Warwick
Medical School

An adaptive seamless phase II/III clinical trial design incorporating short-term endpoint information

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1. Motivating example

A trial in Alzheimer's disease
- experimental treatment at 3 doses and placebo control

Primary endpoint
- ADAS-cog change over 12 weeks

We want to
- select most effective dose
- provide a valid comparison with control

2. Conventional approach

Phase II trial

- exploratory trial compares three doses with placebo
- select best dose
- short-term endpoint: ADAS-cog change over 6 weeks
- go on to phase III if sufficiently promising

Phase III trial

- compares single selected dose with placebo
- long-term endpoint: ADAS-cog change over 12 weeks
- control error rates

3. Combining phases II and III

Trial is conducted in two stages

Stage 1

- 3 doses + placebo
- short and long term endpoints
- conduct interim analysis to select most promising dose

Stage 2

- selected dose + placebo
- long term endpoint

Final analysis

- use all long term endpoint data on selected dose
- control overall type I error rate to provide valid comparison

4. Notation and model

Stage 1: short-term endpoint for N_1 per group
long-term endpoint for $n_1 \leq N_1$ per group
Stage 2: long-term endpoint for $n_2 \geq N_1$ in total per group

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Normally distributed endpoints with mean for dose i given by:
short-term: $\zeta_i, i = 0, \ldots, 3$, long-term: $\xi_i, i = 0, \ldots, 3$

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Stage 1: short-term endpoint, $X \sim N(\zeta_i, \sigma_s^2)$
long and short-term endpoints,

$$\begin{pmatrix} X \\ Y \end{pmatrix} \sim N\left(\begin{pmatrix} \zeta_i \\ \xi_i \end{pmatrix}, \begin{pmatrix} \sigma_s^2 & \rho\sigma\sigma_s \\ \rho\sigma\sigma_s & \sigma^2 \end{pmatrix}\right)$$

Stage 2: long-term endpoint, $Y \sim N(\xi_i, \sigma^2)$

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Stage 2: long-term endpoint, $Y \sim N(\xi_i, \sigma^2)$

Treatment effect of interest: $\theta_i = \xi_i - \xi_0, i = 1, \ldots, 3$

5. Procedure

Stage 1: Obtain $\hat{\theta}_{i1}$ and $var(\hat{\theta_{i1}})$ for each dose
using all short and long-term endpoint data
(using double regression or linear mixed model)
Select dose with largest $\hat{\theta}_{i1}$

Stage 2: Obtain $\hat{\theta}_{i2}$ and $var(\hat{\theta_{i2}})$ for selected dose
using all long-term endpoint data

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$$\hat{\theta}_{i1} \sim N(\theta_i, 2\sigma^2/n_1 - 2\sigma^2\rho^2(1/n_1 - 1/N_1)),$$
$$corr(\hat{\theta}_{i1}, \hat{\theta}_{j1}) = 1/2, i \neq j$$

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Use joint distribution of $\max\{\hat{\theta}_{i1}\}$ and $\hat{\theta}_{i2}$ to construct critical values to control overall type I error rate

6. Example and simulation study

Stage 1: short-term data on 100 patients per group
long-term data on 40 patients per group
Stage 2: long term data on 200 patients per group in total

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ρ	Effective stage 1 n/gp	Expected stage 2 critical value	Power $(\theta_1 = \theta_2 = 0, \theta_3/\sigma = 1/3)$ from 100,000 simulations
0.0	40	2.19	0.784
0.5	47	2.20	0.800
0.6	51	2.21	0.807
0.7	57	2.22	0.816
0.8	65	2.23	0.820
0.9	80	2.25	0.837

7. Conclusions and further notes

New method
- enables combination of phases II and III in a single trial
- gains power through use of short-term endpoint
- maintains control of type I error rate
- does not require estimate of ρ at design stage

Power depends on within-group correlation ρ not on short-term endpoint treatment effect

Can extend to allow
- more than two stages
- early stopping for efficacy or futility
- selection of (pre-specified) number of treatments