OPTIMUM Simulations Notes

OPTimising IMmunisation Using Mixed schedules

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Contents

1 Sample size and accrual

Original design aimed for maximum sample size of 3,000 which provides 90% power to detect reduction from 10% to 7% probability.

1.1 18-month primary end-point

The end-point is food allergy at 18-months. For simplicity, we assume babies are enrolled and randomised at 0 months of age. So, no follow-up data is available until 18-months after the first infant is enrolled.

Suppose accrual is 20 infants per week, then, by the time we have follow-up on the first individual we will have enrolled 1,560 infants (78 weeks $\times$ 20 per week). Assuming the first analysis was at $n = 500$, we would have about 2,000 individuals already enrolled, so 1,500 with missing information at the time of the first interim. Full follow-up would occur at about week 228 (Figure 1).

Suppose accrual is 10 infants per week, then, by the time we have follow-up on the first individual we will have enrolled 780 infants. Assuming the first analysis was at $n = 500$, we would have about 1,300 enrolled, so 800 with missing information at the first interim. Full follow-up would occur at about week 378, beyond the 5-year study span.

The minimum acrrual rate needed to enroll 3,000 infants within 5 years is about 11.5 per week.

1.2 12-month primary end-point

Again assuming 20 infants per week, then, by the time we have follow-up on the first individual we would have enrolled about 1,000 infants. Therefore, at any interim analysis using predictive probability of success, we would need to marginalise over about 1,000 missing responses.

Assuming 10 infants per week, then by the time we have follow-up on the first individual we would have enrolled about 500 infants. Therefore, at any interim analysis using predictive probability of success, we would need to marginalise over about 500 missing responses.

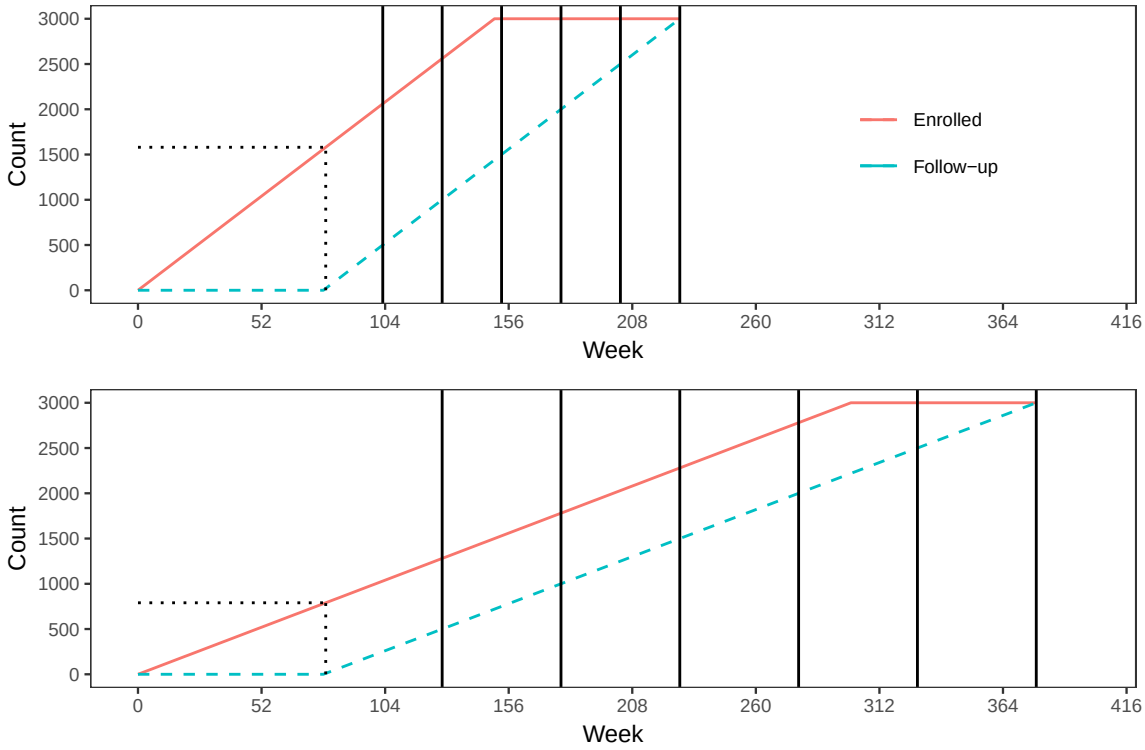


Figure 1: Assumed linear accrual rate and associated delay of information, 18-month end-point.

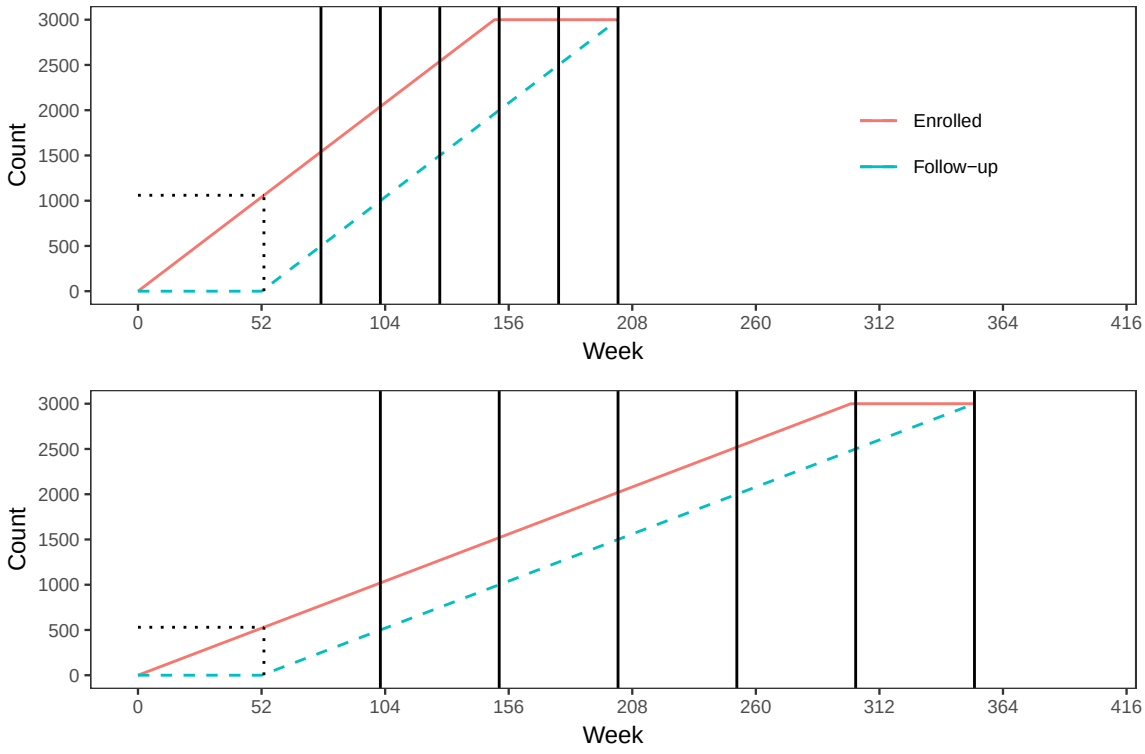


Figure 2: Assumed linear accrual rate and associated delay of information assuming 12-month end-point.

2 Statistical Analysis

2.1 Model

Let θ_a be the probability of food allergy at 18-months amongst infants who receive the acellular pertussis vaccine at first dose, and θ_w the probability of food allergy at 18-months amongst infants received the whole-cell pertussis vaccine at first dose. We are interested in estimating $\delta = \theta_w - \theta_a$ the difference in probability (or $\delta = \ln(\theta_w/(1-\theta_w)) - \ln(\theta_a/(1-\theta_a))$ the difference in log-odds) and investigating the statistical hypothesis

$$H_0 : \delta \geq 0$$
$$H_1 : \delta < 0$$

That is, that θ_w is no lower than θ_a versus θ_w is lower than θ_a.

2.2 Independent Beta-Binomial Models

Suppose that at each analysis $k = 1, ..., K$ we have data on n_k^i individuals with y_k^i responses for $i \in \{a, w\}$. We also assume that we have $m_k^i \geq n_k^i$ total enrolled but not all with data. The number without data is $\tilde{n}_k^i = m_k^i - n_k^i$. At an interim analysis we wish to impute the data for individuals enrolled but without follow-up. We denote these missing number of responses by $\tilde{y}_k^i$.

In addition to enrolled individuals with missing data, there are the yet to be enrolled individuals making up the maximum sample size. At stage K we have n_K^i individuals with y_K^i responses, and so for this end point we have $\tilde{n}_k^i = n_K^i - n_k^i$ data points missing. In either case, the posterior predictive will have the same parameters but with a different sample size parameter. Therefore in what follows we do not distinguish between the two, however, it is standard to use $\tilde{n}_k^i = m_k^i - n_k^i$ in deciding expected success and $\tilde{n}_k^i = n_K^i - n_k^i$ in deciding futility.

We specify the following model for $i \in \{a, w\}$ and $k \in \{1, ..., K\}$,

$$\begin{aligned}
\pi_0^i(\theta^i) &= \text{Beta}(\theta^i | a^i, b^i) \\
f_k^i(y_k^i | \theta^i) &= \text{Binomial}(n_k^i, y_k^i) \\
\pi_k^a(\theta^i | y_k^i) &= \text{Beta}(\theta^i | a^i + y_k^i, b^i + n_k^i - y_k^i) \\
P_k &= \mathbb{P}_{\Theta^a, \Theta^w | Y_k^a, Y_k^w}(\theta^w < \theta^a) \\
&= \int_0^1 \pi_k^a(\theta^a | y_k^a) \left[\int_0^{\theta^a} \pi_k^w(\theta^w | y_k^w) d\theta^w \right] d\theta^a \\
\tilde{f}_k^i(\tilde{y}_k^i | y_k^i) &= \text{Beta-Binomial}(\tilde{y}_k^i | \tilde{n}_k^i, a^i + y_k^i, b^i + n_k^i - y_k^i) \\
\tilde{\pi}_k^i(\theta^i | y_k^i + \tilde{y}_k^i) &= \text{Beta}(\theta^i | a^i + y_k^i + \tilde{y}_k^i, b^i + n_k^i + \tilde{n}_k^i - y_k^i - \tilde{y}_k^i) \\
\tilde{P}_k &= \mathbb{P}_{\Theta^a, \Theta^w | Y_k^a + \tilde{Y}_k^a, Y_k^w + \tilde{Y}_k^w}(\theta^w < \theta^a) \\
&= \int_0^1 \tilde{\pi}_k^a(\theta^a | y_k^a + \tilde{y}_k^a) \left[\int_0^{\theta^a} \tilde{\pi}_k^w(\theta^w | y_k^w + \tilde{y}_k^w) d\theta^w \right] d\theta^a \\
\text{PPoS}_k(q) &= \mathbb{E}_{\tilde{Y}_k^a, \tilde{Y}_k^w | Y_k^a, Y_k^w} \left[\mathbb{I}\left\{ \tilde{P}_k > q \right\} \right] \\
&= \sum_{i=0}^{\tilde{n}_k^a} \sum_{j=0}^{n_k^w} \mathbb{I}\left\{ \tilde{P}_k > q \right\} \tilde{f}_k^w(j | y_k^w) \tilde{f}_k^a(i | y_k^a)
\end{aligned}$$

The quantity P_k cannot be calculated analytically but can be evaluated numerically or estimated using Monte Carlo methods. Although PPoS_k can be computed analytically (assuming we have calculated the relevant $\tilde{P}_k$) it may still be more efficient to estimate using Monte Carlo methods for large sample sizes.

In all that follows we have assumed uniform priors where $a^i = b^i = 1, i = 1, 2$, however it would be useful to consider other priors derived from available information, including both sceptical and enthusiastic versions.

2.3 Decision Rules

At the final analysis (full follow-up on all individuals), a terminal decision is made regarding the difference in response between the two vaccines. This decision rule declares $\delta < 0$, $\delta \geq 0$, or that the study was inconclusive.

$$\delta_K(y_K) = \begin{cases} a_0 \text{ if } P_k \leq \underline{c}_K & \implies \text{accept } H_0 \\ a_1 \text{ if } P_k \geq \overline{c}_K & \implies \text{accept } H_1 \\ a_2 \text{ otherwise} & \implies \text{inconclusive/no-difference} \end{cases}$$

At each interim analysis, a decision is made whether the study should be stopped for futility, expected success, or to continue enrolment. This decision is based on $\text{PPoS}_k(\overline{c}_K)$. The interim decision rule is

$$\delta_k(y_k) = \begin{cases} a_3 \text{ if } \text{PPoS}_k(\overline{c}_K) < \underline{\kappa}_k & \implies \text{futile to continue} \\ a_4 \text{ if } \text{PPoS}_k(\overline{c}_K) > \overline{\kappa}_k & \implies \text{expect success at interim} \\ a_5 \text{ otherwise} & \implies \text{continue to enrol to } k+1. \end{cases}$$

We note that, if $m_k^a + m_k^w = n_K^a + n_K^w$, that is, the number enrolled already equals the maximum sample size in each arm, then there is no point in stopping enrolment for futility or expected success as enrollment is already completed. Therefore, the interim decision only applies for stages where $m_k^a + m_k^w < n_K^a + n_K^w$ is satisfied.

If we stop for futility or expected success, we would undertake a final analysis to estimate the relevant effects when remaining enrolled participants with missing data are followed-up. Note that stopping for expected success does not guarantee success when follow-up is completed, if the true effect is in agreement H_1 then the probability of concluding H_1 after stopping for expected success should be high, however, if we stop for expected success and the true effect is in agreeemnt with H_0, then it is less likely we will actually conclude H_1 after completing follow-up. The variability in these probabilities is a function of how much missing data we are forced to impute at an interim analysis, how accurate the imputation is, and the true value of the effects.

3 Simulations

We want to investigate the operating characteristics of the trial for varying θ^a and θ^w and determine appropriate values of the following trial parameters:

- $(\underline{c}_K, \overline{c}_K)$ - the bounds used for the terminal decision rule
- $(\underline{\kappa}_k, \overline{\kappa}_k)$ - the bounds used for declaring futility and expected success at interim analyses
- The frequency and timing of interim anlayses

The operating characteristics of interest are generally

- The probability of making a wrong decision when there is and isn't an effect
- The probability of making the right decision when there is and isn't an effect
- The probability the trial is stopped early at an interim analysis
- The expected total sample size

3.1 Fixed Sample size

3.1.1 Posterior probability

Assuming a maximum sample size of 3,000 (1,500 in each arm) at a fixed final anlaysis we estimate the following probability of success.

$\theta_w^\star$	$\theta_w^\star$	$\mathbb{P}(\Theta_1 \vert y_K)$
0.10	0.070	0.904
0.03	0.015	0.874
0.28	0.210	0.996

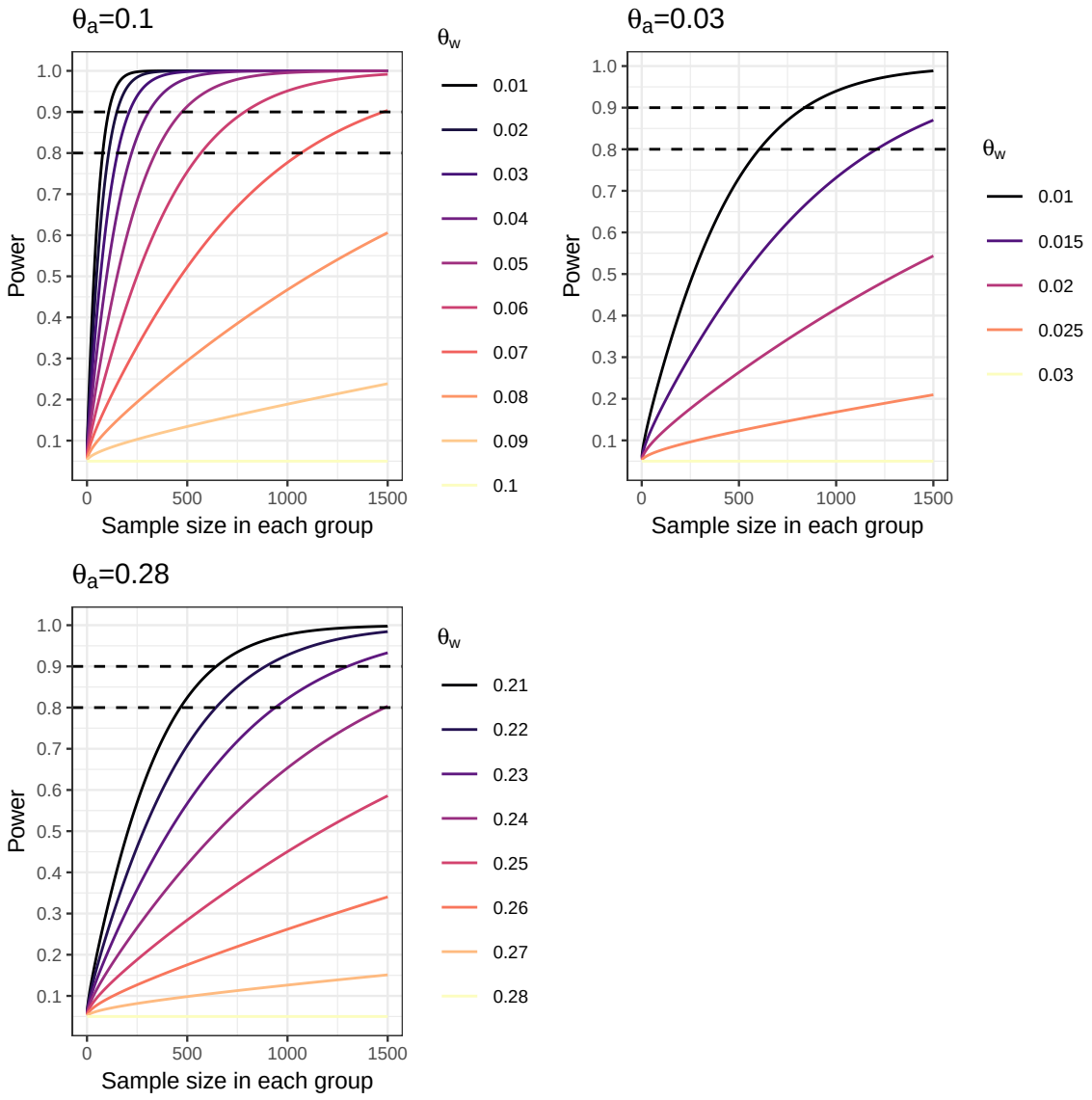
Assuming a maximum sample size of 2,000 participants (1,000 in each group)

$\theta_w^\star$	$\theta_w^\star$	$\mathbb{P}(\Theta_1 \vert y_K)$
0.10	0.070	0.777
0.03	0.015	0.728
0.28	0.210	0.977

3.1.2 Frequentist Power

Assuming $\theta_a^\star = 0.1$ and $\theta_w^\star = 0.07$ with $\alpha = 0.05$ and assuming a one-sided test, to achieve:

- 90% power we need 1478 in each group.
- 80% power we need 1068 in each group.



3.2 Adaptive Sample Size

For assessing interim analyses, we assume the two accrual scenarios mentioned previously: 20 per week and 10 per week. The difference between the two (apart from the total study length required), corresponds to varying the delay in information from follow-up. As previously stated, In the 20 per week case, we expect individuals with follow-up to be about 1,500 behind the number of individuals enrolled at the time of the first interim, whereas for 10 per week we expect individuals with follow-up to be about 800 behind the number enrolled at the time of the first interim. This affects the value of PPoS_k which will generally be closer to P_k the larger the cohort with missing information.

We also investigate the characteristics for parameters $(\underline{\kappa}_k, \overline{\kappa}_k) \in \{(0.1, 0.9), (0.05, 0.95)\}$ while keeping $(\underline{c}_K, \overline{c}_K) = (0.05, 0.95)$ fixed.

For each scenario, we assumed a first analysis when follow-up data is available on 100 individuals in each arm, and then interim analyses for every 200 more individuals with follow-up in each arm. As interim analyses only occur prior to full enrolment of 3,000 individuals, this setup implies 4 interim analyses assuming accrual of 20 participants per week ($n_1 + n_2 = 1,400$) and 5 interim analyses assuming accrual of 10 participants per

week ($n_1 + n_2 = 1,800$). After these interim's, enrolment will have already been completed, so it will not be possible to stop enrolment for futility or expected success.

We ran 1,000 trial simulations for each scenario to obtain estimates of the values of interest.

3.2.1 Example

As an example we simulate two triasl with $\theta_a = \theta_w = 0.1$. In this case the correct conclusion would be $\delta \geq 0$. The procession of posteriors is shown in Figure **??**. One of the trials ends early for futility and the other ends early for expected success.

In the tables that follow the example, estimates of the probabilities of each outcome under each scenario are presented along with expected enrolment at stopping time..

- $\mathbb{P}$(e.s) - probability of stopping early for expected success (early success)
- $\mathbb{P}$(l.s) - probability of declaring H_1 and make it to the maximum sample size (late success)
- $\mathbb{P}$(l.f) - probability of stopping early for futility (early failure)
- $\mathbb{P}$(l.f) - probability of declaring H_0 and make it to the maximum sample size (late failure)
- $\mathbb{P}$(s) - probability of any success
- $\mathbb{P}$(f) - probability of any failure
- $\mathbb{P}$(n.d) - probability we make it to maximum sample size and cannot conclude either H_0 or H_1 (inconclusive/no difference)
- $\mathbb{P}$(s.e) - probability of stopping before we reach maximum enrolment.
- $\mathbb{E}$(enrolled) - Expected number enrolled at stopping time
- Med(enrolled) - Median number enrolled at stopping time

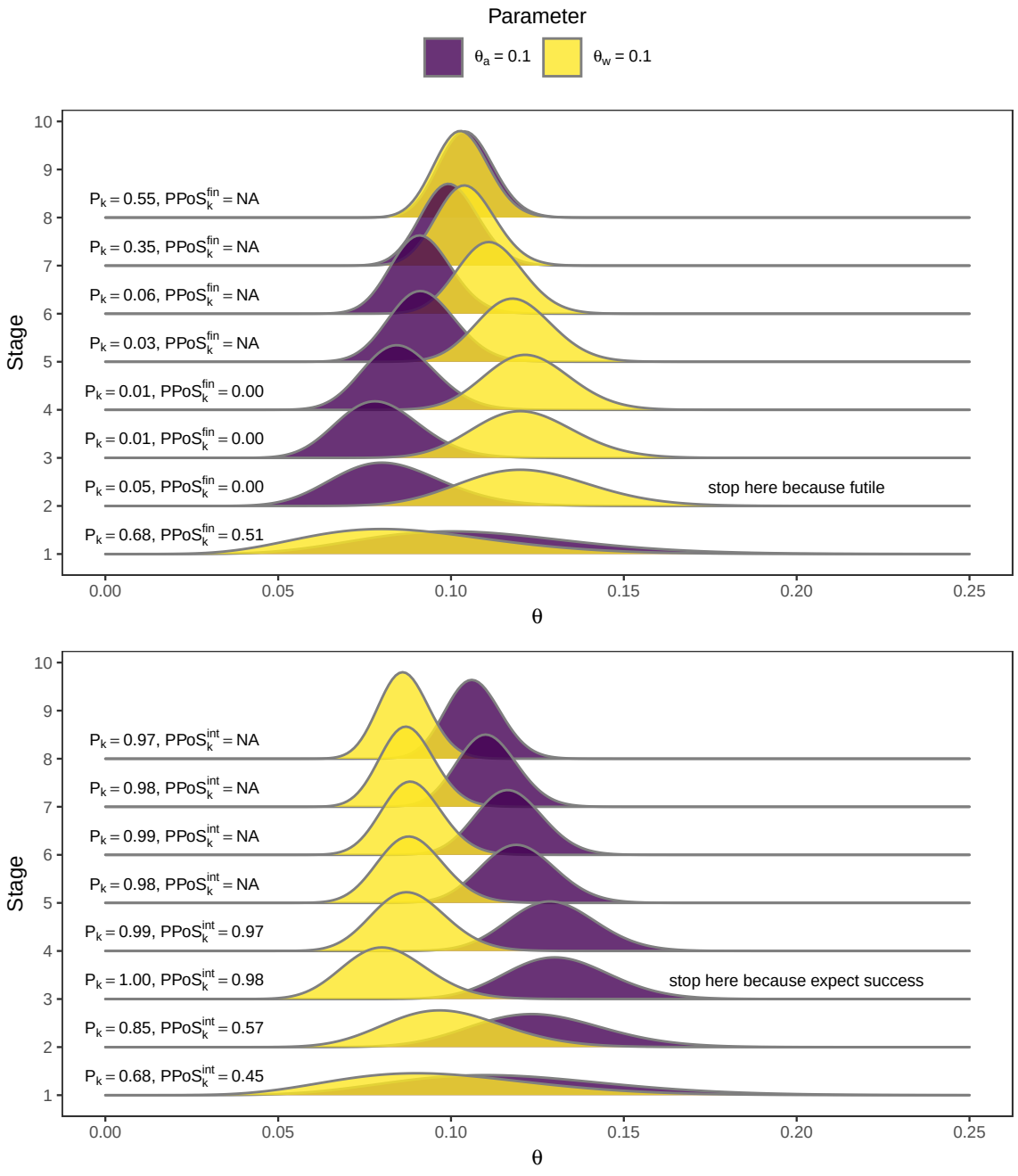


Figure 3: Two example trial procession of posteriors.

3.3 Accrual - 20 per week

3.3.1 18-month Primary End-point

Table 1: Decision probabilities, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.9$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.06	0.03	0.65	0	0.10	0.65	0.25	0.71	2394	2500
2	0.10	0.070	0.56	0.29	0.10	0	0.85	0.10	0.05	0.66	2492	2500
3	0.03	0.030	0.07	0.03	0.66	0	0.10	0.66	0.24	0.73	2429	2500
4	0.03	0.015	0.51	0.30	0.12	0	0.80	0.12	0.07	0.63	2520	2500
5	0.28	0.280	0.07	0.03	0.67	0	0.10	0.67	0.23	0.74	2367	2100
6	0.28	0.210	0.88	0.09	0.03	0	0.97	0.03	0.00	0.91	2209	2100

Table 2: Decision probabilities, ($\underline{\kappa}_k = 0.05, \overline{\kappa}_k = 0.95$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.04	0.04	0.54	0	0.08	0.54	0.38	0.58	2571	2900
2	0.10	0.070	0.43	0.45	0.06	0	0.88	0.06	0.06	0.49	2669	3000
3	0.03	0.030	0.03	0.04	0.54	0	0.08	0.54	0.39	0.57	2621	2900
4	0.03	0.015	0.40	0.43	0.07	0	0.82	0.07	0.11	0.46	2700	3000
5	0.28	0.280	0.04	0.04	0.57	0	0.07	0.57	0.35	0.61	2545	2900
6	0.28	0.210	0.83	0.15	0.01	0	0.99	0.01	0.00	0.84	2359	2500

Table 3: Decision probabilities, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.95$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.04	0.04	0.66	0	0.07	0.66	0.27	0.70	2420	2500
2	0.10	0.070	0.43	0.42	0.10	0	0.84	0.10	0.05	0.53	2629	2900
3	0.03	0.030	0.03	0.04	0.66	0	0.07	0.66	0.27	0.70	2465	2500
4	0.03	0.015	0.39	0.40	0.12	0	0.79	0.12	0.09	0.52	2650	2900
5	0.28	0.280	0.04	0.03	0.68	0	0.07	0.68	0.25	0.72	2399	2500
6	0.28	0.210	0.83	0.14	0.03	0	0.97	0.03	0.00	0.86	2340	2100

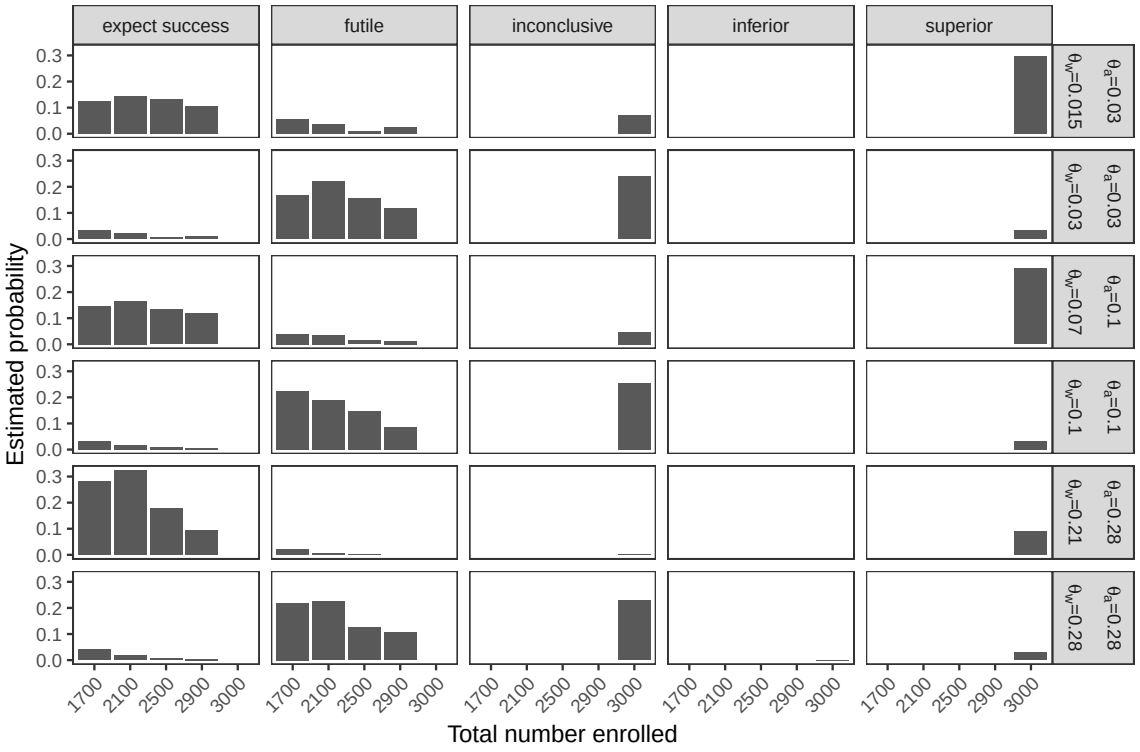


Figure 4: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.9$).

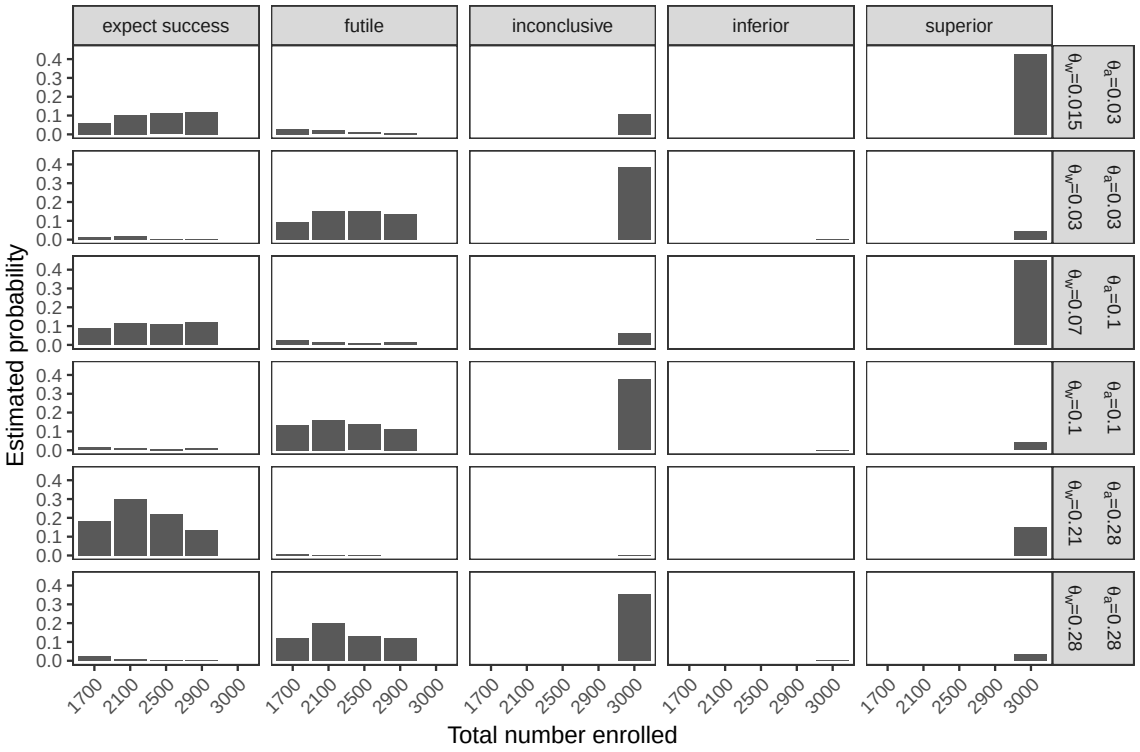


Figure 5: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.05, \overline{\kappa}_k = 0.95$).

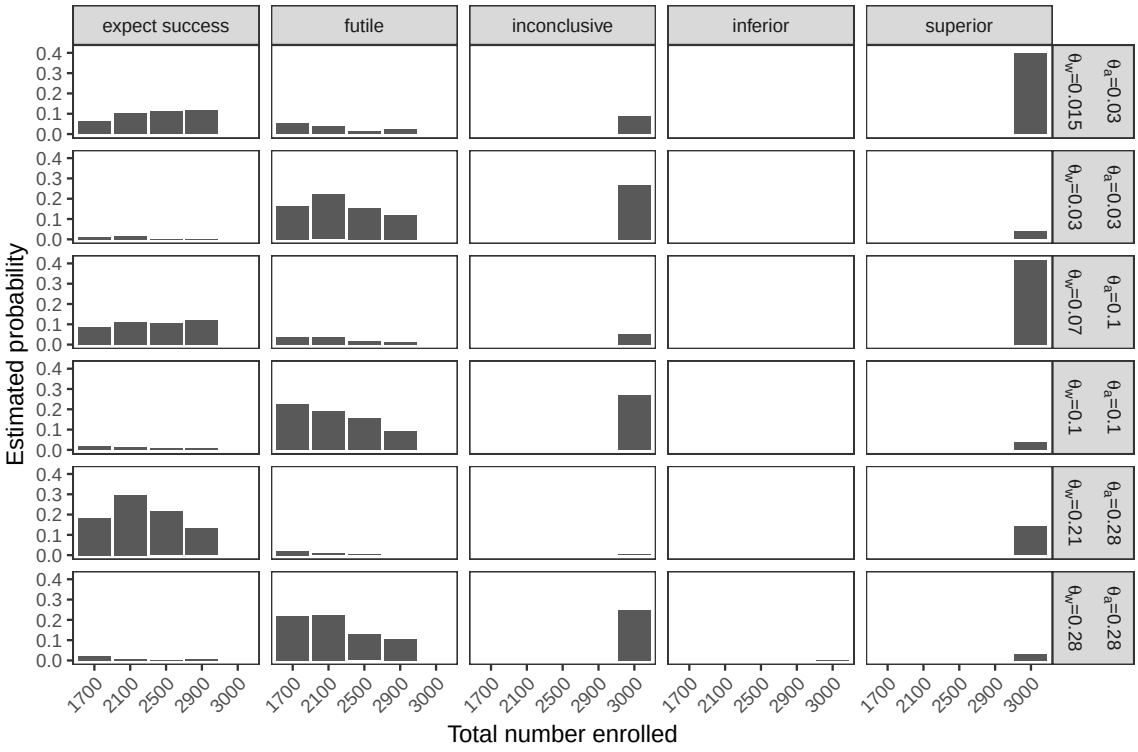


Figure 6: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.95$).

3.3.2 12-month Primary End-point

Table 4: Decision probabilities, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.9$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.05	0.03	0.75	0	0.08	0.75	0.17	0.80	2050	2000
2	0.10	0.070	0.64	0.18	0.13	0	0.82	0.13	0.04	0.78	2113	2000
3	0.03	0.030	0.06	0.03	0.75	0	0.09	0.75	0.16	0.81	2038	2000
4	0.03	0.015	0.61	0.22	0.13	0	0.83	0.13	0.04	0.74	2196	2000
5	0.28	0.280	0.06	0.02	0.77	0	0.08	0.77	0.15	0.82	2054	2000
6	0.28	0.210	0.92	0.04	0.04	0	0.96	0.04	0.00	0.96	1824	1600

Table 5: Decision probabilities, ($\underline{\kappa}_k = 0.05, \overline{\kappa}_k = 0.95$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.02	0.03	0.66	0	0.06	0.66	0.28	0.68	2307	2400
2	0.10	0.070	0.56	0.30	0.07	0	0.86	0.07	0.06	0.64	2376	2400
3	0.03	0.030	0.03	0.04	0.67	0	0.06	0.67	0.27	0.70	2278	2400
4	0.03	0.015	0.52	0.33	0.08	0	0.85	0.08	0.07	0.60	2440	2800
5	0.28	0.280	0.03	0.03	0.67	0	0.06	0.67	0.27	0.69	2296	2400
6	0.28	0.210	0.90	0.08	0.01	0	0.99	0.01	0.00	0.92	2013	2000

Table 6: Decision probabilities, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.95$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.02	0.03	0.76	0	0.05	0.76	0.19	0.78	2084	2000
2	0.10	0.070	0.55	0.26	0.13	0	0.82	0.13	0.05	0.68	2297	2400
3	0.03	0.030	0.03	0.03	0.76	0	0.06	0.76	0.18	0.79	2073	2000
4	0.03	0.015	0.51	0.30	0.13	0	0.82	0.13	0.06	0.64	2370	2400
5	0.28	0.280	0.03	0.03	0.78	0	0.05	0.78	0.17	0.80	2091	2000
6	0.28	0.210	0.89	0.08	0.04	0	0.96	0.04	0.00	0.92	1984	2000

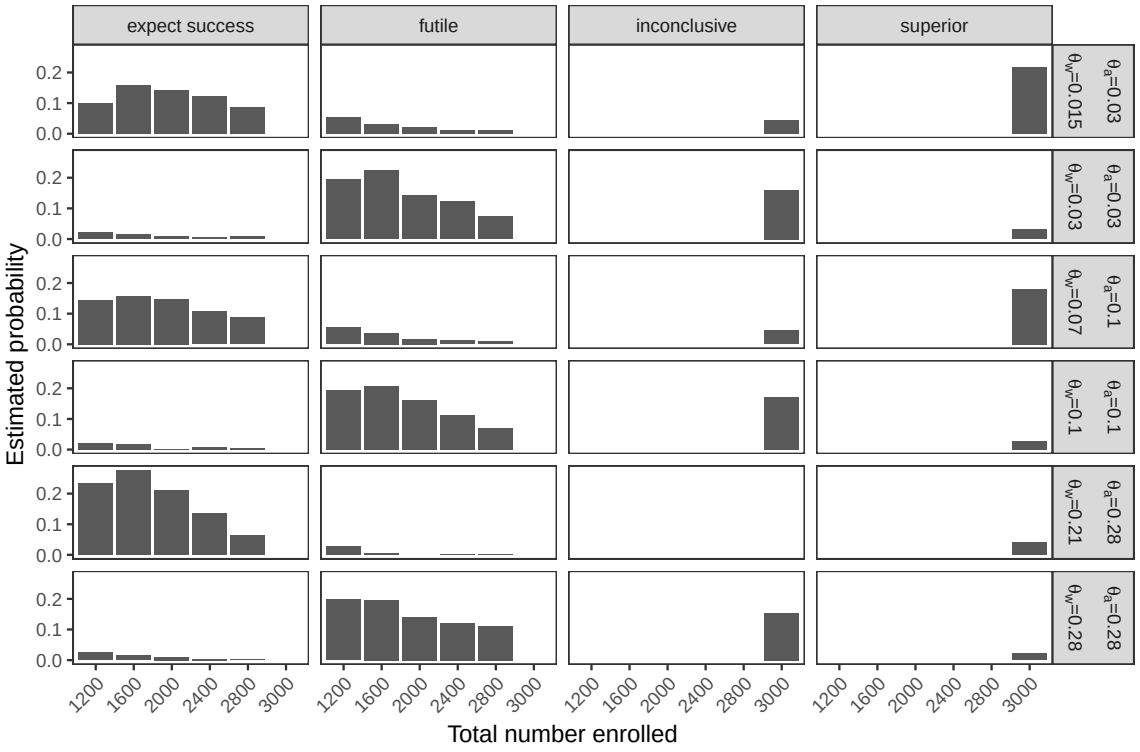


Figure 7: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.9$).

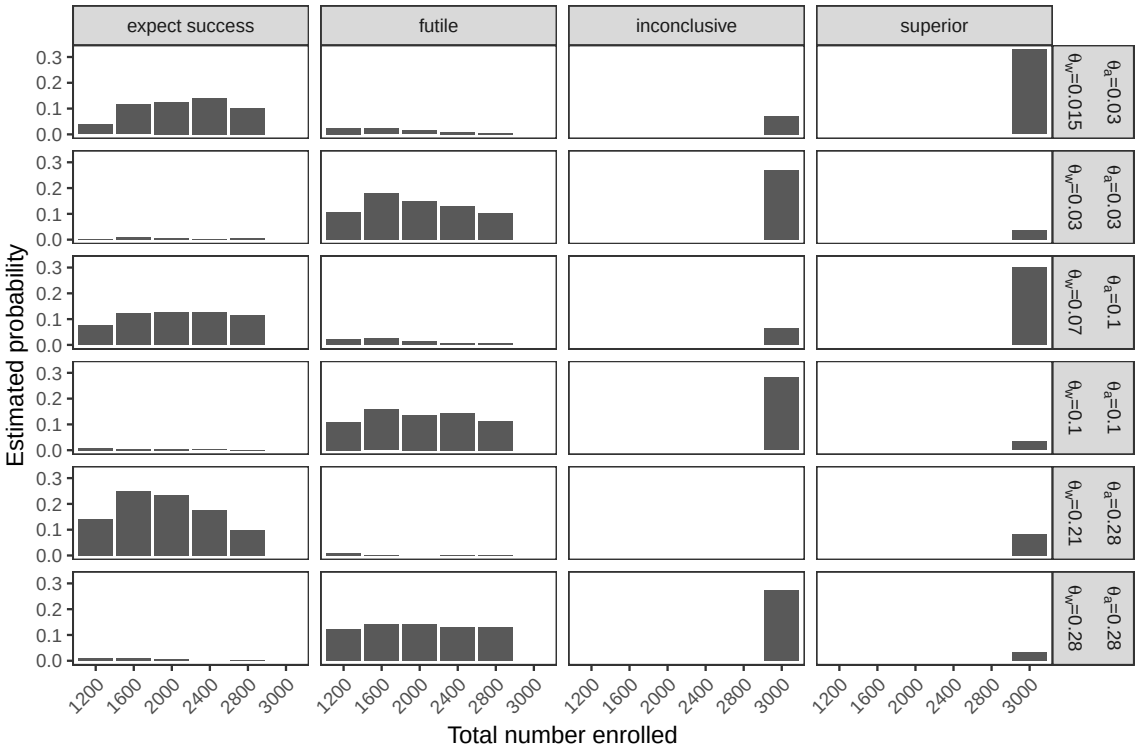


Figure 8: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.05, \overline{\kappa}_k = 0.95$).

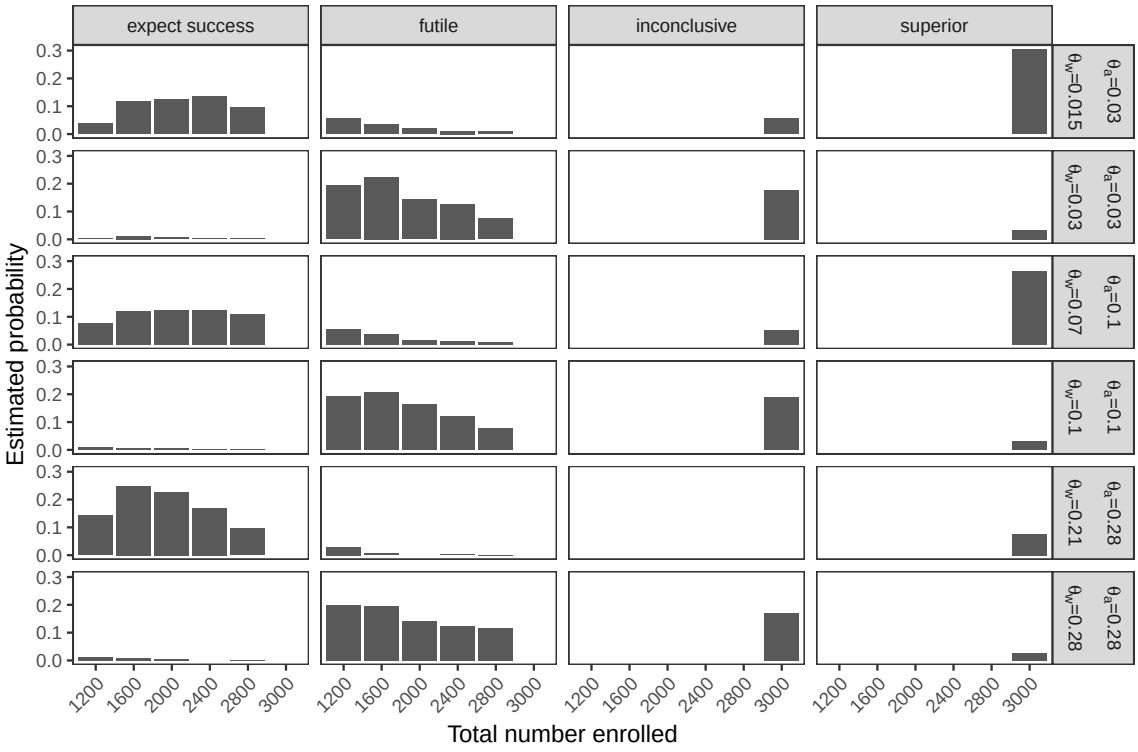


Figure 9: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.05, \overline{\kappa}_k = 0.95$).

3.4 Accrual - 10 per week

3.4.1 18-month primary end-point

Table 7: Decision probabilities, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.9$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.07	0.02	0.76	0	0.09	0.76	0.16	0.82	1841	1800
2	0.10	0.070	0.65	0.19	0.12	0	0.84	0.12	0.04	0.77	2002	1800
3	0.03	0.030	0.06	0.03	0.74	0	0.08	0.74	0.17	0.80	1929	1800
4	0.03	0.015	0.58	0.23	0.14	0	0.81	0.14	0.04	0.73	2096	2200
5	0.28	0.280	0.08	0.02	0.74	0	0.10	0.74	0.16	0.82	1866	1800
6	0.28	0.210	0.92	0.05	0.04	0	0.96	0.04	0.00	0.95	1628	1400

Table 8: Decision probabilities, ($\underline{\kappa}_k = 0.05, \overline{\kappa}_k = 0.95$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.04	0.03	0.67	0	0.07	0.67	0.26	0.71	2116	2200
2	0.10	0.070	0.57	0.31	0.06	0	0.88	0.06	0.06	0.63	2284	2200
3	0.03	0.030	0.03	0.04	0.68	0	0.07	0.68	0.26	0.70	2159	2200
4	0.03	0.015	0.50	0.35	0.08	0	0.85	0.08	0.07	0.58	2362	2600
5	0.28	0.280	0.04	0.03	0.66	0	0.07	0.66	0.27	0.70	2124	2200
6	0.28	0.210	0.89	0.09	0.02	0	0.98	0.02	0.00	0.91	1808	1800

Table 9: Decision probabilities, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.95$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.04	0.03	0.76	0	0.07	0.76	0.17	0.80	1883	1800
2	0.10	0.070	0.56	0.28	0.12	0	0.84	0.12	0.04	0.68	2189	2200
3	0.03	0.030	0.03	0.04	0.75	0	0.06	0.75	0.18	0.78	1962	1800
4	0.03	0.015	0.50	0.31	0.14	0	0.80	0.14	0.05	0.64	2266	2200
5	0.28	0.280	0.04	0.03	0.75	0	0.07	0.75	0.18	0.79	1920	1800
6	0.28	0.210	0.88	0.08	0.04	0	0.96	0.04	0.00	0.92	1780	1800

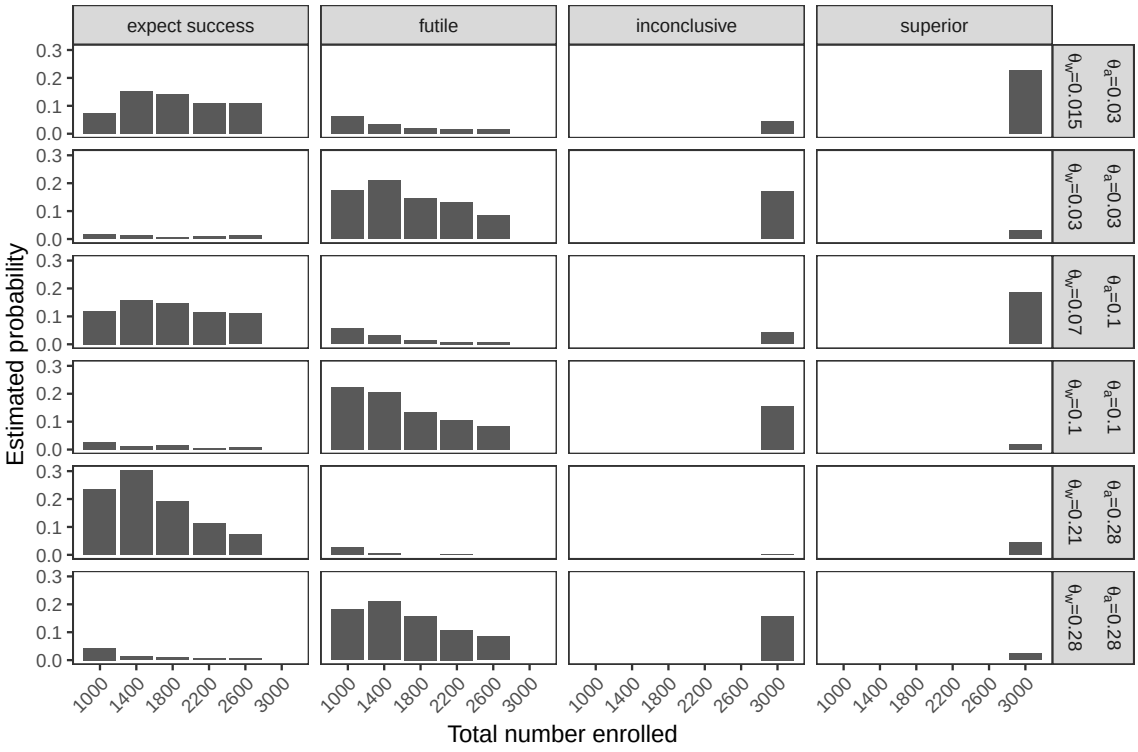


Figure 10: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.9$).

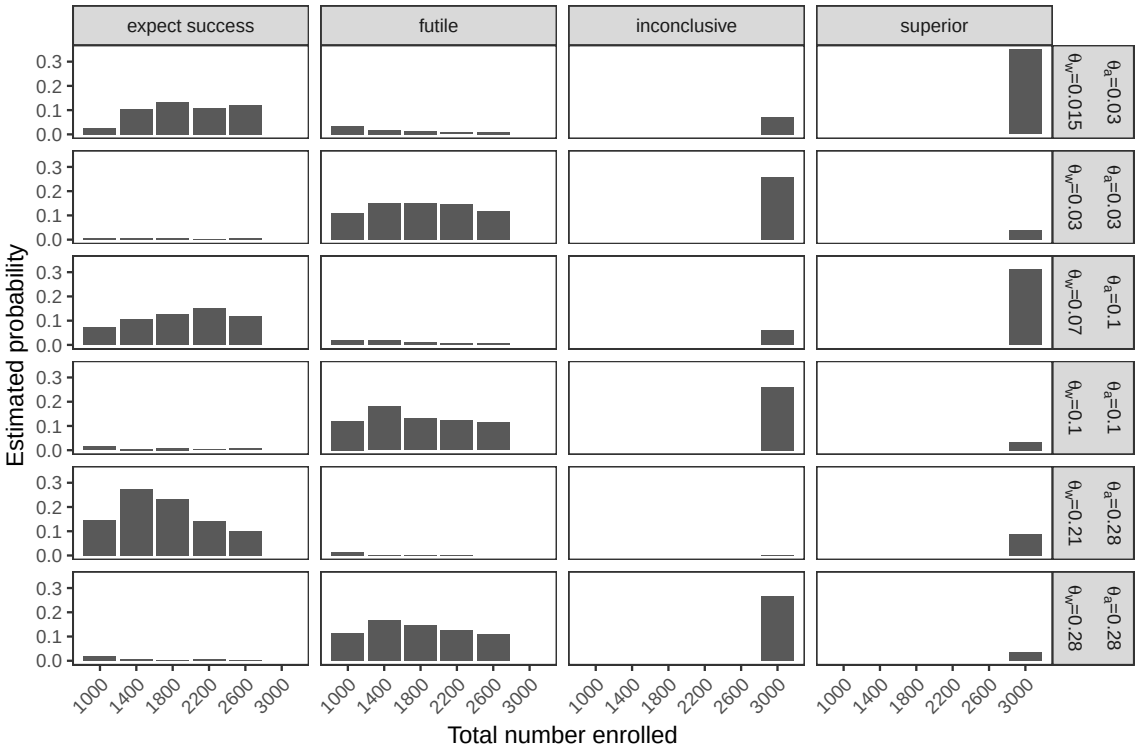


Figure 11: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.05, \overline{\kappa}_k = 0.95$).

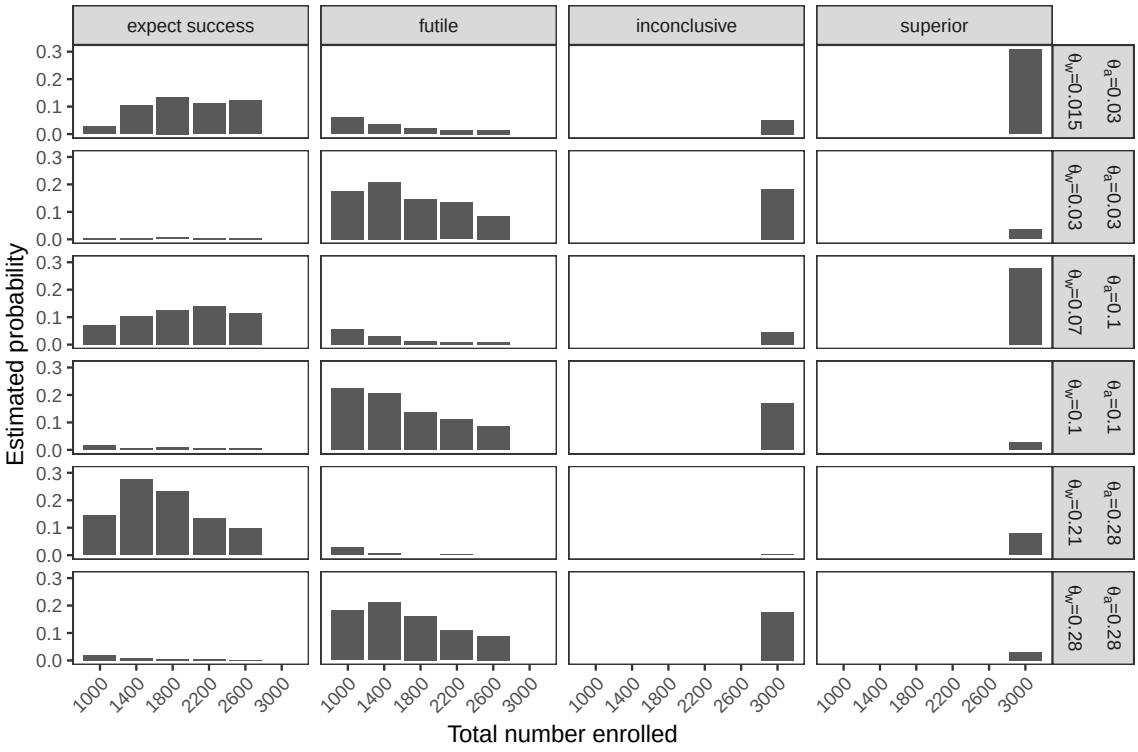


Figure 12: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.95$).

3.4.2 12-month Primary End-point

Table 10: Decision probabilities, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.9$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.06	0.02	0.83	0	0.08	0.83	0.09	0.89	1618	1500
2	0.10	0.070	0.69	0.12	0.14	0	0.82	0.14	0.04	0.84	1742	1500
3	0.03	0.030	0.06	0.02	0.83	0	0.08	0.83	0.10	0.89	1624	1500
4	0.03	0.015	0.66	0.14	0.16	0	0.80	0.16	0.04	0.82	1872	1900
5	0.28	0.280	0.06	0.02	0.82	0	0.08	0.82	0.10	0.88	1609	1500
6	0.28	0.210	0.95	0.02	0.03	0	0.97	0.03	0.00	0.98	1365	1100

Table 11: Decision probabilities, ($\underline{\kappa}_k = 0.05, \overline{\kappa}_k = 0.95$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.03	0.03	0.78	0	0.06	0.78	0.16	0.82	1893	1900
2	0.10	0.070	0.66	0.21	0.07	0	0.87	0.07	0.06	0.73	2052	1900
3	0.03	0.030	0.03	0.02	0.77	0	0.06	0.77	0.17	0.80	1930	1900
4	0.03	0.015	0.62	0.23	0.09	0	0.85	0.09	0.07	0.71	2152	2300
5	0.28	0.280	0.04	0.03	0.76	0	0.07	0.76	0.16	0.81	1905	1900
6	0.28	0.210	0.95	0.03	0.01	0	0.99	0.01	0.00	0.97	1534	1500

Table 12: Decision probabilities, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.95$)

Scenario	$\theta_a^\star$	$\theta_w^\star$	$\mathbb{P}$(e.s)	$\mathbb{P}$(l.s)	$\mathbb{P}$(e.f)	$\mathbb{P}$(l.f)	$\mathbb{P}$(s)	$\mathbb{P}$(f)	$\mathbb{P}$(inc)	$\mathbb{P}$(s.e)	$\mathbb{E}$(enrolled)	Med(enrolled)
1	0.10	0.100	0.03	0.02	0.85	0	0.06	0.85	0.10	0.88	1650	1500
2	0.10	0.070	0.63	0.18	0.14	0	0.81	0.14	0.04	0.78	1926	1900
3	0.03	0.030	0.03	0.02	0.84	0	0.05	0.84	0.11	0.87	1667	1500
4	0.03	0.015	0.60	0.20	0.16	0	0.80	0.16	0.04	0.76	2040	1900
5	0.28	0.280	0.04	0.03	0.83	0	0.07	0.83	0.10	0.87	1641	1500
6	0.28	0.210	0.94	0.03	0.03	0	0.97	0.03	0.00	0.97	1513	1500

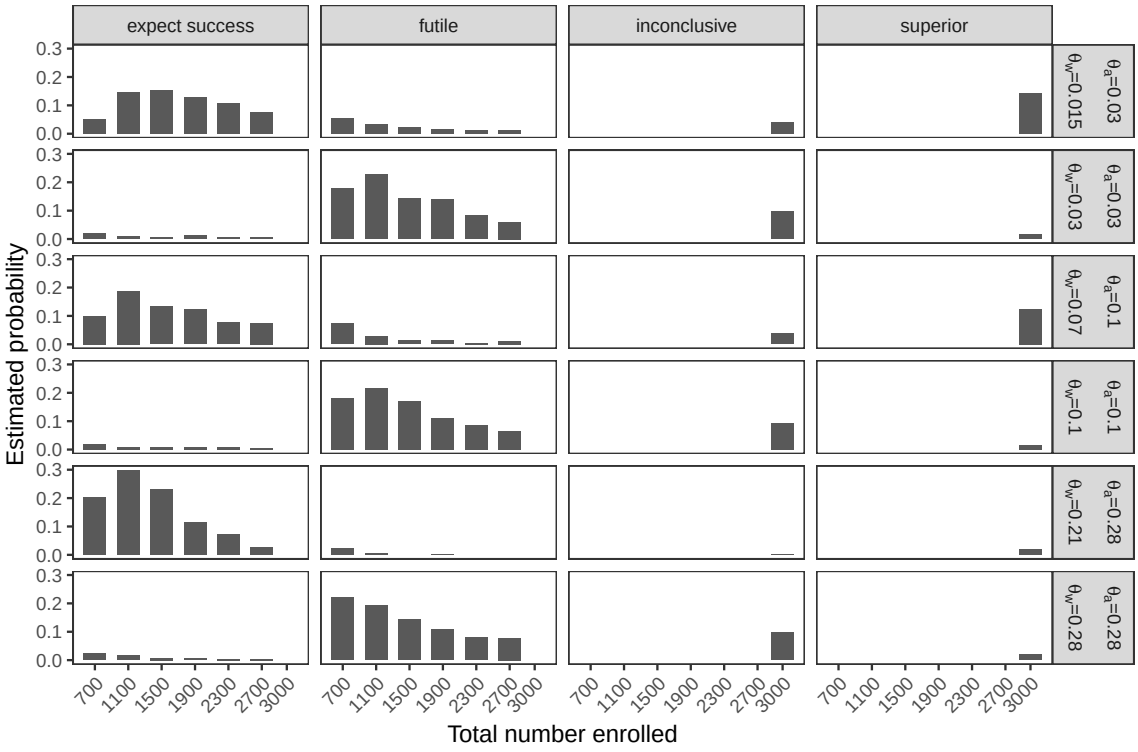


Figure 13: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.9$).

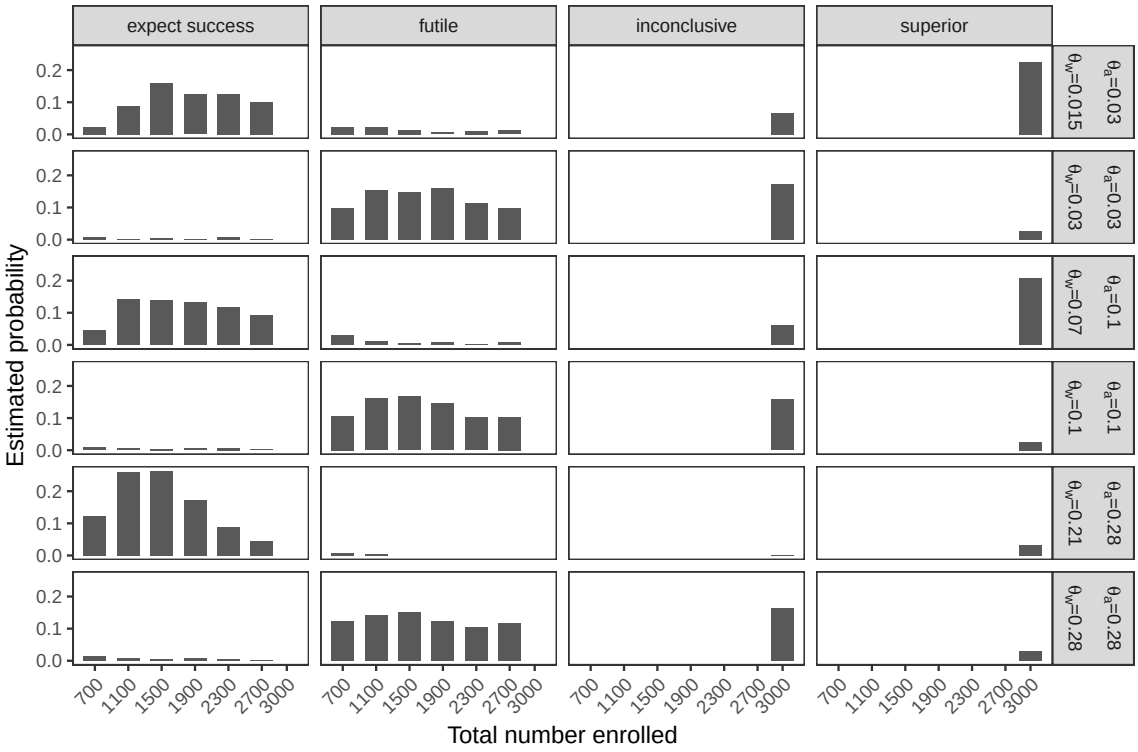


Figure 14: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.05, \overline{\kappa}_k = 0.95$).

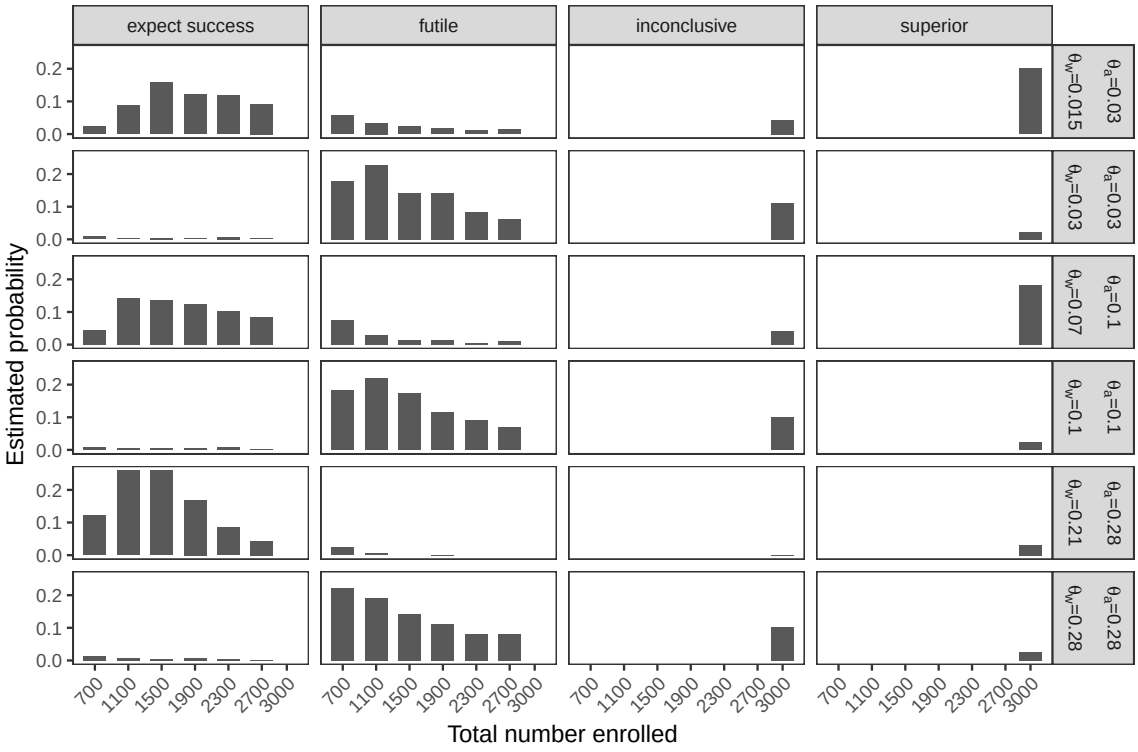


Figure 15: Probability of stopping at stage, by result, ($\underline{\kappa}_k = 0.1, \overline{\kappa}_k = 0.95$).