Efficiency of Promising Zone Designs

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In progress ...

Comparison with **optimal adaptive designs**

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

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Abstract Clinical trials with adaptive sample size re-assessment, based on an analysis of the unblinded interim results (ubSSR), have gained in popularity due to uncertainty regarding the value of δ at which to power the trial at the start of the study. While the statistical methodology for controlling the type-1 error of such designs is well established, there remain concerns that conventional group sequential designs with no ubSSR can accomplish the same goals with greater efficiency. The precise manner

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

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Over the past 25 years, adaptive designs have gradually gained acceptance and are being used with increasing frequency in confirmatory clinical trials. Recent surveys of submissions to the regulatory agencies reveal that the most popular type of adaptation is unblinded sample size re-estimation. Concerns have nevertheless been raised that this type of adaptation is inefficient. We intend to show in our discussion that such concerns are greatly exaggerated in any practical setting and that the advantages of adaptive sample size re-estimation usually outweigh any minor loss of efficiency. Copyright © 2015 John Wiley & Sons, Ltd

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Outline

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

Pivotal Trial in Oncology at a Small Biotech

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

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

- **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 minimal clinically acceptable effect size
  - Early efficacy stopping not of much interest, need adequate drug profile

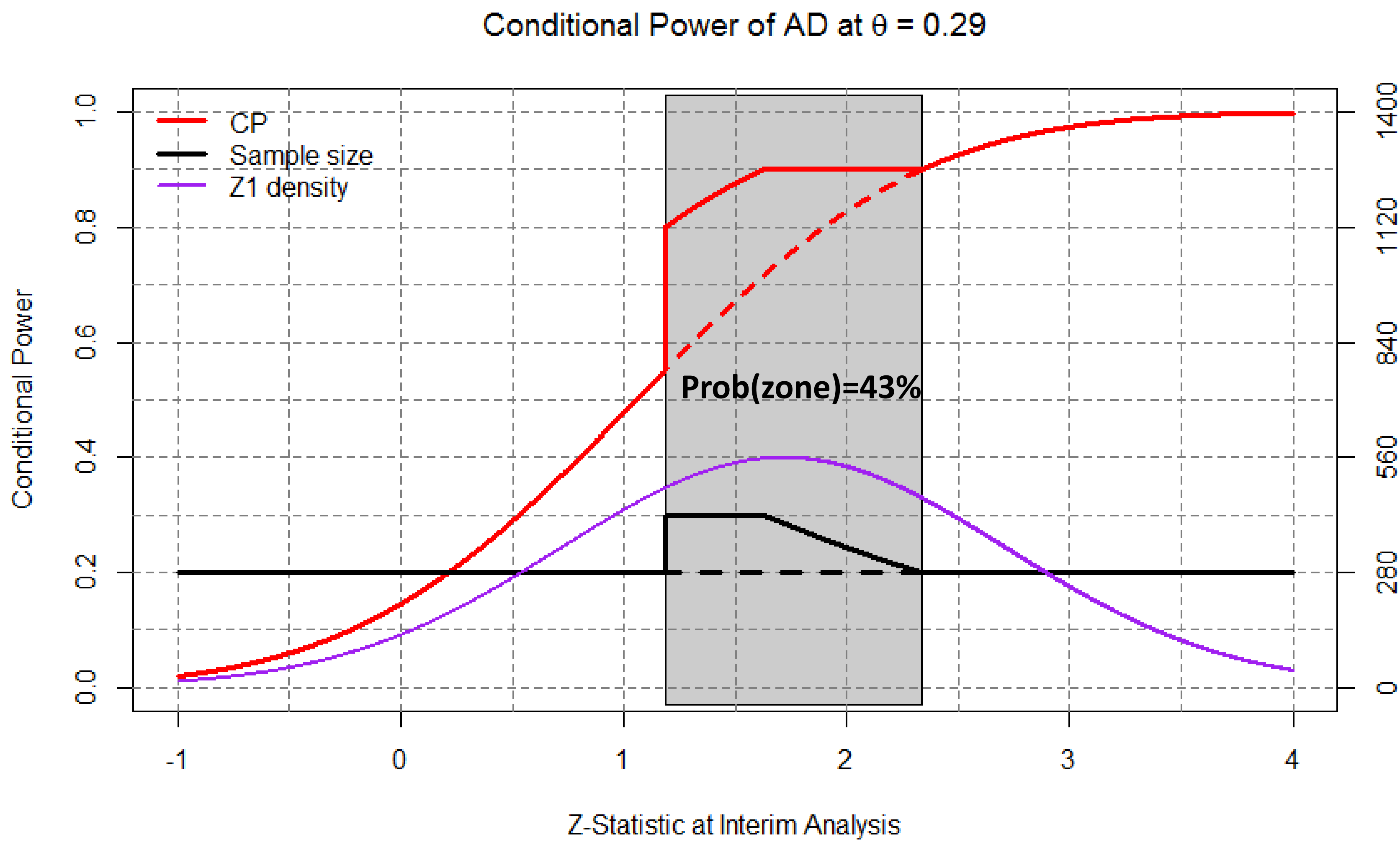
Promising Zone Adaptive Design (AD)

- **Two-Stage AD 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: $n_2 \le n_2^* \le n_{max}$
Constraint 2: $CP_{0.29}(z_1, n_2^*) \ge 80\%$
Constraint 3: $CP_{0.29}(z_1, n_2^*) \le 90\%$

- **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

AD Conditional Power and SSR Rule



Is the Adaptive 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

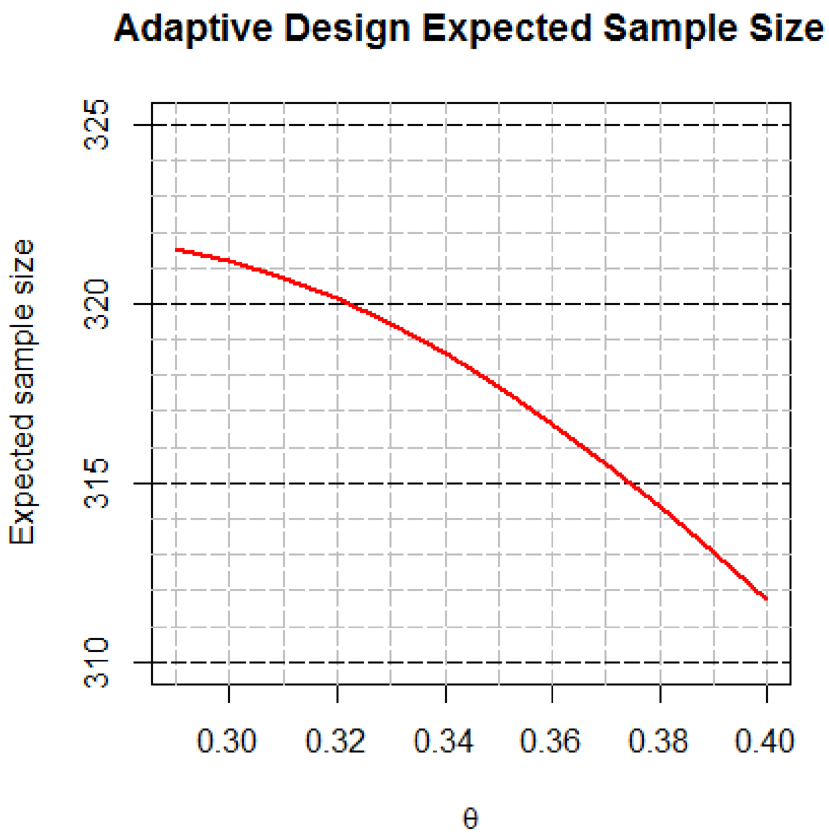
Objective: Maximize $CP_\theta(n_2^*, z_1) - \gamma n_2^*$
Constraint: $n_2 \leq n_2^* \leq n_{max}$

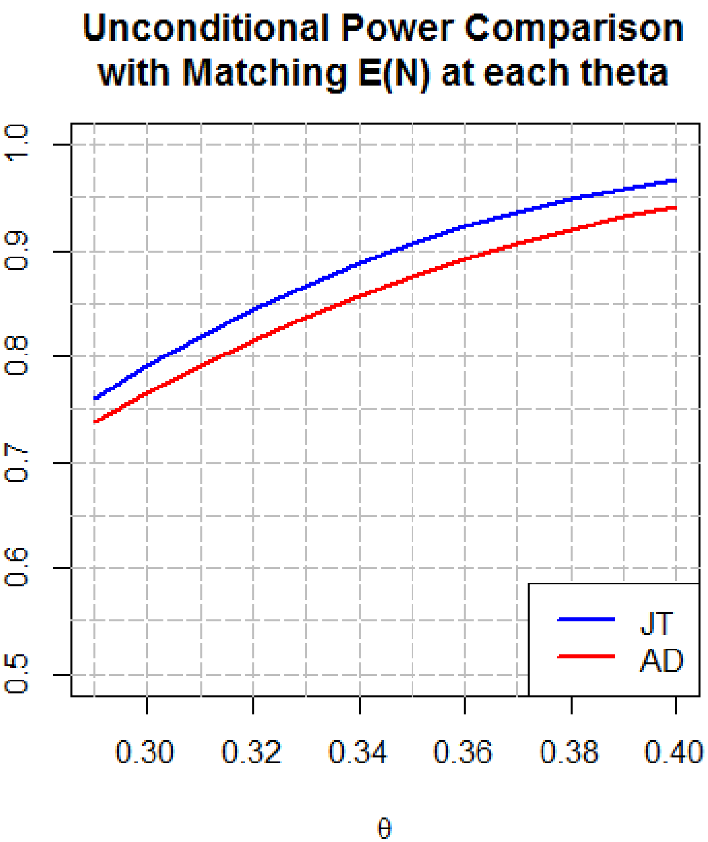
where γ is a constant "exchange rate" between CP and N

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

Efficiency Comparison with JT Optimal Design

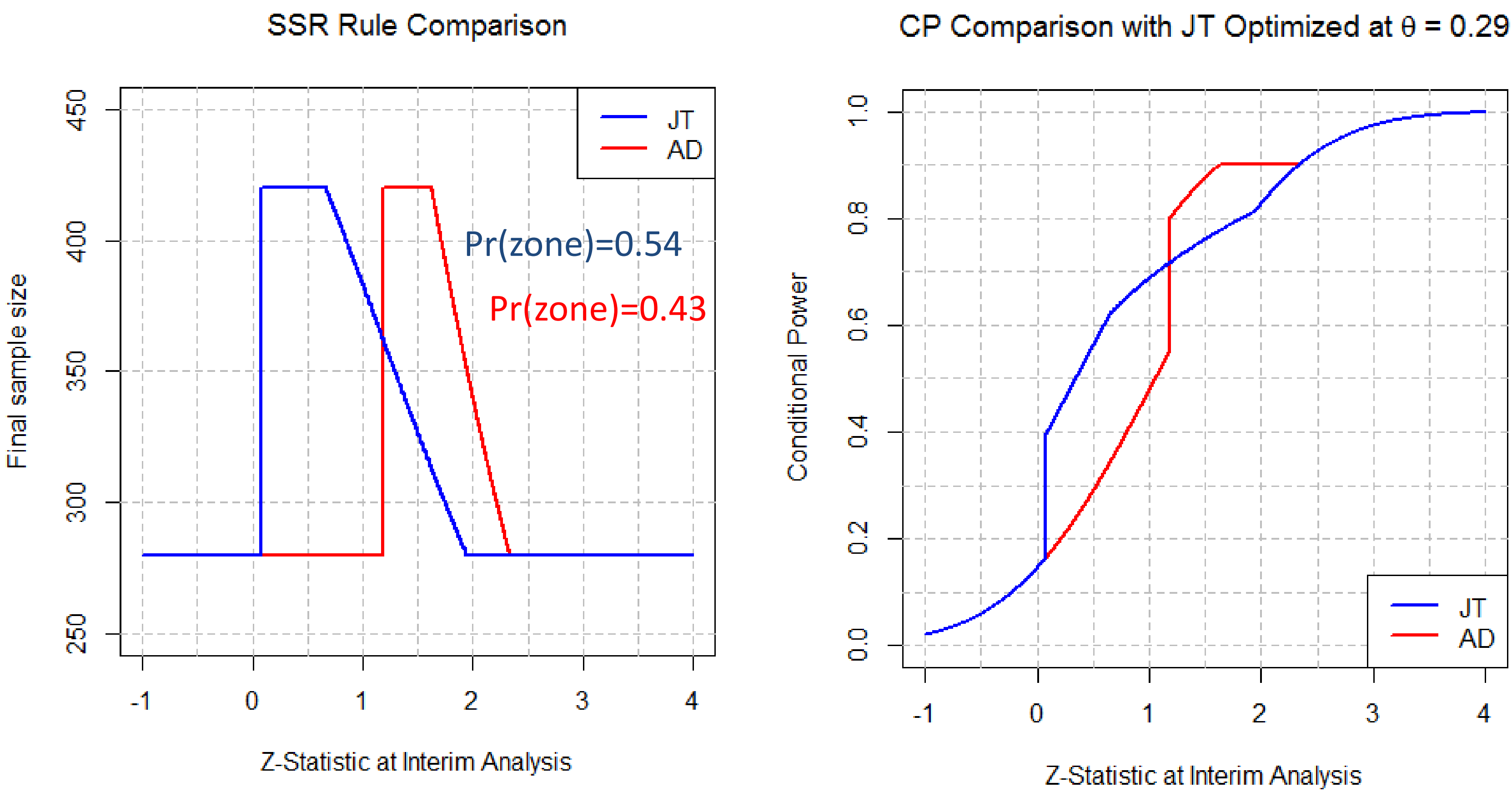
- **Method:** For each θ, compare unconditional power of AD against JT design with γ chosen so expected sample size matches AD





Efficiency Comparison with JT Optimal Design

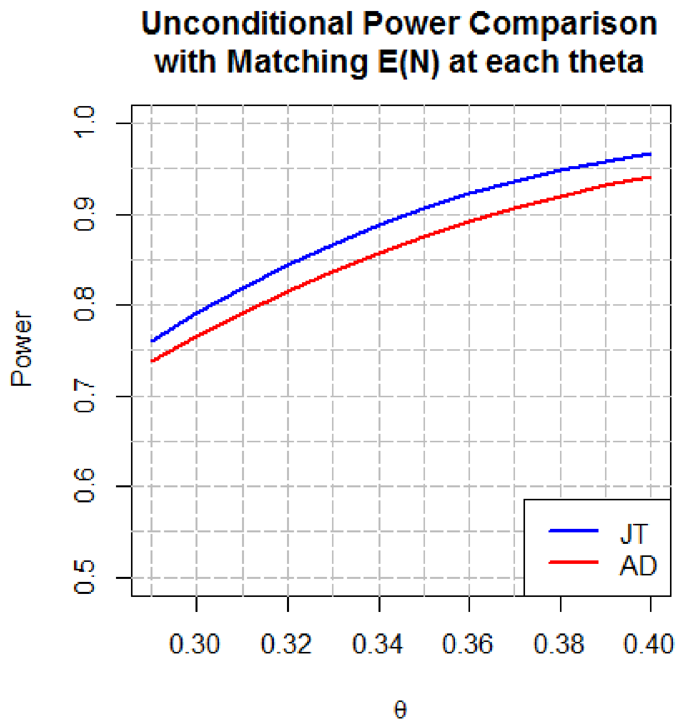
- Comparison at $\theta = 0.29$

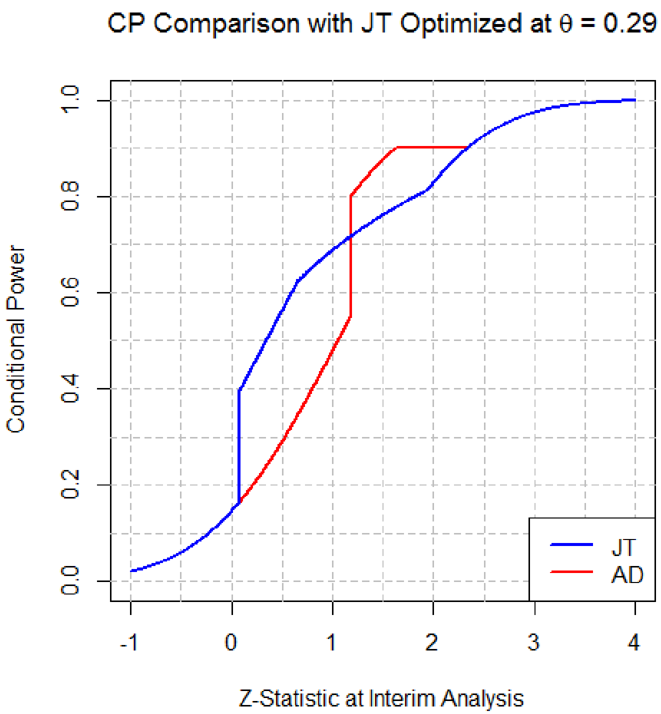


Efficiency Comparison with JT Optimal Design

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

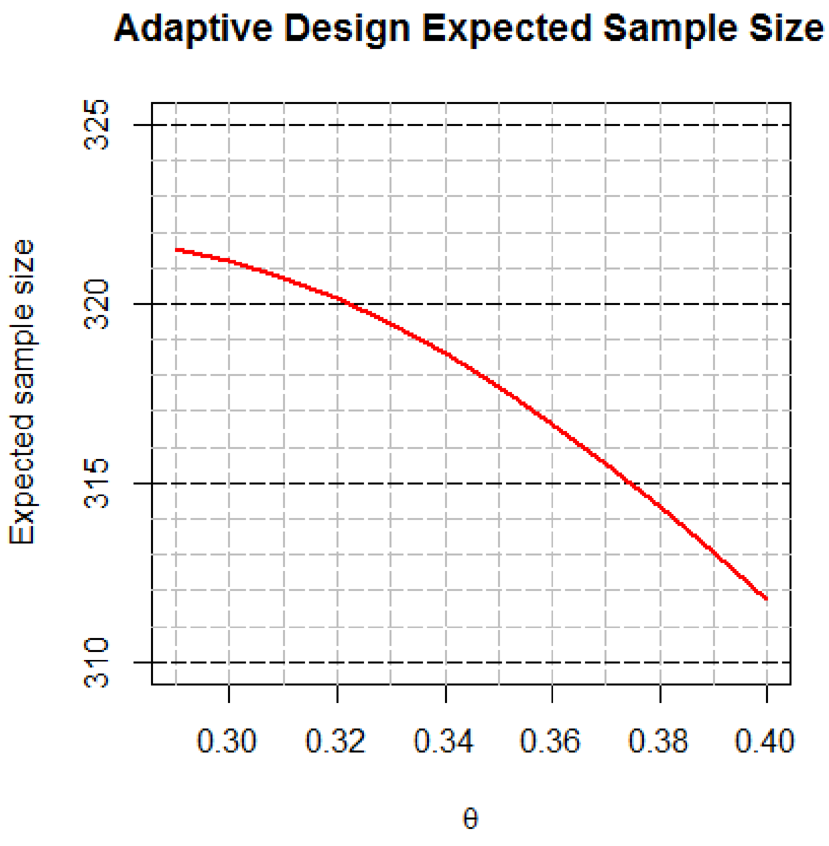
- Impose an additional CP constraint on the JT SSR rule.
- **Constrained SSR Rule:** Final sample size n_2^* determined by:

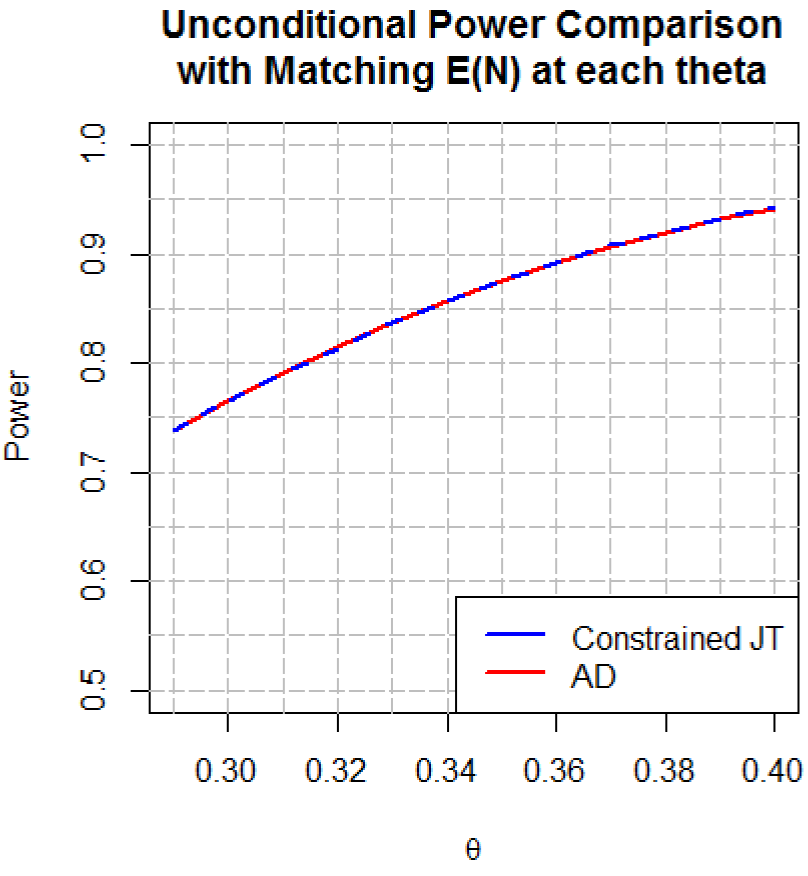
Objective: Maximize $CP_\theta(z_1, n_2^*) - \gamma n_2^*$
Constraint 1: $n_2 \leq n_2^* \leq n_{max}$ **Constraint 2:** $CP_{0.29}(z_1, n_2^*) \geq 80\%$

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

Comparison of AD and Constrained JT

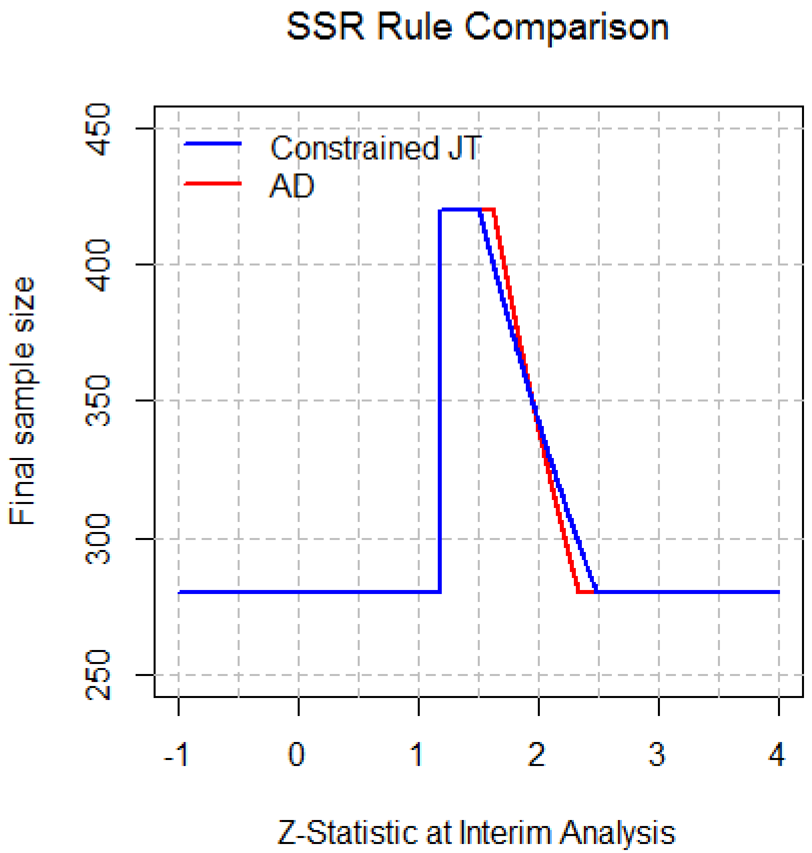
- **Method:** For each θ, compare unconditional power of AD against constrained JT Design with γ chosen so expected sample size matches AD

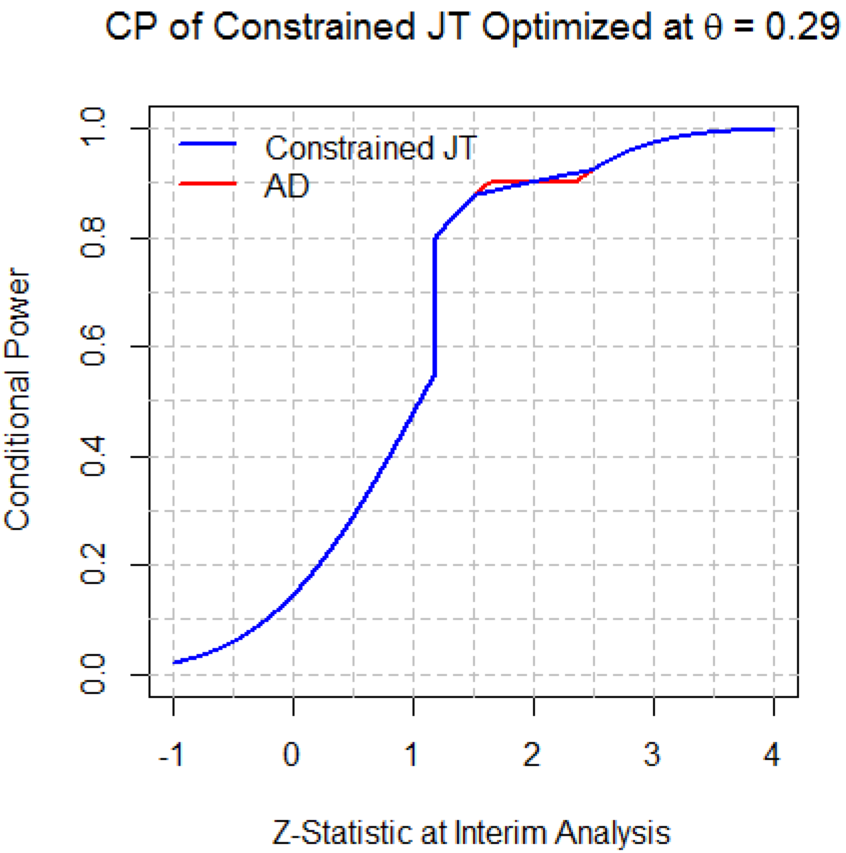




Comparison of AD and Constrained JT

- Comparison at $\theta = 0.29$

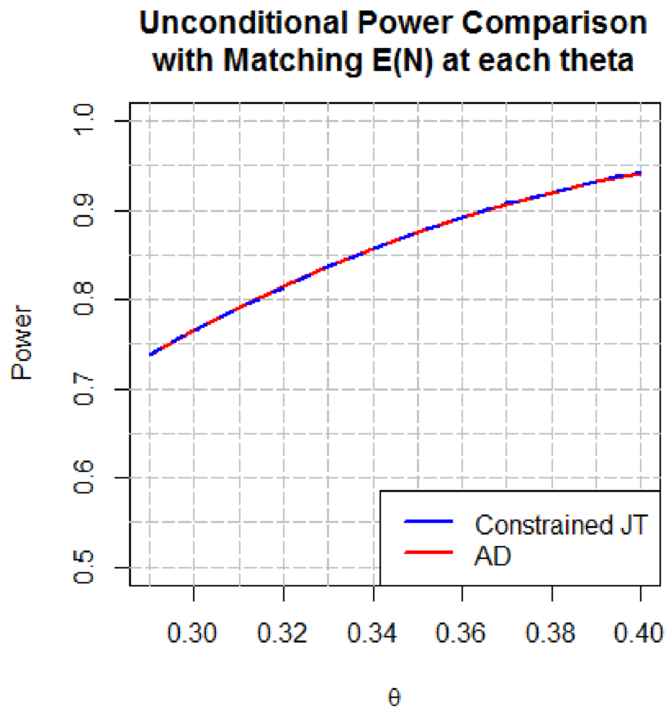


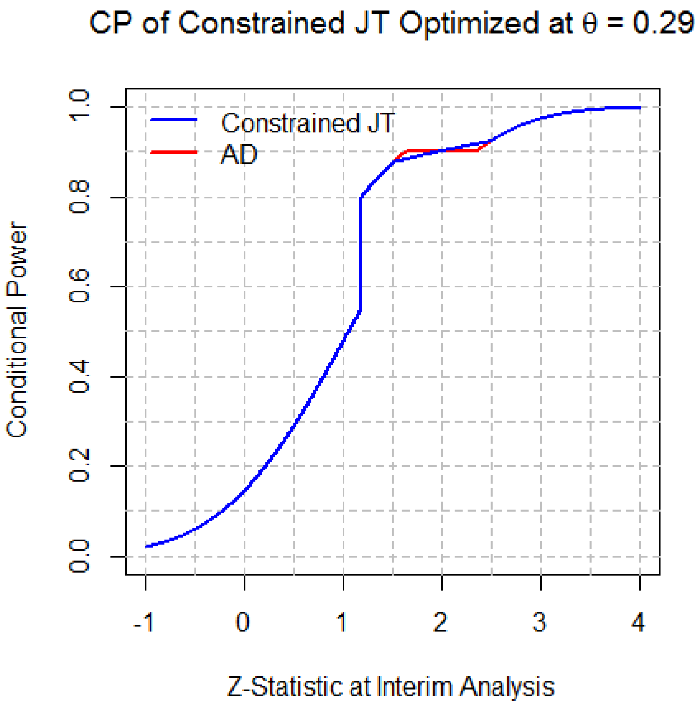


Comparison AD and Constrained JT

Conclusions

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





Conclusions

- We considered a promising zone AD 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 $CP_{0.29}(z_1, n_2^*) > 80\%$
- **Sponsor's utility** will determine whether a CP constraint makes sense, at the cost some efficiency loss compared to JT

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