Two Stage Adaptive Design in Dose Ranging Studies and the Alternatives

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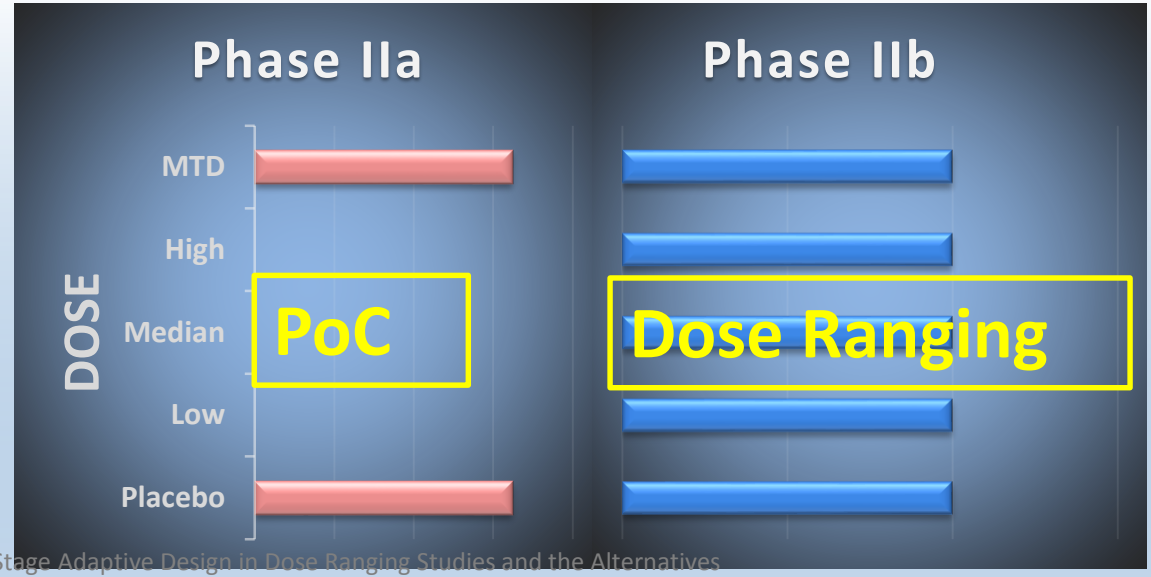
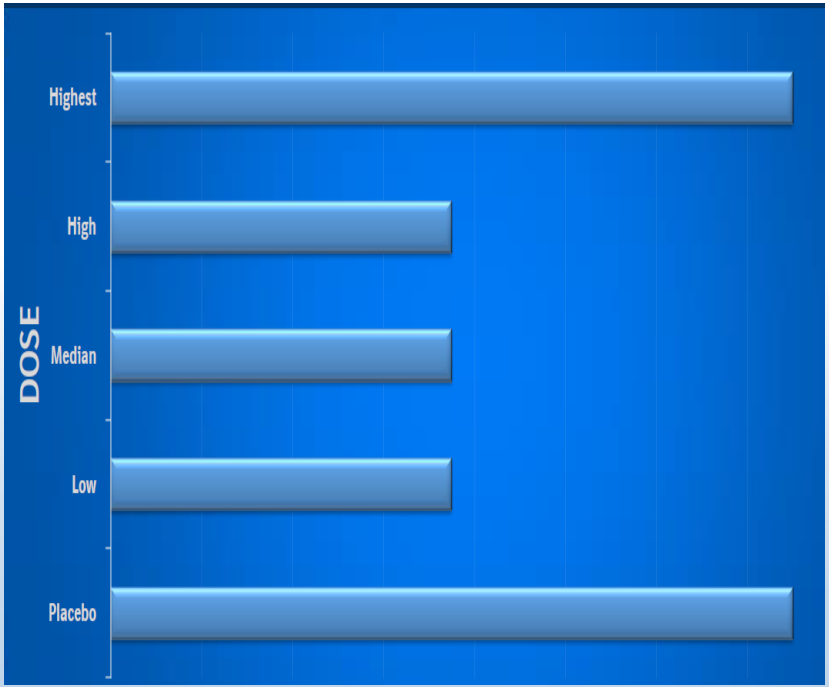
Phase II clinical development for chronic disease

- 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



Combined PoC and Dose ranging



- 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
  - Small early signal of efficacy (ESOE) study. Brown et al (2012)

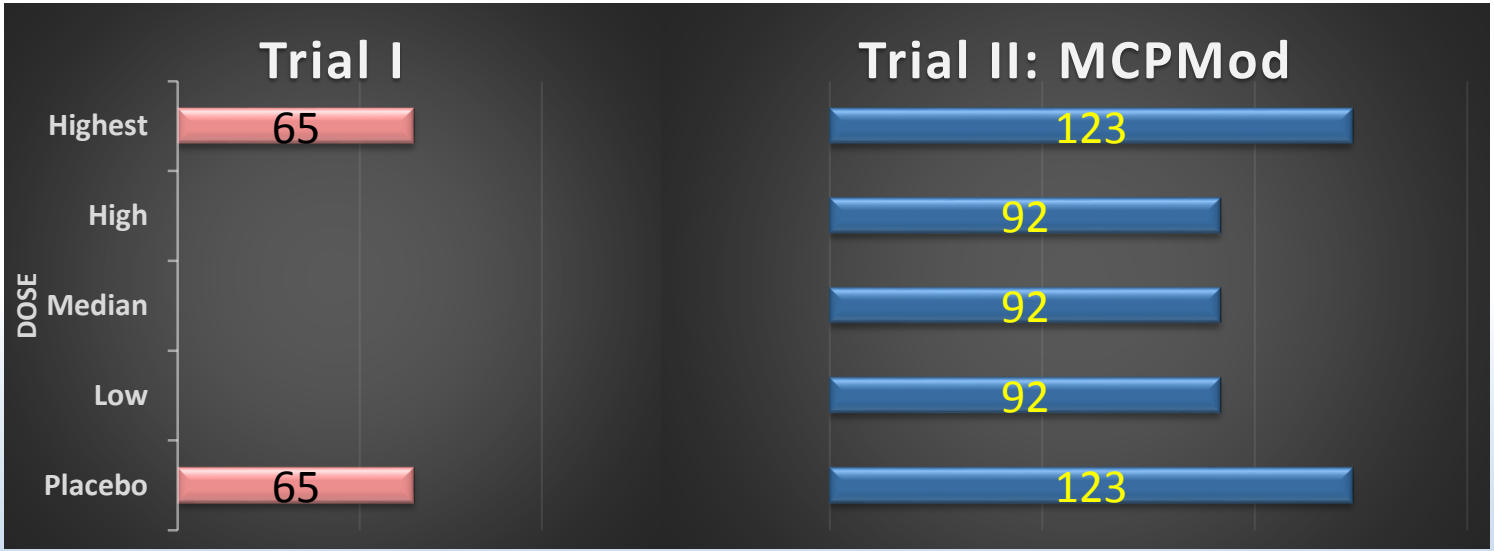
- Two stage Adaptive design
  - E.g. Futility analysis

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

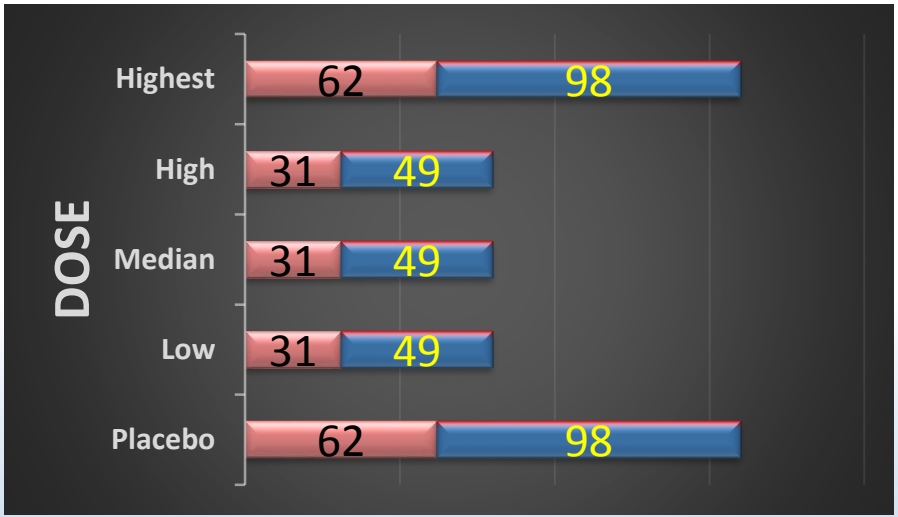
Option 1 – Two trials

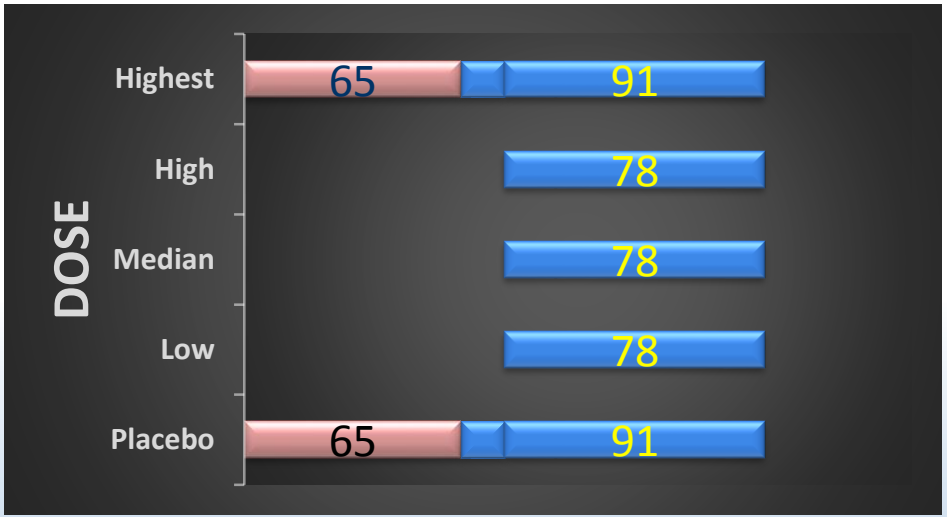


$$\alpha = \alpha_1 \times \alpha_2 = .4 \times .125 = .05$$
$$1 - \beta = (1 - \beta_1) \times (1 - \beta_2) = .95 \times .95 = .9025$$

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)





$$\alpha = .0506, \text{ with } \alpha_1 = .4 \text{ and } \alpha_2 = .06$$
$$1 - \beta = .905, \text{ with } 1 - \beta_1 = .95$$

- 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).

Summary of Various Designs

Table 1 Sample Size Summary for Each Design

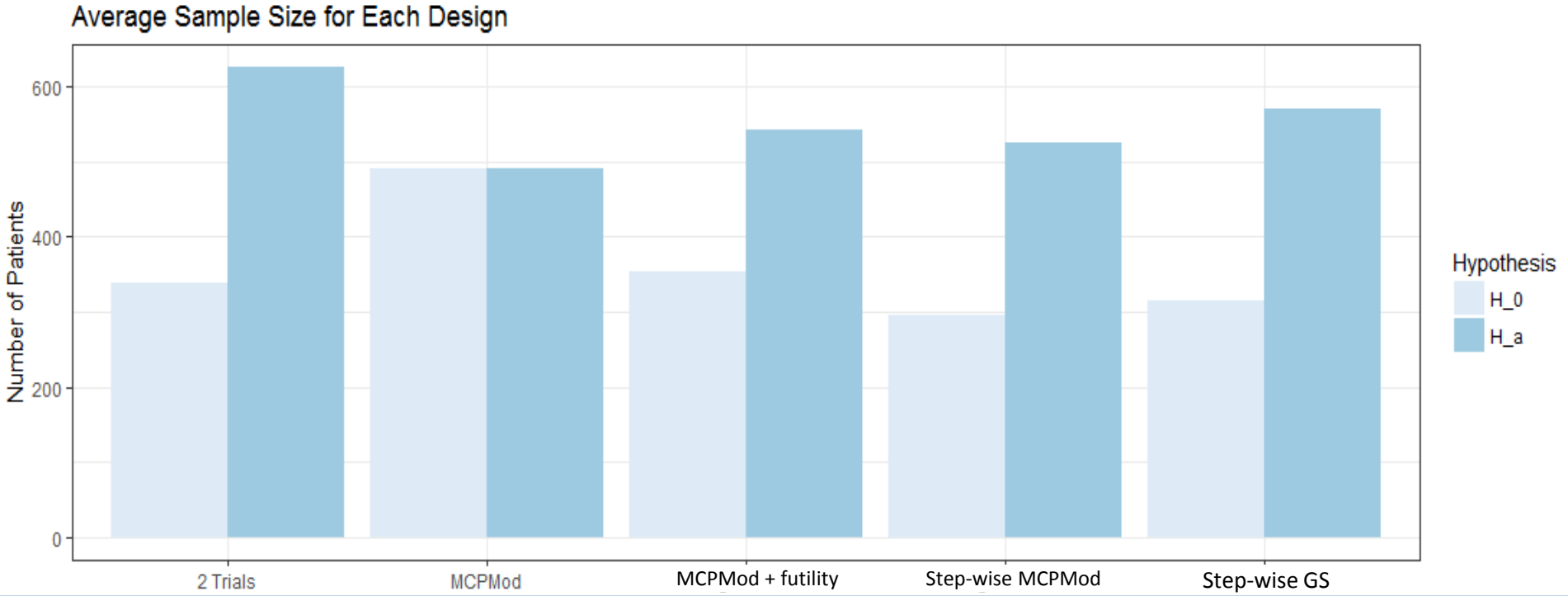
	2 Trials	MCPMod	MCPMod + futility	Step-wise MCPMod	Step-wise GS
Type I	0.050	0.050	0.050	0.051	0.050
Power	0.903	0.900	0.903	0.901	0.900

Table 2 Sample Size Summary for Each Design

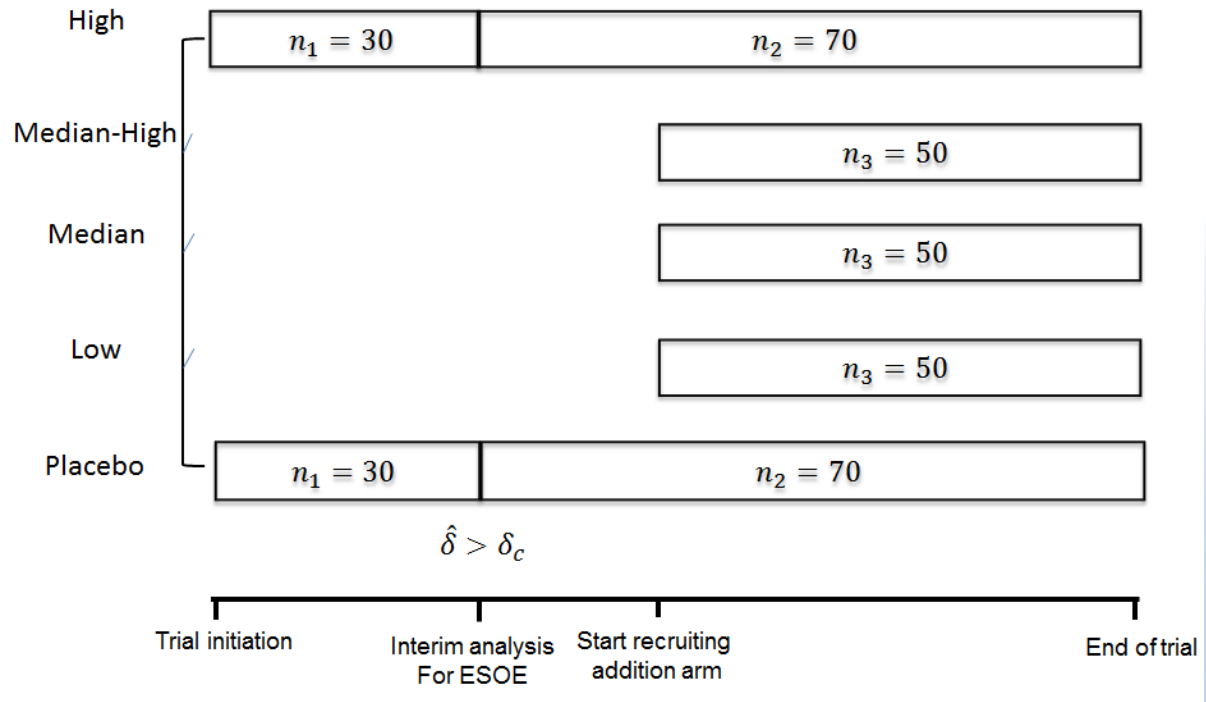
Sample Size	2 Trials	MCPMod	MCPMod + futility	Step-wise MCPMod	Step-wise GS
Stage/Trial I	130		217	130	130
Stage/Trial II	522		336	416	463
Max	652	490	553	546	593
Average (H_0)	338.8	490	351.8	296.4	315.7
Average (H_a)	625.9	490	536.1	525.2	569.8

- 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

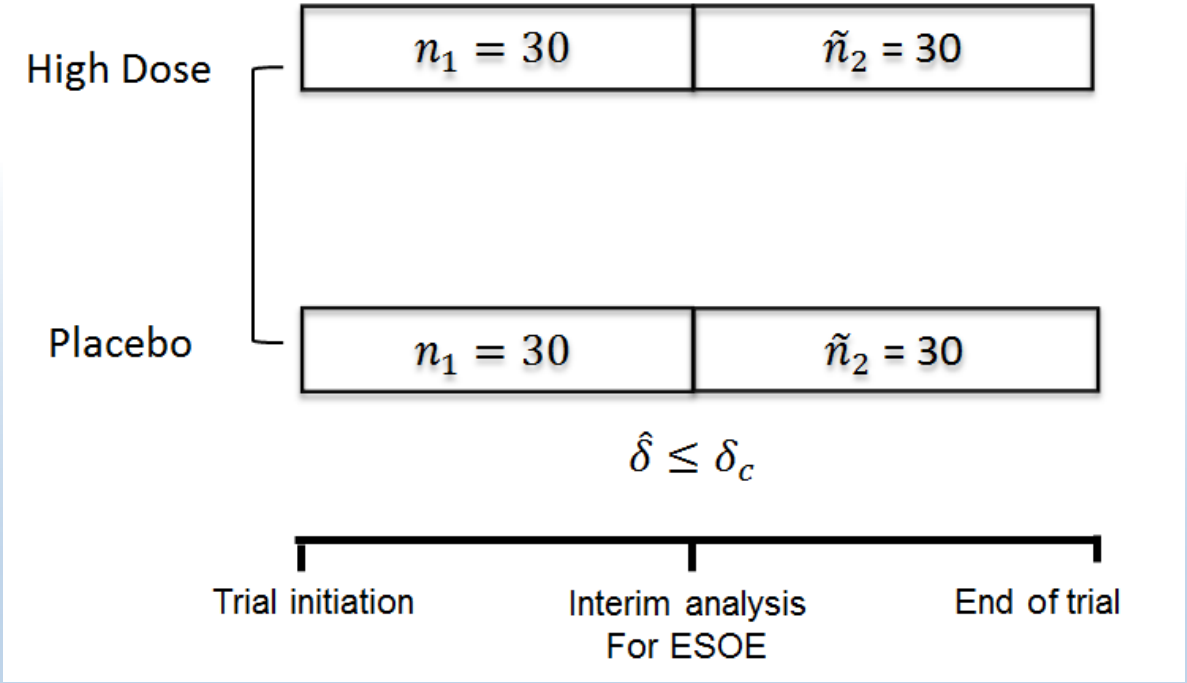


An alternative: A two-stage step-wise design



"Go fast"

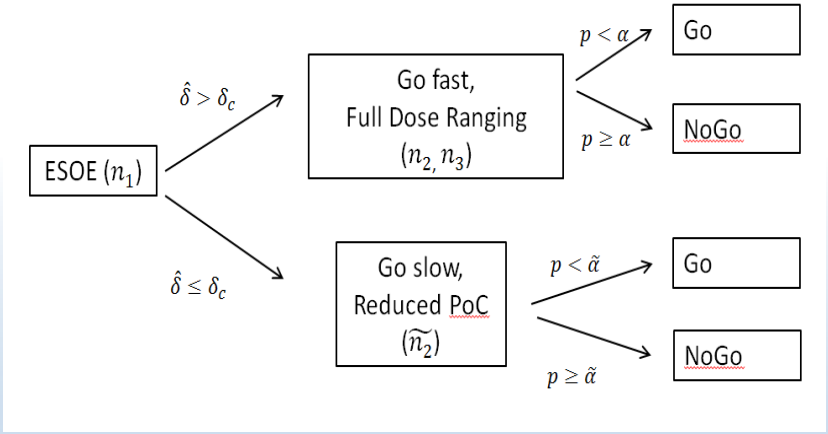
An alternative: A two-stage step-wise design



"Go slow"

An alternative: A two-stage step-wise design

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



Go slow: (Traditional PoC)
- $\delta = 0.4$
- one-sided type I error rate $\tilde{\alpha}$ = 0.15
- power of 88%

=> 60 subjects each in highest dose and Placebo

Go fast: (Dose ranging study)
- $\delta = 0.4$
- one−sided type I error rate α = 0.05
- power of 88%

=> 100 subjects each in highest dose and placebo, 3 additional doses with 50 subjects per dose

“Alpha protection”

- “Alpha protection”

$$
\begin{aligned}
& P(\text{continue development}) \\
&= P(\text{Go fast and succeed}) + P(\text{Go slow and succeed}) \\
&= P(X > c, Z > z_{1-\alpha}) + P(X \le c, \tilde{Z} > z_{1-\tilde{\alpha}}) \\
&< P(X > c, \tilde{Z} > z_{1-\alpha}) + P(X \le c, \tilde{Z} > z_{1-\tilde{\alpha}}) \\
&< P(X > c, \tilde{Z} > z_{1-\tilde{\alpha}}) + P(X \le c, \tilde{Z} > z_{1-\tilde{\alpha}}) \\
&= P(\tilde{Z} > z_{1-\tilde{\alpha}}) = \tilde{\alpha}
\end{aligned}
$$

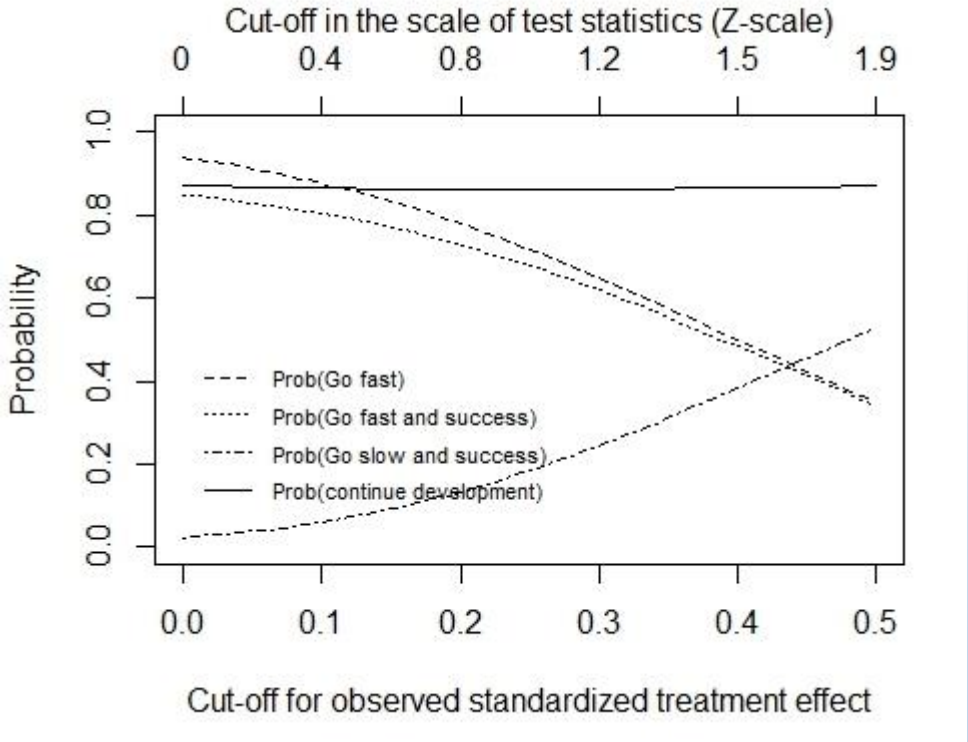
where X = test statistics for interim analysis ESOE

Z = test statistics for final analysis under “Go fast” path

$\tilde{Z}$ = test statistics for final analysis under “Go slow” path

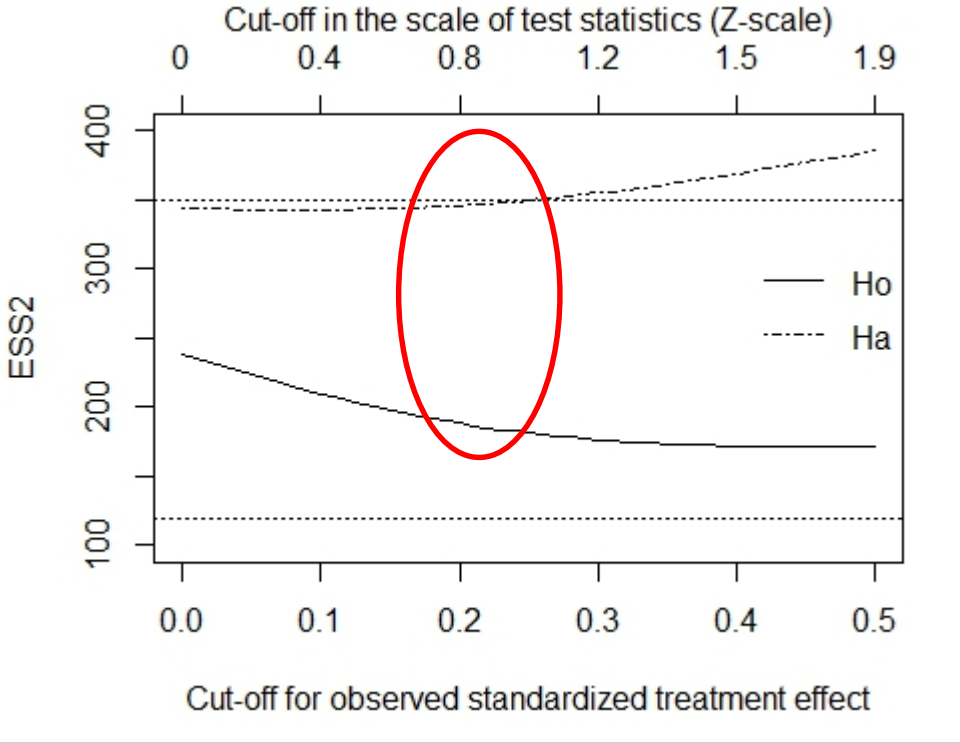
Chen C, Anderson K, Mehrotra DV, Tse A, Rubin EH. A 2-in-1 adaptive Phase 2/3 design for expedited drug development. Contemporary Clinical Trials. 2018 Jan; 64:238-242. doi: 10.1016/j.cct.2017.09.006.

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.

Numerical results – ESS2



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

  - 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

Discussion

- 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

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References

- Qiqi Deng, Xiaofei Bai, Naitee Ting. (2018) Dynamic development paths for expanding a proof-of-concept study to explore dose range. *Statistics in Medicine*.1–10. https://doi.org/10.1002/sim.7840

- Bretz, F., Pinheiro, J. C., and Branson, M. (2005). Combining multiple comparisons and modeling techniques in dose–response studies. *Biometrics* **61**, 738–748.

- Brown MJ, Chuang-Stein C, Kirby S. Designing Studies to Find Early Signals of Efficacy, Journal of Biopharmaceutical Statistics. 2012; 22(6): 1097-1108. DOI: 10.1080/10543406.2011.570466.

- 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.


Thank you