Two Stage Adaptive Design in Dose Ranging Studies and the Alternatives

Qiqi Deng
NISS-Merck Meet-up on Adaptive Studies
Jan 2020
Phase II clinical development for chronic disease

- In clinical development, key objectives for phase II in non-oncology/chronic disease is to prove the concept and establish dose range.
- Classical phase II development consist of a small proof of concept (PoC) study and followed by moderately sized dose ranging studies.
Recent trend in the industry is to combine PoC and dose ranging into one trial.

- Advantage: shorten clinical development time, smaller total investment (compare to two separate studies) if the drug works.
- Disadvantage: higher sunken development cost at risk, if the drug doesn’t work.
Mitigating risk in combined DR study

– Separate trials

– Two stage Adaptive design
  • E.g. Futility analysis
Hypothetical Phase II Trial for comparison

- Continuous endpoint
- 4 active doses, 0.125, 0.25, 0.5, 1.0
- Assumptions for sample size evaluation:
  - Standard deviation = 1
  - Effect size = -.333
  - Type I error: $\alpha = .05$, one-sided
  - Power: $1 - \beta = 1 - .10 = .90$
  - Five candidate set models (linear, 2 emax, exponential, logistic)

- **Statistical Methodology for Proof-of-Concept**
- Highest dose against placebo
- Multiple Comparison Procedure – Modeling (MCPMod)
- Match overall allocation ratio as (2, 1, 1, 1, 2) for a fair comparison
Option 1 – Two trials

Trial I

- Highest: 65
- High: 65
- Median: 65
- Low: 65
- Placebo: 65

Trial II: MCPMod

- Highest: 123
- High: 92
- Median: 92
- Low: 92
- Placebo: 123

\[ \alpha = \alpha_1 \times \alpha_2 = .4 \times .125 = .05 \]
\[ 1 - \beta = (1 - \beta_1) \times (1 - \beta_2) = .95 \times .95 = .9025 \]

Average sample size under null hypothesis: \( N_0 = 65 \times 2 + .4 \times 522 = 338.8 \)
Average sample size under alternative hypothesis: \( N_A = 65 \times 2 + .95 \times 522 = 625.9 \)
Option 2 - Futility analysis
(MCPMod + futility on left, and step-wise futility/2-stage GS on right)

- Interim decision is Go/NGo, it is more efficient to use one high dose if monotonic assumption can be assumed (Indeed a special case under step-wise design).

\[ \alpha = .0506, \text{ with } \alpha_1 = .4 \text{ and } \alpha_2 = .06 \]
\[ 1 - \beta = .905, \text{ with } 1 - \beta_1 = .95 \]
Summary of Various Designs

Table 1 Sample Size Summary for Each Design

<table>
<thead>
<tr>
<th></th>
<th>2 Trials</th>
<th>MCPMod</th>
<th>MCPMod + futility</th>
<th>Step-wise MCPMod</th>
<th>Step-wise GS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td>0.050</td>
<td>0.050</td>
<td>0.050</td>
<td>0.051</td>
<td>0.050</td>
</tr>
<tr>
<td><strong>Power</strong></td>
<td>0.903</td>
<td>0.900</td>
<td>0.903</td>
<td>0.901</td>
<td>0.900</td>
</tr>
</tbody>
</table>

Table 2 Sample Size Summary for Each Design

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>2 Trials</th>
<th>MCPMod</th>
<th>MCPMod + futility</th>
<th>Step-wise MCPMod</th>
<th>Step-wise GS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage/Trial I</td>
<td>130</td>
<td>217</td>
<td>130</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>Stage/Trial II</td>
<td>522</td>
<td>336</td>
<td>416</td>
<td>463</td>
<td>593</td>
</tr>
<tr>
<td>Max</td>
<td>652</td>
<td>553</td>
<td>546</td>
<td>593</td>
<td>593</td>
</tr>
<tr>
<td>Average ($H_0$)</td>
<td>338.8</td>
<td>351.8</td>
<td>296.4</td>
<td>315.7</td>
<td></td>
</tr>
<tr>
<td>Average ($H_a$)</td>
<td>625.9</td>
<td>536.1</td>
<td>525.2</td>
<td>569.8</td>
<td></td>
</tr>
</tbody>
</table>

- MCPMod+futility: Start with multiple doses. The same allocation ratio throughout the trial.
- Step-wise MCPMod: Start with High dose+Pbo. Interim futility analysis by two-sample t test. Final analysis by MCPMod.
- Step-wise GS: Start with High dose+Pbo. Interim and final analysis by two-sample t test.
Comparison of Average sample size

![Average Sample Size for Each Design](image)

- **2 Trials**
- **MCPMod**
- **MCPMod + futility**
- **Step-wise MCPMod**
- **Step-wise GS**

- **Hypothesis**
  - $H_0$
  - $H_a$
An alternative: A two-stage step-wise design

```
High
   n₁ = 30          n₂ = 70

Median-High
    n₃ = 50

Median
   n₃ = 50

Low
   n₃ = 50

Placebo
   n₁ = 30          n₂ = 70

Δ > δₖ
```

“Go fast”
An alternative: A two-stage step-wise design

High Dose

Placebo

Trial initiation
Interim analysis
For ESOE
End of trial

$n_1 = 30$  
$\tilde{n}_2 = 30$

$\hat{\delta} \leq \delta_c$
An alternative: A two-stage step-wise design

- Start with a two group PoC: e.g. MTD vs Placebo

Go fast: (Dose ranging study)
- $\delta = 0.4$
- one-sided type I error rate $\tilde{\alpha} = 0.05$
- power of 88%
- $\Rightarrow$ 100 subjects each in highest dose and placebo, 3 additional doses with 50 subjects per dose

Go slow: (Traditional PoC)
- $\delta = 0.4$
- one-sided type I error rate $\alpha = 0.15$
- power of 88%
- $\Rightarrow$ 60 subjects each in highest dose and Placebo
“Alpha protection”

- “Alpha protection”

\[ P(\text{continue development}) = P(\text{Go fast and succeed}) + P(\text{Go slow and succeed}) \]
\[ = P(X > c, Z > z_{1-\alpha}) + P(X \leq c, \tilde{Z} > z_{1-\alpha}) \]
\[ < P(X > c, \tilde{Z} > z_{1-\alpha}) + P(X \leq c, \tilde{Z} > z_{1-\alpha}) \]
\[ < P(X > c, \tilde{Z} > z_{1-\alpha}) + P(X \leq c, \tilde{Z} > z_{1-\alpha}) \]
\[ = P(\tilde{Z} > z_{1-\alpha}) = \tilde{\alpha} \]

where
- \( X \) = test statistics for interim analysis ESOE
- \( Z \) = test statistics for final analysis under “Go fast” path
- \( \tilde{Z} \) = test statistics for final analysis under “Go slow” path

Numerical results – under alternative hypothesis

- Prob (Continue development) is stable regardless of cut-off.

- Prob (Go slow and success) is the probability to have reversed results. It is not desirable to have reversed results, but it is better than missing a good drug.
Two Stage Adaptive Design in Dose Ranging Studies and the Alternatives

• Two types of expected sample size
  - $ESS_1 = 2n_1 + PF \times (2n_2 + kn_3) + (1 - PF) \times (2\bar{n}_2)$
  - $ESS_2 = 2n_1 + PF \times (2n_2 + kn_3) + (1 - PF) \times (2\bar{n}_2) + PSS \times (2n_1 + 2n_2 + kn_3)$

- Prob(Go fast) -- PF
- Prob(Go fast and success in the end)
- Prob(Go slow and success in the end) -- PSS
- $k$ is the number of additional dosing groups added in the dose ranging study
Two key factors

- Start with two groups (High dose and Placebo), and then expand if promising
- 2-in-1 concept instead of futility analysis
  - Prob(Continue development) is very stable under either pathway
  - can choose a more meaningful interim boundary for decision making
  - Naturally takes care the patient overflow
  - Interim message is different compared to futility analysis

Extension/variations

- Final analysis can use MCPMod or two-group comparison.
- Short term intermediate endpoint for interim analysis

Two separate trials may have operational flexibility

- Smaller initial commitment of resources
- Amount/type of Data to be collect can be different, even different endpoints
Acknowledgement

Thanks to

• Naitee Ting, Xiaofei Bai (co-authors of the paper)
• Yutao Liu, Columbia University
• Cong Chen, Merck
References


• Chen C, Anderson K, Mehrotra DV, Tse A, Rubin EH. A 2-in-1 adaptive Phase 2/3 design for expedited drug development. Accepted by *Contemporary Clinical Trials*. 2017.