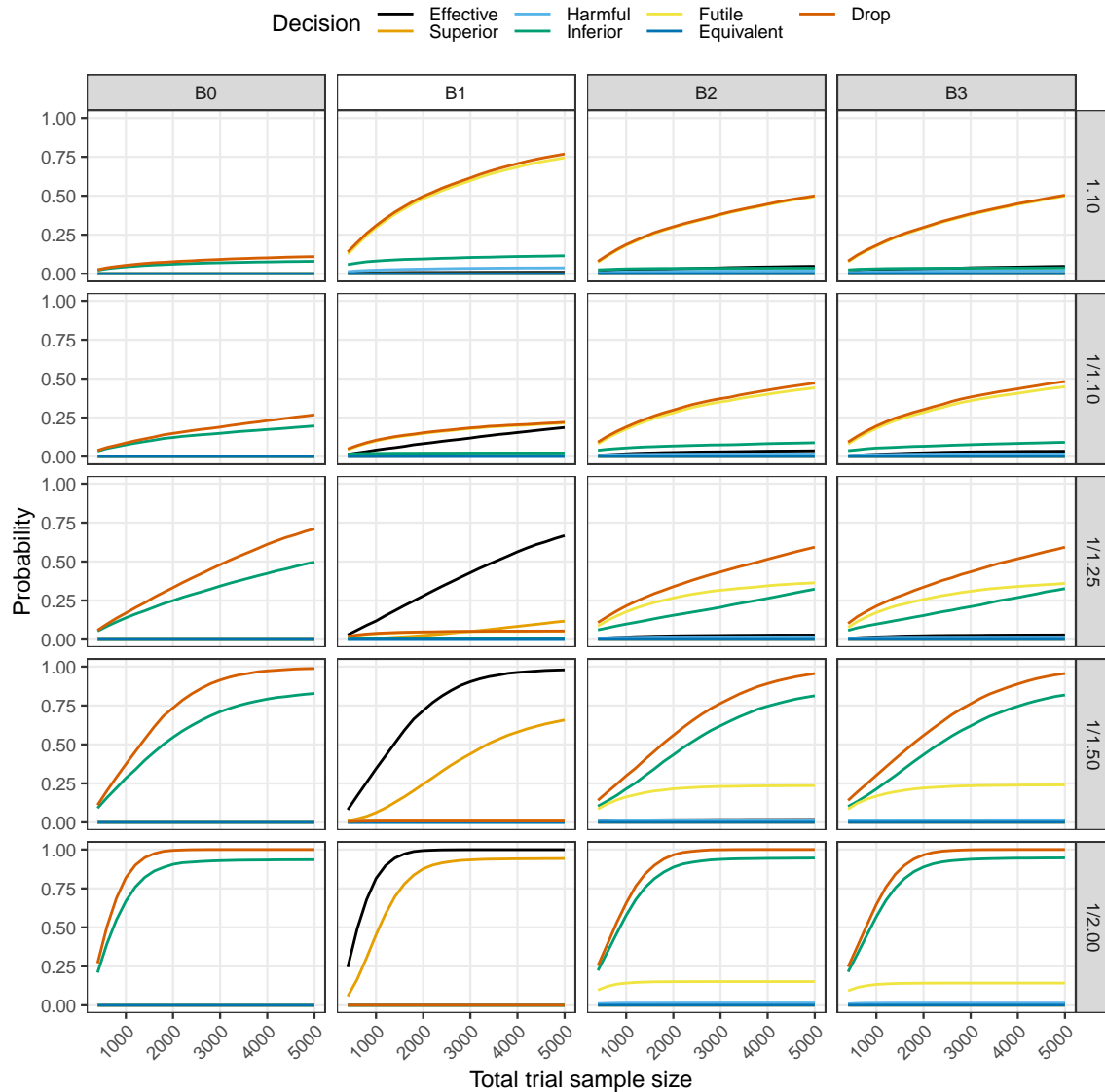


Figure 21: Probability of decision for domain B treatments as trial progresses (white facets are the affected treatments).

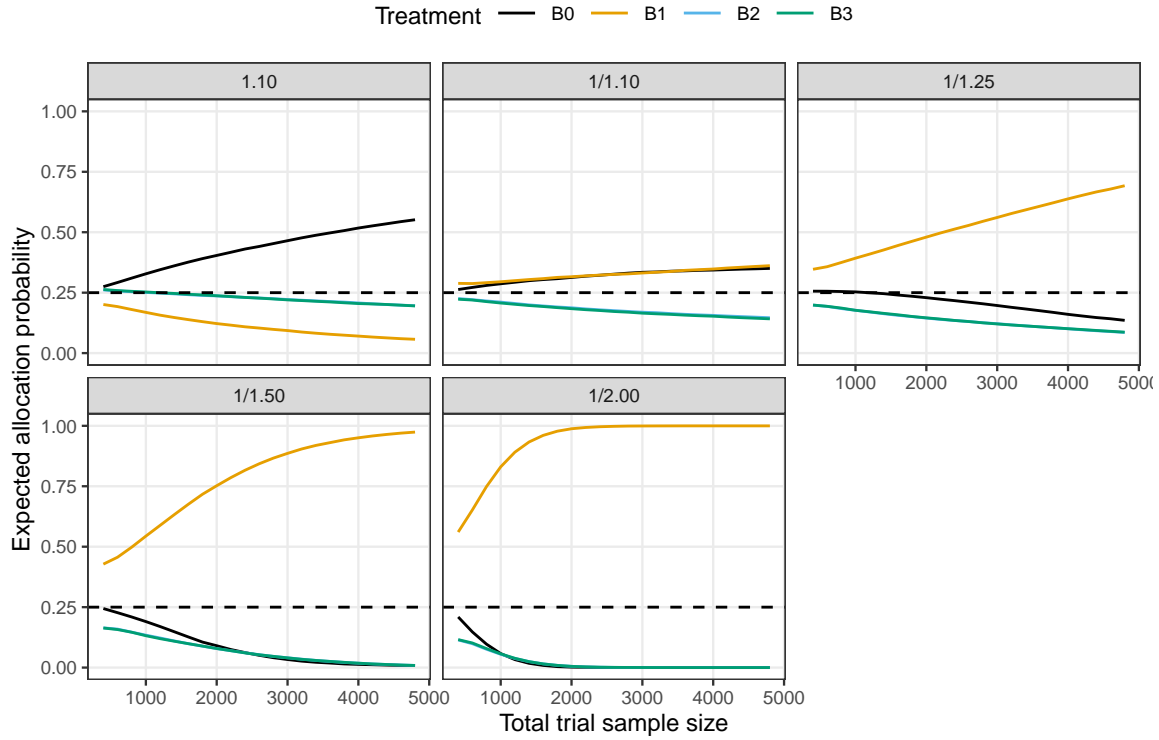


Figure 22: Expected allocation probability in domain B treatments as trial progresses.

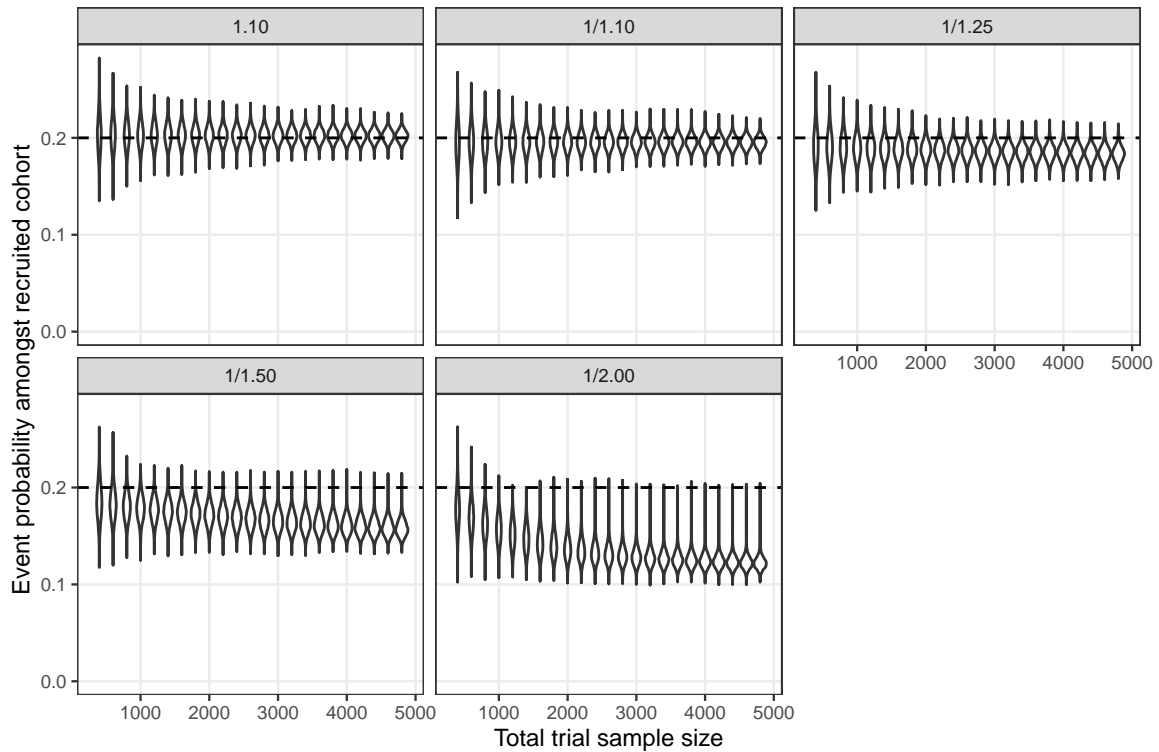


Figure 23: Probability of response as trial progresses.

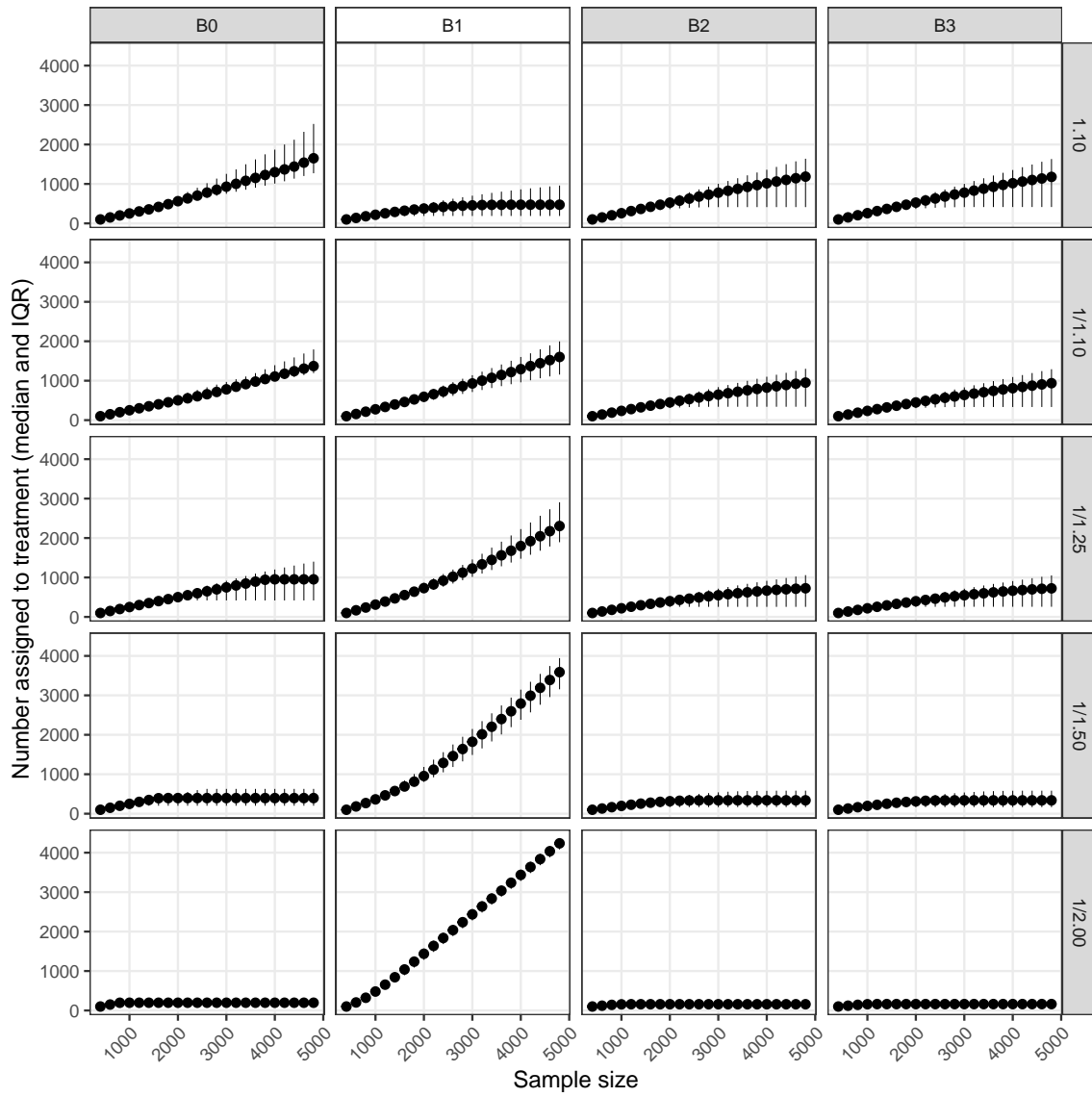


Figure 24: Number assigned to each treatment.

3.2.3 Two Effective

In the following, two treatments in domain B (B_1, B_2) are effective (or harmful).

When the effect size is $1/1.25$, the probability of declaring at least one of B_1 or B_2 effective is approximately 0.74 by 5,000 participants.

When the effect size is $1/1.50$ the probability of declaring at least one of B_1 or B_2 effective exceeds 0.8 by 2,200 participants enrolled and 0.9 by 3,000 participants. The probability of dropping at least one of B_1 or B_2 is below 0.08 by 5,000 participants.

When the effect size is $1/2.00$ the probability of declaring at least one effective exceeds 0.9 by 1,200 participants enrolled. The probability of dropping at least one of B_1 or B_2 is 0.08 by 5,000 participants.

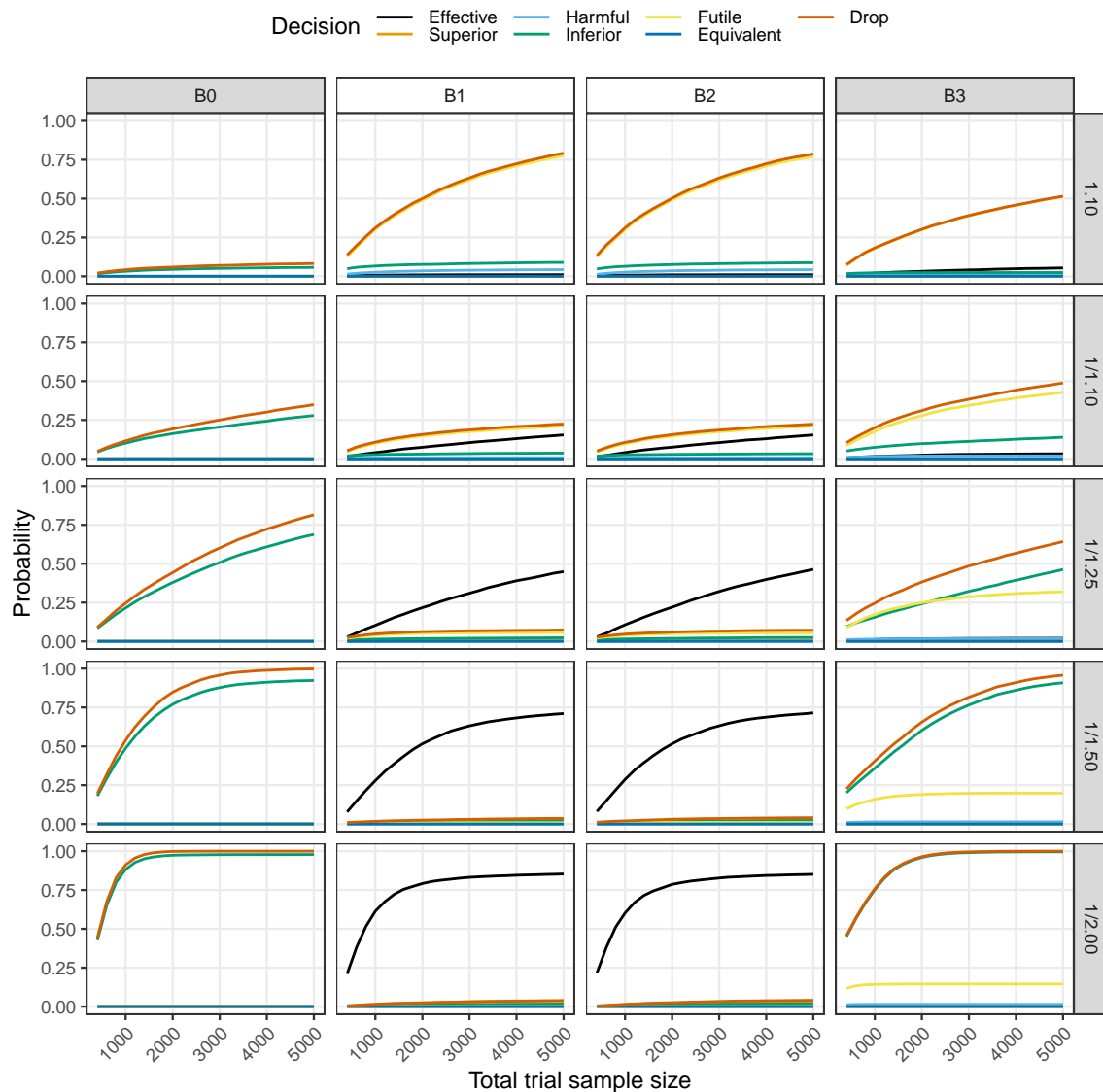


Figure 25: Probability of decision for domain B treatments as trial progresses (white facets are the affected treatments).

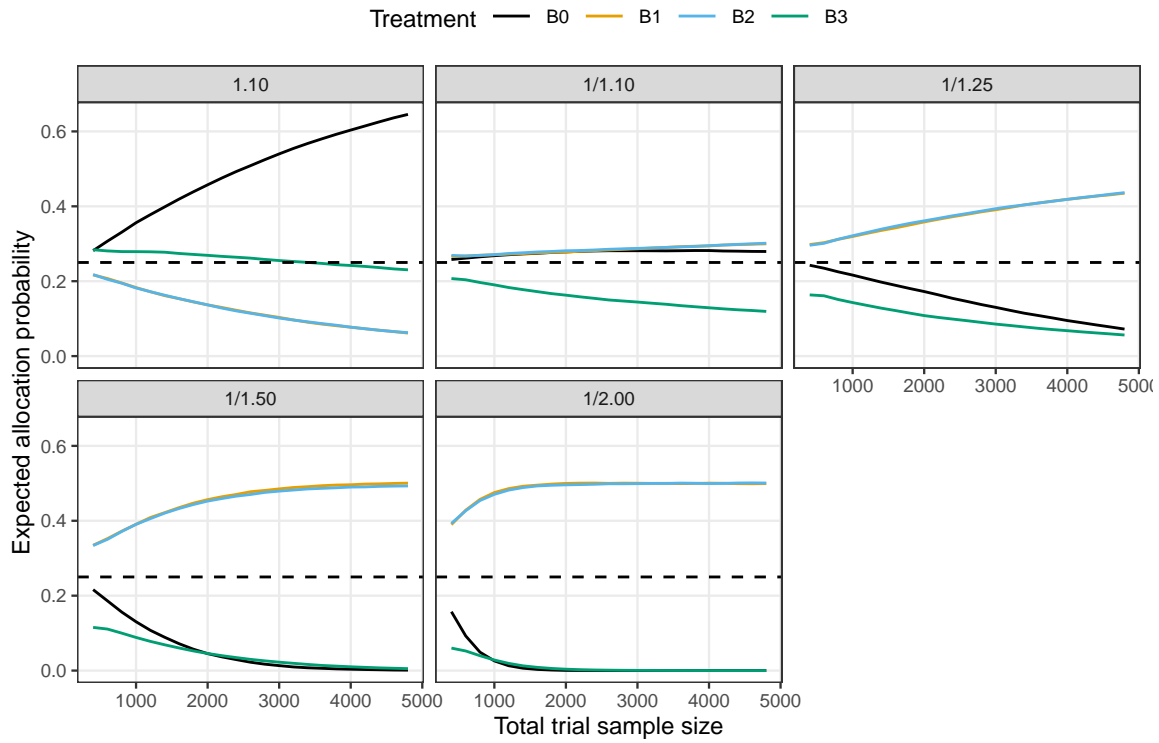


Figure 26: Expected allocation probability in domain B treatments as trial progresses.

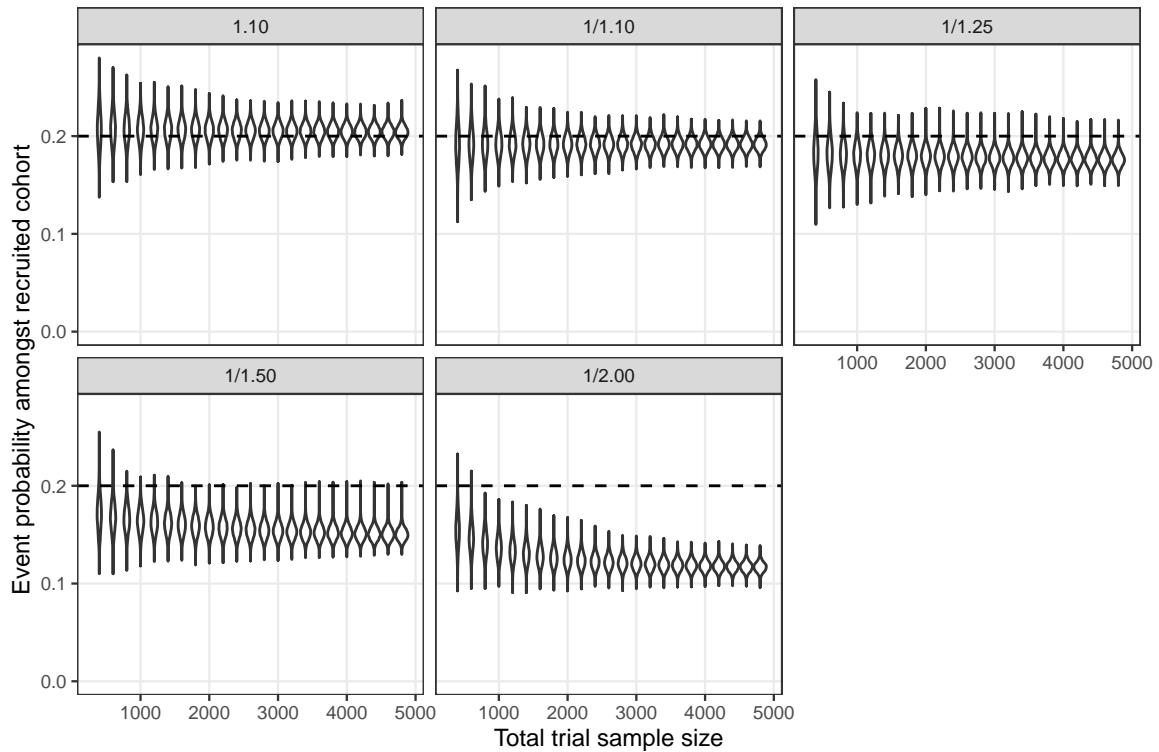


Figure 27: Probability of response as trial progresses.

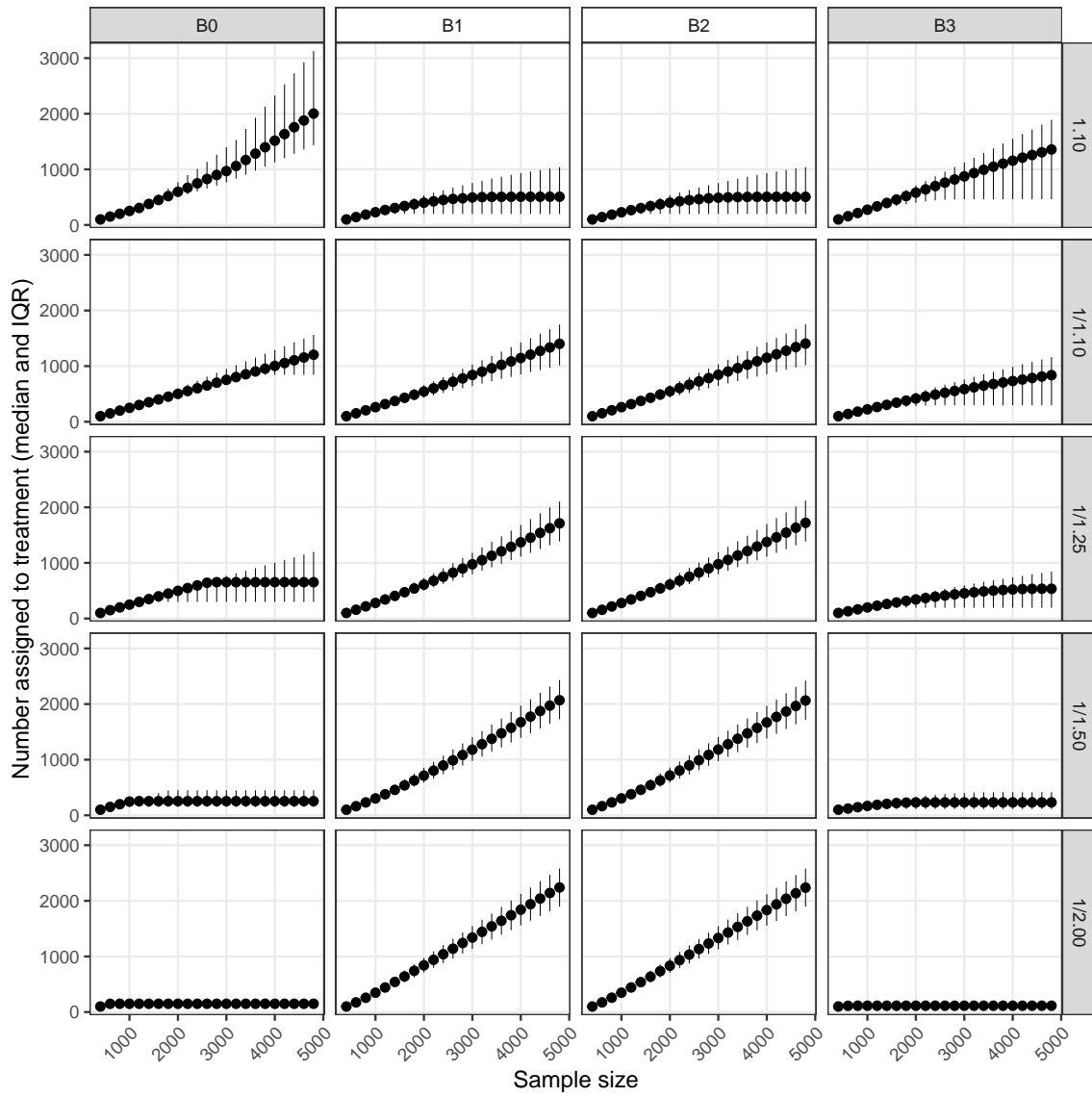


Figure 28: Number assigned to each treatment.

3.3 Domain C (2 treatments)

In what follows, a domain of two treatments is considered under the following design

$$X_C = \begin{matrix} & \beta_{C0} & \beta_{C1} \\ C_0 & \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \\ C_1 & \end{matrix}$$

3.3.1 Global Null

The global null scenario for domain C shows a probability of less than 0.06 of dropping the no treatment option (either due to inferiority or a treatment declared effective) by 5,000 participants enrolled. The lone active intervention option in the domain has less than 0.06 probability of having been declared effective by 5,000 participants enrolled.

There is moderate probability of deciding an ineffective arm as futile by 5,000 participants enrolled (approximately 0.58). As the trial progresses, the expected probability of receiving the no treatment option increases due to the probability of dropping active treatments for futility.

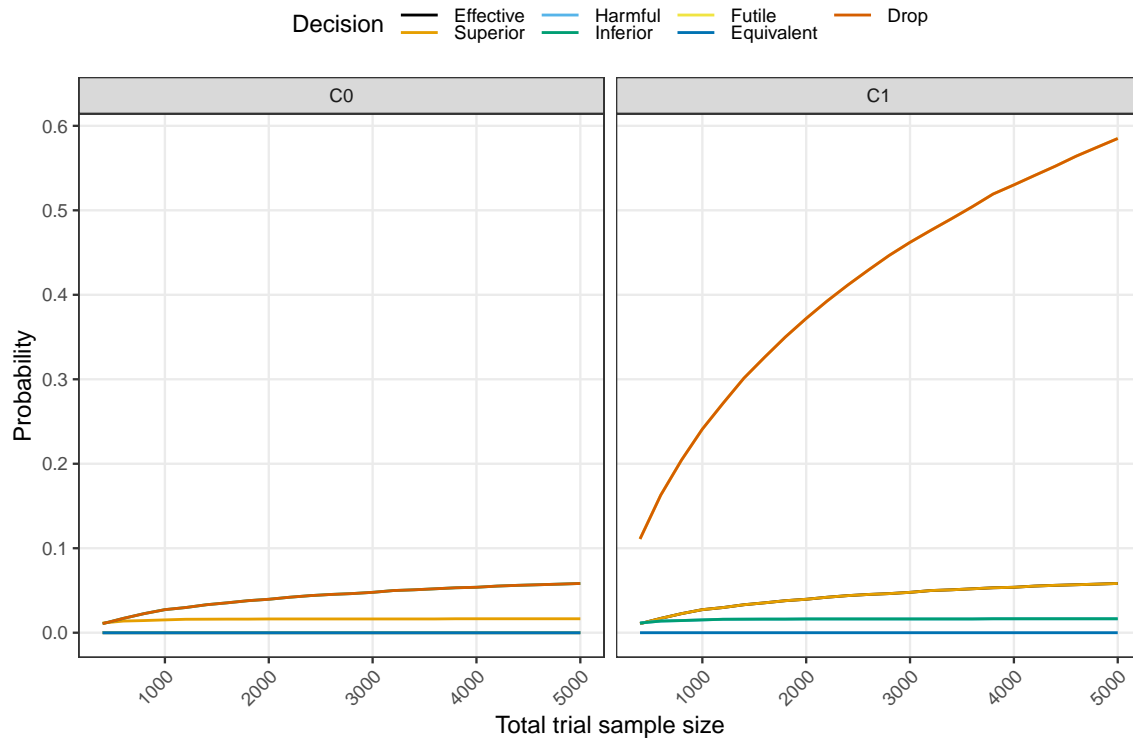


Figure 29: Probability of decision for domain C treatments as trial progresses.

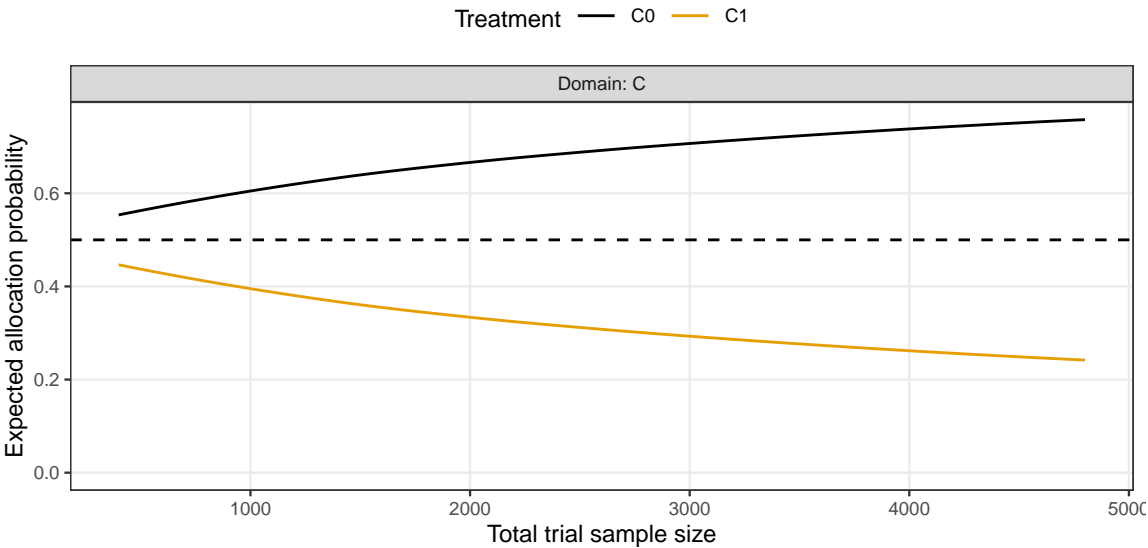


Figure 30: Expected allocation probability in domain C treatments as trial progresses.

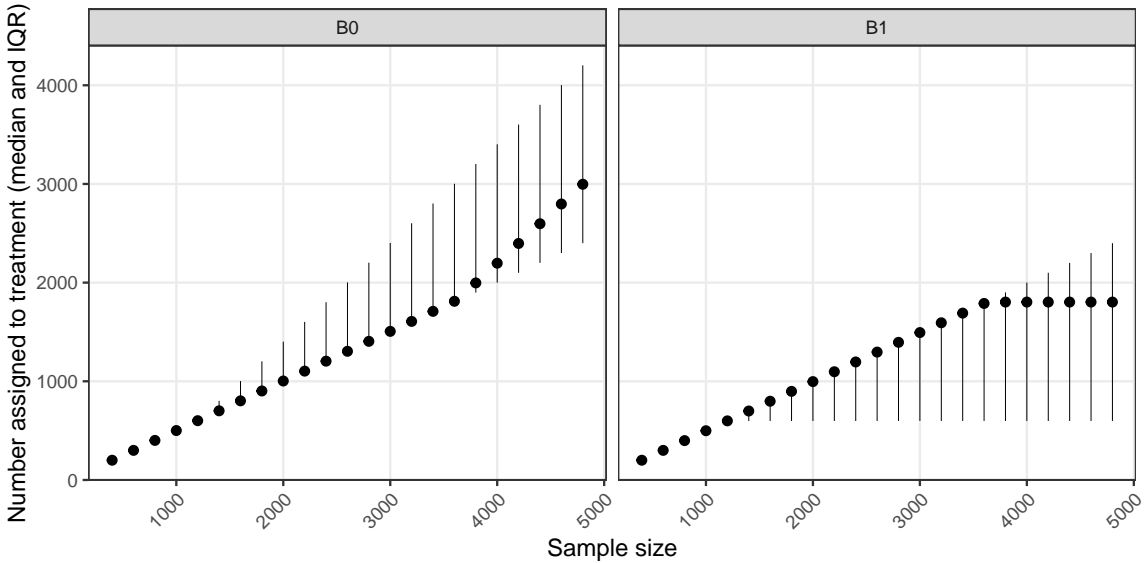


Figure 31: Number assigned to each treatment.

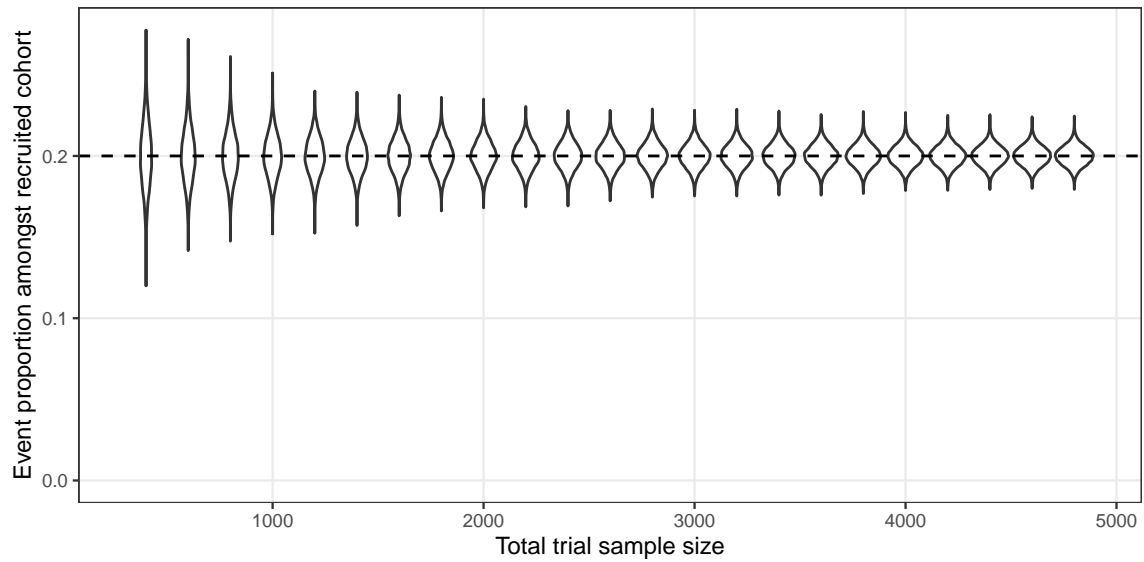


Figure 32: Probability of response as trial progresses.

3.3.2 One Effective Treatment

In the following, the one active treatment in domain C (C_1) is effective (or harmful).

The probability of deciding effectiveness/superiority exceeds 0.9 by 2,200 participants enrolled when C_1 changes the odds of the outcome by a factor of 2/3 and exceeds 0.9 by 800 participants enrolled when C_1 changes the odds of the outcome by a factor of 0.5. When C_1 reduces the odds of the outcome by 1/1.25, the probability of dropping C_1 remains below 0.04 by 5,000 participants enrolled.

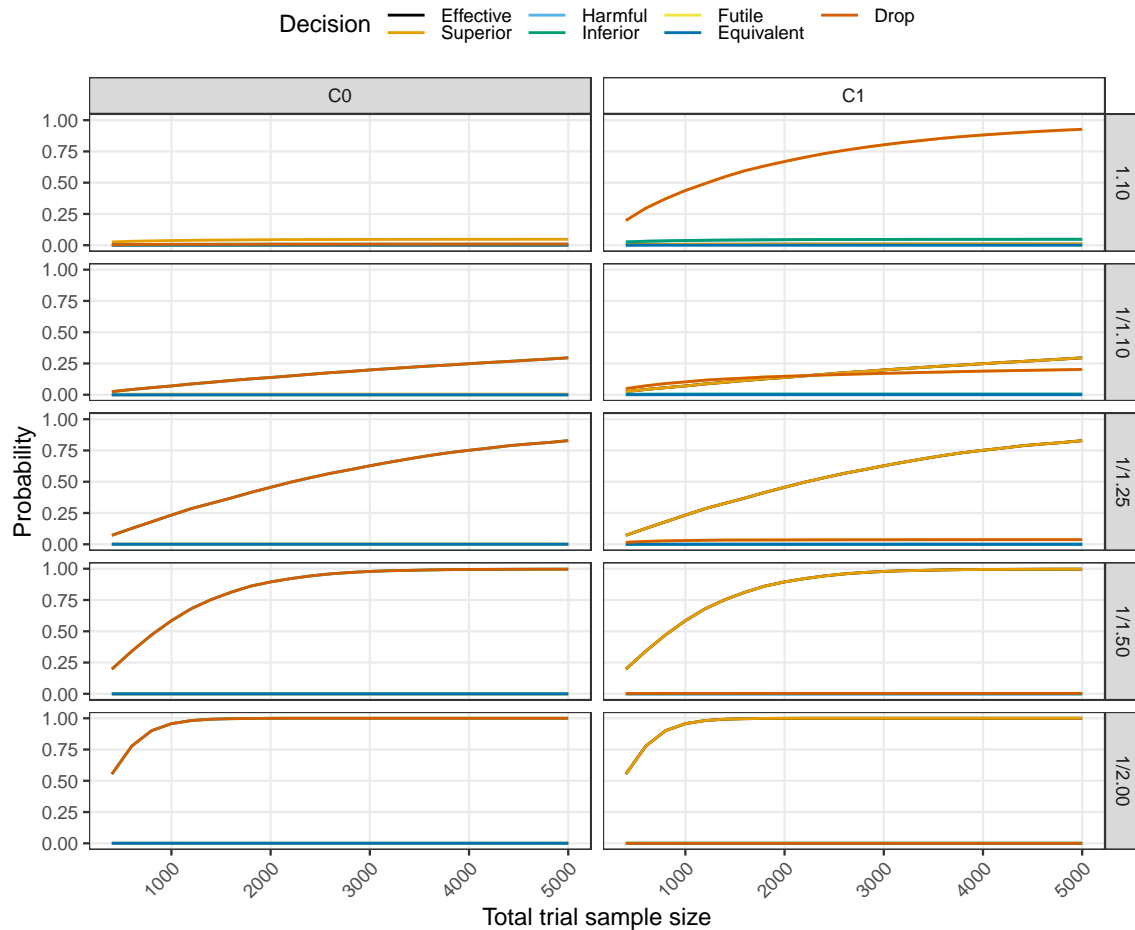


Figure 33: Probability of decision for domain C treatments as trial progresses (white facets are the affected treatments).

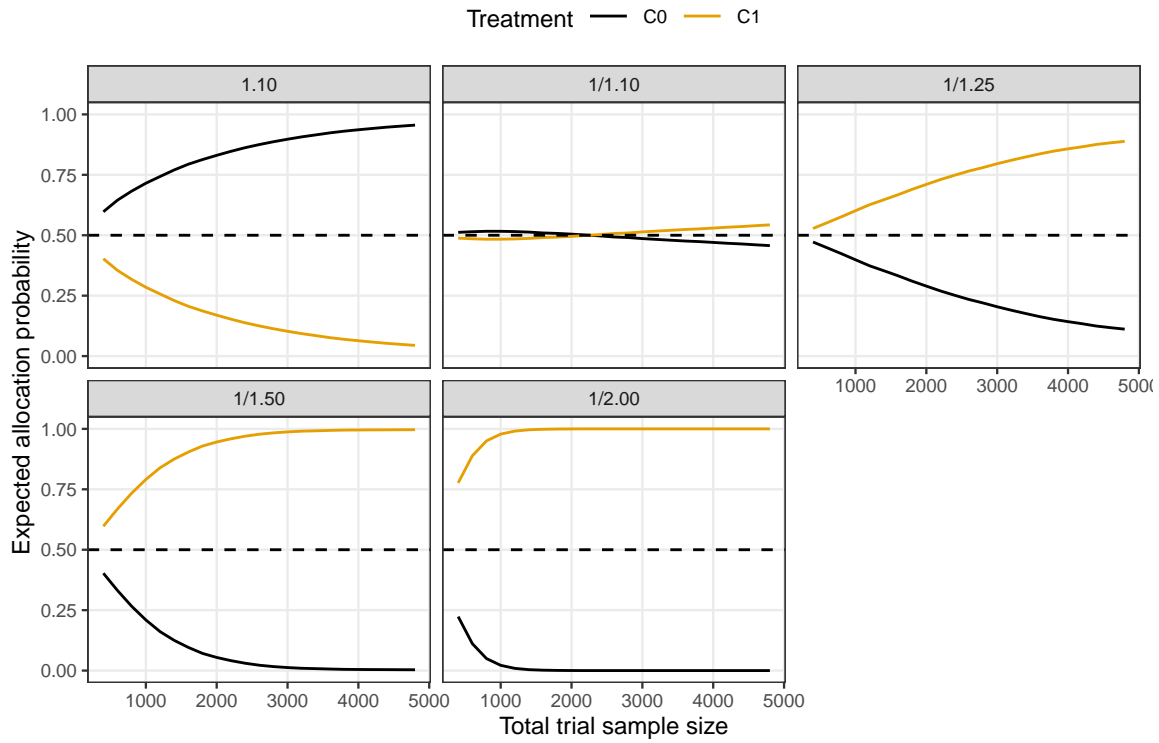


Figure 34: Expected allocation probability in domain C treatments as trial progresses.

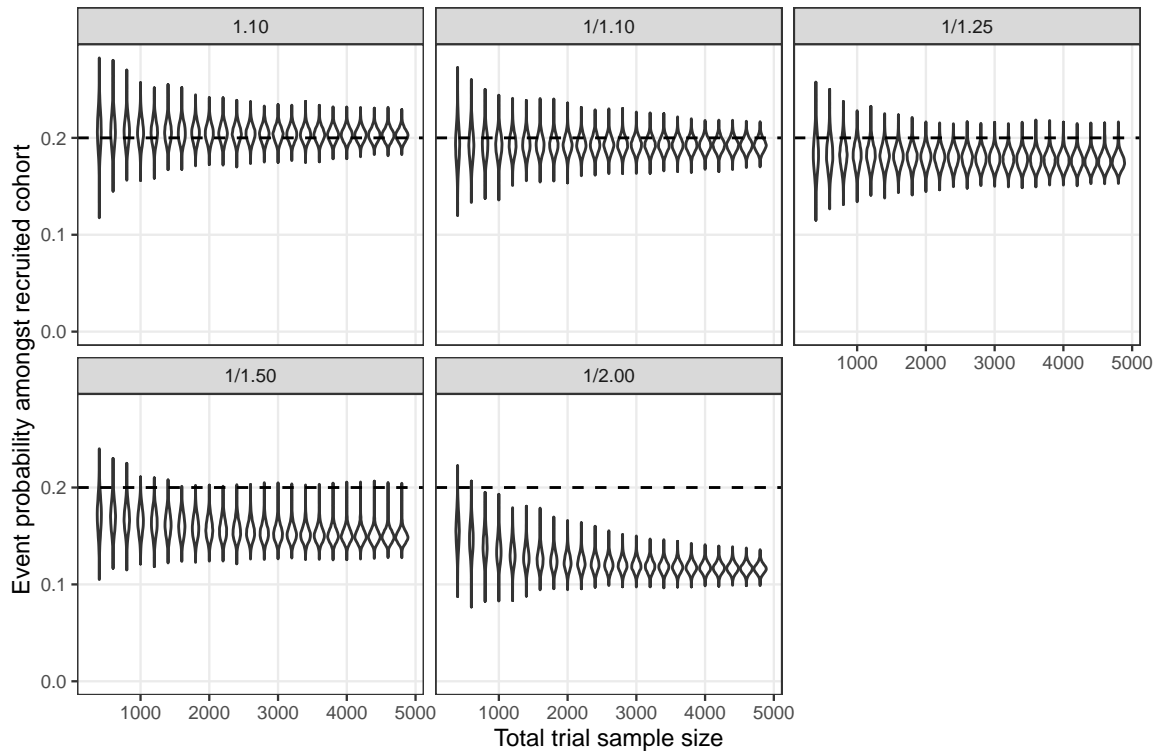


Figure 35: Probability of response as trial progresses.

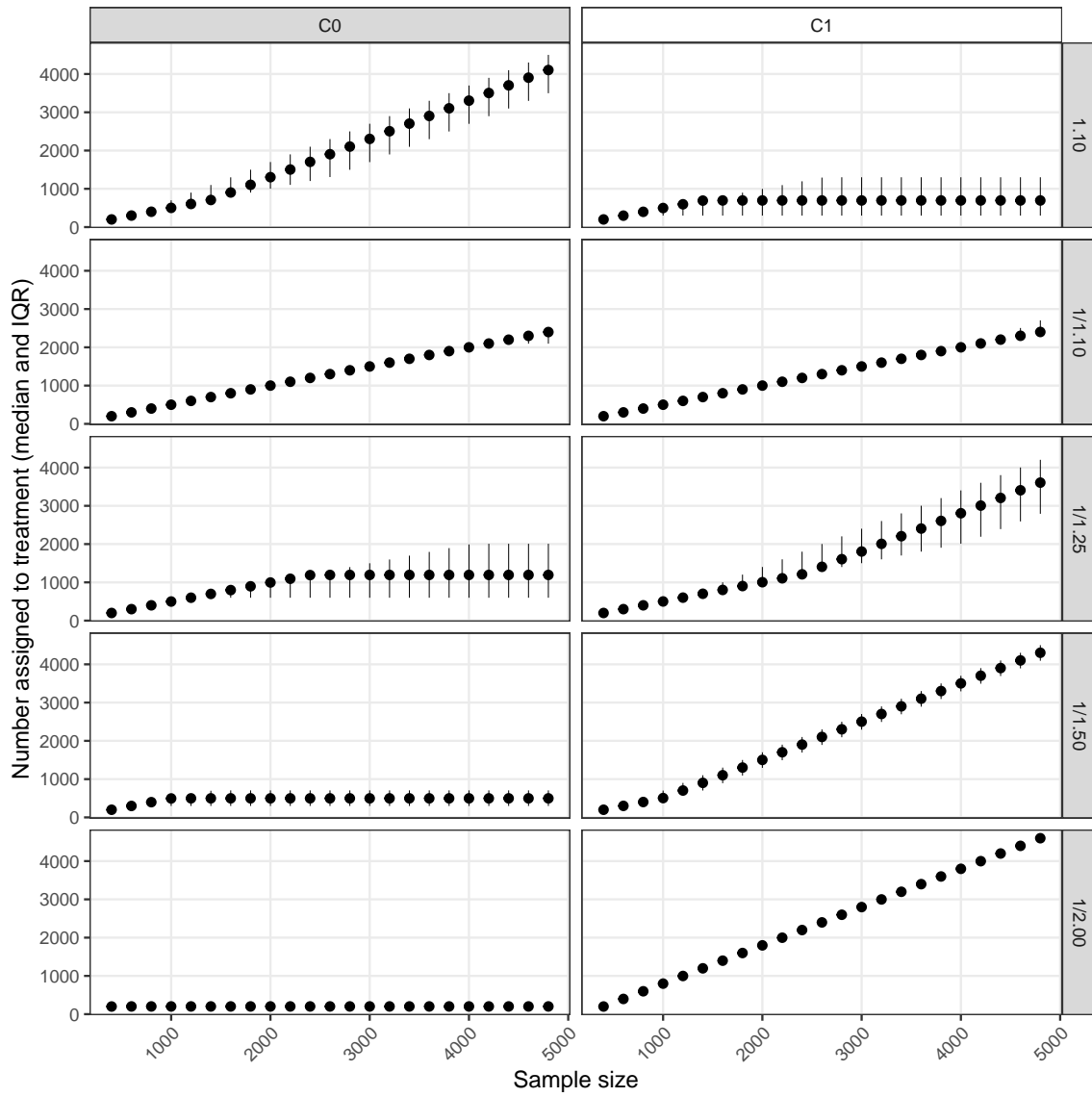


Figure 36: Number assigned to each treatment.