Sequential Enrichment Designs for Early Phase Clinical Trials

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1. Background

Early phase clinical trials in oncology

- Single-arm design with limited sample size
- Subgroup identifications are typically done via post-hoc-analysis
- Exact binomial test and Simon two-stage design are commonly used
- Need evidence-based and clinically meaningful quantitative framework to facilitate patient subpopulation for further development

Objective

- Developing a robust GO/NO-GO decision-making framework by considering both statistical significance and clinical relevance
- Identify the right population to increase likelihood of success

We propose a Bayesian adaptive enrichment strategy and dual criterion design for sub-population selection in early phase trials.

2. Example

Study objective

- PoC study of Drug A to evaluate its anti-tumor activity in gastric cancer

Endpoint

- Objective response rate (ORR)

Study population

- All patients irrespective of status for biomarker of interest Y

Study design

- Single-arm with biomarker of interest Y

3. Dual Criteria Design

- Formal inclusion of statistical significance and clinical relevance in design:
- Decide GO
  - Strong evidence: effect ≥ no effect or null value (NV)
  - Estimated effect ≥ decision value (DV)
- DV : minimum effect with clinical relevance; not classical alternative hypothesis
  - Need discussion with nonstatisticians
- Sample size requires consideration of DV
  - Adequate sample size is required to ensure statistical significance when clinical relevance observed
- Need simulation to calculate design operating characteristics (e.g., type-I error, power)

4. Subpopulation Selection in Early Phase

Demand for a new design

- A competitor Drug B failed for all-comers but show promising efficacy in patients with Y+ in post-hoc subgroup analysis

Goal

- Assess activity of Drug A for all patients irrespective of biomarker status
- If it is **not active for all patients**, assess activity of Drug A for Y+ patients

5. Single-stage Design with Population Selection

- **Study populations**

All-comers (F) = Y+ patients + Y- patients

- **Bayesian triplet criterion for all-comers**

1. Pr(ORR (F) ≥ 16% | data) ≥ 0.975
2. Posterior median (F) ≥ 24%
3. Pr(ORR (Y-) ≥ 16% | data) ≥ 0.75
   (activity assurance in Y- patients)

The third criteria ensures that the effect of Drug A in F is not solely driven by Y+

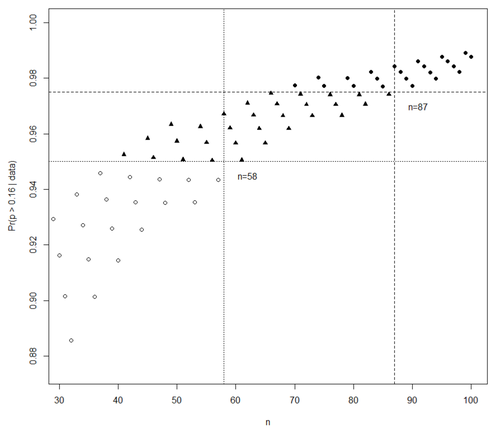
- **Bayesian dual criteria for Y+ patients**

1. Pr(ORR (Y+) ≥ 16% | data) ≥ 0.95
2. Posterior median (Y+) ≥ 24%

- **Minimum sample size (SS_{min})**

All-comers: 87 (with number of responders ≥21)
Y+ patients: 58 (with number of responders ≥14)
Sample size bigger than SS_{min} ensures statistical significance when clinical relevance is observed

Figure 1. Grid Search for Minimum Sample Size



Sample size

6. Design Characteristics (single-stage)

Figure 6.1: Flow Chart for Single-stage Enrichment Design

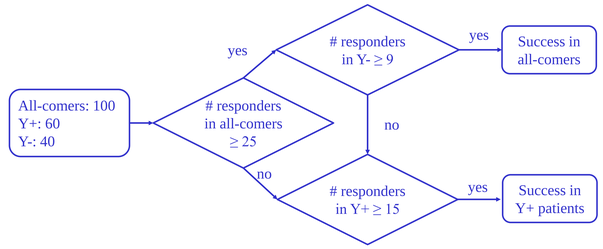


Figure 6.2: OC for One-stage Enrichment Design

Scenario	Probability of crossing efficacy boundary in all-comers (%)	Probability of crossing efficacy boundary in Y+ patients (%)
ORR (Y+) = ORR (Y-) = 16%	1.1	4.1
ORR (Y+) = 32%, ORR (Y-) = 16%	16.0	74.8
ORR (Y+) = 16%, ORR (Y-) = 32%	29.8	0.5
ORR (Y+) = ORR (Y-) = 32%	90.1	6.6

7. Two-stage Design with Adaptive Population Enrichment

- **Sequential enrichment**

Use probability of success (POS) at interim to allow early stopping for futility.

- **Use POS for interim decision making**

POS(F): PP(posterior median (F) ≥ 24% at final analysis | interim data); PP=predictive probability
POS(Y+): PP(posterior median (Y+) ≥ 24% at final analysis | interim data)
POS(Y-): PP (Pr(ORR (Y-) ≥ 16% | data) ≥ 0.75 at final analysis | interim data)

- **Interim decision rules**

Continue with F: POS(F) ≥ 10% and POS(Y-) ≥ 10%
Continue with Y+: POS(F) ≥ 10% but POS(Y-) < 10% and POS(Y+) ≥ 10% OR
POS(F) < 10% but POS(Y+) ≥ 10%
Otherwise stop for futility

8. Design Characteristics (two-stage)

Figure 8.2: Interim OC for Sequential Enrichment Design

Scenario	Probability of crossing interim boundary in all-comers (%)	Probability of crossing interim boundary in Y+ patients (%)	Probability of early stop for futility (%)
ORR (Y+) = ORR (Y-) = 16%	24.7	16.0	59.3
ORR (Y+) = 32% ORR (Y-) = 16%	60.4	35.5	4.1
ORR (Y+) = 16% ORR (Y-) = 32%	71.3	1.6	27.1
ORR (Y+) = ORR (Y-) = 32%	96.1	2.6	1.3

Figure 8.1: Flow Chart for Sequential Enrichment Design

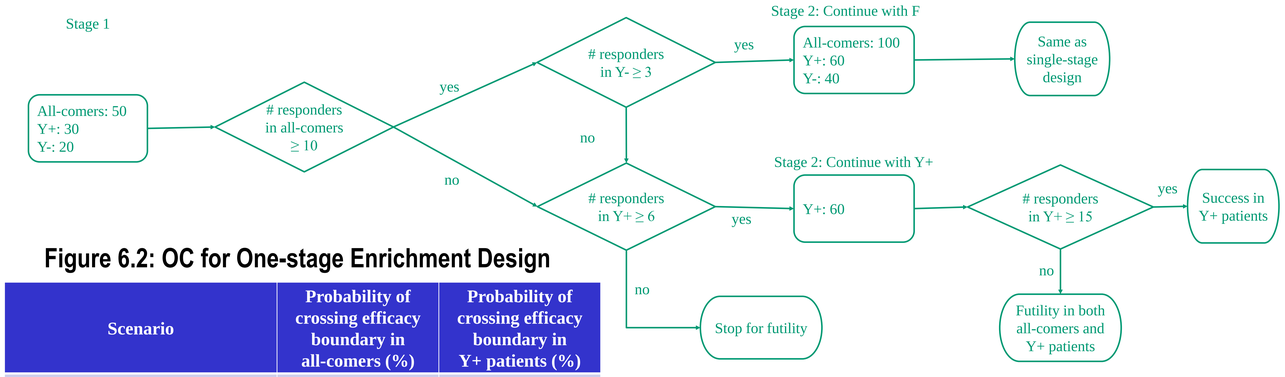


Figure 8.3: Final OC for Sequential Enrichment Design

Scenario	Probability of crossing efficacy boundary in all-comers (%)	Probability of crossing efficacy boundary in Y+ patients (%)
ORR (Y+) = ORR (Y-) = 16%	1.0	3.8
ORR (Y+) = 32%, ORR (Y-) = 16%	15.2	73.9
ORR (Y+) = 16%, ORR (Y-) = 32%	28.6	0.5
ORR (Y+) = ORR (Y-) = 32%	88.5	7.4

9. Conclusions/Discussions

- We have provided an evidence-based approach for subgroup selection in single arm trial
- Complement statistical–clinical criterion and intrinsic population selection algorithm in the interim analysis
- Can be extended to single-arm studies with other endpoints, such as time-to-event endpoints (e.g., 1-year PFS rate)

10. References

1. Roychoudhury, S., Scheuer, N., & Neuenschwander, B. (2018). Beyond p-values: A phase II dual-criterion design with statistical significance and clinical relevance. Clinical Trials, 15(5), 452–461.