Isotonic design for a single-arm trial with a biomarker: Supplementary Materials

Exact calculation of the probability of rejecting null hypothesis

There are three routes defined in Section 3. Here, we present how we calculate the probability of rejecting hypotheses through each route.

For Route 1 and Route 2, the interim decision rule requires $\widetilde{X_1^-} \geq k_1^-$ and $\widetilde{X_1^+} \geq k_1^+$ for both subgroups to proceed to the second stage. Recall that PAVA would pool the response rates if $p_1^- \geq p_1^+$. We can express the interim decision rule by solving:

$$X_1^- = \frac{(X_1^- + X_1^+)}{N_1^- + N_1^+} \times N_1^- \geq k_1^- .$$

This yields the constraint on the observed X_1^+ as:

$$X_1^+ \geq \frac{k_1^-(N_1^- + N_1^+)}{N_1^-} - X_1^- .$$

Similar scenario might happen in the second stage for Route 1.The probability of rejecting the null hypothesis through Route 1 given the response rate of p^-, p^+, $R_1(p^-, p^+)$, can be calculated using the two conditions below:

1. (Stage 1) $X_1^- \geq k_1^-$ and $X_1^+ \geq \frac{k_1^-(N_1^- + N_1^+)}{N_1^-} - X_1^-$ and,
2. (Stage 2) $X^- \geq k^-$ and $X^+ \geq \frac{k^-(N^- + N^+)}{N^-} - X^-$

For Route 2, the Stage 1 decision will be the same. For Stage 2, there are two scenarios. Scenario 1 is when $X^- < k^-$ and $\widetilde{X^+} \geq k^+$. So we can solve for X^+:

$$\widetilde{X^{+}} = \frac{(X^{-} + X^{+})}{N^{-} + N^{+}} \times N^{+} \geq k^{+} .$$

Thus the constraint on the observed X^{+} as

$$X^{+} \geq \frac{k^{+}(N^{-} + N^{+})}{N^{+}} - X^{-} .$$

In some rare cases, even when $X^{-} \geq k^{-}$, we can still reject through Route 2 after applying PAVA. This would happen when

$$\frac{k^{+}(N^{-} + N^{+})}{N^{+}} - X^{-} \leq X^{+} < \frac{k^{-}(N^{-} + N^{+})}{N^{-}} - X^{-} .$$

So to summarize, the probability we reject null hypothesis through Route 2 given the response rate of p^{-}, p^{+}, $R_2(p^{-}, p^{+})$, can be calculated using the conditions below:

1. (Stage 1) $X_1^{-} \geq k_1^{-}$ and $X_1^{+} \geq \frac{k_1^{-}(N_1^{-} + N_1^{+})}{N_1^{-}} - X_1^{-}$ and,
2. (Stage 2 option 1) $X^{-} < k^{-}$ and $X^{+} \geq \frac{k^{+}(N^{-} + N^{+})}{N^{+}} - X^{-}$ or,
3. (Stage 2 option 2) $X^{-} \geq k^{-}$ and $\frac{k^{+}(N^{-} + N^{+})}{N^{+}} - X^{-} \leq X^{+} < \frac{k^{-}(N^{-} + N^{+})}{N^{-}} - X^{-}$.

Route 3 is to reject only H_0^{+} when only A^{+} groups proceed to the second stage. Very similar to Route 2 but the second stage decision rules apply in the first stage. The second stage only involves testing about N_e^{+}. the probability we reject null hypothesis through Route 3 given the response rate of p^{-}, p^{+}, $R_3(p^{-}, p^{+})$, can be calculated using the conditions below:

1. (Stage 1 option 1) $X_1^- \geq k_1^-$ and

$$\frac{k_1^+(N_1^- + N_1^+)}{N_1^+} - X_1^- \leq X_1^+ < \frac{k_1^-(N_1^- + N_1^+)}{N_1^-} - X_1^- \text{ or,}$$

2. (Stage 1 option 2) $X_1^- < k_1^-$ and $X_1^+ \geq \dfrac{k_1^+(N_1^- + N_1^+)}{N_1^+} - X_1^-$ and,

3. (Stage 2) $X_e^+ \geq k_e^+$.

Using the framework shown above, we can calculate the expected sample size and probability of early stopping. Using the conditions outlined above, define the probability of passing the interim analysis for both subgroup as p_{i1} and the probability of having only A^+ groups passing the interim analysis as p_{i2}, the probability of early stopping for futility (PET) can be calculated as:

$$\text{PET} = 1 - p_{i1} - p_{i2}.$$

The expected sample size $EN(p^+, p^-)$ can be calculated as:

$$EN(p^+, p^-) = N_1^- + N_1^+ \times PET + p_{i1} \times (N^- + N^+) + p_{i2} \times (N_1^- + N_e^+).$$