Flexible group-sequential designs with treatment selection

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Outline

1. Aim – Seamless phase II/III designs

2. Background
   - 2.1 Standard group-sequential approach
   - 2.2 Select best treatment at first analysis
   - 2.3 Strong control of FWER

3. Flexible group-sequential boundary

4. Simulation study

5. Conclusions

1. Aim - Seamless phase II/III clinical trials

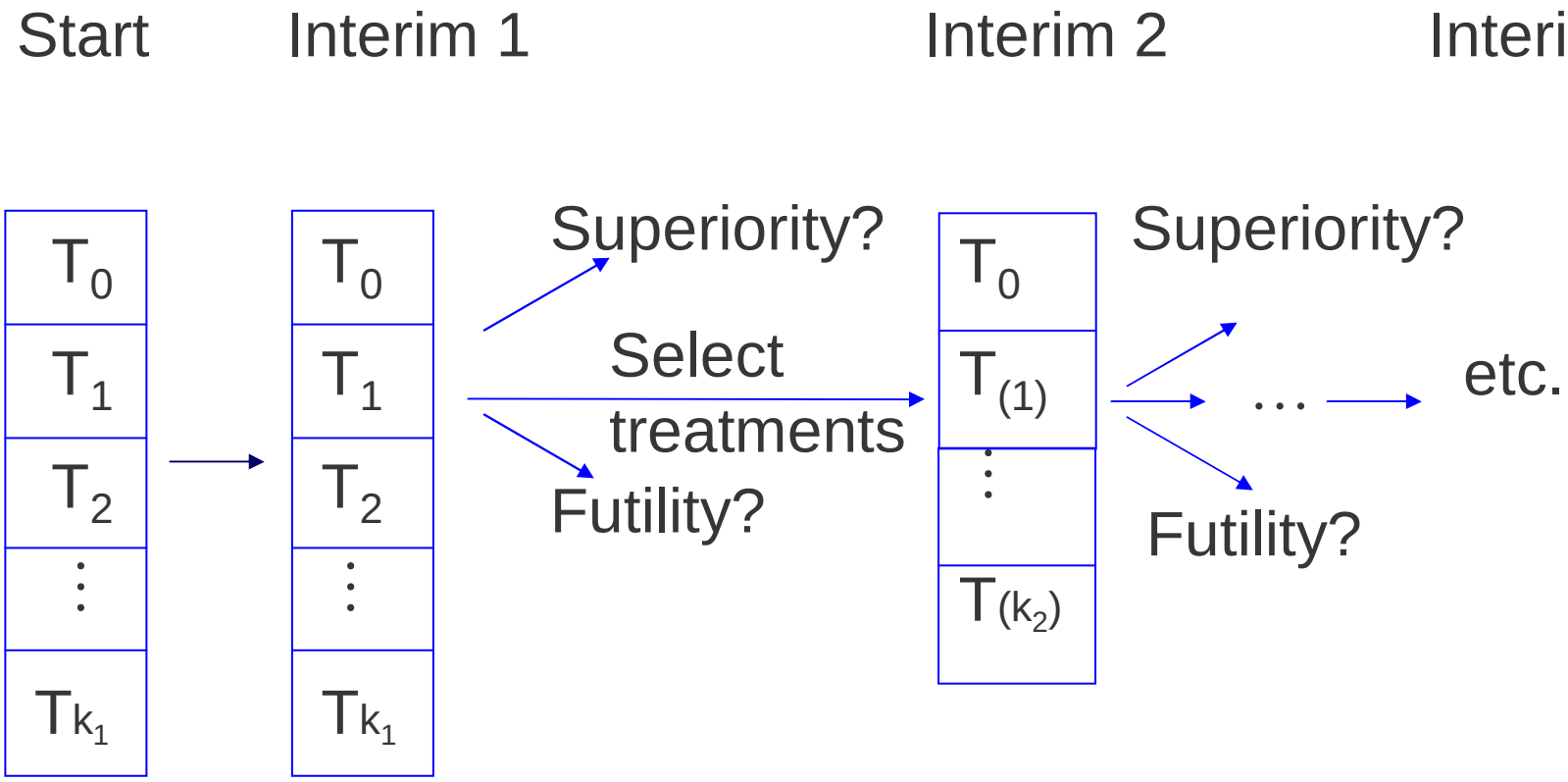
Phase II trials (exploratory)

- Early trials to assess treatment efficacy
- Error rates not tightly controlled
- Select one of several treatments/doses for further development

Phase III trials (confirmatory)

- Large-scale controlled trials
- Comparison of single experimental treatment with control
- Error rates controlled - definitive conclusions

Aim: combine these two phases in a seamless design



T_0: Control Treatment $T_1,\ldots, T_{k_1}$ Experimental Treatments

Aim: control FWER in strong sense

2. Background

2.1 Standard group-sequential approach ($k_1 = 1$)

(Jennison and Turnbull, 2000)

θ measures superiority of T_1 over T_0

Test H_0: $\theta = 0$ vs. H_A: $\theta > 0$

At look j

calculate $(S_j, \mathcal{I}_j)$, efficient score and information for θ

stop if $S_j \leq l_j$, stop and reject H_0 if $S_j \geq u_j$

Obtain null distribution of S numerically using

$S_1 \sim N(\theta\mathcal{I}_1, \mathcal{I}_1)$, $S_j - S_{j-1} \sim N(\theta(\mathcal{I}_j - \mathcal{I}_{j-1}), \mathcal{I}_j - \mathcal{I}_{j-1})$

Find boundaries with Pr(reject H_0 by look j; H_0) = $\alpha^*(j)$

for specified $\alpha^*(1) \leq \ldots \leq \alpha^*(N) = \alpha$

2.2 Select best treatment at first analysis ($k_2 = 1$)

(Stallard and Todd, 2003)

θ_i measures T_i over T_0

Test global null hypothesis H_0: $\theta_1 = \ldots \theta_k = 0$

At look 1

calculate $(S_{i1}, \mathcal{I}_{i1})$, efficient score and information for θ_i

let $\lambda = \text{argmax}\{S_i\}$

stop if $S_{\lambda 1} \leq l_1$, stop and reject H_0 if $S_{\lambda 1} \geq u_1$

else continue with T_λ and T_0

At look j $(1 < j \leq N)$

calculate $(S_{\lambda j}, \mathcal{I}_{\lambda Ij})$

stop if $S_{\lambda j} \leq l_j$, stop and reject H_0 if $S_{\lambda j} \geq u_j$

Obtain null distribution of $S_{\lambda j}$

Find boundary to satisfy spending function constraint

2.3 Strong control of FWER

Consider test of H_{0K}: $\theta_i = 0 \; \forall \; i \in K \subseteq \{1, \ldots, k_1\}$

$\max_{i \in K} \{S_{i1}; H_{0K}\} \leq_{st} \max\{S_{i1}; H_0\} \Rightarrow$ control error rate for H_{0K}

Hence by CTP control I error rate for H_{0i} in strong sense

Can also select treatment other than best and use same stopping boundary

3. Flexible group-sequential boundary

At look j
calculate $(S_{i1}, \mathcal{I}_{i1})$ for all current treatments
let $X_{ij} = S_{ij} - S_{ij-1}$
let $X_j^{max} = \max\{X_{ij}\}$
let $S_j^{max} = X_1^{max} + \ldots + X_j^{max}$

Obtain null distribution of S_j^{max}
Find boundary to control type I error rate for monitoring S_j^{max}

Stop T_i if $S_{ij} \leq l_j$, stop T_i and reject H_{0i} if $S_{ij} \geq u_j$

Can select any treatments since $S_{ij} \leq_{st} S_j^{max}$
Control FWER in strong sense as previously

4. Simulation study

Start with $k_1 = 3$ treatments

Use triangular test spending function with 5 looks

with power 0.8 when $\theta_1 = \theta_2 = 0$, $\theta_3 = 0.5$ if $k_2 = 1$

Drop T_i if $S_{ij} \geq u_j$ or $S_{ij} \leq l_j$ or if $\hat{\theta}_i < \max\left\{\hat{\theta}_i\right\} - \varepsilon$

Estimate type I error rates

pr(reject any H_{0i}; H_0)

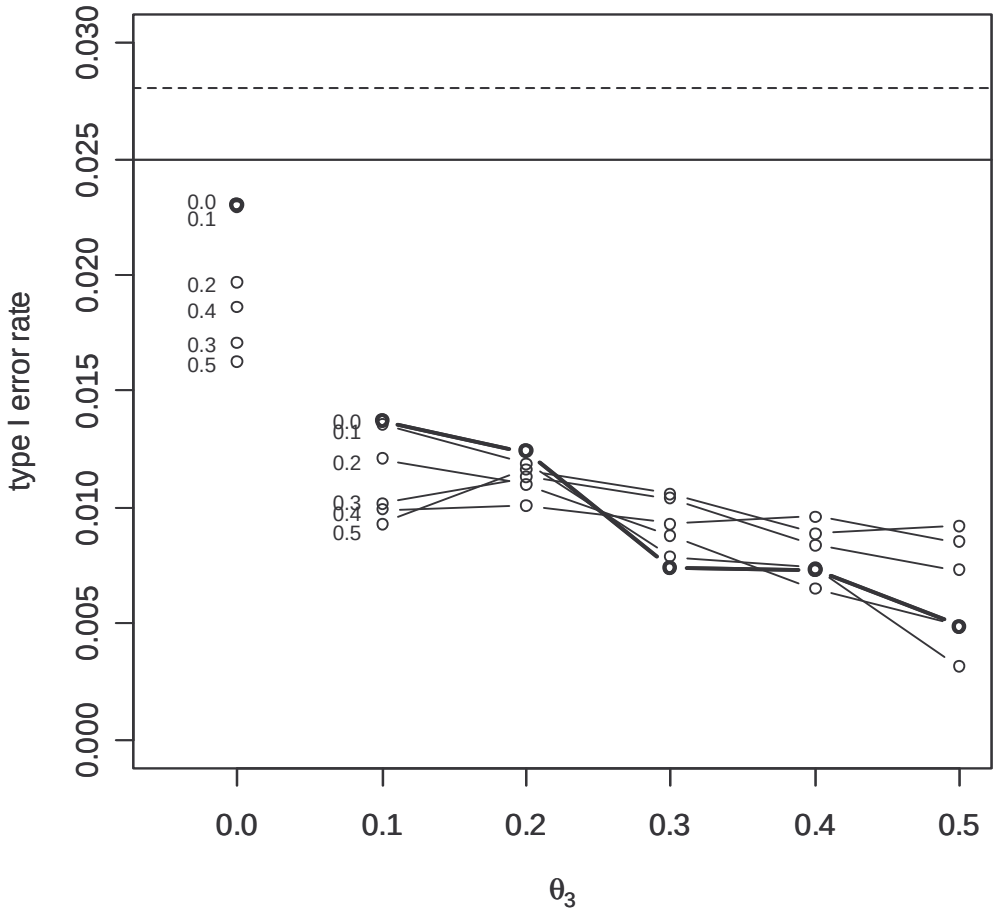
pr(reject H_{01} or H_{02}; H_{01}, H_{02}) for range of θ_3 values

Estimate power

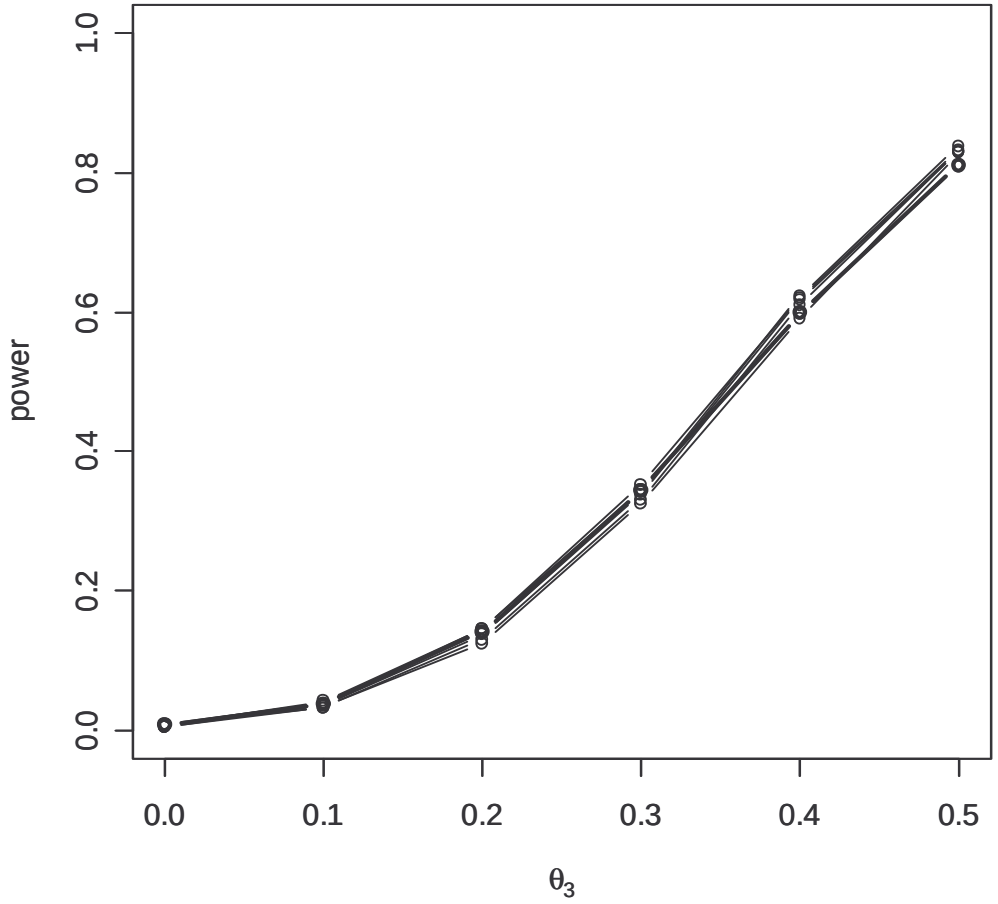
pr(reject H_{03}; H_{01}, H_{02}) for range of θ_3 values

Based on 10,000 simulated trials per scenario

Simulated type I error rates for range of ε and θ_3 values



Simulated power for range of ε and θ_3 values



4. Conclusions

The new approach

- enables construction of boundary using group-sequential approach
- allows flexible dropping of treatments at any stage
- strongly controls FWER
- maintains power relative to Stallard and Todd design