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 adaptive design is unblinded sample size re-estimation. Concerns have nevertheless been raised that this type of design is not validated in any standard and may lead to a minor loss of power. In this commentary, we provide an objective re-evaluation of adaptive sample size re-estimation, based on an analysis of its popularity due to uncertainty in the interim analyses, the start of the study. While the potential of such designs is well recognized, the practical implementation and sample sizes for sequential designs with this flexibility is important to efficiency. The precise manner

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

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Optimal promising zone designs

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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 (δ = 0.4 on log scale), but consider HR=0.75 to be minimally acceptable (δ = 0.29)

| Power | \( \delta = 0.29 \) | \( \delta = 0.4 \) |
|-------|----------------|----------------|
| 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 $n_2 = 280$, interim analysis $n_1 = 140$, maximum $n_{max} = 420$
  - 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

Conditional power and final sample size at $\delta = 0.29$

- Conditional Power
- Sample Size
- Density of Z1

Prob(zone) = 43%

Z-Statistic at Interim Analysis

Sample Size
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 $\gamma$ is a constant “exchange rate” between CP and N, and $\delta_0$ 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 $\delta$, compare unconditional power of CPZ against JT design with $\gamma$ chosen so expected sample size matches.
Efficiency Comparison with JT Optimal Design

- Comparison at $\delta = 0.29$

SSR Rule Comparison

CP Comparison at $\delta = 0.29$

Pr(zone) = 0.54

Pr(zone) = 0.43
Efficiency Comparison with JT Optimal Design

Conclusions

• JT Optimal Design gains 2-3% unconditional power
• Requirement of high CP at lowest meaningful $\theta$ 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: | $n_2 \leq n_2^* \leq n_{\text{max}}$ |
  | 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 $\delta$, compare unconditional power of AD against constrained JT Design with $\gamma$ 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
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