Sample Size

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Contents

1 Conditional Power Fixed Sample Size

Assuming two arms with outcome probabilities θ_0 in control and θ_1 in treatment, interest is in

$$H_0 : \delta > 0$$

where $\delta = \theta_0 - \theta_1$.

The Bayesian model assumed for the purposes of sample size calculation is:

$$\begin{aligned}
\theta_i &\sim \text{Beta}(\alpha_i, \beta_i) \\
y_i|\theta_i; n_i &\sim \text{Binomial}(\theta_i, n_i) \\
\theta_i|y_i; n_i &\sim \text{Beta}(\alpha_i + y_i, \beta_i + n_i - y_i)
\end{aligned}$$

for $i = 0, 1$. Although in practice, this would be a logistic regression model adjusting for relevant covariates.

For reference, conditional classical sample size under assumed control proportion and effect size are given in Figure 1. Conditional Bayesian sample size assuming an uninformative prior will be very similar, i.e.

$$\mathbb{E}_{\theta_0,\theta_1}[\Pr(\delta > 0|y_0, y_1) > 1 - \alpha] \approx \mathbb{E}_{\theta_0,\theta_1}[\phi(y_0, y_1)].$$

For example, assuming $\theta_0 = 0.15$ a reduction of $\delta = 0.11$ would require a sample size of 1209 per arm for 90% power.

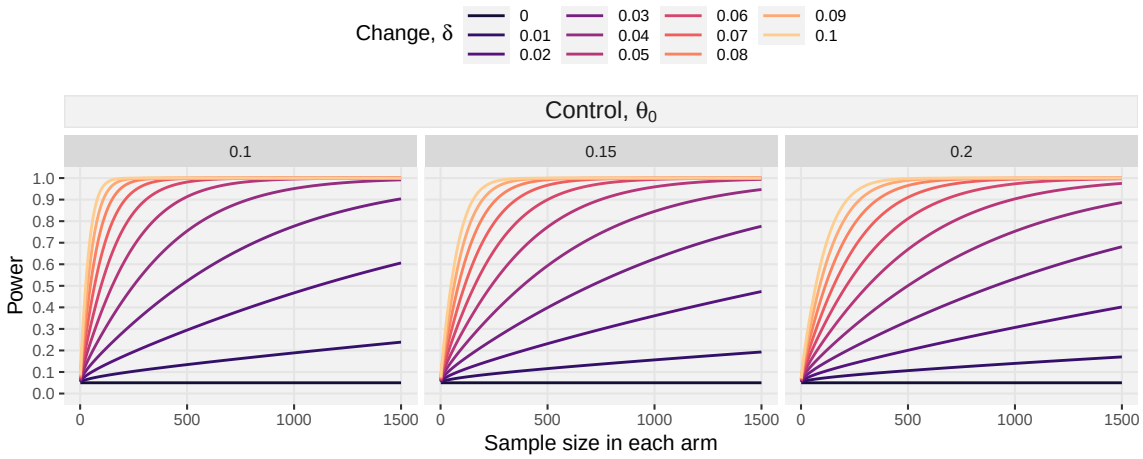

Figure 1: Frequentist power by sample size for given control proportion and effect size at level $\alpha = 0.05$.

2 Sequential Sample Size

We are interested in a group-sequential type design assuming two arms where effectiveness (or lack thereof) may be declared early if there is sufficient evidence.

At each interim we would assess $\pi_t = \Pr(\theta_0 - \theta_1 > 0 | \mathcal{D}_t)$ and decide

$$d_t^1 = \begin{cases} 1 & \text{if } \pi_t > \overline{\epsilon}_t \text{ (trigger superiority)} \\ 2 & \text{if } \pi_t < \underline{\epsilon}_t \text{ (trigger inferiority)} \\ 0 & \text{if } \pi_t \in [\underline{\epsilon}_t, \overline{\epsilon}_t] \text{ (continue).} \end{cases}$$

Additionally, we could consider $\varpi_t = \Pr(|\theta_0 - \theta_1| < \Delta | \mathcal{D}_t)$ and decide

$$d_t^2 = \begin{cases} 1 & \text{if } \varpi_t > \kappa_t \text{ and } d_t^1 = 0 \text{ (trigger equivalence)} \\ 0 & \text{if } \varpi_t \leq \kappa_t \text{ and } d_t^1 = 0 \text{ (continue).} \end{cases}$$

The results assume two arms with fixed 1:1 allocation. If other arms are added as the trial progresses, either the maximum sample size would need to be increased to accommodate the arm, or power would be reduced compared to what is displayed. The results are idealistic in that they assume no drop-out and no missing information at each interim analysis.

The thresholds vary according to

$$\begin{aligned} \underline{\epsilon}_t &= a_0 (n/N)^{b_0} \\ \overline{\epsilon}_t &= a_1^{(n/N)^{b_1}} \\ \kappa_t &= a_2^{(n/N)^{b_2}}. \end{aligned}$$

where a is a vector of target thresholds at maximum information and b a vector of scaling parameters.

The parameters considered are given in the table.

Table 1: Threshold parameters considered.

id	a0	a1	a2	b0	b1	b2
1	0.05	0.95	0.95	0.0	0.0	0
2	0.05	0.99	0.90	0.0	0.0	0
3	0.10	0.99	0.90	0.0	0.0	0
4	0.10	0.98	0.90	1.0	1.0	0
5	0.10	0.97	0.90	1.5	1.5	0
6	0.10	0.96	0.90	3.0	3.0	0
7	0.10	0.95	0.90	3.5	3.5	0

2.1 Effect size 0.00

Table 2: Expected trial outcomes.

Threshold	a0	a1	a2	b0	b1	b2	Parameter	theta0	theta1	superior	inferior	equivalent	triggered	early
1	0.05	0.95	0.95	0.0	0.0	0	1	0.20	0.20	0.20	0.19	0.00	0.39	0.38
1	0.05	0.95	0.95	0.0	0.0	0	7	0.15	0.15	0.19	0.19	0.01	0.40	0.38
1	0.05	0.95	0.95	0.0	0.0	0	13	0.10	0.10	0.20	0.19	0.41	0.80	0.75
2	0.05	0.99	0.90	0.0	0.0	0	1	0.20	0.20	0.05	0.19	0.21	0.46	0.31
2	0.05	0.99	0.90	0.0	0.0	0	7	0.15	0.15	0.05	0.19	0.48	0.72	0.66
2	0.05	0.99	0.90	0.0	0.0	0	13	0.10	0.10	0.05	0.19	0.66	0.90	0.87
3	0.10	0.99	0.90	0.0	0.0	0	1	0.20	0.20	0.05	0.33	0.18	0.56	0.44
3	0.10	0.99	0.90	0.0	0.0	0	7	0.15	0.15	0.05	0.32	0.41	0.78	0.73
3	0.10	0.99	0.90	0.0	0.0	0	13	0.10	0.10	0.05	0.31	0.56	0.92	0.90
4	0.10	0.98	0.90	1.0	1.0	0	1	0.20	0.20	0.05	0.19	0.23	0.46	0.30
4	0.10	0.98	0.90	1.0	1.0	0	7	0.15	0.15	0.05	0.18	0.52	0.74	0.67
4	0.10	0.98	0.90	1.0	1.0	0	13	0.10	0.10	0.05	0.16	0.71	0.92	0.89
5	0.10	0.97	0.90	1.5	1.5	0	1	0.20	0.20	0.06	0.16	0.23	0.45	0.28
5	0.10	0.97	0.90	1.5	1.5	0	7	0.15	0.15	0.06	0.16	0.53	0.74	0.66
5	0.10	0.97	0.90	1.5	1.5	0	13	0.10	0.10	0.06	0.13	0.74	0.93	0.89
6	0.10	0.96	0.90	3.0	3.0	0	1	0.20	0.20	0.06	0.13	0.24	0.42	0.23
6	0.10	0.96	0.90	3.0	3.0	0	7	0.15	0.15	0.05	0.13	0.54	0.72	0.62
6	0.10	0.96	0.90	3.0	3.0	0	13	0.10	0.10	0.06	0.10	0.76	0.93	0.88
7	0.10	0.95	0.90	3.5	3.5	0	1	0.20	0.20	0.06	0.12	0.24	0.43	0.23
7	0.10	0.95	0.90	3.5	3.5	0	7	0.15	0.15	0.06	0.12	0.55	0.73	0.62
7	0.10	0.95	0.90	3.5	3.5	0	13	0.10	0.10	0.07	0.10	0.77	0.93	0.88

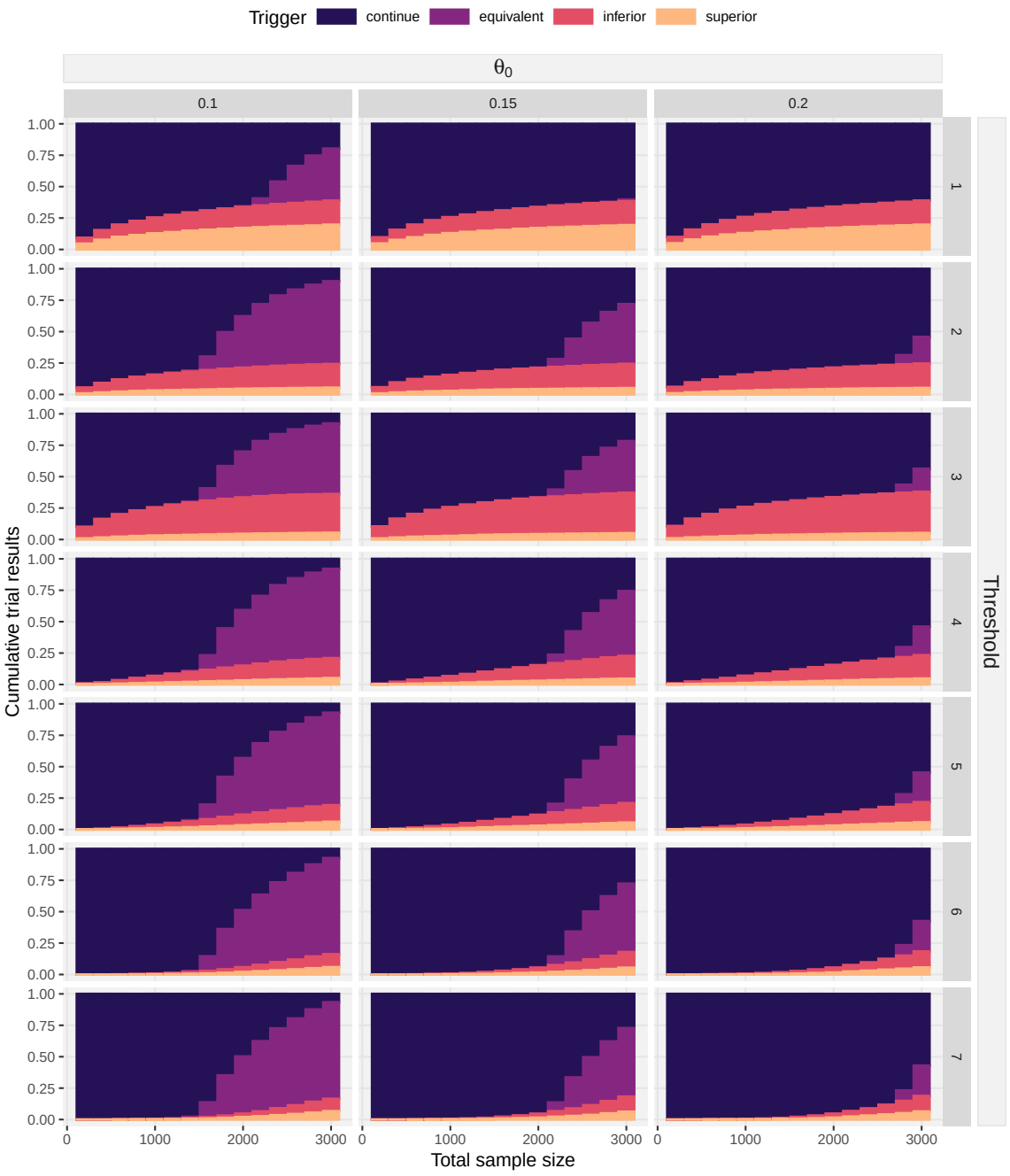

Figure 2: Expected trial progression.

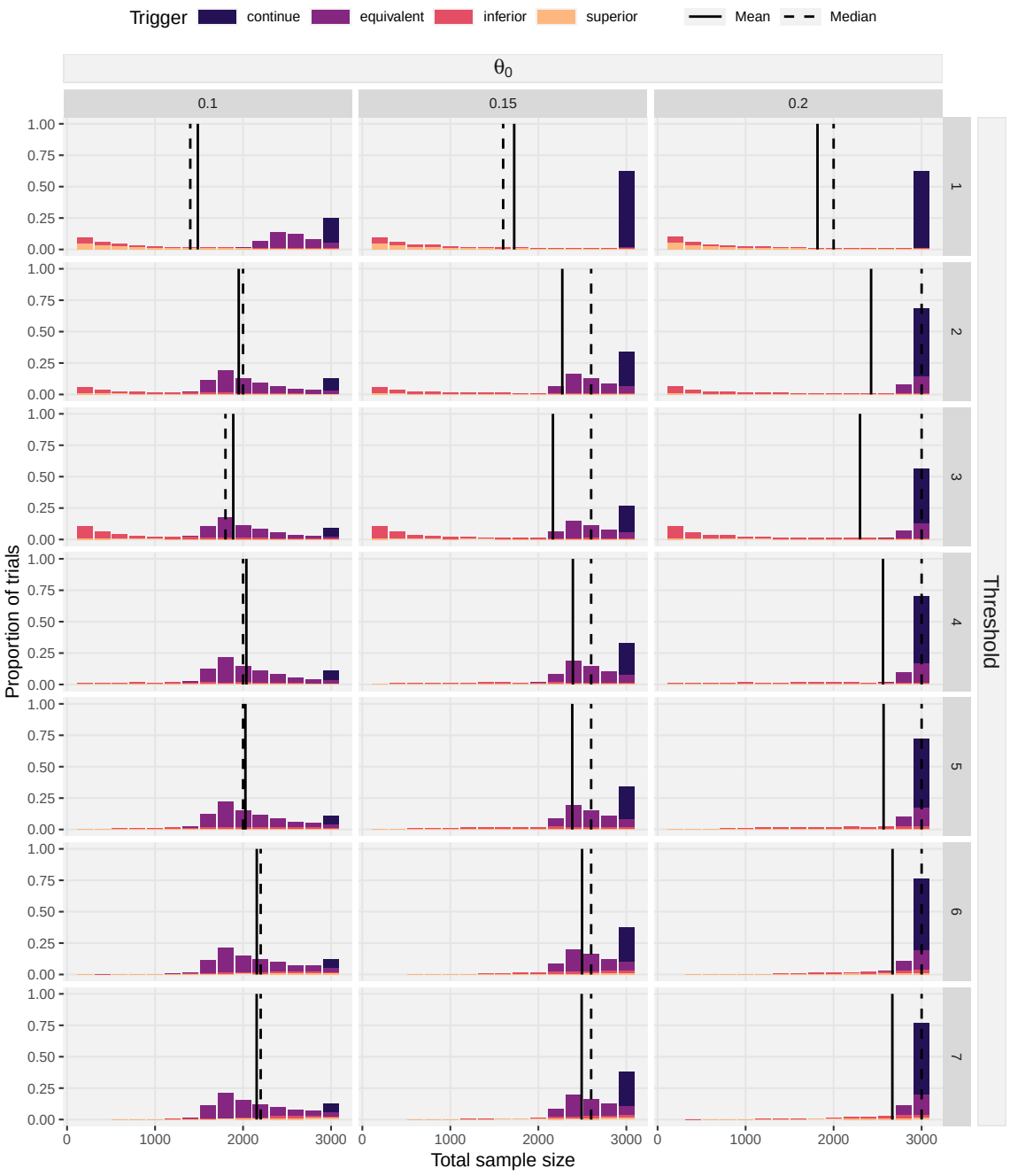

Figure 3: Distribution of trial sample sizes.

2.2 Effect size 0.01

Table 3: Expected trial outcomes.

Threshold	a0	a1	a2	b0	b1	b2	Parameter	theta0	theta1	superior	inferior	equivalent	triggered	early
1	0.05	0.95	0.95	0.0	0.0	0	2	0.20	0.19	0.35	0.10	0.00	0.45	0.44
1	0.05	0.95	0.95	0.0	0.0	0	8	0.15	0.14	0.39	0.08	0.02	0.50	0.46
1	0.05	0.95	0.95	0.0	0.0	0	14	0.10	0.09	0.42	0.07	0.34	0.83	0.78
2	0.05	0.99	0.90	0.0	0.0	0	2	0.20	0.19	0.13	0.10	0.19	0.42	0.32
2	0.05	0.99	0.90	0.0	0.0	0	8	0.15	0.14	0.15	0.08	0.39	0.62	0.57
2	0.05	0.99	0.90	0.0	0.0	0	14	0.10	0.09	0.17	0.07	0.58	0.81	0.78
3	0.10	0.99	0.90	0.0	0.0	0	2	0.20	0.19	0.13	0.19	0.17	0.48	0.39
3	0.10	0.99	0.90	0.0	0.0	0	8	0.15	0.14	0.14	0.16	0.35	0.65	0.61
3	0.10	0.99	0.90	0.0	0.0	0	14	0.10	0.09	0.17	0.15	0.51	0.82	0.79
4	0.10	0.98	0.90	1.0	1.0	0	2	0.20	0.19	0.14	0.07	0.21	0.43	0.30
4	0.10	0.98	0.90	1.0	1.0	0	8	0.15	0.14	0.16	0.05	0.42	0.64	0.58
4	0.10	0.98	0.90	1.0	1.0	0	14	0.10	0.09	0.19	0.04	0.61	0.84	0.80
5	0.10	0.97	0.90	1.5	1.5	0	2	0.20	0.19	0.17	0.05	0.22	0.44	0.31
5	0.10	0.97	0.90	1.5	1.5	0	8	0.15	0.14	0.19	0.04	0.43	0.67	0.59
5	0.10	0.97	0.90	1.5	1.5	0	14	0.10	0.09	0.22	0.03	0.63	0.87	0.82
6	0.10	0.96	0.90	3.0	3.0	0	2	0.20	0.19	0.17	0.03	0.22	0.43	0.28
6	0.10	0.96	0.90	3.0	3.0	0	8	0.15	0.14	0.19	0.03	0.44	0.67	0.58
6	0.10	0.96	0.90	3.0	3.0	0	14	0.10	0.09	0.22	0.02	0.64	0.88	0.82
7	0.10	0.95	0.90	3.5	3.5	0	2	0.20	0.19	0.20	0.03	0.22	0.45	0.29
7	0.10	0.95	0.90	3.5	3.5	0	8	0.15	0.14	0.22	0.03	0.45	0.69	0.59
7	0.10	0.95	0.90	3.5	3.5	0	14	0.10	0.09	0.24	0.01	0.64	0.90	0.84

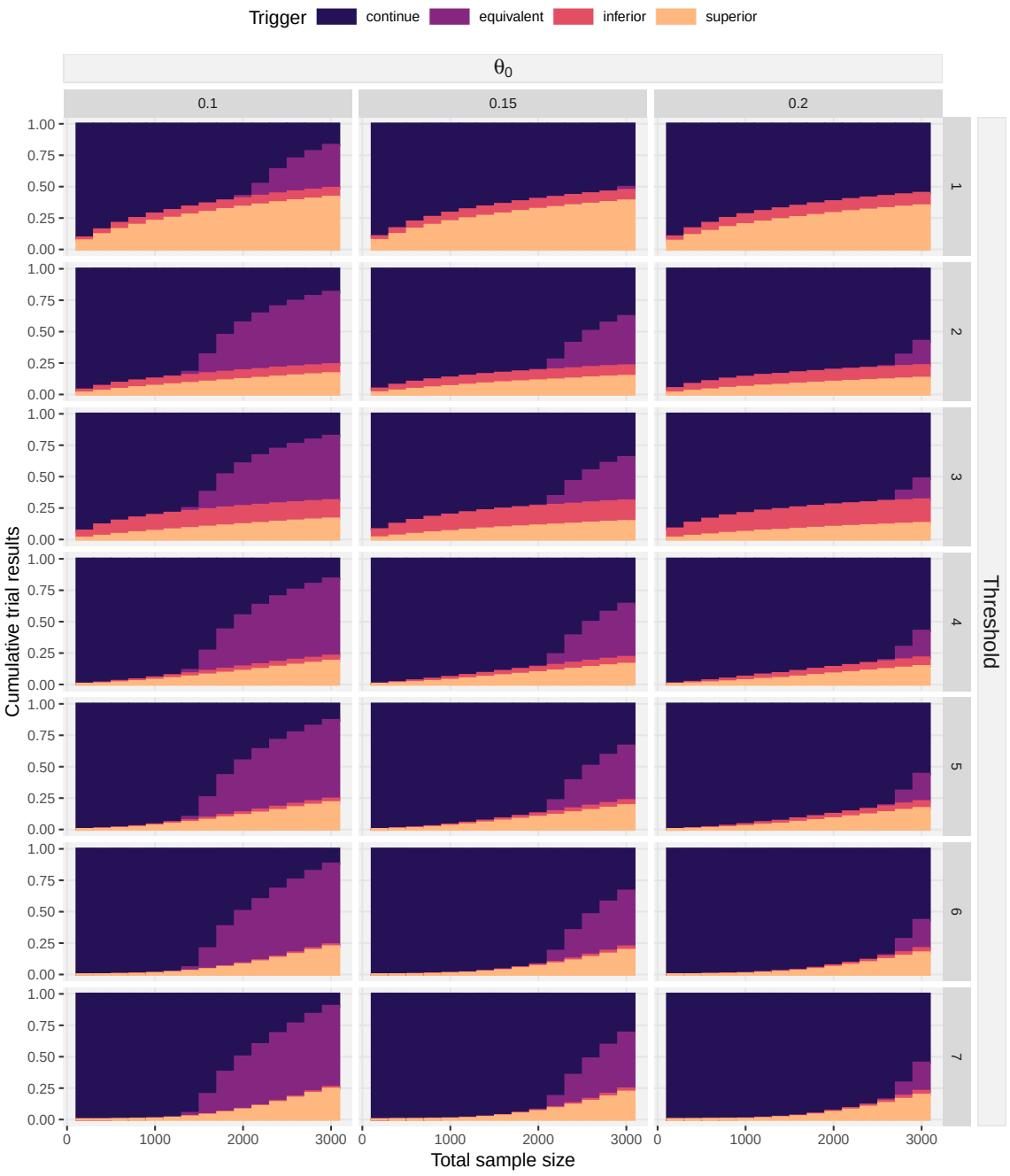

Figure 4: Expected trial progression.

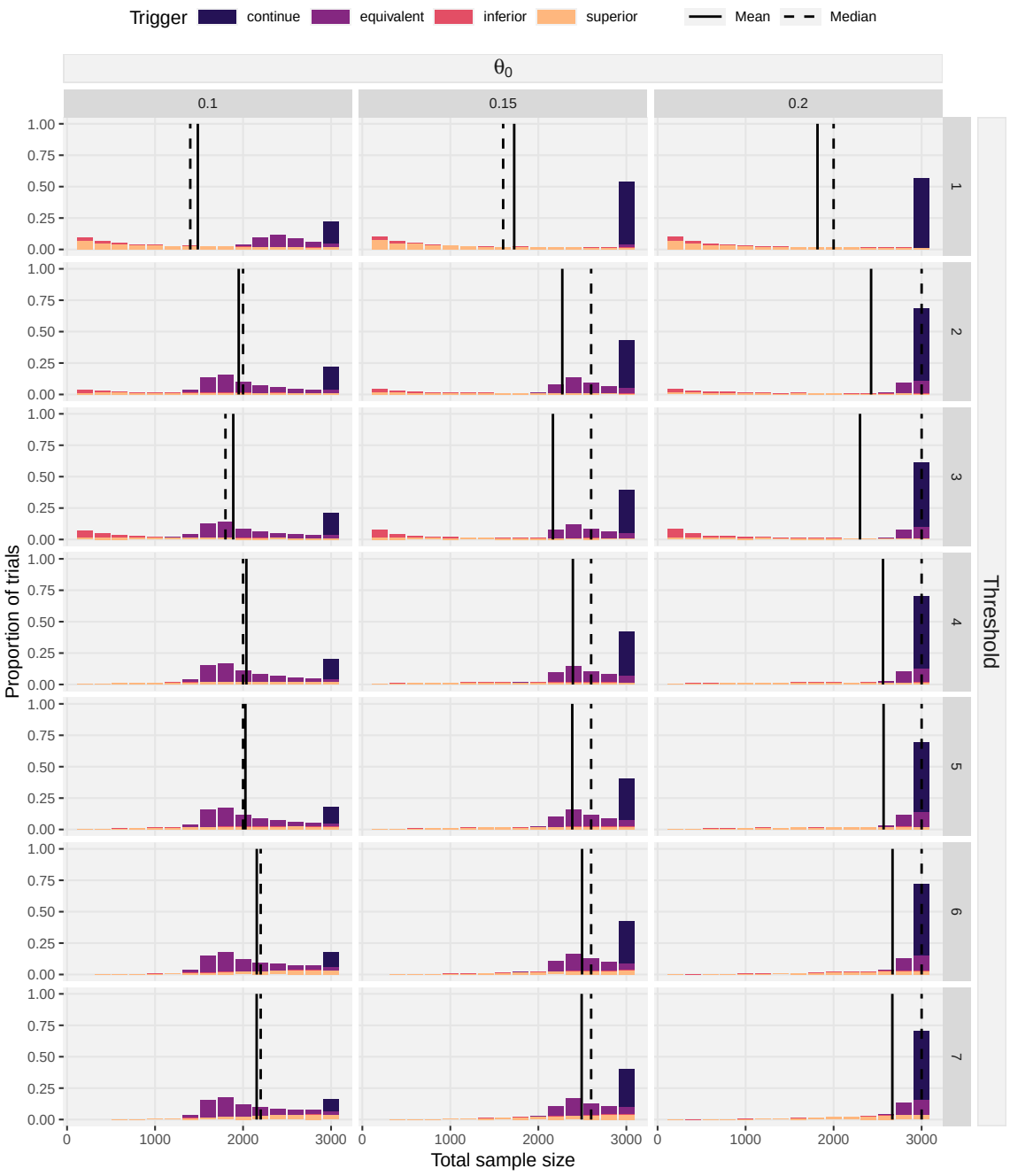

Figure 5: Distribution of trial sample sizes.

2.3 Effect size 0.02

Table 4: Expected trial outcomes.

Threshold	a0	a1	a2	b0	b1	b2	Parameter	theta0	theta1	superior	inferior	equivalent	triggered	early
1	0.05	0.95	0.95	0.0	0.0	0	3	0.20	0.18	0.59	0.04	0.00	0.63	0.61
1	0.05	0.95	0.95	0.0	0.0	0	9	0.15	0.13	0.64	0.04	0.02	0.71	0.66
1	0.05	0.95	0.95	0.0	0.0	0	15	0.10	0.08	0.74	0.03	0.13	0.90	0.87
2	0.05	0.99	0.90	0.0	0.0	0	3	0.20	0.18	0.29	0.04	0.12	0.45	0.39
2	0.05	0.99	0.90	0.0	0.0	0	9	0.15	0.13	0.35	0.04	0.21	0.60	0.56
2	0.05	0.99	0.90	0.0	0.0	0	15	0.10	0.08	0.46	0.03	0.30	0.78	0.75
3	0.10	0.99	0.90	0.0	0.0	0	3	0.20	0.18	0.29	0.10	0.10	0.49	0.43
3	0.10	0.99	0.90	0.0	0.0	0	9	0.15	0.13	0.35	0.09	0.19	0.62	0.58
3	0.10	0.99	0.90	0.0	0.0	0	15	0.10	0.08	0.45	0.06	0.27	0.79	0.75
4	0.10	0.98	0.90	1.0	1.0	0	3	0.20	0.18	0.33	0.02	0.12	0.48	0.40
4	0.10	0.98	0.90	1.0	1.0	0	9	0.15	0.13	0.40	0.02	0.23	0.64	0.59
4	0.10	0.98	0.90	1.0	1.0	0	15	0.10	0.08	0.51	0.01	0.32	0.84	0.79
5	0.10	0.97	0.90	1.5	1.5	0	3	0.20	0.18	0.38	0.01	0.13	0.52	0.43
5	0.10	0.97	0.90	1.5	1.5	0	9	0.15	0.13	0.45	0.01	0.23	0.69	0.63
5	0.10	0.97	0.90	1.5	1.5	0	15	0.10	0.08	0.56	0.00	0.32	0.88	0.84
6	0.10	0.96	0.90	3.0	3.0	0	3	0.20	0.18	0.40	0.01	0.13	0.53	0.42
6	0.10	0.96	0.90	3.0	3.0	0	9	0.15	0.13	0.47	0.00	0.24	0.71	0.63
6	0.10	0.96	0.90	3.0	3.0	0	15	0.10	0.08	0.57	0.00	0.33	0.90	0.84
7	0.10	0.95	0.90	3.5	3.5	0	3	0.20	0.18	0.43	0.00	0.13	0.57	0.45
7	0.10	0.95	0.90	3.5	3.5	0	9	0.15	0.13	0.50	0.00	0.24	0.74	0.66
7	0.10	0.95	0.90	3.5	3.5	0	15	0.10	0.08	0.60	0.00	0.33	0.92	0.86

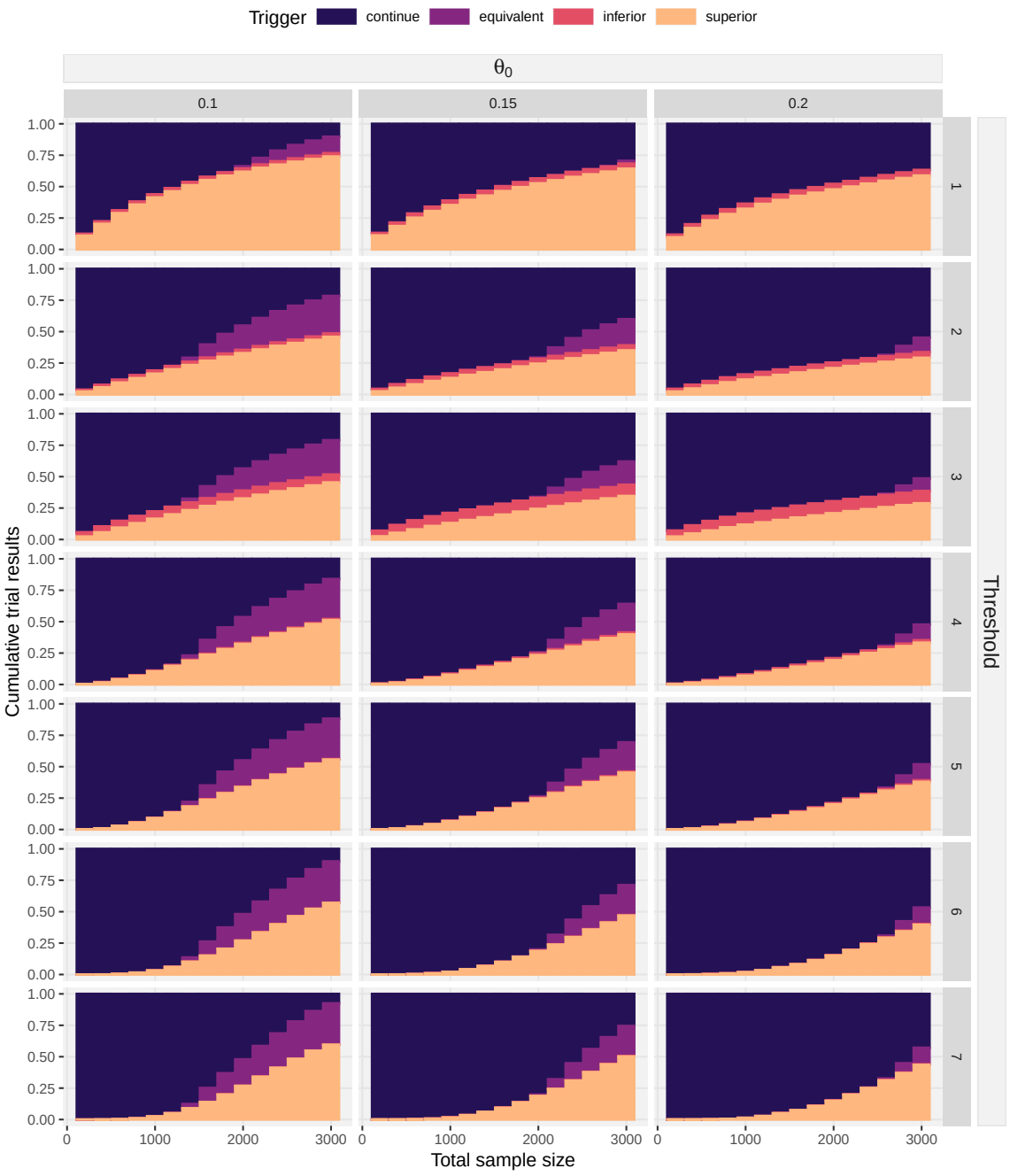

Figure 6: Expected trial progression.

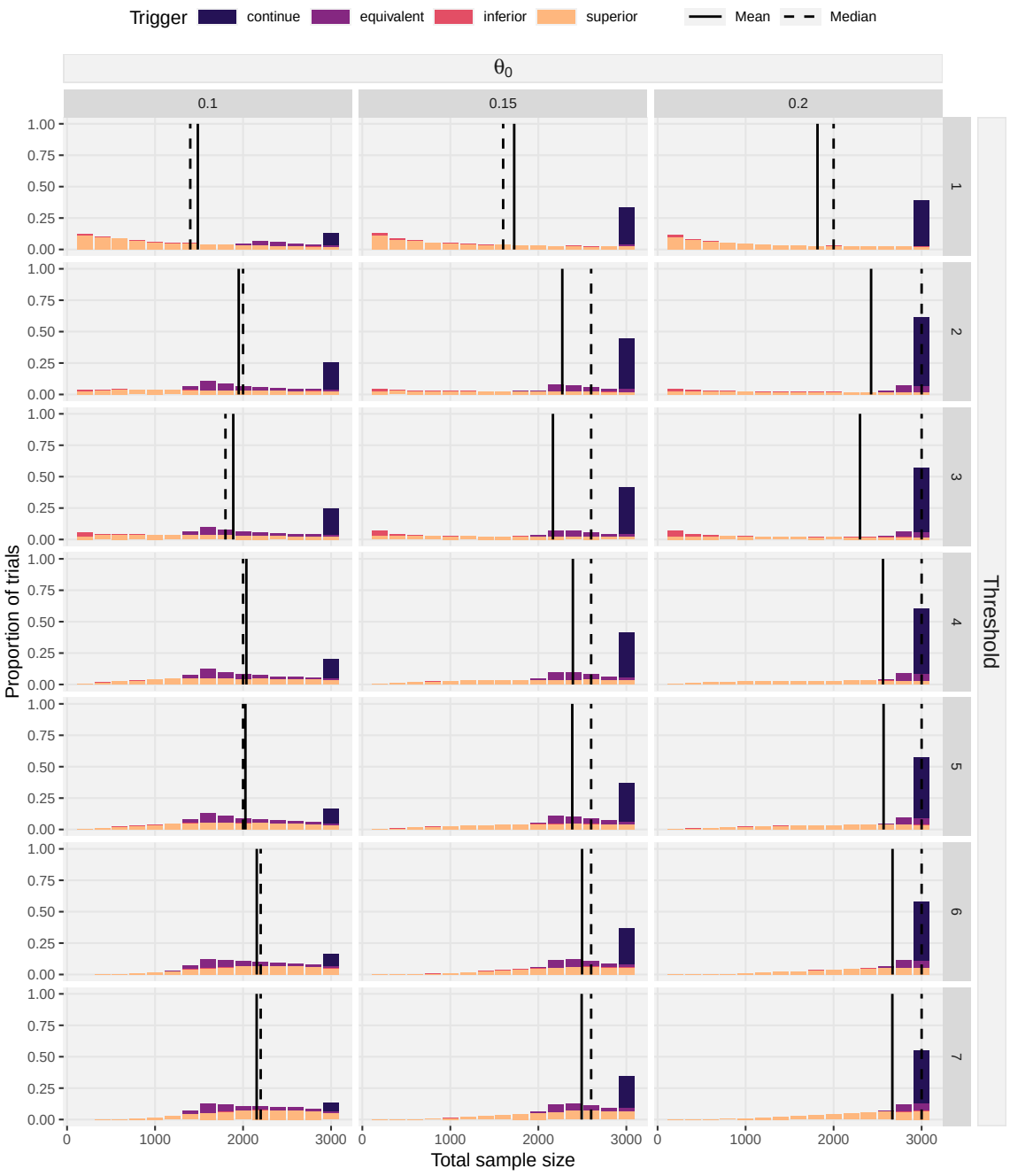

Figure 7: Distribution of trial sample sizes.

2.4 Effect size 0.03

Table 5: Expected trial outcomes.

Threshold	a0	a1	a2	b0	b1	b2	Parameter	theta0	theta1	superior	inferior	equivalent	triggered	early
1	0.05	0.95	0.95	0.0	0.0	0	4	0.20	0.17	0.80	0.02	0.00	0.83	0.80
1	0.05	0.95	0.95	0.0	0.0	0	10	0.15	0.12	0.86	0.02	0.01	0.89	0.87
1	0.05	0.95	0.95	0.0	0.0	0	16	0.10	0.07	0.94	0.01	0.03	0.98	0.96
2	0.05	0.99	0.90	0.0	0.0	0	4	0.20	0.17	0.54	0.02	0.04	0.60	0.56
2	0.05	0.99	0.90	0.0	0.0	0	10	0.15	0.12	0.64	0.02	0.07	0.73	0.69
2	0.05	0.99	0.90	0.0	0.0	0	16	0.10	0.07	0.80	0.01	0.09	0.90	0.87
3	0.10	0.99	0.90	0.0	0.0	0	4	0.20	0.17	0.53	0.06	0.03	0.62	0.58
3	0.10	0.99	0.90	0.0	0.0	0	10	0.15	0.12	0.64	0.04	0.06	0.74	0.70
3	0.10	0.99	0.90	0.0	0.0	0	16	0.10	0.07	0.79	0.03	0.08	0.90	0.87
4	0.10	0.98	0.90	1.0	1.0	0	4	0.20	0.17	0.60	0.01	0.04	0.65	0.60
4	0.10	0.98	0.90	1.0	1.0	0	10	0.15	0.12	0.71	0.00	0.07	0.78	0.74
4	0.10	0.98	0.90	1.0	1.0	0	16	0.10	0.07	0.84	0.00	0.10	0.94	0.91
5	0.10	0.97	0.90	1.5	1.5	0	4	0.20	0.17	0.66	0.00	0.04	0.70	0.64
5	0.10	0.97	0.90	1.5	1.5	0	10	0.15	0.12	0.75	0.00	0.07	0.83	0.78
5	0.10	0.97	0.90	1.5	1.5	0	16	0.10	0.07	0.87	0.00	0.10	0.96	0.94
6	0.10	0.96	0.90	3.0	3.0	0	4	0.20	0.17	0.68	0.00	0.05	0.72	0.64
6	0.10	0.96	0.90	3.0	3.0	0	10	0.15	0.12	0.77	0.00	0.07	0.84	0.78
6	0.10	0.96	0.90	3.0	3.0	0	16	0.10	0.07	0.87	0.00	0.10	0.97	0.94
7	0.10	0.95	0.90	3.5	3.5	0	4	0.20	0.17	0.71	0.00	0.05	0.76	0.67
7	0.10	0.95	0.90	3.5	3.5	0	10	0.15	0.12	0.80	0.00	0.07	0.87	0.81
7	0.10	0.95	0.90	3.5	3.5	0	16	0.10	0.07	0.88	0.00	0.10	0.98	0.96

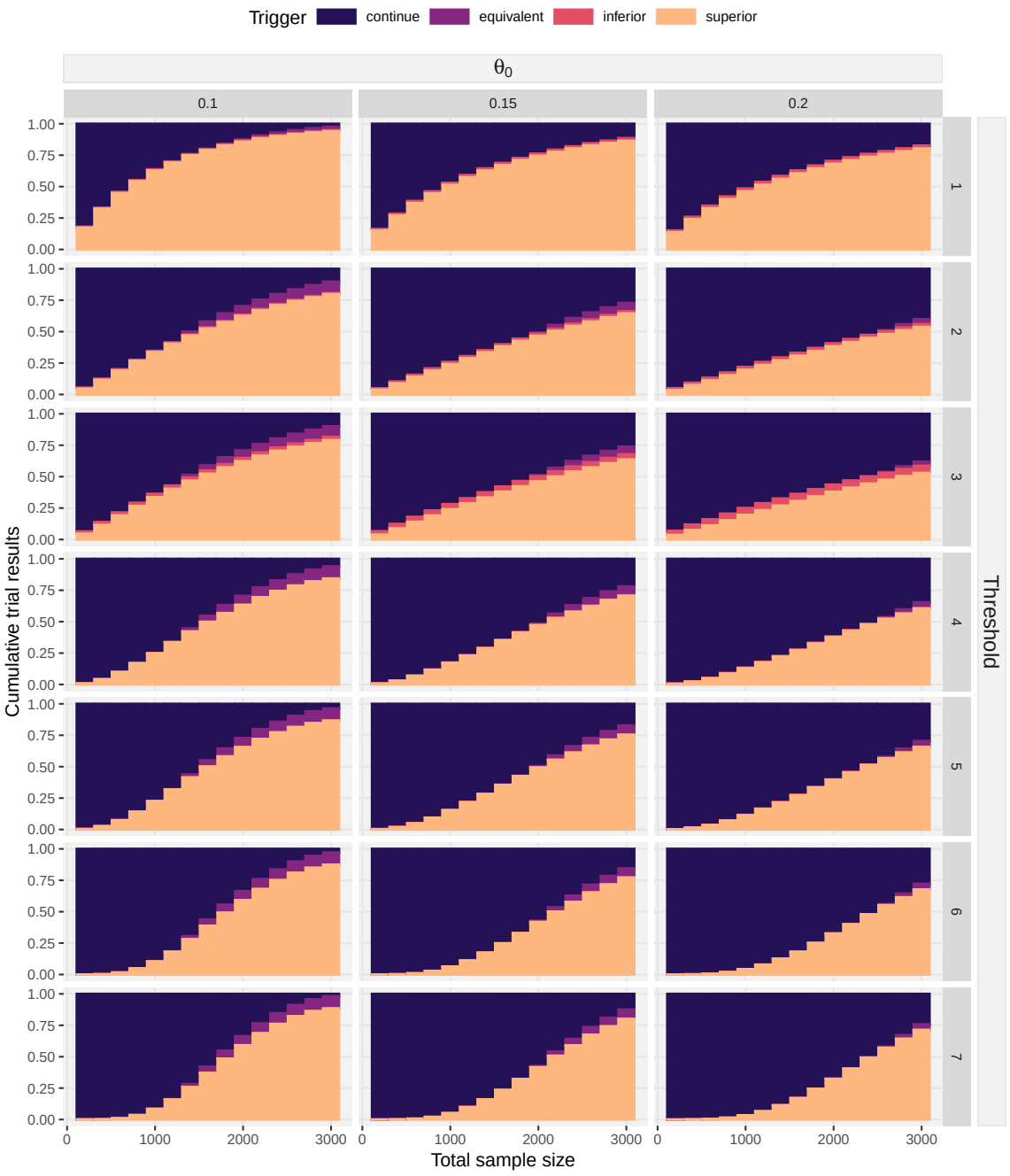

Figure 8: Expected trial progression.

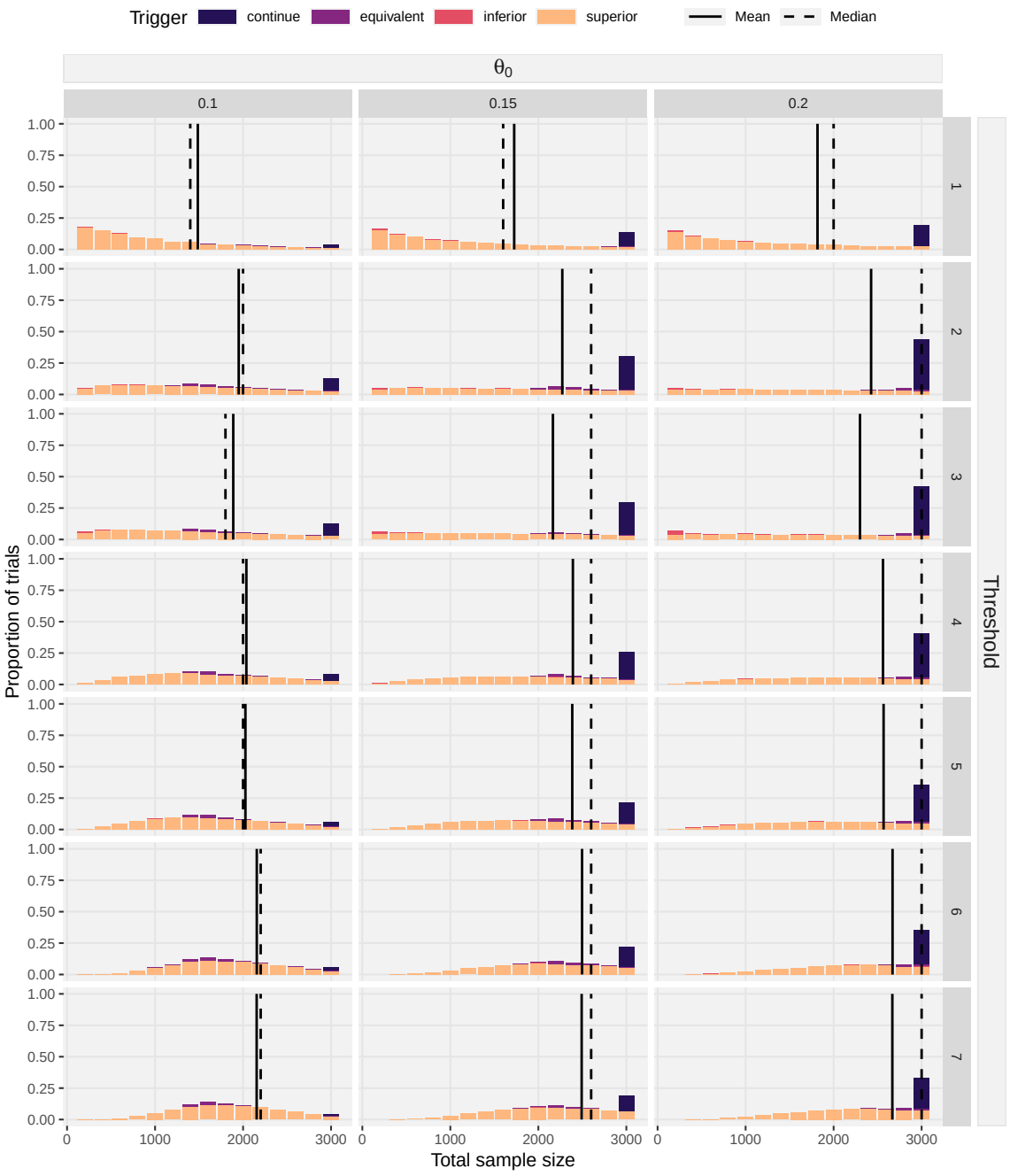

Figure 9: Distribution of trial sample sizes.

2.5 Effect size 0.04

Table 6: Expected trial outcomes.

Threshold	a0	a1	a2	b0	b1	b2	theta0	theta1	superior	inferior	equivalent	triggered	early
1	0.05	0.95	0.95	0.0	0.0	0	0.20	0.16	0.93	0.01	0.00	0.94	0.92
1	0.05	0.95	0.95	0.0	0.0	0	0.15	0.11	0.97	0.01	0.00	0.98	0.97
1	0.05	0.95	0.95	0.0	0.0	0	0.10	0.06	0.99	0.00	0.00	1.00	1.00
2	0.05	0.99	0.90	0.0	0.0	0	0.20	0.16	0.77	0.01	0.01	0.79	0.76
2	0.05	0.99	0.90	0.0	0.0	0	0.15	0.11	0.87	0.01	0.01	0.90	0.87
2	0.05	0.99	0.90	0.0	0.0	0	0.10	0.06	0.97	0.00	0.02	0.99	0.98
3	0.10	0.99	0.90	0.0	0.0	0	0.20	0.16	0.76	0.03	0.01	0.80	0.77
3	0.10	0.99	0.90	0.0	0.0	0	0.15	0.11	0.87	0.02	0.01	0.90	0.88
3	0.10	0.99	0.90	0.0	0.0	0	0.10	0.06	0.96	0.01	0.01	0.99	0.98
4	0.10	0.98	0.90	1.0	1.0	0	0.20	0.16	0.83	0.00	0.01	0.84	0.80
4	0.10	0.98	0.90	1.0	1.0	0	0.15	0.11	0.92	0.00	0.02	0.93	0.91
4	0.10	0.98	0.90	1.0	1.0	0	0.10	0.06	0.98	0.00	0.02	0.99	0.99
5	0.10	0.97	0.90	1.5	1.5	0	0.20	0.16	0.86	0.00	0.01	0.87	0.84
5	0.10	0.97	0.90	1.5	1.5	0	0.15	0.11	0.94	0.00	0.02	0.95	0.93
5	0.10	0.97	0.90	1.5	1.5	0	0.10	0.06	0.98	0.00	0.02	1.00	0.99
6	0.10	0.96	0.90	3.0	3.0	0	0.20	0.16	0.88	0.00	0.01	0.89	0.84
6	0.10	0.96	0.90	3.0	3.0	0	0.15	0.11	0.94	0.00	0.02	0.96	0.93
6	0.10	0.96	0.90	3.0	3.0	0	0.10	0.06	0.98	0.00	0.02	1.00	0.99
7	0.10	0.95	0.90	3.5	3.5	0	0.20	0.16	0.89	0.00	0.01	0.90	0.86
7	0.10	0.95	0.90	3.5	3.5	0	0.15	0.11	0.95	0.00	0.02	0.97	0.94
7	0.10	0.95	0.90	3.5	3.5	0	0.10	0.06	0.98	0.00	0.02	1.00	1.00

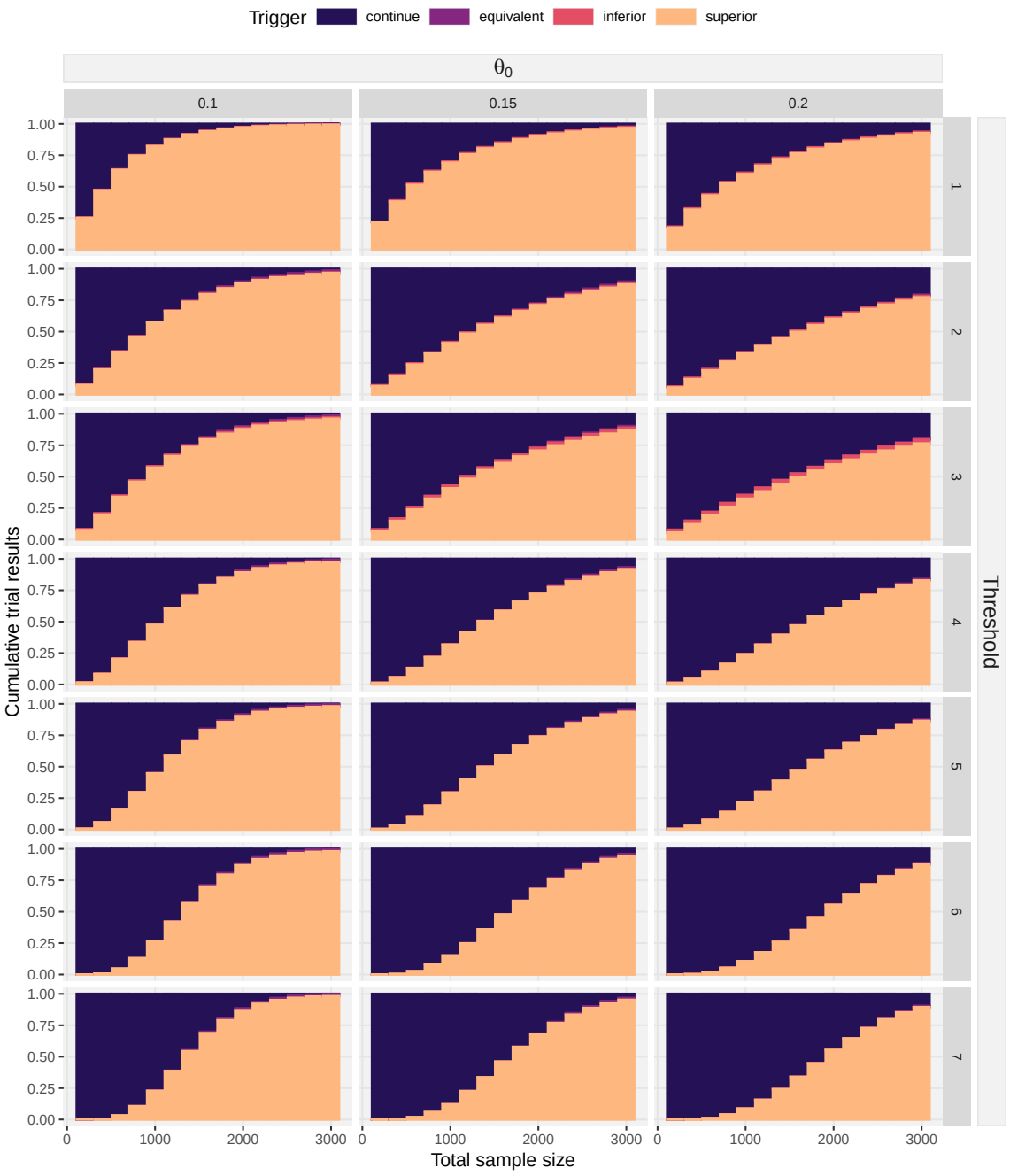

Figure 10: Expected trial progression.

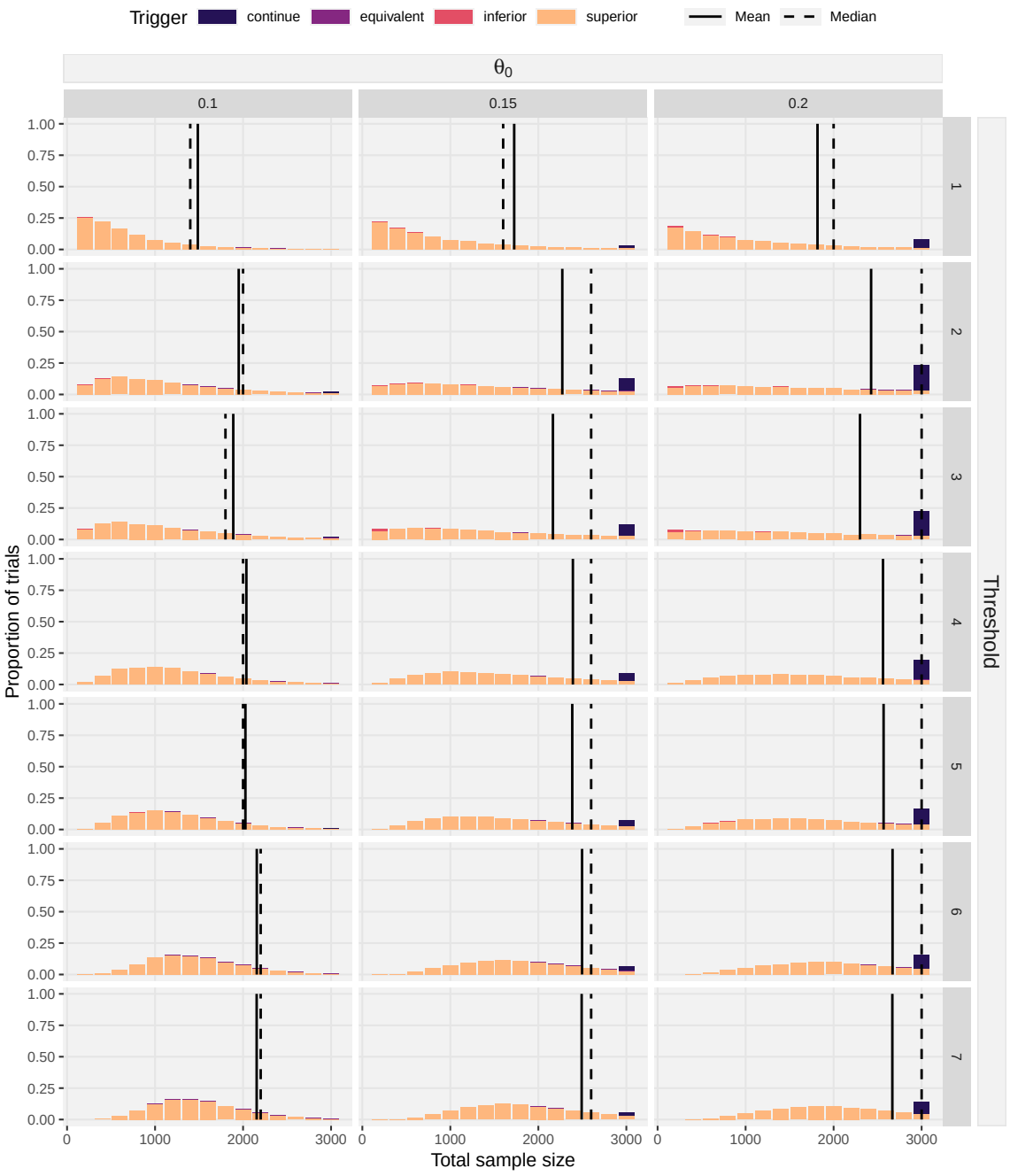

Figure 11: Distribution of trial sample sizes.

2.6 Effect size 0.05

Table 7: Expected trial outcomes.

Threshold	a0	a1	a2	b0	b1	b2	theta0	theta1	superior	inferior	equivalent	triggered	early
1	0.05	0.95	0.95	0.0	0.0	0	0.20	0.15	0.98	0.01	0	0.99	0.98
1	0.05	0.95	0.95	0.0	0.0	0	0.15	0.10	0.99	0.00	0	1.00	1.00
1	0.05	0.95	0.95	0.0	0.0	0	0.10	0.05	1.00	0.00	0	1.00	1.00
2	0.05	0.99	0.90	0.0	0.0	0	0.20	0.15	0.93	0.01	0	0.94	0.92
2	0.05	0.99	0.90	0.0	0.0	0	0.15	0.10	0.98	0.00	0	0.98	0.97
2	0.05	0.99	0.90	0.0	0.0	0	0.10	0.05	1.00	0.00	0	1.00	1.00
3	0.10	0.99	0.90	0.0	0.0	0	0.20	0.15	0.92	0.02	0	0.94	0.92
3	0.10	0.99	0.90	0.0	0.0	0	0.15	0.10	0.97	0.01	0	0.98	0.97
3	0.10	0.99	0.90	0.0	0.0	0	0.10	0.05	1.00	0.00	0	1.00	1.00
4	0.10	0.98	0.90	1.0	1.0	0	0.20	0.15	0.95	0.00	0	0.96	0.94
4	0.10	0.98	0.90	1.0	1.0	0	0.15	0.10	0.99	0.00	0	0.99	0.98
4	0.10	0.98	0.90	1.0	1.0	0	0.10	0.05	1.00	0.00	0	1.00	1.00
5	0.10	0.97	0.90	1.5	1.5	0	0.20	0.15	0.97	0.00	0	0.97	0.95
5	0.10	0.97	0.90	1.5	1.5	0	0.15	0.10	0.99	0.00	0	0.99	0.99
5	0.10	0.97	0.90	1.5	1.5	0	0.10	0.05	1.00	0.00	0	1.00	1.00
6	0.10	0.96	0.90	3.0	3.0	0	0.20	0.15	0.97	0.00	0	0.98	0.96
6	0.10	0.96	0.90	3.0	3.0	0	0.15	0.10	0.99	0.00	0	0.99	0.99
6	0.10	0.96	0.90	3.0	3.0	0	0.10	0.05	1.00	0.00	0	1.00	1.00
7	0.10	0.95	0.90	3.5	3.5	0	0.20	0.15	0.98	0.00	0	0.98	0.96
7	0.10	0.95	0.90	3.5	3.5	0	0.15	0.10	1.00	0.00	0	1.00	0.99
7	0.10	0.95	0.90	3.5	3.5	0	0.10	0.05	1.00	0.00	0	1.00	1.00

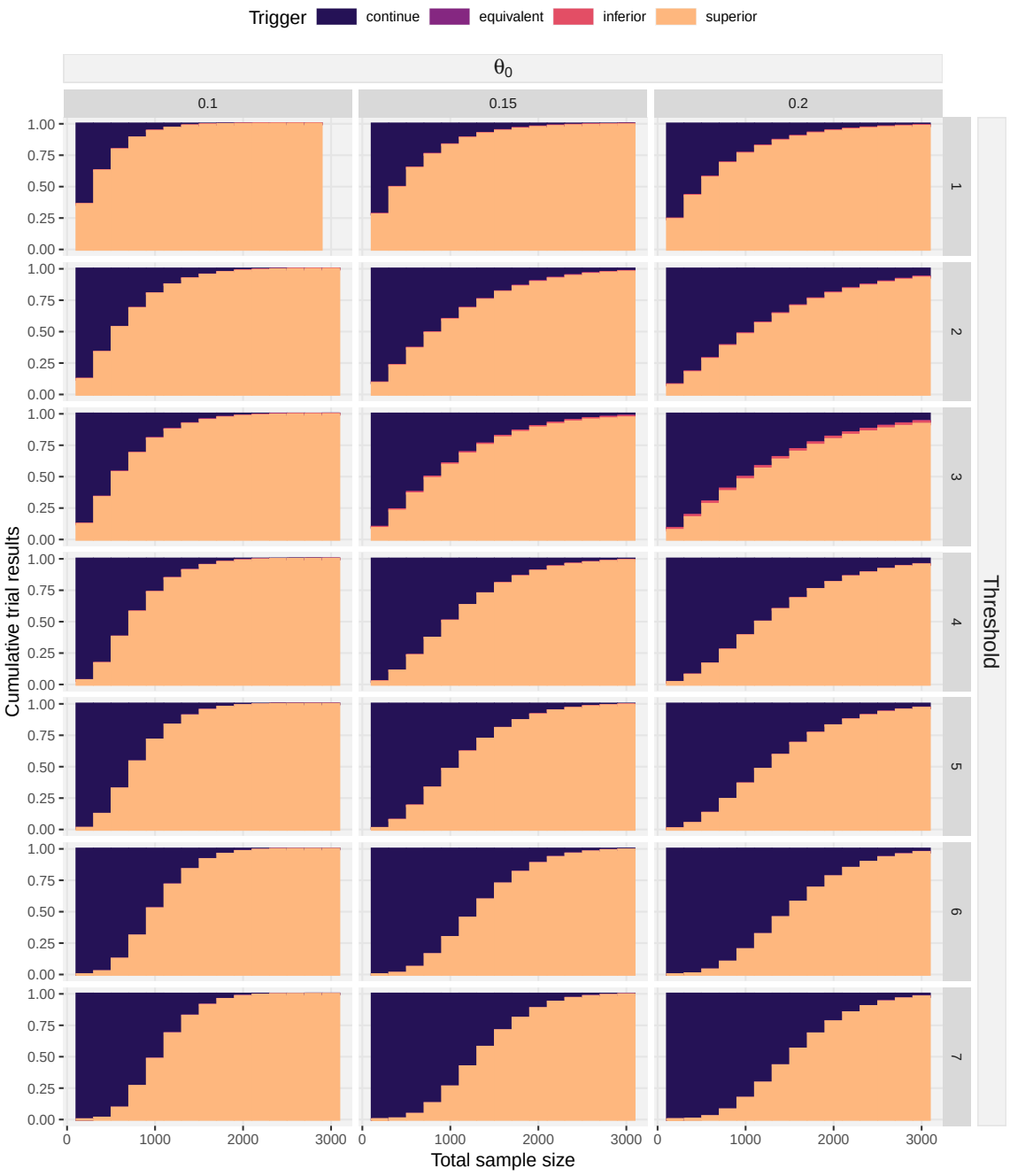

Figure 12: Expected trial progression.

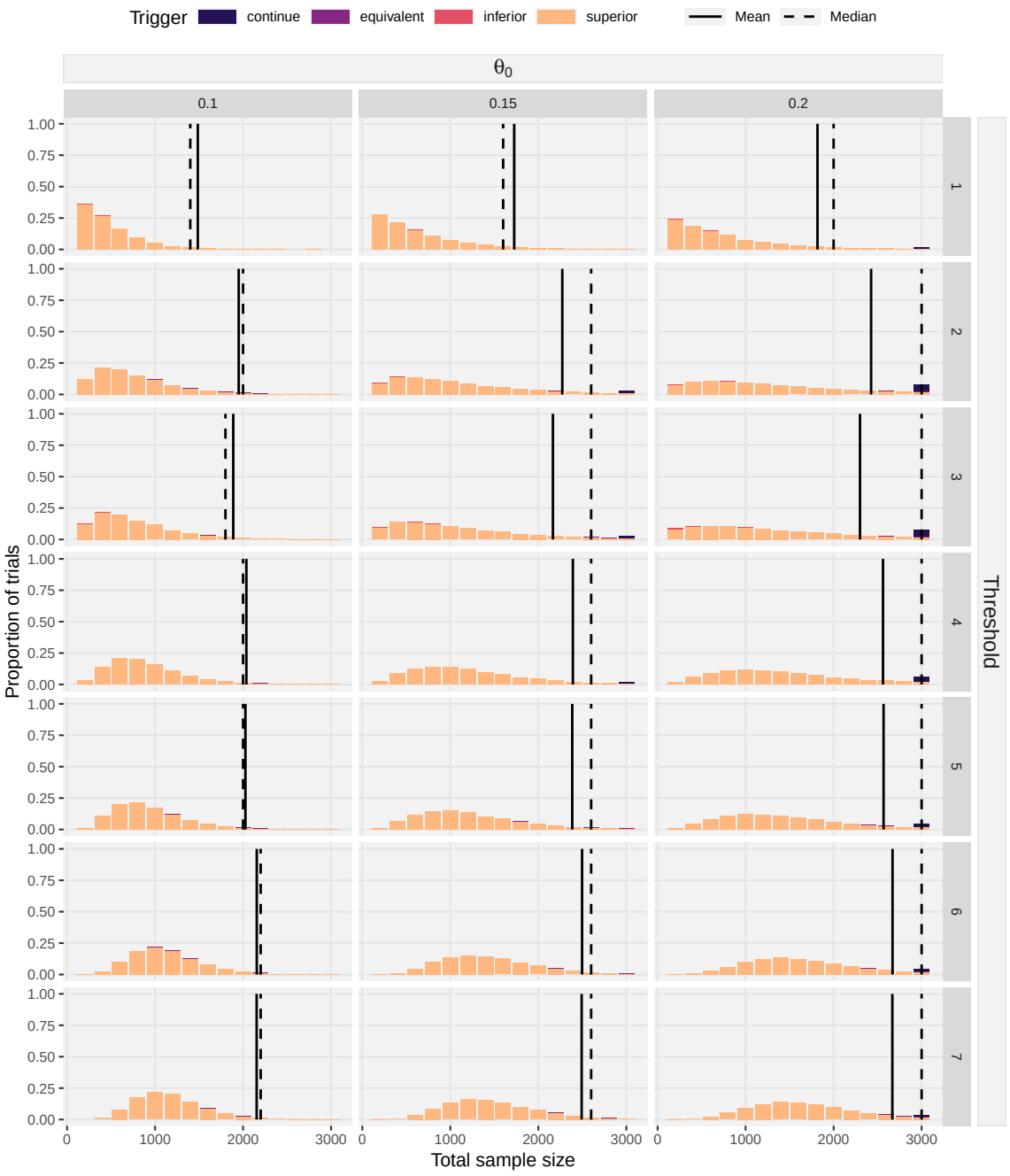

Figure 13: Distribution of trial sample sizes.