Sample Size

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1 Conditional Power Fixed Sample Size

Just assuming a two arm case of θ_0 in control and θ_1 in treatment arms respectively. 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 $\theta_0 = 0.2$ a reduction of $\delta = 0.05$ would require about a sample size of 1,000 for 90% power.

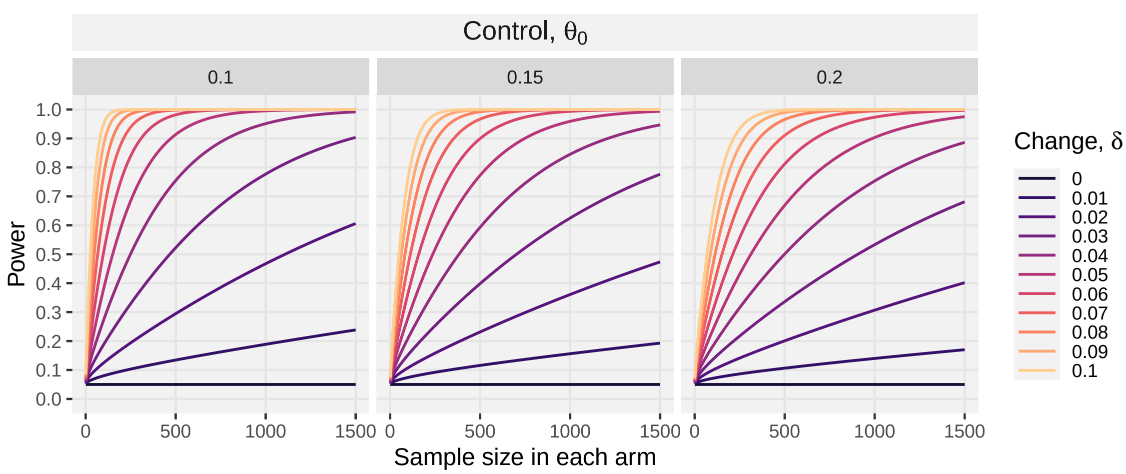

Figure 1: Frequentist power by sample size for given control proportion and effect size at level $\alpha = 0.05$.

2 Group 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 here.

The results are idealistic in that they assume no drop-out and no missing information at each interim analysis. The actually amount of missing data will be dependent on the accrual rate and time to primary endpoint. Early outcome data could be used to impute missing primary endpoint data for participants already enrolled at the time of the interim.

Table 1: Expected trial outcomes.

Scenario	superior	inferior	equivalent	triggered	early
Null	0.19	0.19	0	0.39	0.38
Small	0.70	0.04	0	0.73	0.71
Moderate	0.98	0.01	0	0.99	0.99
Large	1.00	0.00	0	1.00	1.00

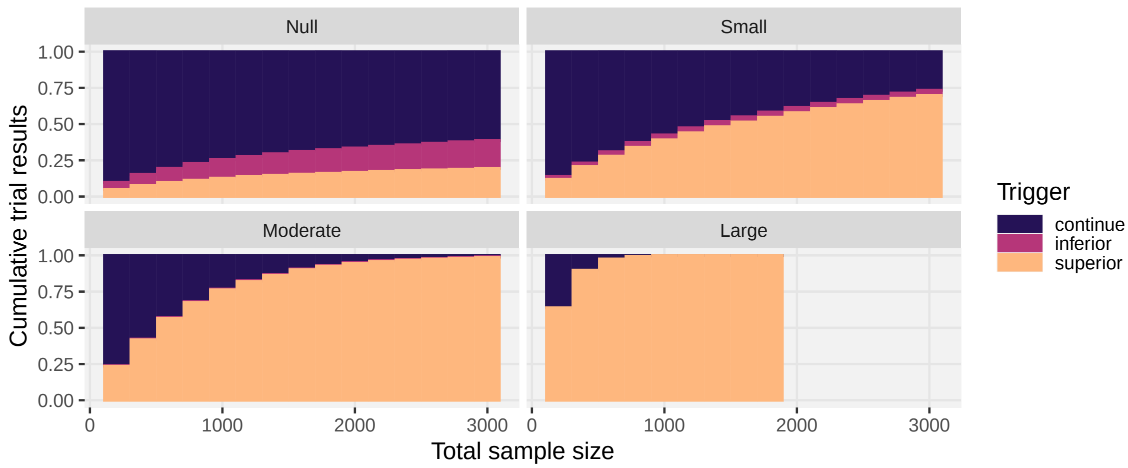

Figure 2: Expected trial progression under ($\underline{\epsilon}_t = 0.05, \bar{\epsilon}_t = 0.95, \kappa_t = 0.95, \Delta = 0.025$).

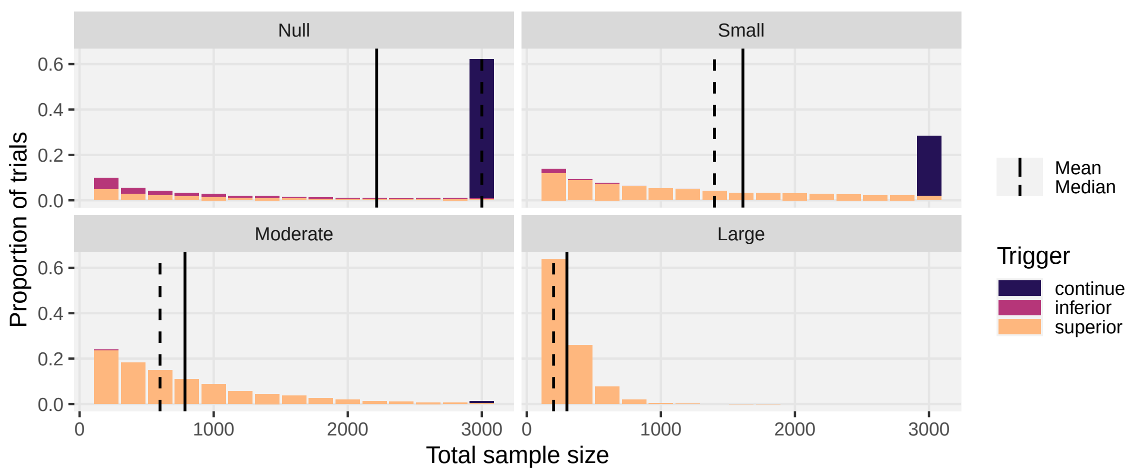

Figure 3: Distribution of trial sample sizes under ($\underline{\epsilon}_t = 0.01, \bar{\epsilon}_t = 0.99, \kappa_t = 0.9, \Delta = 0.025$).

Table 2: Expected trial outcomes.

Scenario	superior	inferior	equivalent	triggered	early
Null	0.05	0.05	0.24	0.34	0.18
Small	0.42	0.01	0.08	0.50	0.45
Moderate	0.94	0.00	0.00	0.94	0.92
Large	1.00	0.00	0.00	1.00	1.00

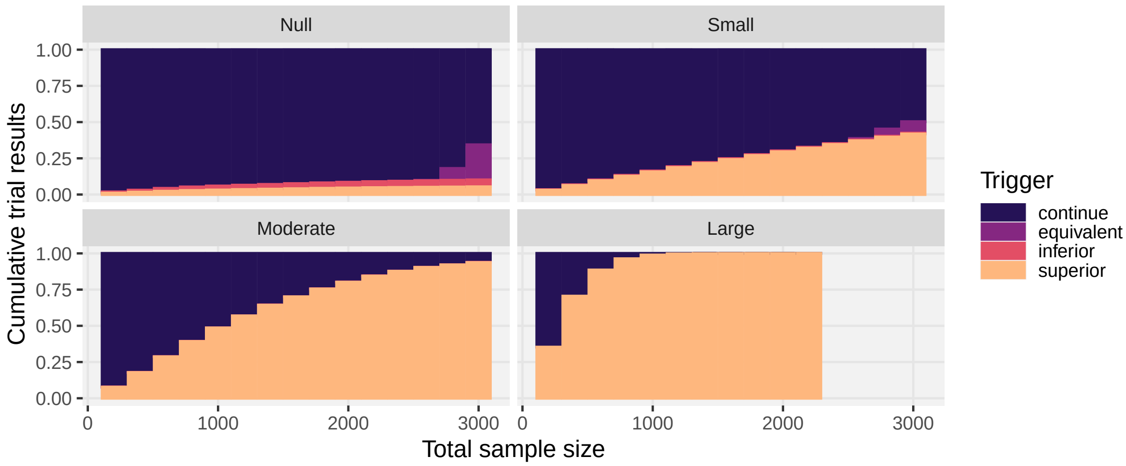

Figure 4: Expected trial progression under ($\underline{\epsilon}_t = 0.01, \overline{\epsilon}_t = 0.99, \kappa_t = 0.9, \Delta = 0.025$).

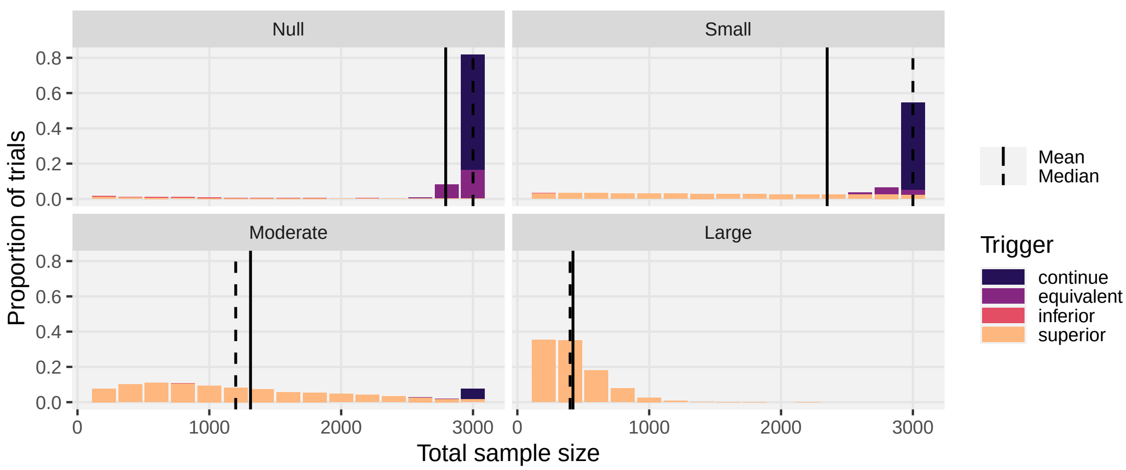

Figure 5: Distribution of trial sample sizes under ($\underline{\epsilon}_t = 0.01, \overline{\epsilon}_t = 0.99, \kappa_t = 0.9, \Delta = 0.025$).

Table 3: Expected trial outcomes.

Scenario	superior	inferior	equivalent	triggered	early
Null	0.05	0.19	0.49	0.74	0.69
Small	0.41	0.04	0.17	0.62	0.59
Moderate	0.93	0.01	0.01	0.95	0.93
Large	1.00	0.00	0.00	1.00	1.00

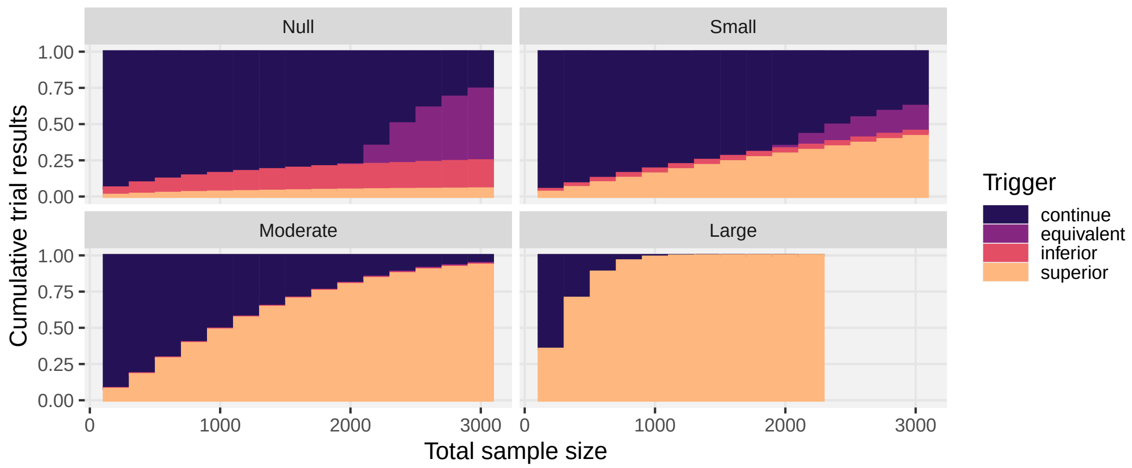

Figure 6: Expected trial progression under ($\underline{\epsilon}_t = 0.05, \overline{\epsilon}_t = 0.99, \kappa_t = 0.85, \Delta = 0.025$).

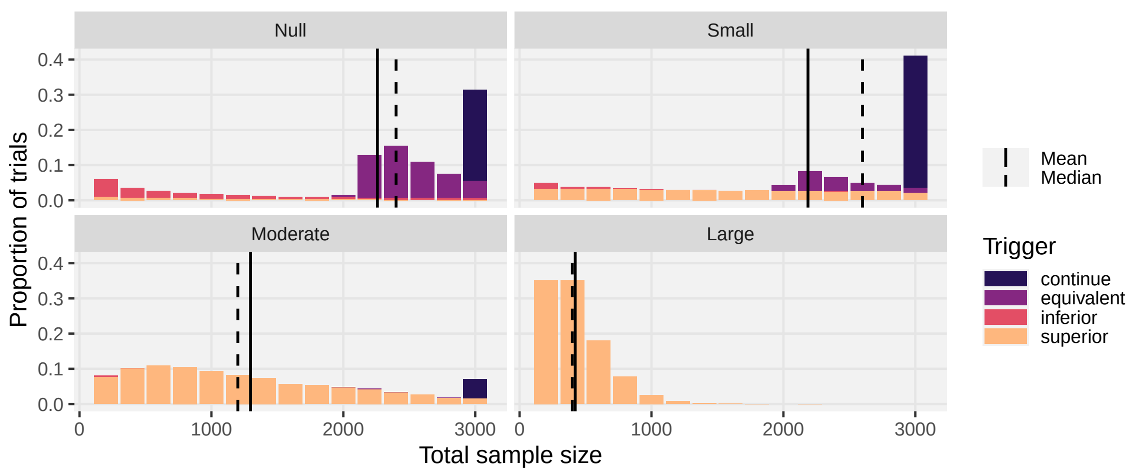

Figure 7: Distribution of trial sample sizes under ($\underline{\epsilon}_t = 0.05, \overline{\epsilon}_t = 0.99, \kappa_t = 0.85, \Delta = 0.025$).

Table 4: Expected trial outcomes.

Scenario	superior	inferior	equivalent	triggered	early
Null	0.05	0.32	0.42	0.80	0.76
Small	0.41	0.08	0.15	0.64	0.61
Moderate	0.92	0.02	0.01	0.95	0.93
Large	1.00	0.00	0.00	1.00	1.00

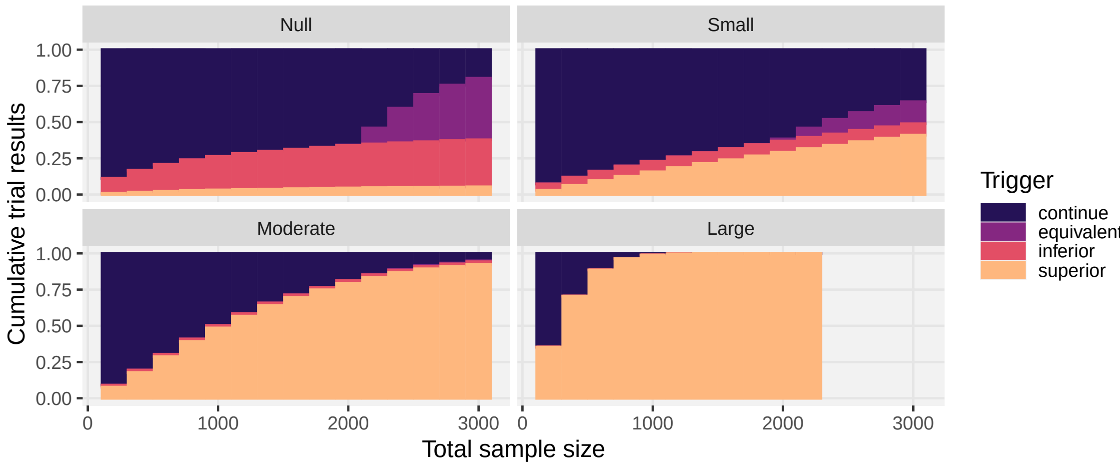

Figure 8: Expected trial progression under $(\underline{\epsilon}_t = 0.1, \bar{\epsilon}_t = 0.99, \kappa_t = 0.8, \Delta = 0.025)$.

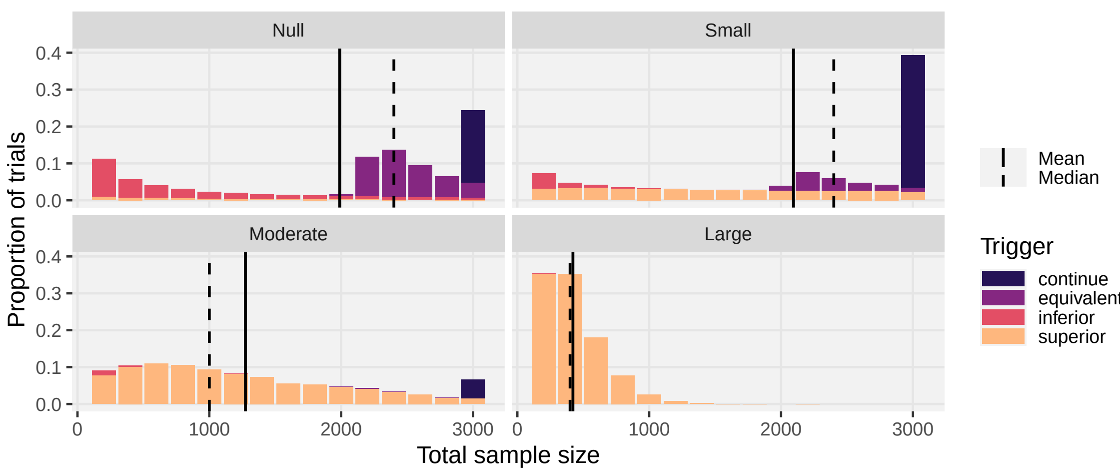

Figure 9: Distribution of trial sample sizes under $(\underline{\epsilon}_t = 0.1, \bar{\epsilon}_t = 0.99, \kappa_t = 0.8, \Delta = 0.025)$.

Table 5: Expected trial outcomes.

Scenario	superior	inferior	equivalent	triggered	early
Null	0.05	0.16	0.55	0.76	0.69
Small	0.49	0.01	0.19	0.69	0.63
Moderate	0.96	0.00	0.01	0.97	0.96
Large	1.00	0.00	0.00	1.00	1.00

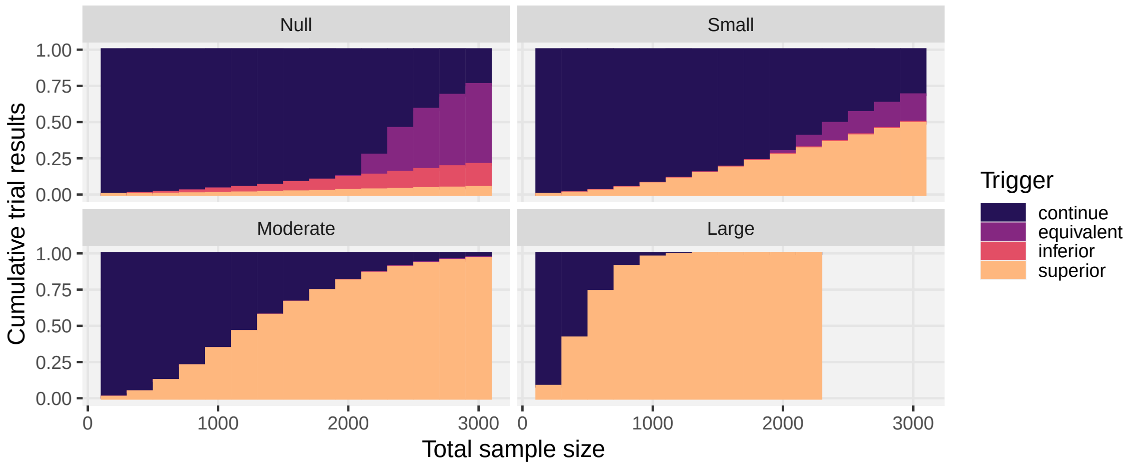

Figure 10: Expected trial progression under ($\underline{\epsilon}_t = 0.1, \bar{\epsilon}_t = 0.99, \kappa_t = 0.8, \Delta = 0.025$).

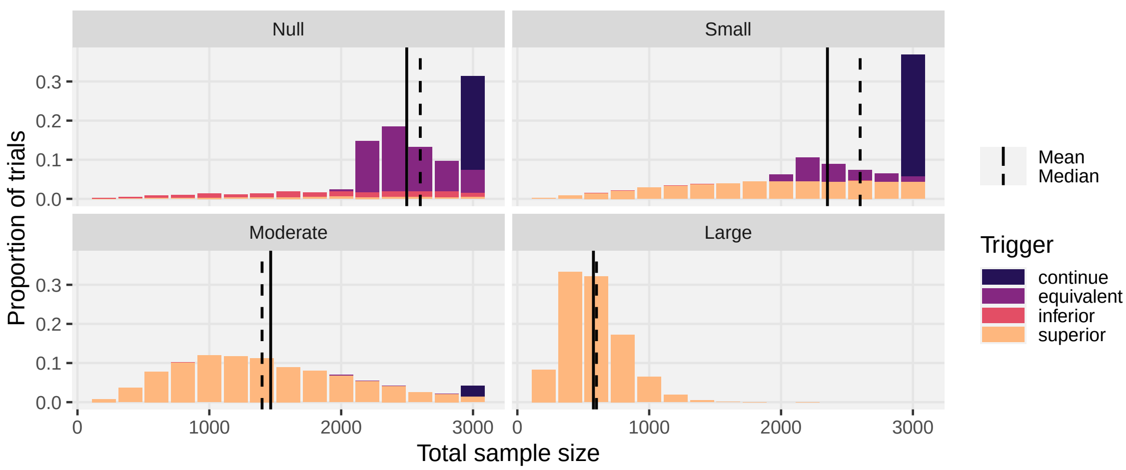

Figure 11: Distribution of trial sample sizes under ($\underline{\epsilon}_t = 0.1, \bar{\epsilon}_t = 0.99, \kappa_t = 0.8, \Delta = 0.025$).

Table 6: Expected trial outcomes.

Scenario	superior	inferior	equivalent	triggered	early
Null	0.07	0.12	0.57	0.76	0.67
Small	0.58	0.00	0.19	0.78	0.70
Moderate	0.98	0.00	0.01	0.99	0.98
Large	1.00	0.00	0.00	1.00	1.00

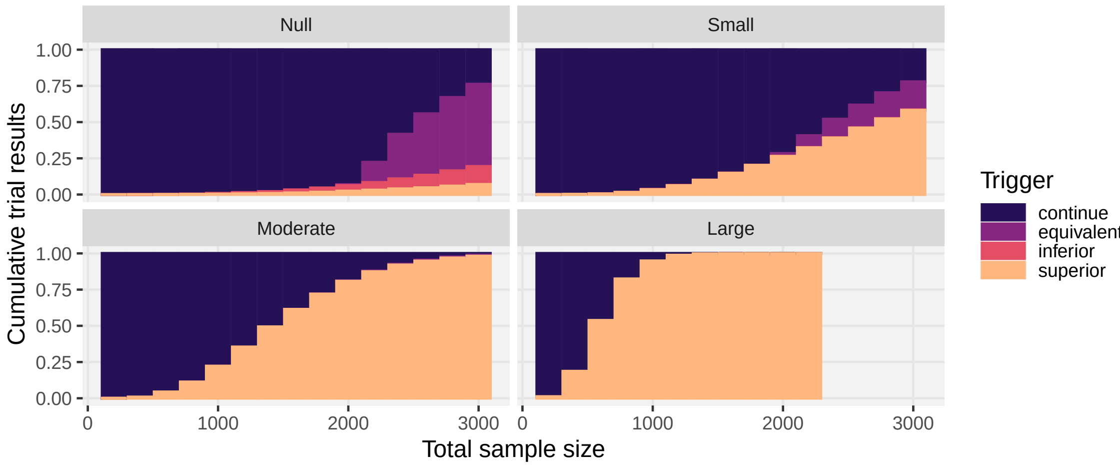

Figure 12: Expected trial progression under ($\underline{\epsilon}_t = 0.1, \overline{\epsilon}_t = 0.99, \kappa_t = 0.8, \Delta = 0.025$).

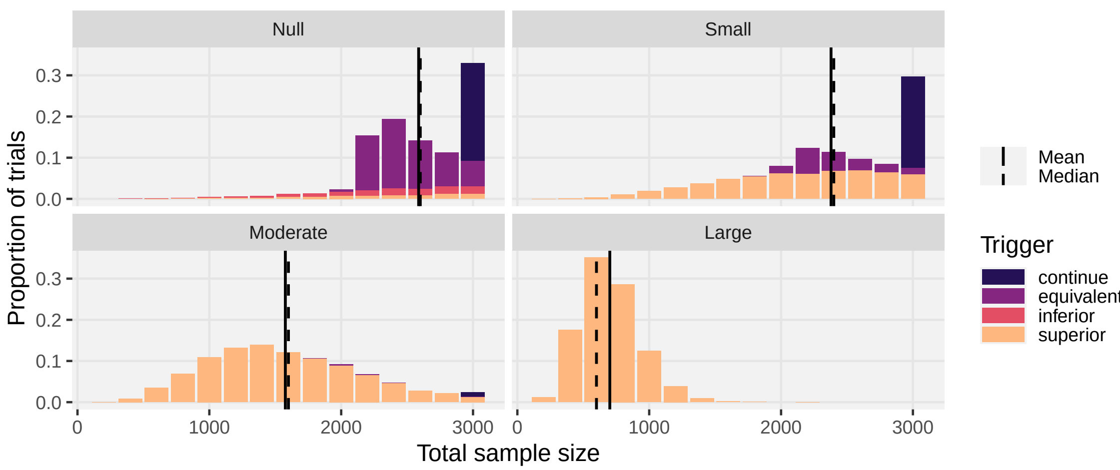

Figure 13: Distribution of trial sample sizes under ($\underline{\epsilon}_t = 0.1, \overline{\epsilon}_t = 0.99, \kappa_t = 0.8, \Delta = 0.025$).