

One- and two-stage design proposals for a phase II trial comparing three active treatments with control using an ordered categorical endpoint

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Outline

- 1 Background
- 2 Details of the Method
- 3 Sample size comparisons
- 4 Discussion

Setting

- Dose/Treatment selection
- Test for promise of efficacy (Phase II)
- Ordered categorical response

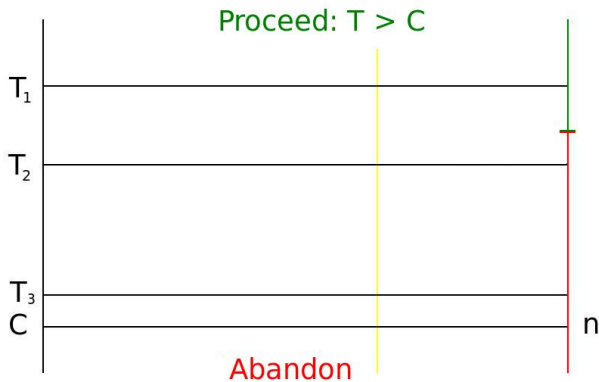
Examples

- Oncology
 - Compare different doses or different combinations of therapy
 - Ordered categorical outcome e.g. complete response, partial response, stable disease, progression or death
- Neurological diseases e.g Alzheimers disease
 - Compare different doses
 - Clinician's Global Impression of Change
- Stroke

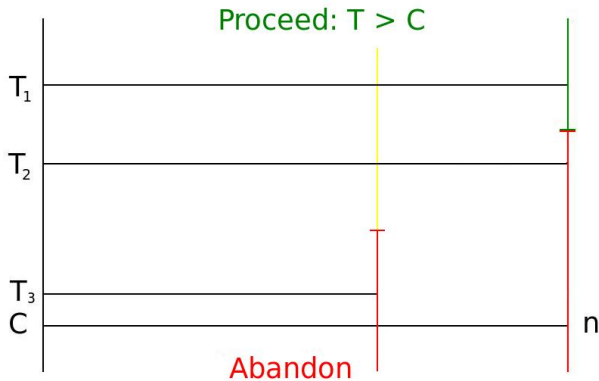
Related work

- One-stage designs
 - One treatment vs control (Pocock, 1983)
 - Multiple treatments vs control (Dunnett, 1984)
- Multi-stage designs
 - Two-stage design with dose selection and futility stopping with binary endpoint (Thall *et al.* 1988)
 - Extension to multiple interim analysis and other responses (Stallard and Todd, 2003)

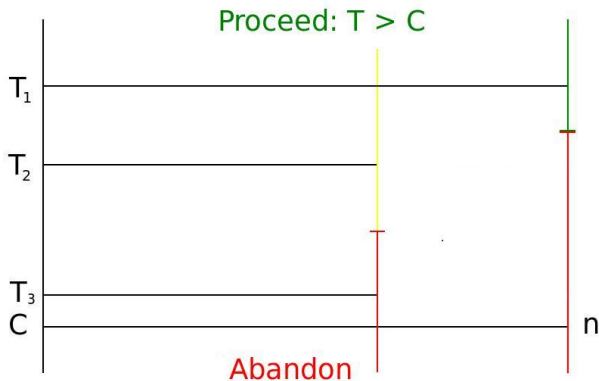
One-stage design



One-stage design with futility



Two-stage design



Log-odds Ratio

$$\theta_{jk} = \log \left(\frac{Q_{jk}(1 - Q_{0k})}{Q_{0k}(1 - Q_{jk})} \right) \quad j = 1, 2, 3; k = 1, \dots, (a - 1)$$

where $Q_{jk} = p_{j1} + \dots + p_{jk}$; probability of category C_k or better

- $\theta_{jk} < 0$ indicates disadvantage
- $\theta_{jk} = 0$ indicates equivalence
- $\theta_{jk} > 0$ indicates advantage

Assumptions

- proportional odds assumption
odds ratio for being in a chosen category or higher compared to being in a lower category is the same regardless of which category is chosen
- δ is a worthwhile treatment effect on log-odds scale
- δ_0 is a treatment effect that is negligible
- sample sizes are equal in each treatment arm

Hypotheses

$$H_0 : \theta_1 = \theta_2 = \theta_3 = 0$$

$$H_a : \text{at least one } \theta_j > 0$$

- Test is based on pairwise efficient score statistic (pairwise Mann-Whitney tests)
- Satisfy
 $P(\text{take any treatment to phase III} | \theta_1 = \theta_2 = \theta_3 = 0) = \alpha$
- Key requirement: Covariance between two score statistics

Error control

$$\alpha = P(\text{take any treatment to Phase III} | \theta_1 = \theta_2 = \theta_3 = 0)$$

$$1 - \beta = P(\text{take treatment } T_1 \text{ to Phase III} | \theta_1 = \delta, \theta_2 = \theta_3 = \delta_0)$$

Two-stage design

Find n and k , such that

$$1 - \alpha = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \left(\Phi \left(u + k\sqrt{2r} - s\sqrt{2(r-1)} \right) \right)^3 \phi(u)\phi(s) du ds$$

$$1 - \beta = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \left(\Phi \left(w + \frac{\sqrt{n_1}(\delta - \delta_0)}{\sigma} \right) \right)^2 \phi(w)\phi(u)\Phi(G(w, u)) dw du$$

where $G(w, u) = w - k\sqrt{2r} + u\sqrt{2(r-1)} + r\sqrt{n_1}\delta/\sigma$

A stroke example

- Therapy in acute ischemic stroke
- Four treatment arms: placebo T_0 , low T_1 , medium T_2 and high T_3 doses + standard care
- Barthel score 90 days after therapy

Ordered categorical outcome

22-point extended Barthel score

-5	0	...	100
death	vegetative state	...	complete recovery

Preliminary data

Category	C1	C2	C3	C4	C5	C6
Outcome	100	70 – 95	40 – 65	5 – 35	0	death
Probability	0.075	0.182	0.319	0.243	0.015	0.166

- $\delta = 1.1$... doubling the percent of patients in C2 or better

Sample Sizes

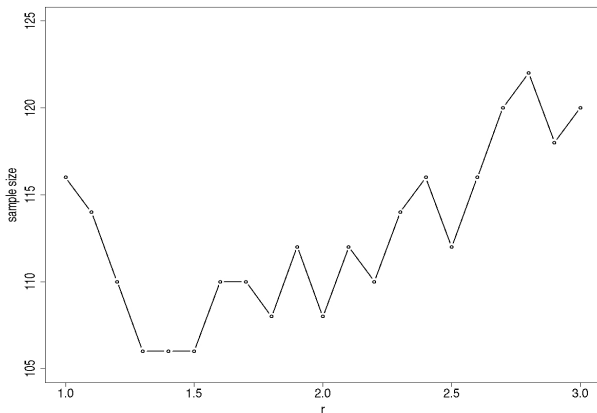
Table 1: Sample sizes for different designs with $(\delta, \delta_0) = (1.1, 0.275)$.

		$1 - \beta$	0.8			0.9		
		Design	n_1	n_2	n	n_1	n_2	n
α	0.200	1-stage	29	–	116	40	–	160
		optimal 2-stage	19	15	106	34	9	154
		2:1 2-stage	18	18	108	27	27	162
	0.100	1-stage	37	–	148	50	–	200
		optimal 2-stage	21	21	126	36	18	180
		2:1 2-stage	21	21	126	30	30	180
	0.050	1-stage	46	–	184	60	–	240
		optimal 2-stage	21	32	148	31	39	202
		2:1 2-stage	25	25	150	34	34	204
	0.025	1-stage	55	–	220	70	–	280
		optimal 2-stage	24	36	168	32	48	224
		2:1 2-stage	29	29	174	38	38	228

Optimal 2-stage design

Figure 1: Sample sizes for different allocations between stages.

$\alpha = \beta = 0.2$, $\delta = 1.1$, $\delta_0 = 0.275$.



Simulation Results

Table 2: Simulated type I error and power for different designs based on 10,000 replicate simulations.

		(θ, θ_0)	$(0,0)$		$(1.1, 0.275)$	
			target $1 - \beta$			
		Design	0.80	0.90	0.80	0.90
target α	0.200	1-stage	0.2023	0.1959	0.7968	0.8936
		1-stage*	0.2042	0.2084	0.7955	0.8945
		2-stage	0.2019	0.2008	0.7980	0.8934
		2-stage*	0.2026	0.2080	0.7842	0.8915
	0.025	1-stage	0.0250	0.0264	0.7867	0.8921
		1-stage*	0.0240	0.0256	0.7881	0.8894
		2-stage	0.0276	0.0255	0.7915	0.8963
		2-stage*	0.0251	0.0252	0.7953	0.8904

* stopping for futility allowed

Choice of Design

- Interim analysis
 - stopping for futility
 - sample size re-estimation
- 2-stage design
 - yield smaller sample sizes
- 1-stage design
 - allow for selection of k^{th} best treatment

Future Work

- Allow for covariate adjustment
- Extend to multiple interim analysis
- Allow for bivariate endpoint

References

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