Exact Sample Size Determination for Basket Trials with Competitive Enrollment

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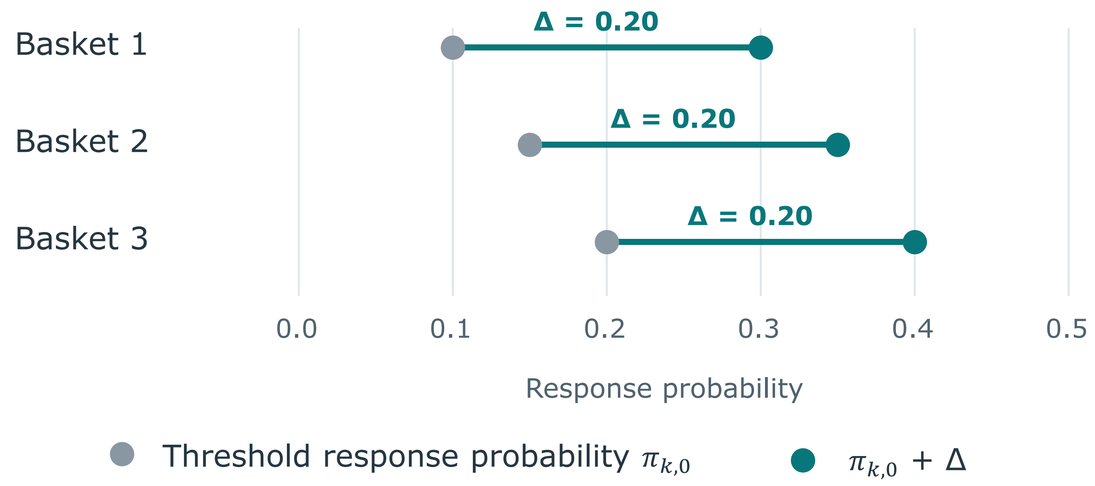
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01 Background: A frequentist framework for phase II basket trials in oncology

Hattori and Morita[1] proposed a one-sample Mantel–Haenszel framework that extends conventional single-arm inference to basket trials, allowing basket-specific response thresholds while borrowing information under a common treatment effect.

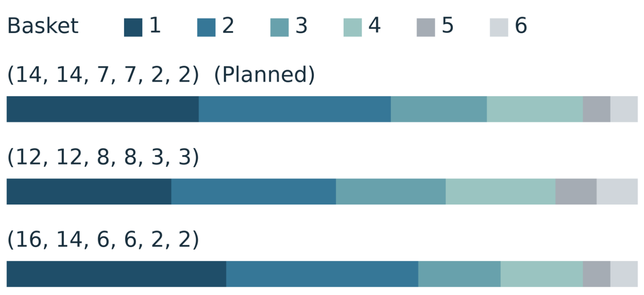
	Traditional single-arm design	Basket trial framework
Model	$\mathbf{Y} \sim \mathbf{Bin}(\mathbf{N}, \boldsymbol{\pi})$	$\mathbf{Y_k} \sim \mathbf{Bin}(\mathbf{n_k}, \boldsymbol{\pi_{k,0}} + \boldsymbol{\Delta})$
Hypothesis testing	$\mathbf{H_0}: \boldsymbol{\pi} \le \boldsymbol{\pi_0}$ Exact test based on $\mathbf{T} = \mathbf{Y}$	$\mathbf{H_0}: \boldsymbol{\Delta} \le \mathbf{0}$ Exact test based on $\mathbf{T} = \sum_{k=1}^{K} \mathbf{Y_k}$[3]
Estimation	$\widehat{\boldsymbol{\pi}} = \frac{\mathbf{Y}}{\mathbf{N}}$	$\widehat{\boldsymbol{\Delta}}^{\mathbf{RD}} = \frac{\sum_{k=1}^{K}(\mathbf{Y_k} - \mathbf{n_k}\boldsymbol{\pi_{k,0}})}{\sum_{k=1}^{K}\mathbf{n_k}}$ $If\ n_k \to \infty\ or\ K \to \infty, \quad \widehat{\Delta}^{RD} \to \Delta$
Confidence intervals	**Clopper–Pearson method**[2]	$\widehat{\boldsymbol{\Delta}}^{\mathbf{RD}} \pm \mathbf{z_{1-\alpha/2}}\,\widehat{\mathbf{SE}}(\widehat{\boldsymbol{\Delta}}^{\mathbf{RD}})$
Selection of baskets to pool	—	**GIC selection based on $\widehat{\boldsymbol{\Delta}}$**
Sample-size determination (without interim analysis)	**Smallest N admitting a cutoff r** $\mathbf{Pr}_{\pi_0}(\mathbf{Y} \ge \mathbf{r}) \le \boldsymbol{\alpha}$ $\mathbf{Pr}_{\pi_1}(\mathbf{Y} \ge \mathbf{r}) \ge \mathbf{1} - \boldsymbol{\beta}$	**★This Study**

Different thresholds, the same improvement (ex : $\Delta = 0.20$)



02 Problem: the final mix can shift

Under competitive enrollment, the final basket mix may differ from that planned.The planned composition requires $(N = 46)$ for 90% power. For each composition below, we recalculated the exact cutoff to control the one-sided type I error at 2.5%.



	Type I error	Power
(14, 14, 7, 7, 2, 2) (Planned)	2.22%	90.79%
(12, 12, 8, 8, 3, 3)	1.37%	**88.6%**
(16, 14, 6, 6, 2, 2)	1.13%	**85.6%**

Targets: type I error ≤ 2.5%, power ≥ 90%. Exact calculations (§05).
At $(N = 46)$, power can fall below 90% even with a composition-specific cutoff.

03 Objective: protect every allowed mix

Prespecify enrollment bounds and target effect Δ_1. Find the smallest N with one cutoff r satisfying:

$$P_k^L \le n_k/N \le P_k^U$$

$$\mathcal{N}(N) = \left\{\mathbf{n} \in \mathbb{Z}_{\ge 0}^K : \sum_k n_k = N, \quad \lceil NP_k^L \rceil \le n_k \le \lfloor NP_k^U \rfloor\right\}$$

Maximum type I error

$$\max_{\mathbf{n} \in \mathcal{N}(N)} \Pr_0(T \ge r \mid \mathbf{n}) \le \alpha$$

Minimum power

$$\min_{\mathbf{n} \in \mathcal{N}(N)} \Pr_{\Delta_1}(T \ge r \mid \mathbf{n}) \ge 1 - \beta$$

04 Proposed design: two worst cases, then search over N

For Fixed N, cutoff r and Δ, if $\pi_{i,0} \le \pi_{j,0}$ and all other basket sizes remain unchanged, then

$$\Pr_\Delta(T \ge r \mid \ldots, n_i - 1, \ldots, n_j + 1) \ge \Pr_\Delta(T \ge r \mid \ldots, n_i, \ldots, n_j)$$

Set $n_k = \lceil NP_k^L \rceil$ for each basket.

$\mathbf{n}^{(0)}(N)$ — Maximize type I error at $\Delta = 0$

Allocate the remaining patients in descending order of $\pi_{k,0}$, up to each basket's upper bound

$\mathbf{n}^{(1)}(N)$ — Minimize Power at $\Delta = \Delta_1$

Allocate the remaining patients in ascending order of $\pi_{k,0}$, up to each basket's upper bound

For each feasible N, these two compositions are worst-case for every cutoff r; no enumeration is needed.

Initialize N = 1

1 Update bounds and feasible counts
Empty set: increase N and try again

↓

2 Control α using the null maximum

$$r_N = \min\{r : \Pr_0(T \ge r \mid \mathbf{n}^{(0)}(N)) \le \alpha\}$$

↓

3 Check power at the worst mix

$$\Pr_{\Delta_1}(T \ge r_N \mid \mathbf{n}^{(1)}(N)) \ge 1 - \beta\ ?$$

No → N + 1

Yes ↓

STOP: first qualifying N and its cutoff

Recompute at every N. Integer bounds and cutoffs can make power nonmonotone.

05 Results: the cost of allowing the basket mix to vary

Six baskets: $\pi_{k,0}$ = (0.20, 0.15, 0.10, 0.10, 0.05, 0.05). Δ_1 = 0.20, type I error = 0.025, target power = 0.90.

Scenario

Design	P_1	P_2	P_3	P_4	P_5	P_6
Fixed	0.3	0.3	0.15	0.15	0.05	0.05
Narrow	0.27–0.33	0.28–0.32	0.12–0.18	0.13–0.17	0.02–0.08	0.03–0.07
Moderate	0.25–0.35	0.25–0.35	0.1–0.2	0.1–0.2	0–0.1	0–0.1
Wide	0.15–0.45	0.15–0.45	0.05–0.25	0.05–0.25	0.02–0.08	0.02–0.08

Design	N	n_1	n_2	n_3	n_4	n_5	n_6	Cutoff r_N	Max. type I error	Min. power
Fixed	46	14	14	7	7	2	2	12	2.22%	90.79%
Narrow	50	14–16	14–16	6–9	7–8	1–4	2–3	13	2.23%	90.22%
Moderate	58	15–20	15–20	6–11	6–11	0–5	0–5	15	2.31%	90.66%
Wide	74	12–33	12–33	4–18	4–18	2–5	2–5	19	2.32%	90.56%

06 Conclusion: an extension of exact single-arm design

We extend exact sample size planning to single-arm phase II basket trials with competitive enrollment in oncology.The design controls type I error and achieves the target power for every basket composition within prespecified enrollment bounds.

<References>

[1] Hattori S, Morita S. *Stat Med.* 2023;42:4824–4849.
[2] Clopper CJ, Pearson ES. *Biometrika.* 1934;26:404–413.
[3] London WB, Chang MN. *Stat Med.* 2005;24:2597–2611.