Evolution of the Promising Zone Design - Let's have a try

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SBF 2020.9.25

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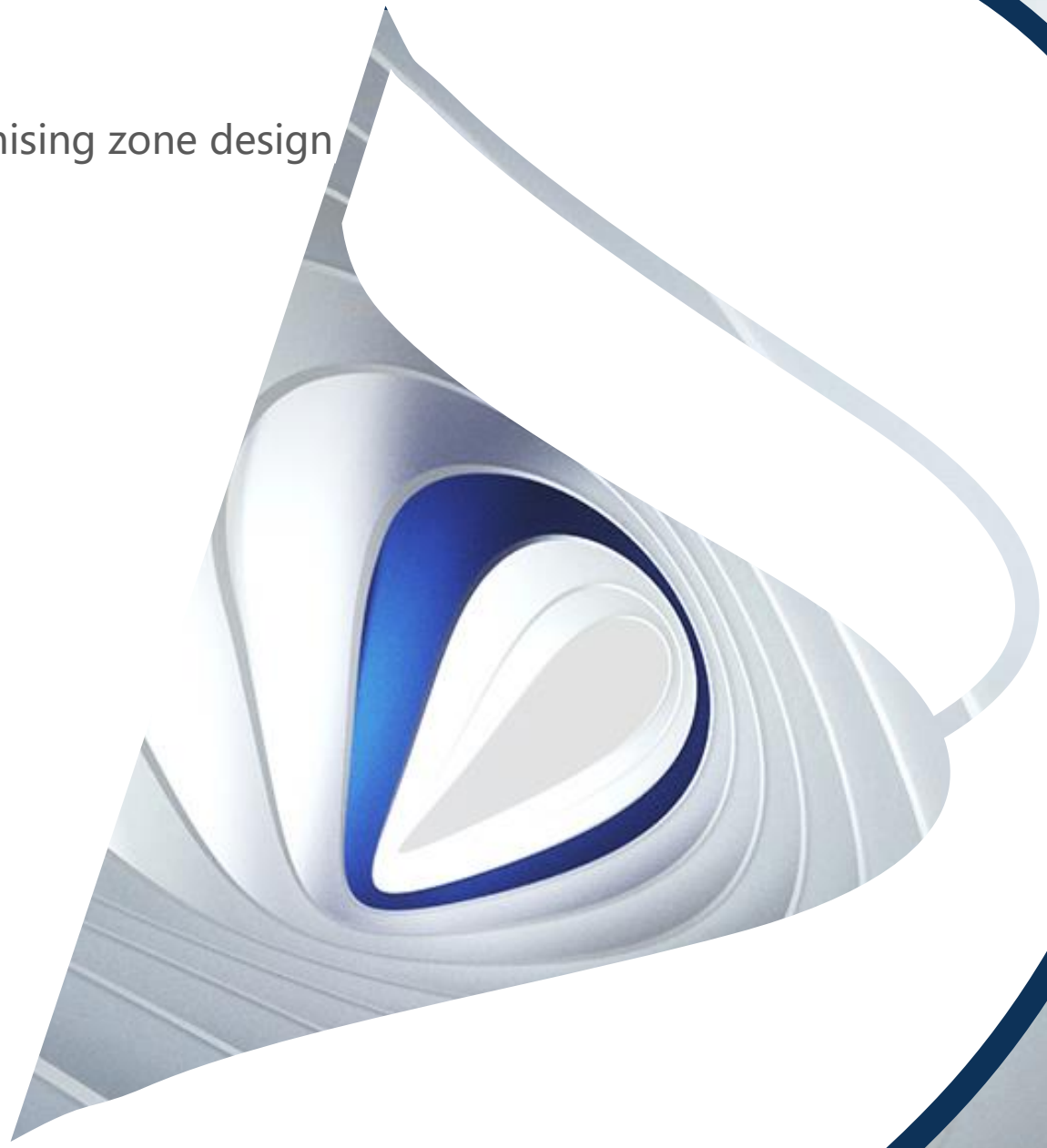

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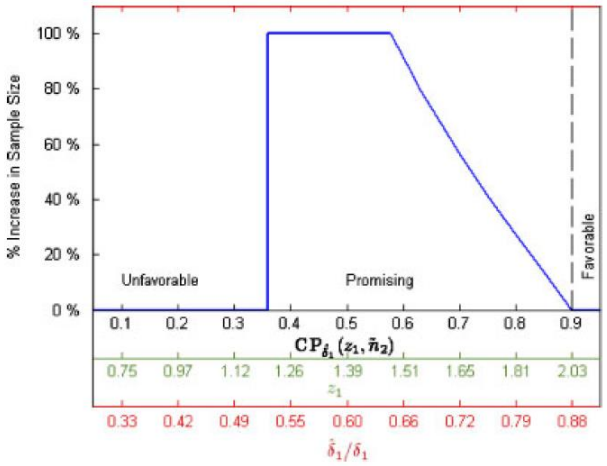
01

A brief literature review on promising zone design

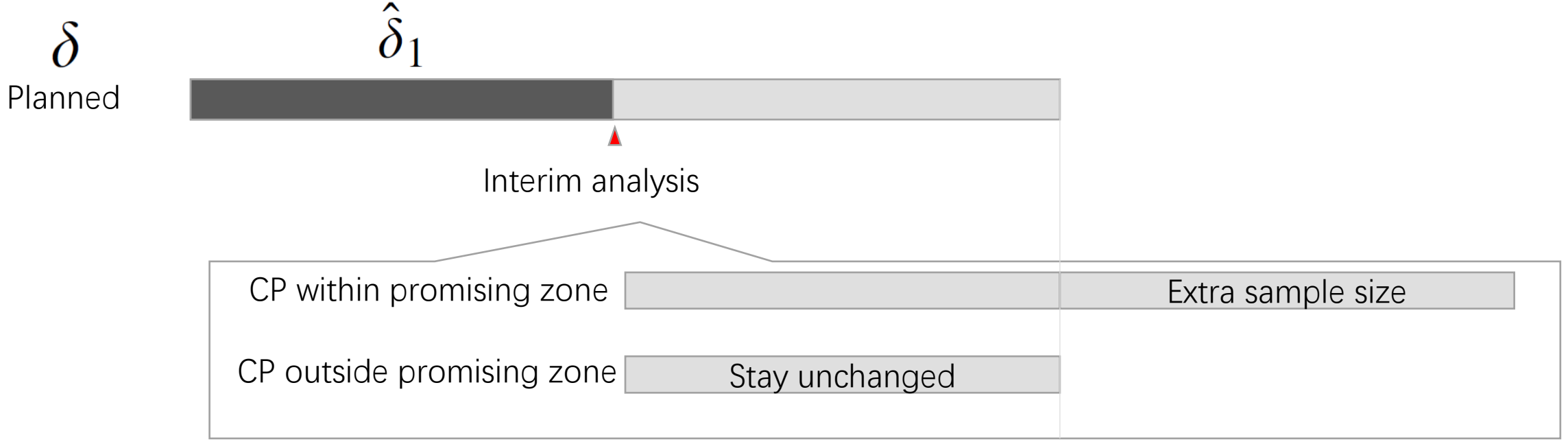
Promising zone design

- Promising zone method have been proposed for 10+ years, e.g.
  - Chen et.al 2004
  - Gao et.al 2008
- General idea:
  - Do **unblinded sample size re-estimation** at an interim only when the interim result is promising
    - Only sample size increasing is allowed
    - Keep planned sample size when interim result is not promising
  - How to define PZ, interim results, rules for sample size increase, adjustment for type-I error rate…

- Mehta and Pock published their PZ design with a practical guide in 2011, based on the work of Gao et al 2008
  - Define PZ in terms of **conditional power (CP)**
    - CP: conditional on interim results, the probability of a significant final result
    - E.g. PZ: 0.5<CP<0.9
  - SSR decision
    - IA CP lies in the PZ, increase sample size, otherwise stay as planed
      - Raise CP to a planned level (e.g. 90%), or reach n_{max} (e.g. 2 folds)
  - Can also combine with futility/efficacy interim analysis
  - Final analysis
    - Follow **conventional method**, type-I error rate not inflated

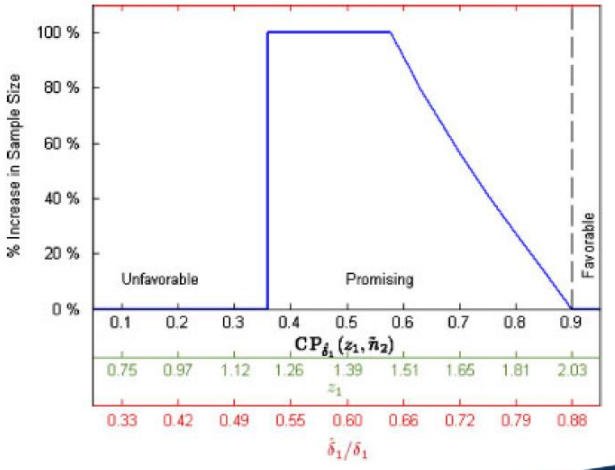


$$\mathrm{CP}_{\hat{\delta}_1}(z_1, \tilde{n}_2) = 1 - \Phi\left(\frac{z_\alpha\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\tilde{n}_2}} - \frac{z_1\sqrt{\tilde{n}_2}}{\sqrt{n_1}}\right)$$



Recap on MP's PZ design

- Plan a design with IA
- At IA: unblinded SSR
  - Define PZ: e.g 0.5<CP<0.9
  - Calculate CP using parameter **estimate from IA** as true estimate
  - CP lies in PZ: increase sample size
  - CP lies outside PZ: as planned
- At final: **conventional test** using pooled data



- Immediately following Mehta and Pocock's paper, two commentaries published:
  - By Glimm:
    - Using interim result as the true effect and in CP calculation may not be reliable due to the **uncertainty of interim result**
    - The formula for CP calculation used interim result **twice**, which may result in an extreme value of CP when the interim estimate deviates from true value much

$$\mathrm{CP}_{\hat{\delta}_1}(z_1, \tilde{n}_2) = 1 - \Phi\left(\frac{z_\alpha\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\tilde{n}_2}} - \frac{z_1\sqrt{\tilde{n}_2}}{\sqrt{n_1}}\right)$$

- By Emerson, Levin and Emerson
  - **Criteria** of comparing PZ method and other methods is not proper
    - Overall power increase is at the cost of sample size increase, and this sample size increase may not be efficient
    - Suggested criteria: fixed the power curve for all methods and compare their expected sample size curve
    - They found the PZ method is obviously **inferior** to traditional fixed sample design and group sequential design: expected sample size is much larger after aligning the power curve
    - Do not recommend using this PZ method

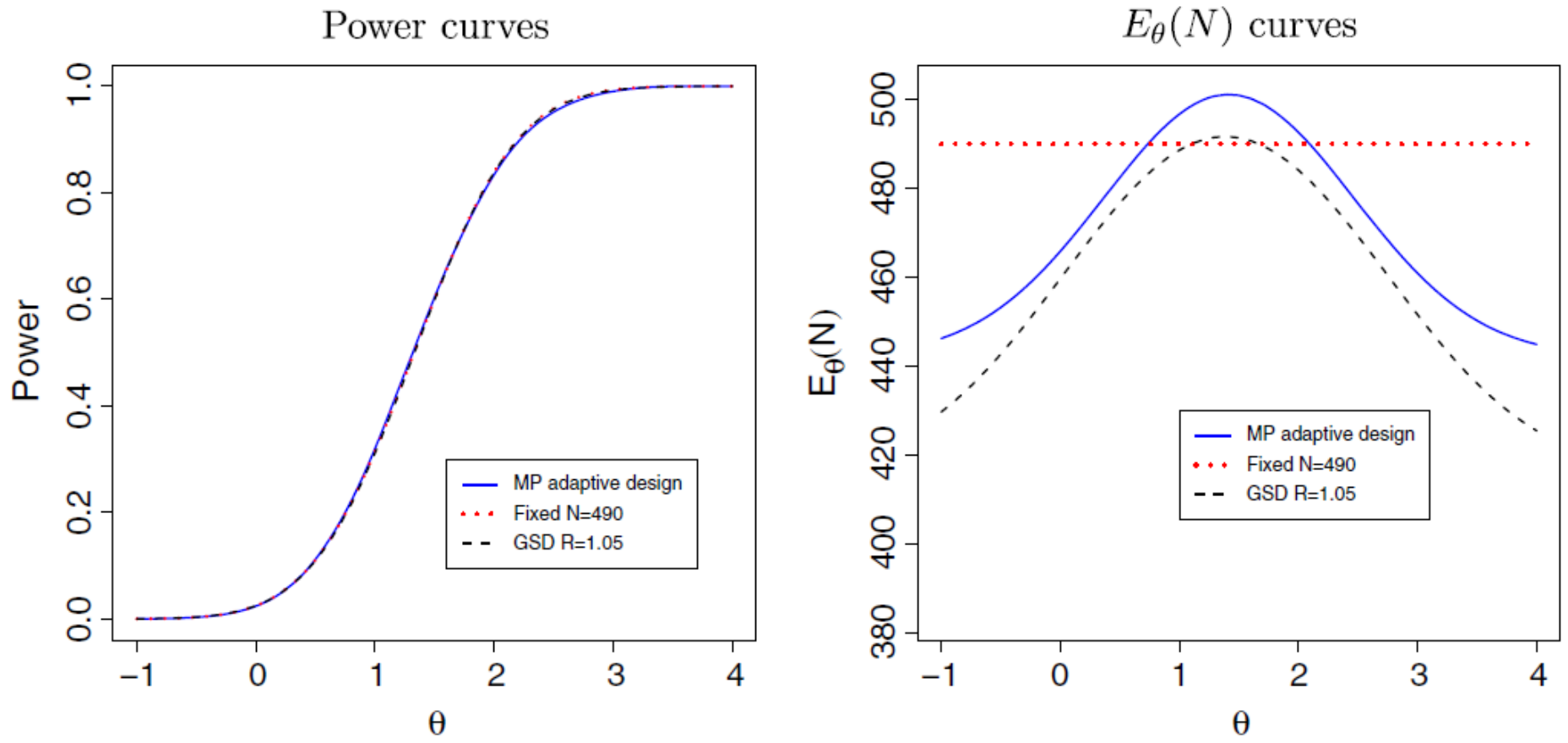


Figure 7. Power and average sample size curves for three designs.

- Fixed N=490
- GSD R=1.05: GSD with total sample size 514 (490*1.05), IA at 208 completers (week26, total 416 enrolled). Rho-family error spending function with rho=2. this is to match the power curve with MP design

- Jennison and Turnbull updated the promising zone method in 2015:
  - High increase in sample size for a small range of interim outcomes, but may be more efficient to make **moderate increase over a wider range**
  - Propose a design that overcome the pitfalls:
    - Choosing sample size to balance the gain in CP under fixed effect size (not IA estimate) against extra sample size

$$CP_{\tilde{\theta}}(z_1, n_2^*) - \gamma(n_2^* - 442)$$

$$CP_{\hat{\delta}_1}(z_1, \tilde{n}_2) = 1 - \Phi\left(\frac{z_\alpha\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\tilde{n}_2}} - \frac{z_1\sqrt{\tilde{n}_2}}{\sqrt{n_1}}\right)$$

(Note here the CP calculation is different from MP's paper)

    - Using weighted inverse normal combination test to control alpha

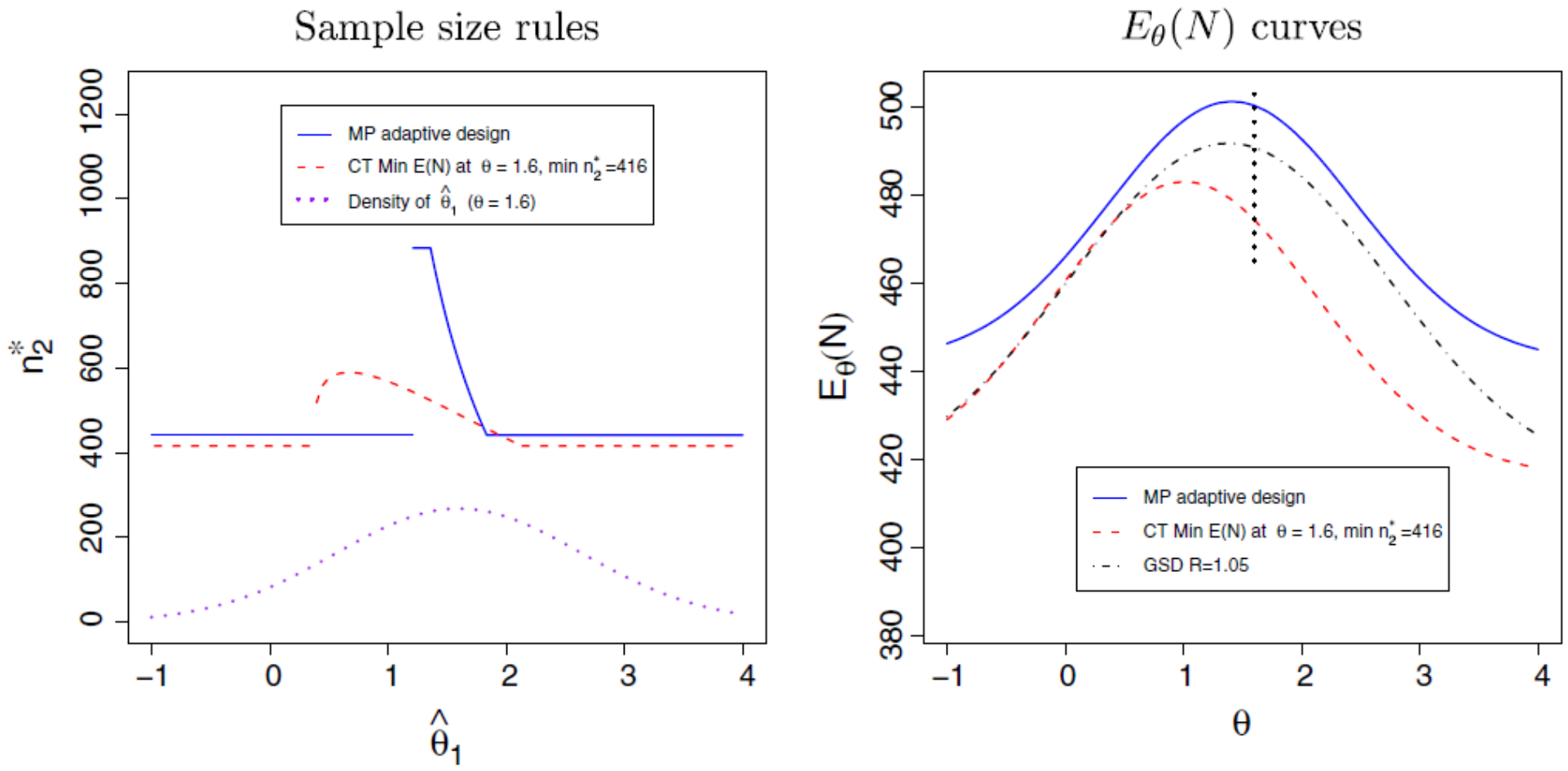


Figure 10. Efficient combination test (CT) designs.

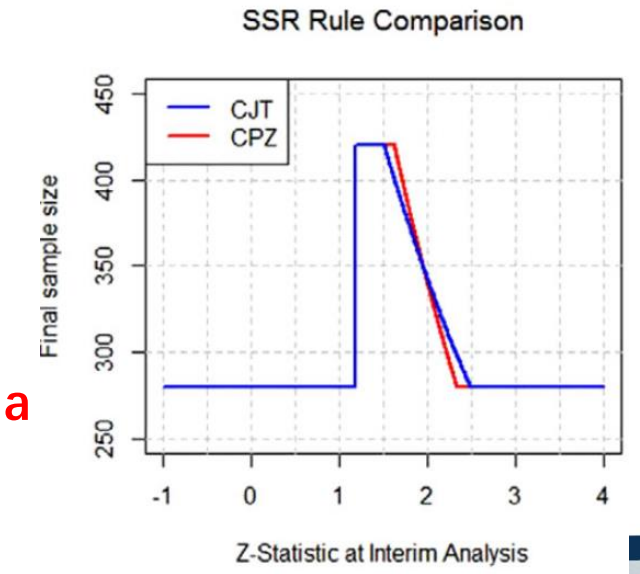
02

Optimal promising zone design

by Hsiao, Liu and Mehta, 2018

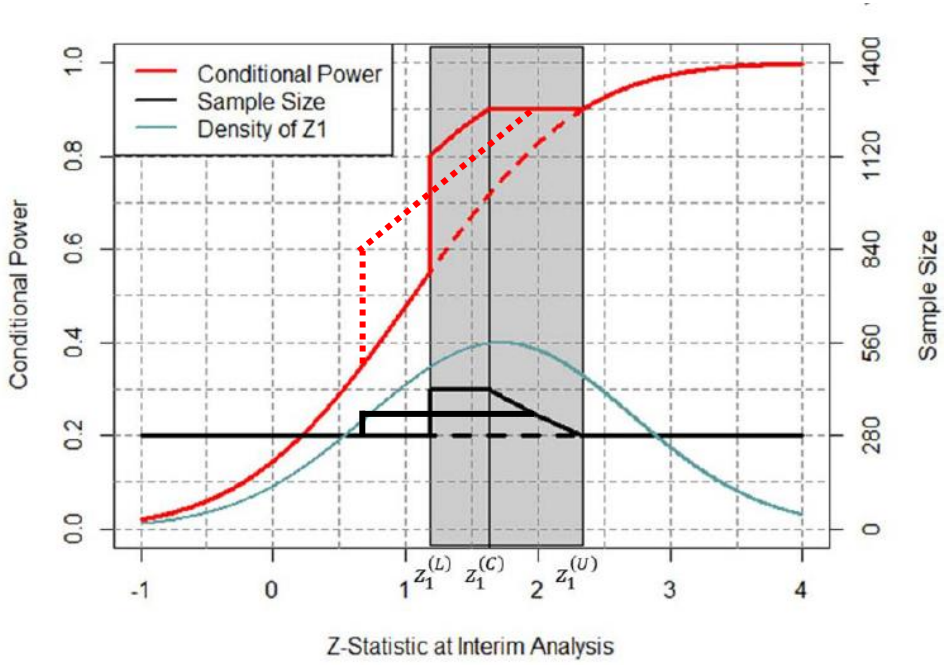
Optimal PZ design (compared with MP)

- Plan a design with IA
- At IA: unblinded SSR
  - Define PZ: ~~e.g. 0.5<CP<0.9~~ **through definition of cp_{min}, cp_{max}**
  - Calculate CP using ~~parameter estimate from IA~~ **minimum clinical meaningful estimate** as true estimate
  - CP lies in PZ: increase sample size
  - CP lies outside PZ: as planned
- At final:
  - ~~conventional test using pooled data~~
  - **Using weighted inverse normal combination test to control alpha**

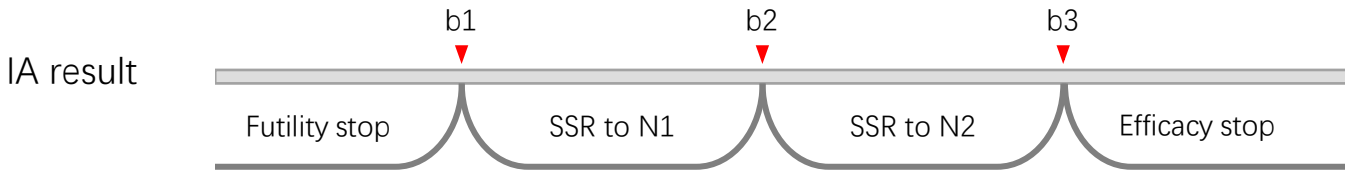


$$Z^*_{2,\mathrm{chw}} = \sqrt{\frac{n_1}{n_2}} Z_1 + \sqrt{\frac{\tilde{n}_2}{n_2}} \tilde{Z}^*_2$$

- Specification of $\boldsymbol{cp_{min}}$:
  - cp_{min}: minimum requirement for CP inside PZ
    - $cp_{min} = 0.8$: based on IA result, CP is, say 0.55, and we increase sample size to n_{max}, and the CP will be 0.8
    - $cp_{min} = 0.6$ – acceptable?
      - Say, IA CP is 0.35, is it worth to invest extra money to increase the CP to 0.6?
      - Or, High increase (n_{max}) for a small range or moderate increase over a wider range?



- Type-I error rate control is critical
  - Combination test is used
- Below method that we experienced may not control type-I error rate well:



With final analysis using conventional method

  - Simulation can show that in most cases the type-I error rate **uncontrolled**

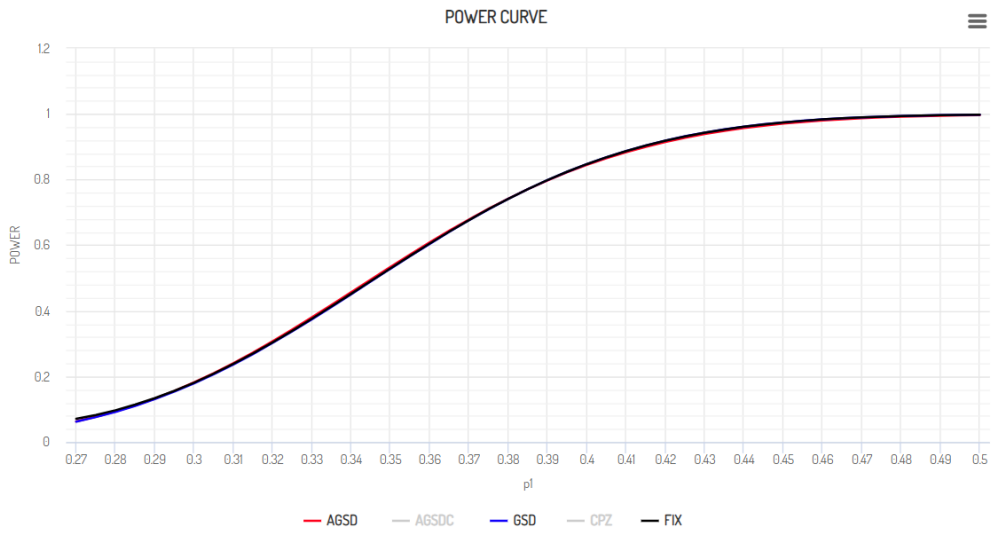
03

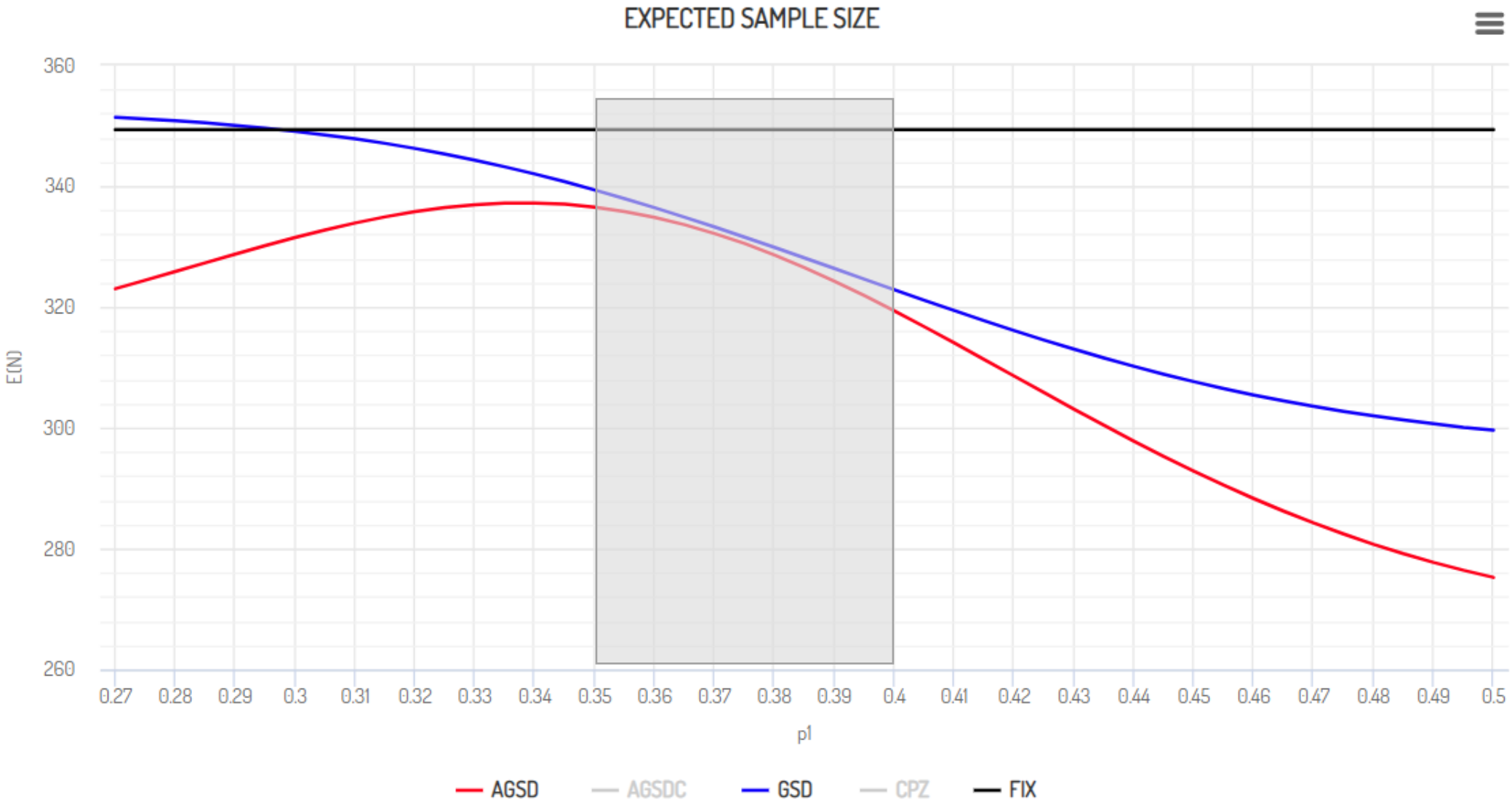
A hypothetical example

- Design setting:
  - Randomized, double blind phase III
  - Primary endpoint: week 6 remission rate
  - Control P0: 0.25； treatment P1: 0.4 (minimum clinical meaningful P1 0.35)
  - 1:1 randomization, alpha 1-sided 0.025, power 0.8

- Designs to consider:
  - Fixed design (FIX): without any interim
  - Group sequential design (GSD): efficacy interim at 70%, OBF
  - GSD with SSR (GSD-SSR): efficacy interim at 70% + SSR with promising zone method
    - n_{max} 1.5 fold; cp_{min} 0.6; cp_{max} 0.8

	n1	n2	n2max	IA.eff	IA.fut	SSR
FIX		350		No	No	No
GSD	247	353		Yes,70%	No	No
AGSD	217	310	465	Yes,70%	No	Yes,70%




EXPECTED SAMPLE SIZE
E(N)
360
340
320
300
280
260
0.27
0.28
0.29
0.3
0.31
0.32
0.33
0.34
0.35
0.36
0.37
0.38
0.39
0.4
0.41
0.42
0.43
0.44
0.45
0.46
0.47
0.48
0.49
0.5
p1
AGSD
AGSDC
GSD
CPZ
FIX

04

Summary

Summary

- In general, promising zone method is intuitive
  - Promising? Then increase sample size
  - Some parameters need to be discussed carefully
- The optimal promising zone method (2018)
  - may be more efficient compared to GSD and earlier promising zone method (2011)
  - Also more flexible: width of promising zone
- Type-I error rate control is critical
- Simulations help understand the properties of this method

Acknowledgment

- Wengang He
- Mingming Guo
- Long Qu
- Yuan Lv
- Wenting Li

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THANK YOU.