Introduction

Designing a phase II clinical trial for the evaluation and validation of a biomarker-guided personalized targeted therapy can be challenging. We outlined two design considerations illustrated by an example named TTAML (targeted therapy for acute myeloid leukemia) trial.

Background

The TTAML trial evaluates five widely used FDA approved drugs for AML patients.

Goal of the trial: to validate the clinical utility of a newly developed in-vitro screening technique for personalized drug selection based on drug sensitivity assay for AML patients with identifiable targets of tyrosine kinases.

Primary objective: to evaluate whether receiving a sensitive drug brings more therapeutic benefits than receiving a non-sensitive drug.

Primary endpoint: treatment response, a binary variable indicating whether the reduction in white blood cell counts is more than 25% from the baseline in 30 days.

Note:
- Each patient has its own set of “sensitive” and “non-sensitive” drugs.
- The response rate may differ for the 5 drugs, and for the same drug depending on its “sensitivity” to the patient.

Design Considerations

A: Single-arm or randomized trial?

Single-arm trial:

Reasons that favor single-arm trial:
- Ethical consideration: (Physician’s opinion) the assay-matched targeted therapy should be at least no worse than the tradition standard treatment.
- Sample size consideration: requires relatively a small sample size compared with a randomized trial.

Randomized trial:
Biomarker-stratified design

Stage 1: Fixed ratio randomization

Assess Biomarker

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<tr>
<th>Pts sensitive to all 5 drugs</th>
<th>Stage 1: Fixed ratio randomization</th>
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<td>Stage 2: Adaptive randomization</td>
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<td>Pts sensitive to r = 1-4 drugs</td>
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Stage 2: Adaptive randomization

Assess Biomarker

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B: How to determine the adaptive allocation ratios A, B, and C?

Six different allocation rules were considered:

- BRAR-01: Allocation ratio is proportional to the estimated response rate.
- BRAR-02: Allocation ratio proportional to \( \frac{p_j + p_{j+}}{\sqrt{p_j} + \sqrt{p_{j+}}} \).
- BRAR-11: Allocation ratio partially follows RSIHR ratio.
  - A: same as BRAR-02; B: \( \frac{\sqrt{p_j}}{\sqrt{p_{j}} + \sqrt{p_{j+}}} \).
  - C: \( \frac{\sqrt{p_{j+}}}{\sqrt{p_j} + \sqrt{p_{j+}}} \).
- BRAR-12: Allocation ratio using \( \frac{p_j + p_{j+}}{p_j + p_{j+}} \) where \( c = 1/2 \).
- BRAR-14: Allocation ratio the same as BARA-12 except for \( c = n/2N \) (as proposed by Thall and Wathen).
- BRAR-16: Apply doubly adaptive biased coin design (DBCD) to BRAR-12.

Methods for making choice: Broadly evaluate the performance (Probability of assigning patients to more effective treatment in stage 2. Power and Type I error rate) for all six allocation rules in a simulation study. Pick the allocation rule with best performance.

Final Choice: BRAR-12

It has good power with type I error rate controlled within 5% for a total of 150 patients, 30 in the stage 1.

Its performance is robust to the number of sensitive drugs a patient may have.

Its probability of assigning patients to the more promising group is much higher than a traditional randomized trial with equal allocation.

Conclusion

The design considerations largely depends on the primary objective and available resources for a clinical trial. An interactive discussion between clinical researchers and physicians is crucial in making important decisions.

The performance of different adaptive allocation ratio can be quite different. Simulation is a powerful tool in making choice of adaptive randomization ratio for the adaptive stage.

Acknowledgement

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