Optimal Promising Zone Designs

Sam Hsiao

Cytel Inc

May 2019

Statistics in Medicine

Commentary

(wileyonlinelibrary.com) DOI: 10.1002/sim.6614 Published online in Wiley Online Li

An objective re-evaluation of adaptive sample size re-estimation: commentary on 'Twenty-five years of confirmatory adaptive designs'

Cyrus Mehta[a,b*†] and Lingyun Liu[a]

Over the past 25 years, adaptive designs have gradually gained acceptance and are being used with increa frequency in confirmatory clinical trials. Recent surveys of submissions to the regulatory agencies reveal tha most popular type of adaptation is unblinded sample size re-estimation. Concerns have nevertheless been r that this type of gerated in any p any minor loss o

Stat Biosci
DOI 10.1007/s12561-017-9188-x

CrossMark

Efficiency Considerations for Group Sequential Designs with Adaptive Unblinded Sample Size Re-assessment

Lingyun Liu[1] · Sam Hsiao[1] · Cyrus R. Mehta[1,2]

Received: 20 August 2016 / Accepted: 15 February 2017

ment, based on an analysis pularity due to uncertainty start of the study. While r of such designs is well p sequential designs with iency. The precise manner

Received: 12 December 2017 | Revised: 18 September 2018 | Accepted: 19 September 2018

DOI: 10.1002/bimj.201700308

RESEARCH PAPER

Biometrical Journal

Optimal promising zone designs

Samuel T. Hsiao[1] | Lingyun Liu[1] | Cyrus R. Mehta[1,2]

[1]Cytel Corporation, Cambridge, Massachusetts, USA

[2]Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA

Correspondence
Cyrus R. Mehta, Cytel Corporation, Cambridge, MA 02139; Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA.
Email: mehta@cytel.com

Abstract

Clinical trials with adaptive sample size reassessment based on an unblinded analysis of interim results are perhaps the most popular class of adaptive designs (see Elsäßer et al., 2007). Such trials are typically designed by prespecifying a zone for the interim test statistic, termed the promising zone, along with a decision rule for increasing the sample size within that zone. Mehta and Pocock (2011) provided some examples of promising zone designs and discussed several procedures for controlling

Outline

- Example from oncology trial
- Constrained promising zone design
- Efficiency comparisons with:
  - Optimal adaptive design (Jennison & Turnbull 2015)
  - Constrained optimal design
- Conclusions

Oncology Trial at a Small Biotech

- **Indication -** Advanced pancreatic cancer
- **Endpoint -** Progression free survival
- **Effect size -** Hypothesized hazard ratio HR=0.67 ($\boldsymbol{\delta = 0.4}$ on log scale), but consider HR=0.75 to be minimally acceptable ($\boldsymbol{\delta = 0.29}$)
- **Power**

	$\boldsymbol{\delta = 0.29}$	$\boldsymbol{\delta = 0.4}$
N = 280	68%	92%
N = 500	90%	99%

N = number of events

- **Considerations for Adaptive Design (AD)**
  - Difficult to get upfront commitment to power at low effect size
  - Stakeholders expressing **conditional utility**, investment linked to interim milestone, requiring good chance of success at minimally acceptable effect size
  - No early efficacy stopping, need adequate volume of data for regulatory review

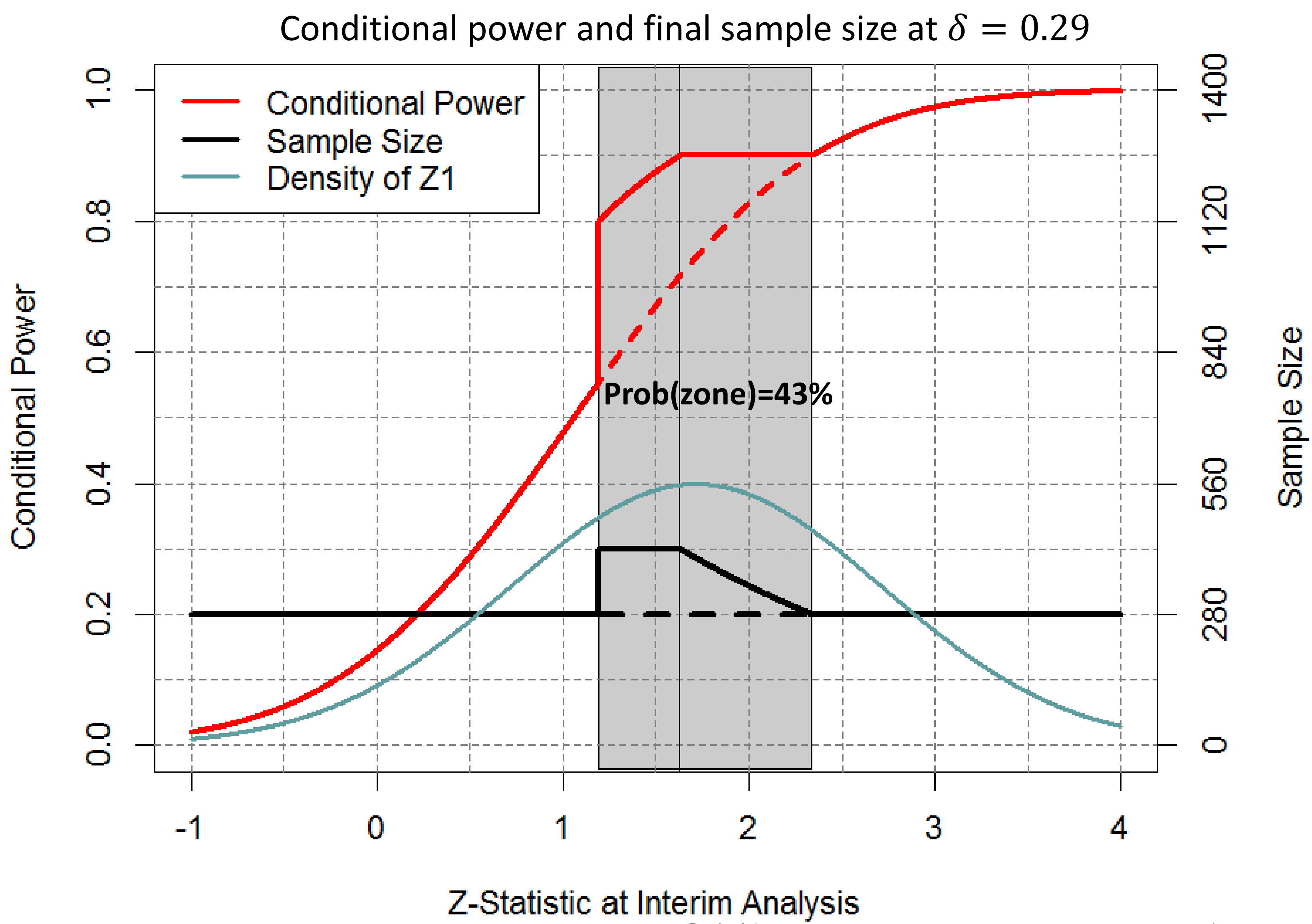
Constrained Promising Zone Design (CPZ)

- **Two-Stage design with sample size re-assessment (SSR)**
- Plan $n_2 = \mathbf{280}$, interim analysis $n_1 = \mathbf{140}$, maximum $n_{max} = \mathbf{420}$
- Given interim statistic z_1, choose final sample size n_2^* as follows:

Objective: Maximize conditional power $CP_{0.29}(z_1, n_2^*)$
Constraint 1: $n_2 \leq n_2^* \leq n_{max}$
Constraint 2: $CP_{0.29}(z_1, n_2^*) \geq 80\%$
Constraint 3: $CP_{0.29}(z_1, n_2^*) \leq 90\%$

- **Promising zone** consists of z_1 for which all constraints can be satisfied
- No sample size modification outside of promising zone
- Testing uses CHW combination statistic

CPZ Design Conditional Power and SSR Rule



Is the CPZ Design Optimal?

Can unconditional power be improved using a different SSR rule, keeping expected sample size the same?

Jennison Turnbull (JT) Optimal SSR Rule

- Optimize tradeoff between CP and N
- **SSR Rule:** Choose final sample size n_2^* such that

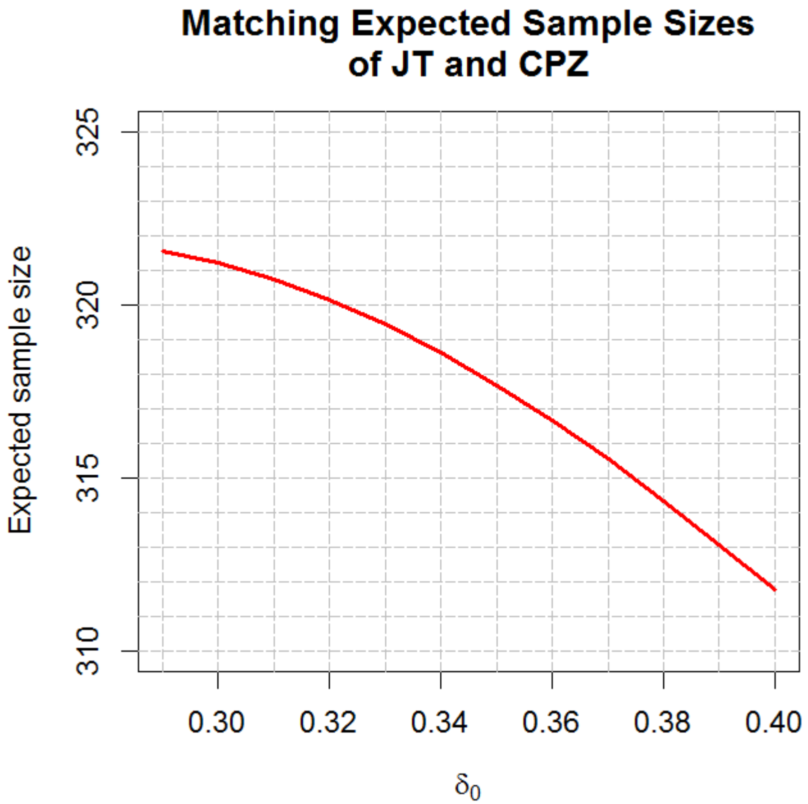
Objective: Maximize $CP_{\delta_0}(n_2^*, z_1) - \gamma n_2^*$
Constraint: $n_2 \leq n_2^* \leq n_{max}$

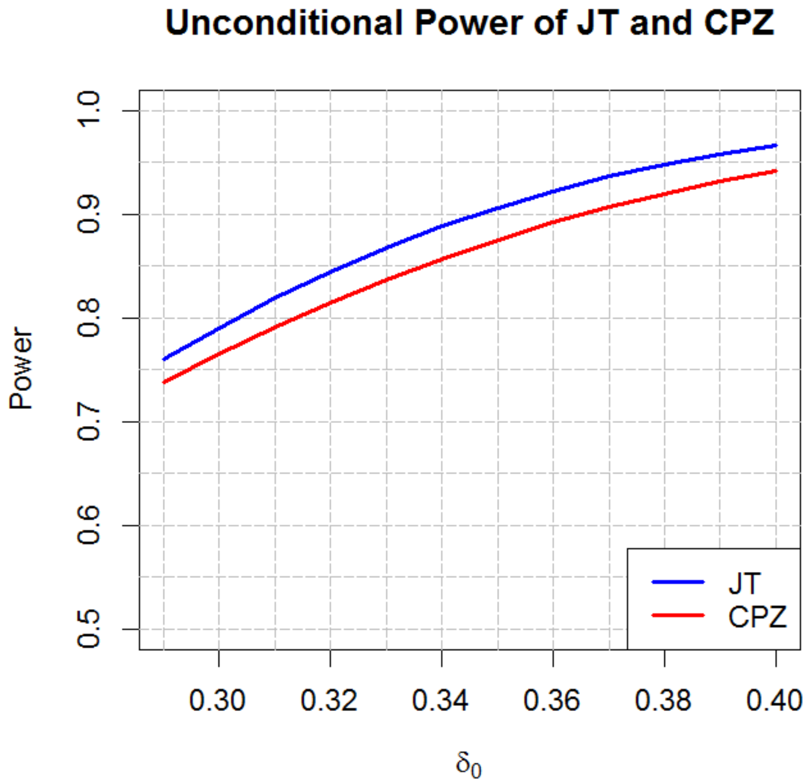
where γ is a constant “exchange rate” between CP and N, and δ_0 is effect size at which to optimize

- **Optimality property**: Highest possible unconditional power among SSR rules with matching E(N)
- **Benchmarking tool** for adaptive designs

Efficiency Comparison with JT Optimal Design

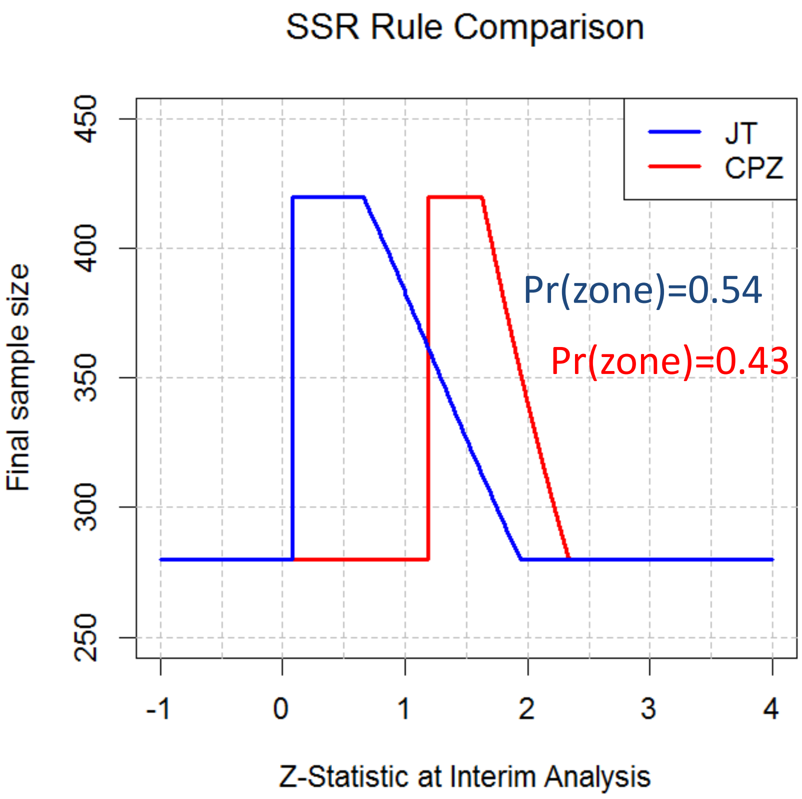
- **Method:** For each δ, compare unconditional power of CPZ against JT design with γ chosen so expected sample size matches

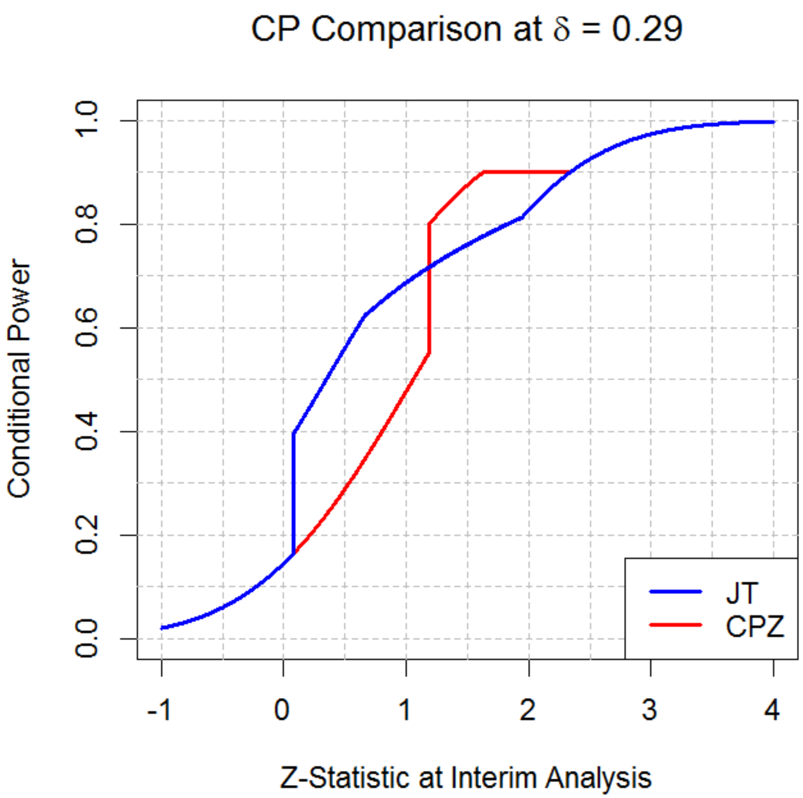




Efficiency Comparison with JT Optimal Design

- Comparison at $\delta = 0.29$

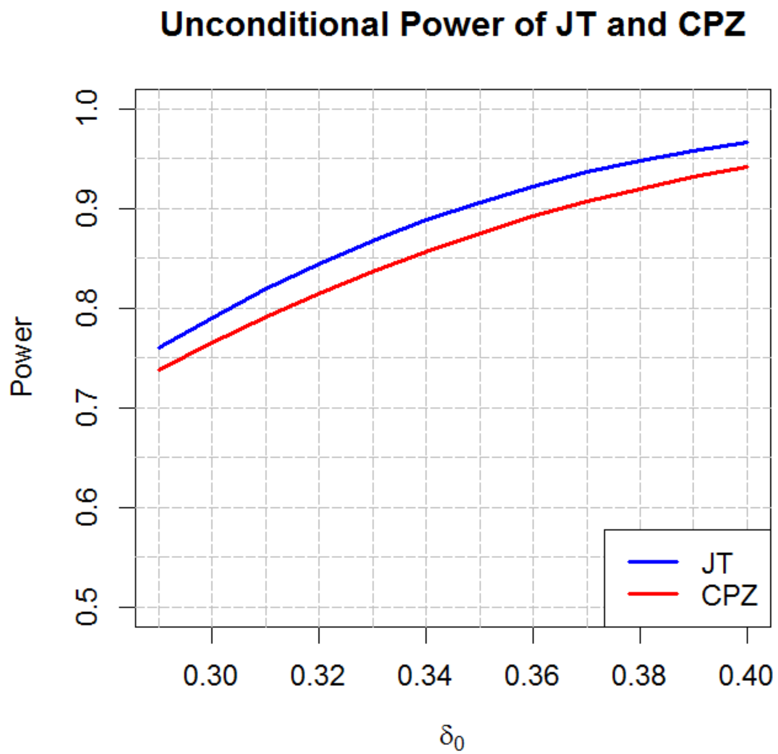


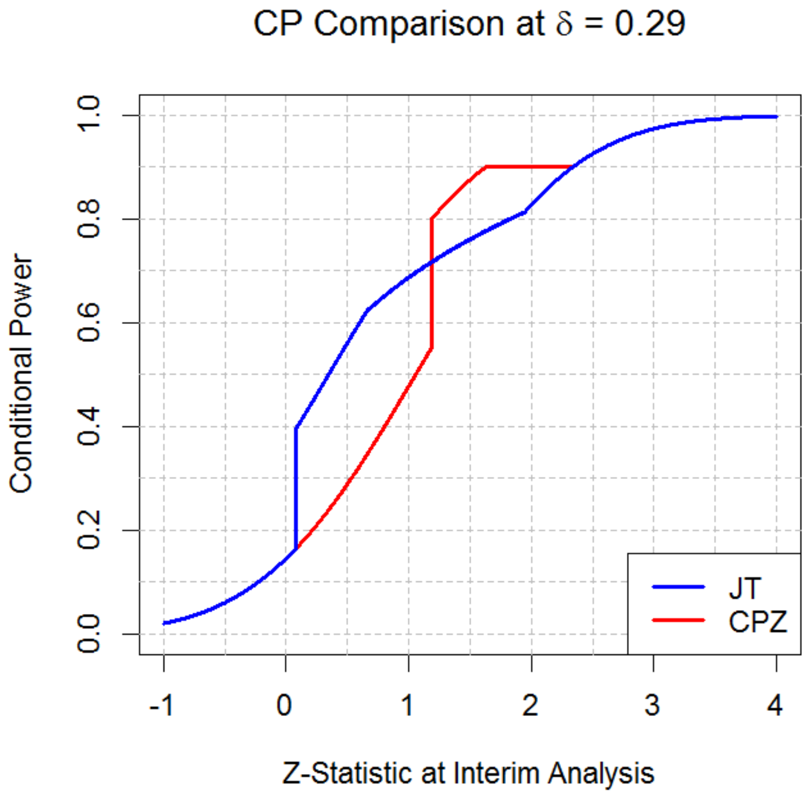


Efficiency Comparison with JT Optimal Design

Conclusions

- JT Optimal Design gains 2-3% unconditional power
- Requirement of high CP at lowest meaningful θ is not met by JT Design





Constrained JT Rule (CJT)

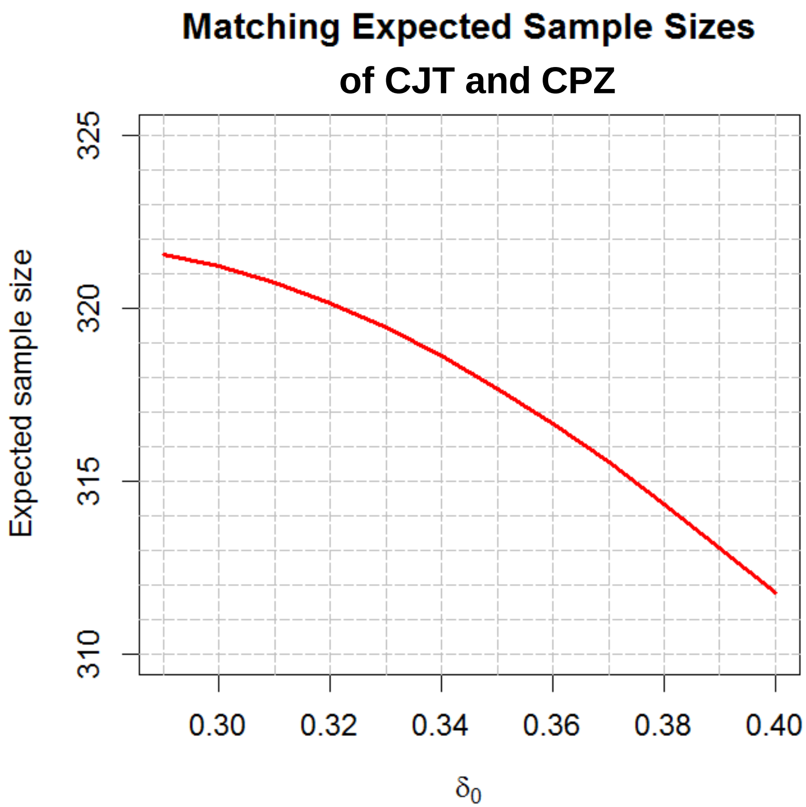
- Impose an additional CP constraint on the JT SSR rule.
- **Constrained SSR Rule:** Final sample size n_2^* determined by:

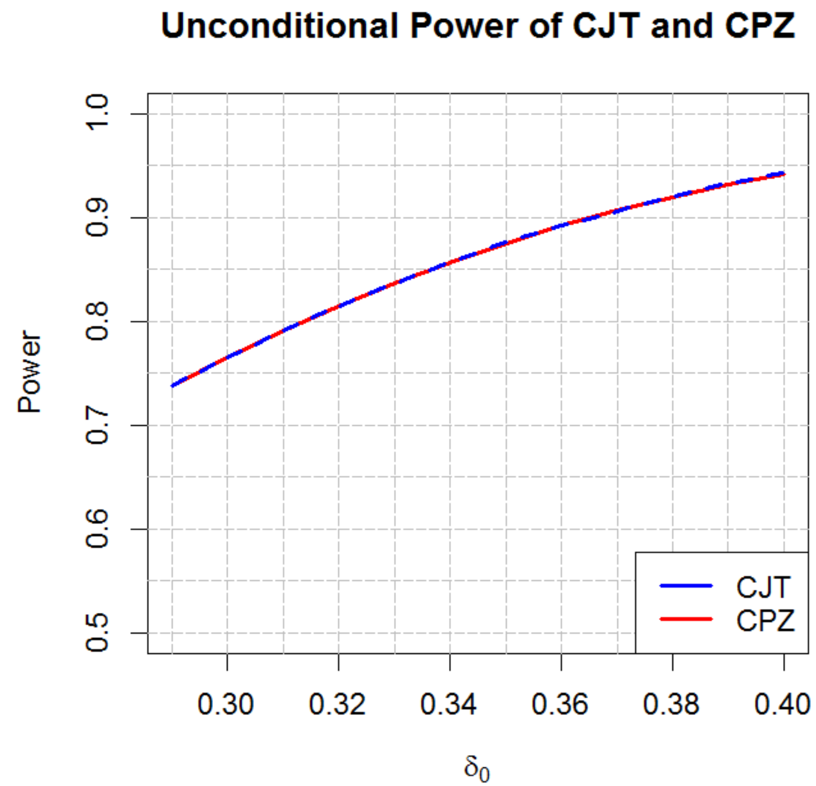
Objective: Maximize $CP_{\delta_0}(z_1, n_2^*) - \gamma n_2^*$
Constraint 1: $n_2 \leq n_2^* \leq n_{max}$
Constraint 2: $CP_{0.29}(z_1, n_2^*) \geq 80\%$

- **Optimality property**: Highest unconditional power among promising zone designs satisfying same constraints and matching E(N)

Comparison of CPZ and CJT

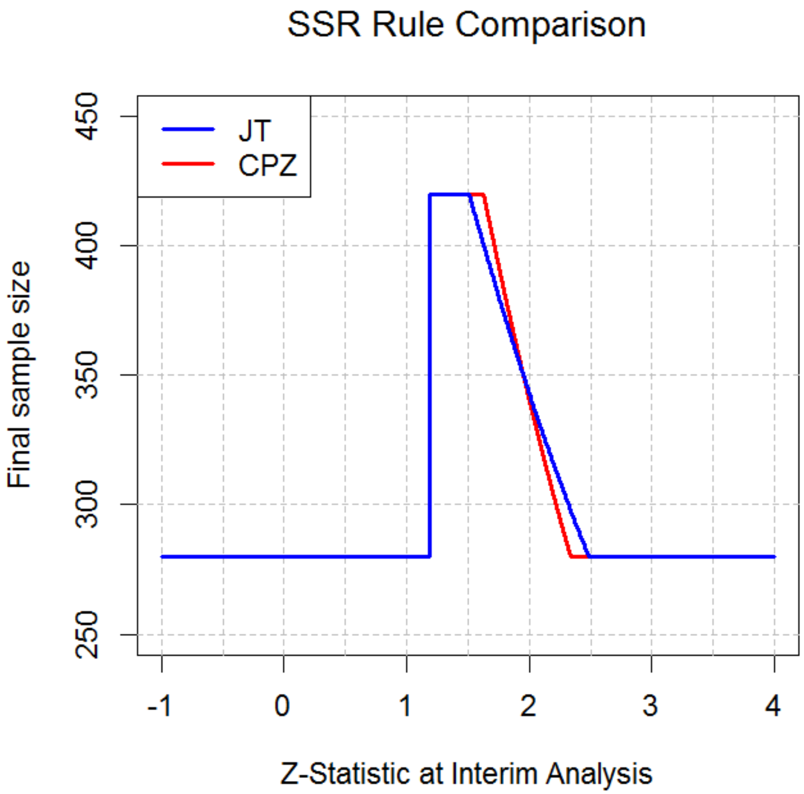
- **Method:** For each δ, compare unconditional power of AD against constrained JT Design with γ chosen so expected sample size matches AD

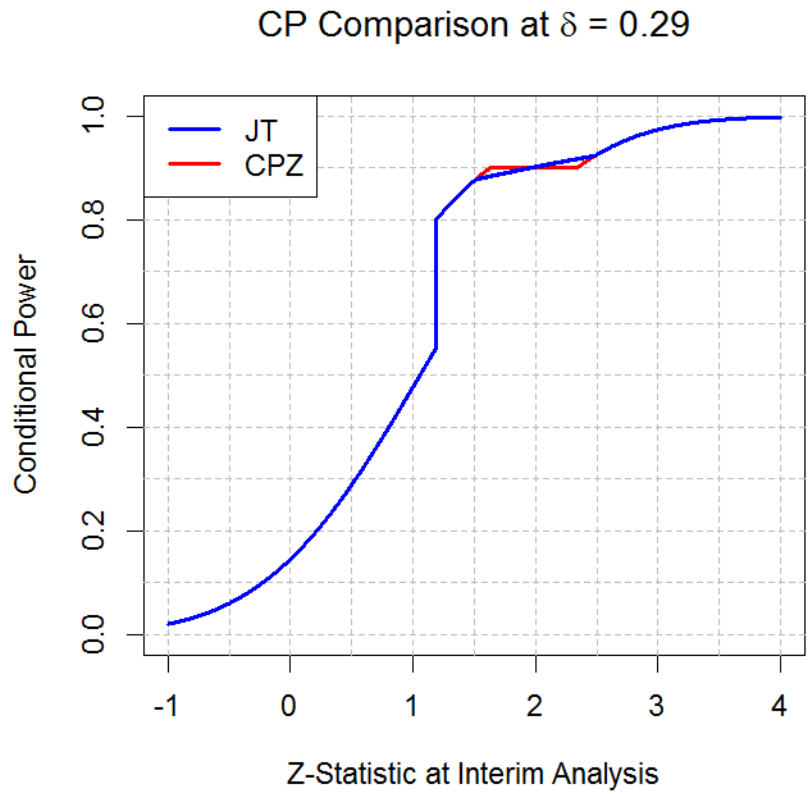




Comparison of CPZ and CJT

- Comparison at $\delta = 0.29$

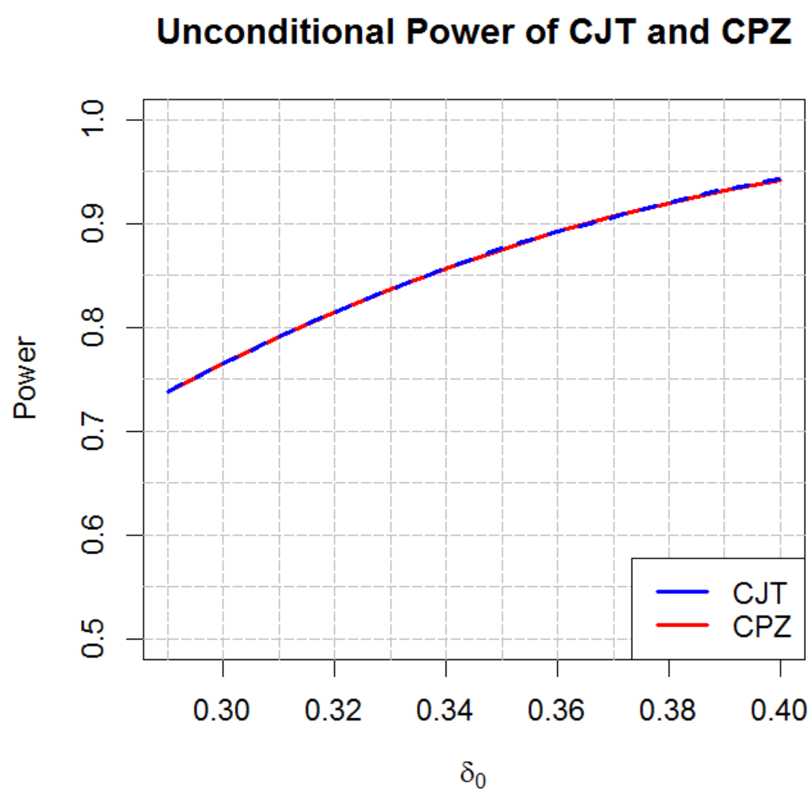


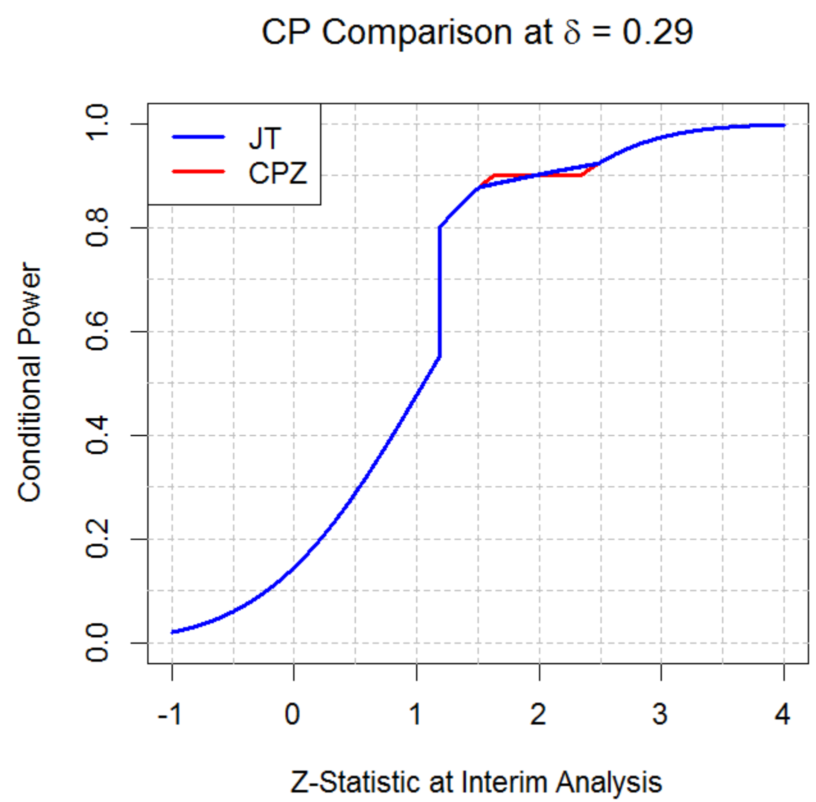


Comparison of CPZ and CJT

Conclusions

- Equally efficient in terms of unconditional power
- Similar conditional power profiles





Using a Smaller CP Constraint

Objective: Maximize conditional power $CP_{0.29}(z_1, n_2^*)$

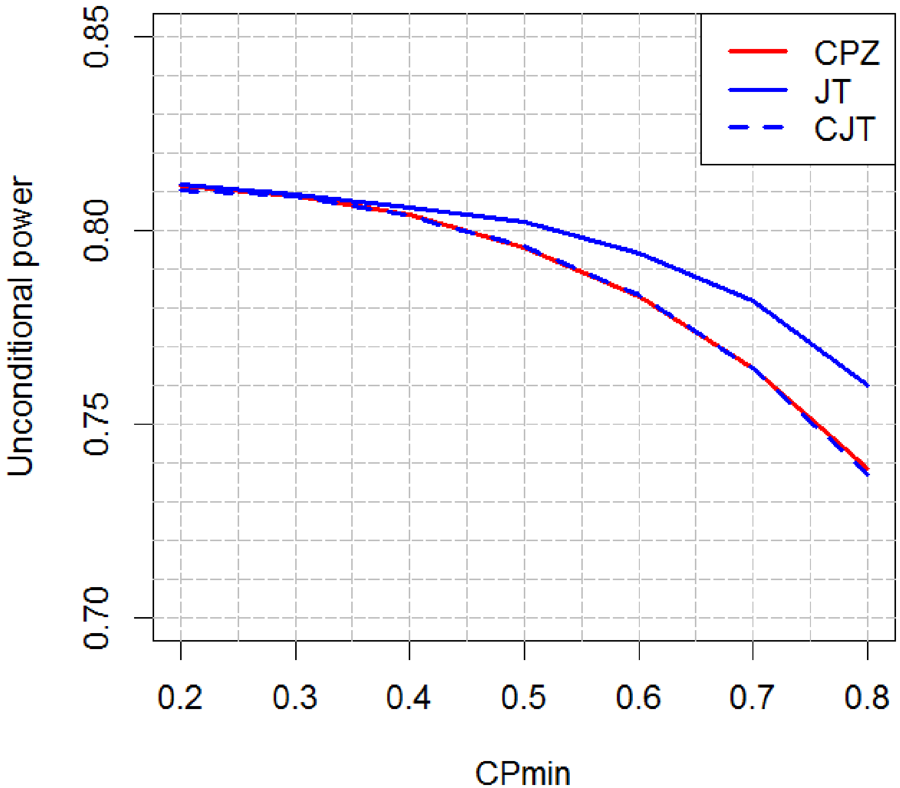
Constraint 1: $n_2 \leq n_2^* \leq n_{max}$

Constraint 2: $CP_{0.29}(z_1, n_2^*) \geq 80\%$ **70%, 60%, 50%,…**

Constraint 3: $CP_{0.29}(z_1, n_2^*) \leq 90\%$

Using a Smaller CP Constraint

Comparison of unconditional power at $\delta = 0.29$



Comparison with Group Sequential Designs

- Discussed in Mehta & Liu 2016, and Liu et al. 2017.
- Relative efficiency depends on aggressiveness of SSR rule, final test statistic, number and timing of interim looks.
- Compare apples to apples

Conclusions

- We considered a constrained promising zone design for an oncology trial
  - Maximize CP
  - Require sufficiently high CP to justify sample size increase
- Provide method for objective efficiency comparison
- 2-3% loss of unconditional power compared to optimal JT design which has wider SSR zone and recommends increasing N at lower z_1 values
- No loss of efficiency compared to optimal constrained JT design which requires $CP_{0.29}(z_1, n_2^*) > 80\%$
- Thus CPZ is optimal among designs with same CP and sample size constraints
- **Sponsor's utility** will determine whether a CP constraint makes sense, at the cost some efficiency loss compared to JT

References

- Liu, Lingyun, Sam Hsiao, and Cyrus R. Mehta. 2017. "Efficiency Considerations for Group Sequential Designs with Adaptive Unblinded Sample Size Re-Assessment." *Statistics in Biosciences*
- Mehta, Cyrus, and Lingyun Liu. 2016. "An Objective Re-Evaluation of Adaptive Sample Size Re-Estimation: Commentary on 'Twenty-Five Years of Confirmatory Adaptive Designs.'" *Statistics in Medicine* 35: 350–58.
- Hsiao SK, Liu L, Mehta CR. 2018. Optimal promising zone designs. *Biometrical Journal.*
- Jennison, Christopher, and Bruce W. Turnbull. 2015. "Adaptive Sample Size Modification in Clinical Trials: Start Small Then Ask for More?" *Statistics in Medicine* 34 (29): 3793–3810.