MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Bayesian Methods for Clinical Trials

Lecture 5: Two- or multi-stage clinical trials

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A simple fixed-sample design

Context:	a phase II trial of a new cancer drug (E)
Subjects:	patients for whom other treatments have failed
Endpoint:	response to treatment, which is shrinkage or disappearance of the tumour

A patient will be said to SUCCEED if they respond within some given time period (such as 4 weeks)

$p = P(SUCCEED)$ for a patient on the experimental therapy

$p_0 = P(SUCCEED)$ for a patient on standard therapy

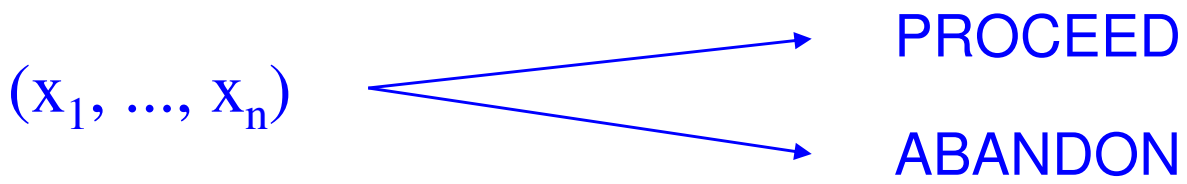
p_1 is a success rate that would be considered "promising"

n patients will be treated in the trial: all will receive E

$x_h = 1$ if the hth patient succeeds, and = 0 otherwise, $h = 1, \ldots, n$

$S = x_1 + \cdots + x_n$ is the total number of successes

We need a rule:



such that

$$P(PROCEED|p = p_0) \leq \alpha \quad \text{and}$$
$$P(PROCEED|p = p_1) \geq 1 - \beta$$

Clearly, the rule should be based on S alone (it is a sufficient statistic):

$$S \geq u \longrightarrow \text{PROCEED}$$

$$S < u \longrightarrow \text{ABANDON}$$

The trial can be expressed as a test of

$$H_0 : p = p_0 \text{ versus } H_1 : p = p_1$$

with rejection of H_0 ($\Rightarrow$ PROCEED) if the one-sided p-value is $\leq \alpha$, and with power $\geq 1 - \beta$.

Sample size for a fixed sample design

Assume that all patients succeed independently, with probability p

Then $S \sim B(n, p)$ and

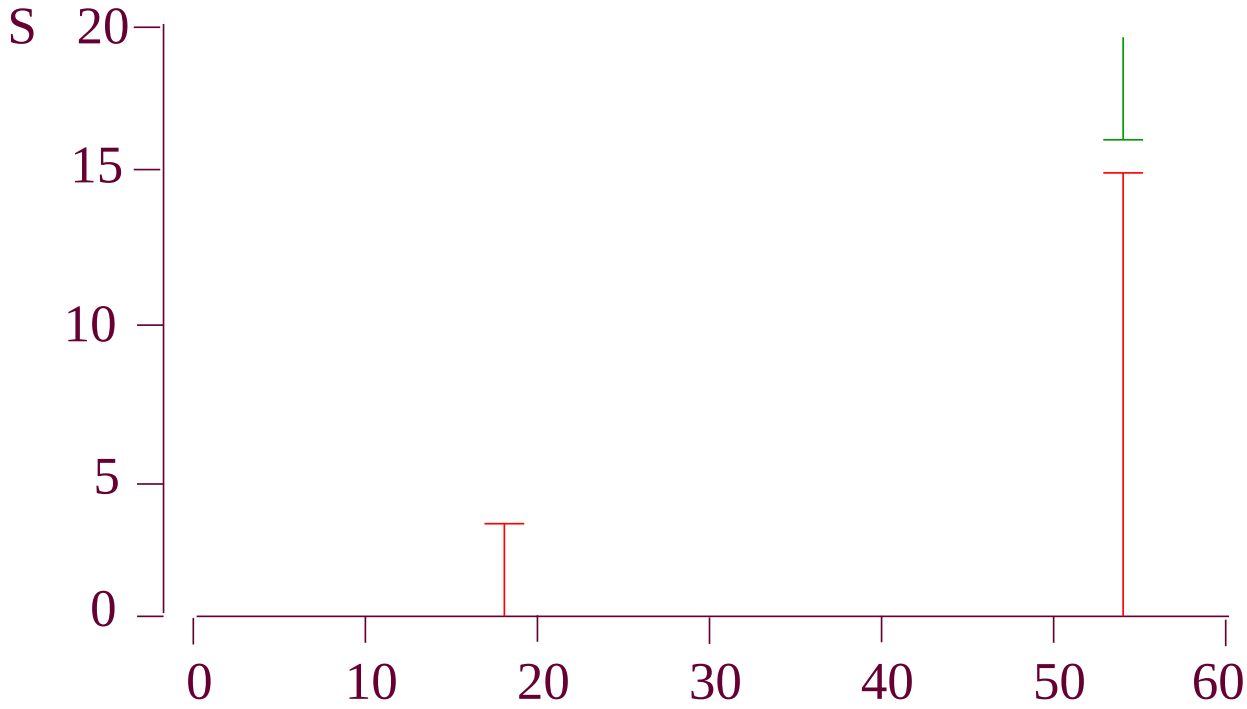
$$P(PROCEED; p) = P(S \geq u; p) = \sum_{h=1}^{n} \binom{n}{h} p^h (1-p)^{n-h}$$

Find values of n and u such that

$$P(PROCEED; p_0) \leq \alpha \text{ and } P(PROCEED; p_1) \geq 1 - \beta$$

and take the pair with the smallest n

Simon's two-stage design Simon (1989)



After n_i observations

PROCEED if $S_2 \geq u$
ABANDON if $S_i \leq \ell_i$, with $\ell_2 = u - 1$
take $(n_2 - n_1)$ more observations if $S_1 \geq \ell_1$.

Simon's frequentist two-stage design

Choose n_1, n_2, ℓ_1 and ℓ_2 to minimise $\mathbb{E}(n^\star; p_0)$, where $n^\star$ is the (random) sample size on termination.

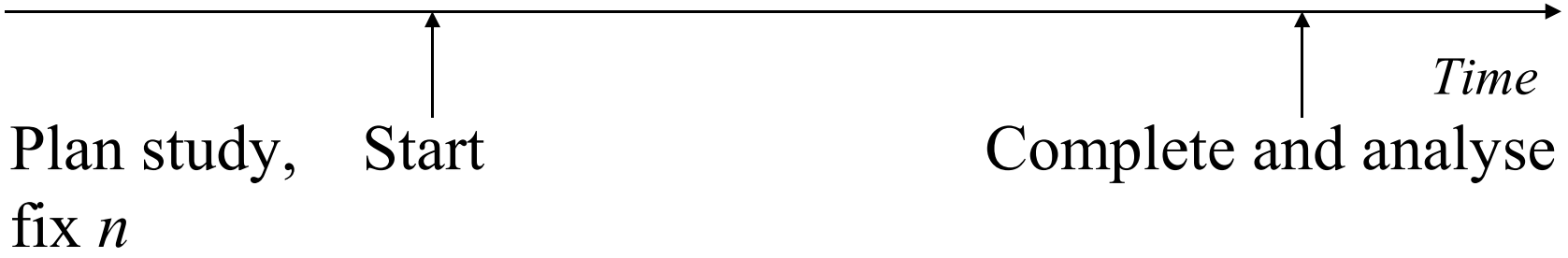
Simon's design is appropriate when it is more important to discard a bad treatment than to progress a good one

- patients in the trial are to be protected from a bad treatment, but will benefit from a good one

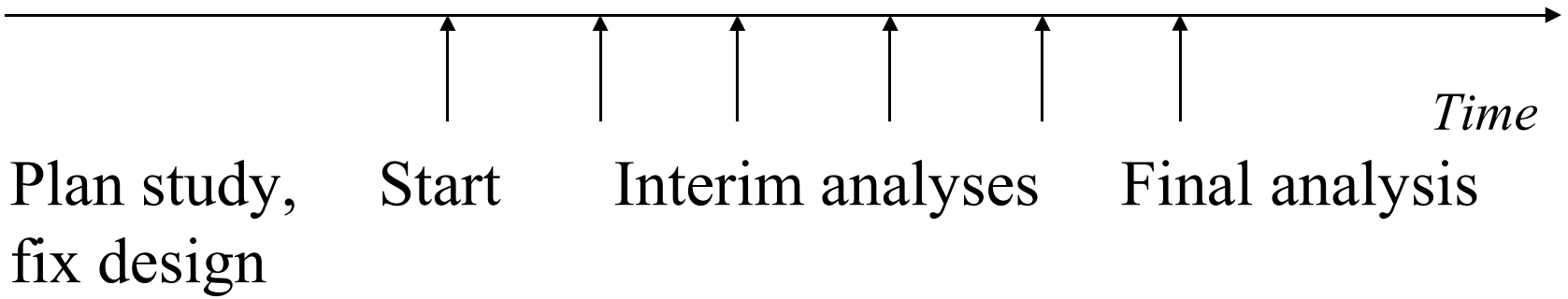
Thus, there is no early stopping to `PROCEED`, and the sample size is to be minimised in the null case of no benefit

Introduction: Sequential Designs

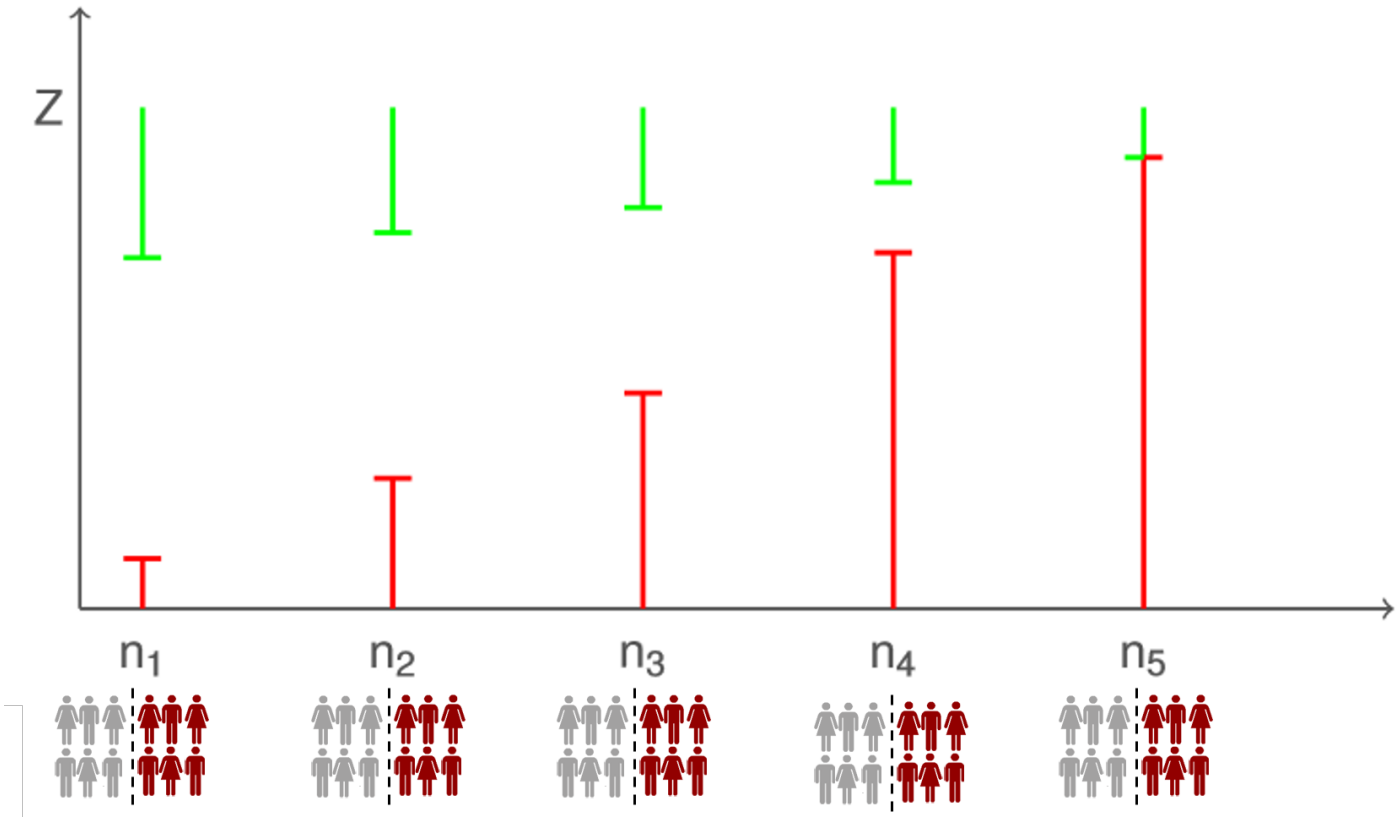
Fixed sample design:



Adaptive Design:



Group-Sequential Trial:



- “Proceed” = Move to next phase of drug development
- Each interim aims to answer if E $>$ C
- Reasons: ethical; administrative; economic

General Setting

Setting: For Phase II or Phase III, randomized controlled trial

- **Two Treatment arms:** Experimental (**E**) and Control (**C**)
- **Equal allocation:** $n_E = n_C = \frac{n}{2}$
- **Advantage measurement** of E over C: θ
- **Objective:** Whether or not to `PROCEED` to next phase, such as
  - from Phase II to Phase III
  - from Phase III to registration

For Normal responses

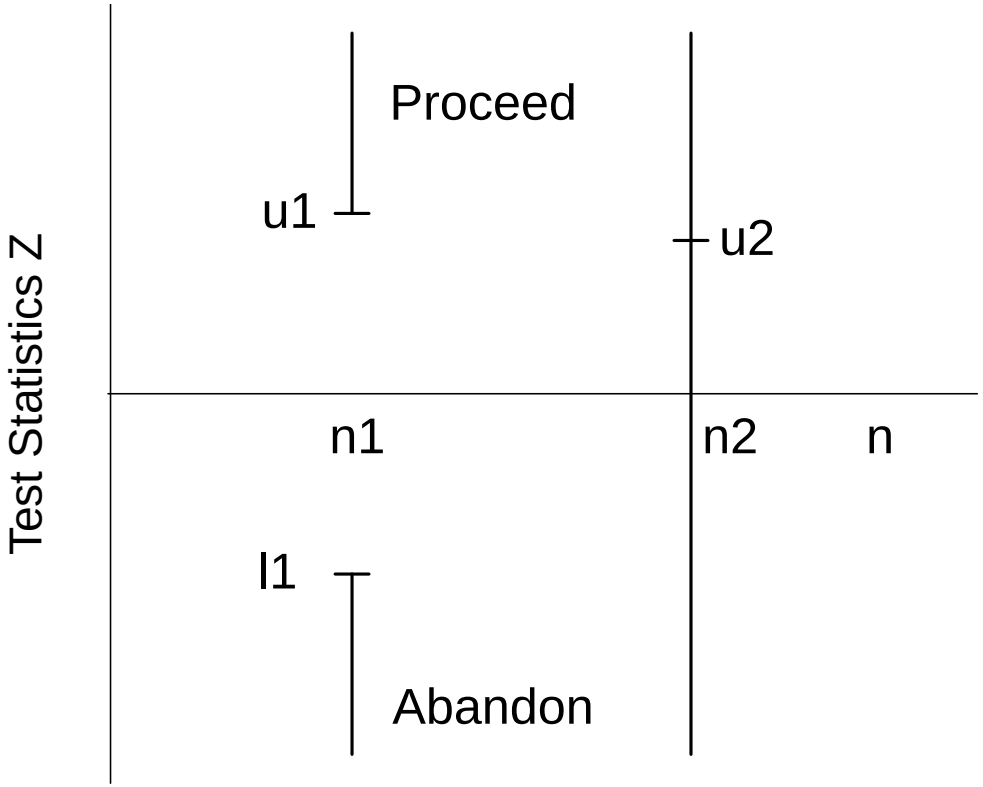
- $X_{jk} \sim N(\mu_j, \sigma^2)$ where $j = E$ or C, $k = 1 \ldots n/2$, known σ^2
- $\theta = \mu_E - \mu_C$
- $Z = \frac{\sqrt{n}}{2\sigma}(\bar{X}_E - \bar{X}_C)$;
- $Z \sim N(\frac{\theta\sqrt{n}}{2\sigma}, 1)$
- PROCEED if $Z \geq c$

General Setting: Two Requirements

$$\begin{aligned} \mathbb{P}\{\texttt{PROCEED}|\theta = 0\} &= \alpha \\ \mathbb{P}\{\texttt{PROCEED}|\theta = \theta_R\} &\geq 1 - \beta \end{aligned}$$

- $\texttt{PROCEED} \equiv$ Reject $H_0 : \theta = 0$ of no treatment advantage in favour of alternative $H_A : \theta > 0$
- θ_R: Treatment advantage worthwhile for development
- Set a small α: Type I error rate
- Set a big $1 - \beta$: Power

Two-Stage Design



- Two looks (one interim). Each look calculate Z_i.
- Stop at first interim if $Z_1 \notin (l_1, u_1)$
- $\mathbb{P}(\texttt{PROCEED}) = \mathbb{P}(Z_1 \geq u_1 \cup \{Z_1 \in (l_1, u_1) \cap Z_2 \geq u_2\})$
  $= \mathbb{P}(Z_1 \geq u_1) + \mathbb{P}(Z_1 \geq l_1 \cap Z_2 \geq u_2\} - \mathbb{P}\{Z_1 \geq u_1 \cap Z_2 \geq u_2)$

Specifying a Two-Stage Design

Five unknowns: $n_1,\ n_2,\ l_1,\ u_1,\ u_2$

Two equations

- $\mathbb{P}\{\texttt{PROCEED}|\,\theta = 0\} = \alpha = \Phi(-u_1) + \Phi_2(-l_1, -u_2, \rho) + \Phi_2(-u_1, -u_2, \rho)$
- $\mathbb{P}\{\texttt{PROCEED}|\,\theta = \theta_R\} = 1 - \beta =$
  $\Phi\left(-u_1 + \theta_R\frac{\sqrt{n_1}}{2\sigma}\right) + \Phi_2\left(-l_1 + \theta_R\frac{\sqrt{n_1}}{2\sigma}, -u_2 + \theta_R\frac{\sqrt{n_2}}{2\sigma}, \rho\right) +$
  $\Phi_2\left(-u_1 + \theta_R\frac{\sqrt{n_1}}{2\sigma}, -u_2 + \theta_R\frac{\sqrt{n_2}}{2\sigma}, \rho\right)$

So 3 more constraints needed:

$l_1 = au_1;\ u_2 = bu_1;\ n_1 = \nu n_2$, and $a,\ b,\ \nu$ are known constants

Example

Design a two-stage trial with $\alpha = 0.025$, $1 - \beta = 0.9$, $\theta_R = 0.7$

- assume $\sigma^2 = 1$
- Set $l_1 = -u_1$, $u_2 = \sqrt{\frac{n_1}{n_2}} u_1$, $\frac{n_1}{n_2} = 0.6$
- **Solution:** $n_1 = 54$, $n_2 = 90$, $u_1 = 2.572$, $l_1 = -2.572$, $u_2 = 1.9923$

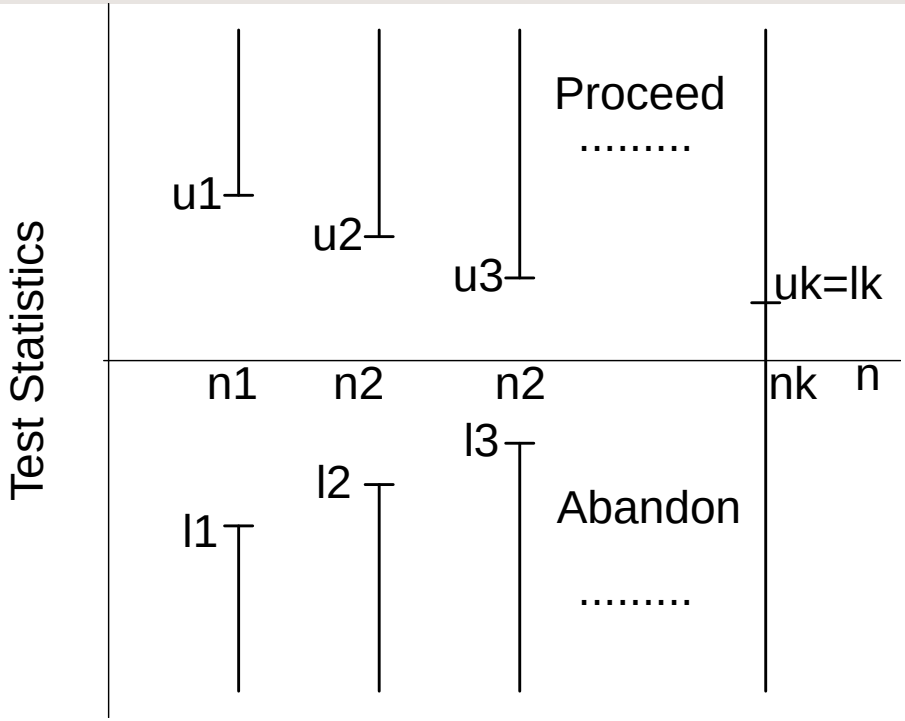
θ	$\mathbb{P}\{Z_1 < l_1\}^{(1)}$	$\mathbb{P}\{Z_1 > u_1\}^{(2)}$	$\mathbb{E}(n)^{(3)}$	$\mathbb{P}\{\texttt{PROCEED}\}$
0.00	0.00506	0.00506	89.6	0.02499
0.35	0.00001	0.09922	86.4	0.37676
0.70	0.00000	0.50000	72.0	0.90991

(1) $\mathbb{P}\{Z_1 < l_1\}$: Prob of `ABANDON` at first stage = $\Phi(l_1 - \theta\sqrt{n_1}/(2\sigma))$

(2) $\mathbb{P}\{Z_1 > u_1\}$: Prob of `PROCEED` at first stage = $1 - \Phi(u_1 - \theta\sqrt{n_1}/(2\sigma))$

(3) Expected sample size: $\mathbb{E}(n) = n_1\delta + n_2(1 - \delta)$
$\delta = \mathbb{P}\{\text{Stop at first stage}\} = \mathbb{P}\{Z_1 < l_1\} + \mathbb{P}\{Z_1 > u_1\}$

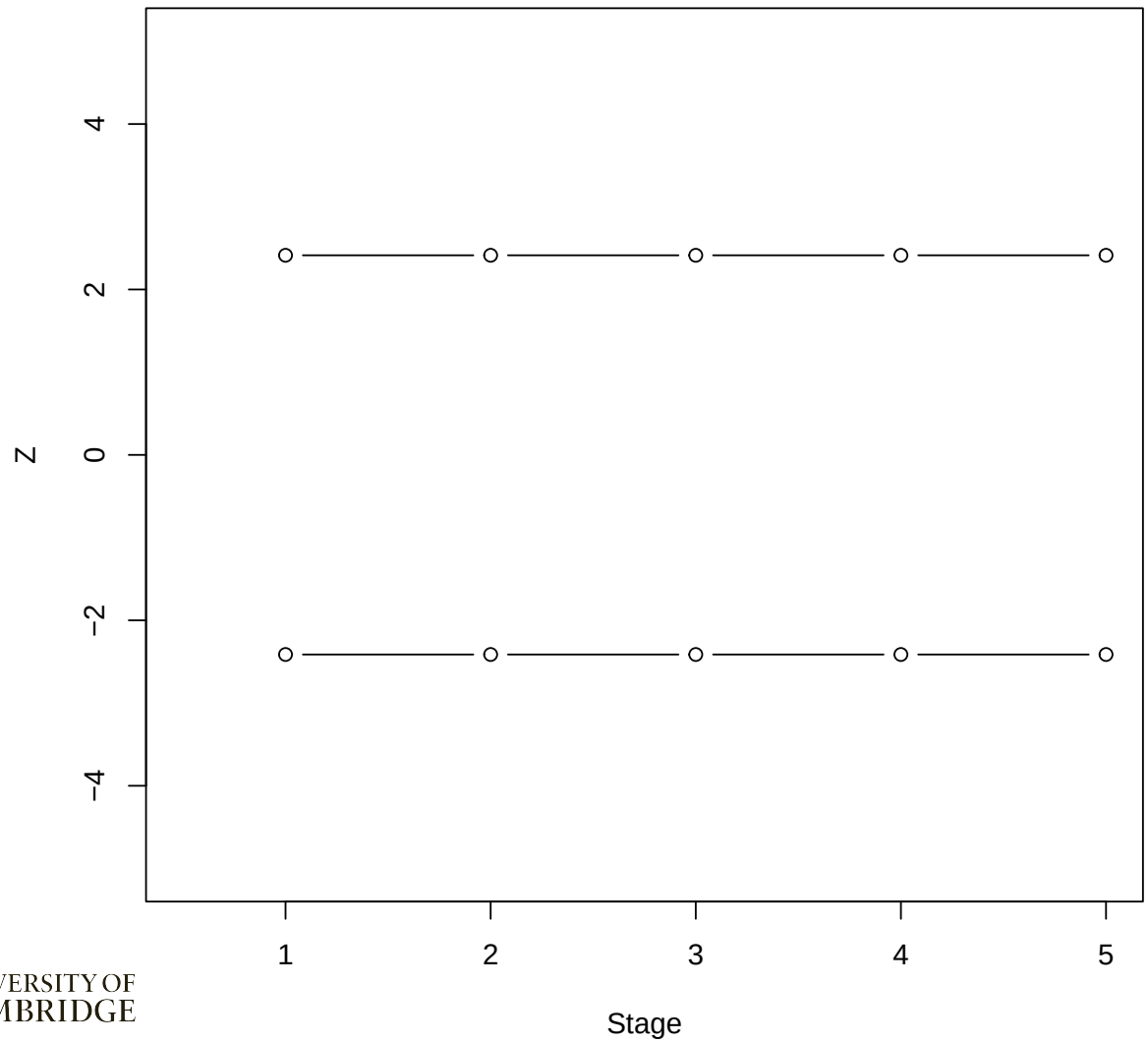
Multi-Stage Design



- Need to find $\mathbf{3k - 1}$ unknowns: $n_i,\ l_i,\ u_i;\ i = 1, \ldots k$
- Still only two equations
- Additional constraints needed
  - Specify $r = \{r_i,\ i = 2, \ldots, k\}$ that $n_i = r_i n_1$
  - Define functions $l_i = l_i(a),\ u_i = u_i(a)$
  - Simplify problem to n_1 and $a \Rightarrow$ two unknowns

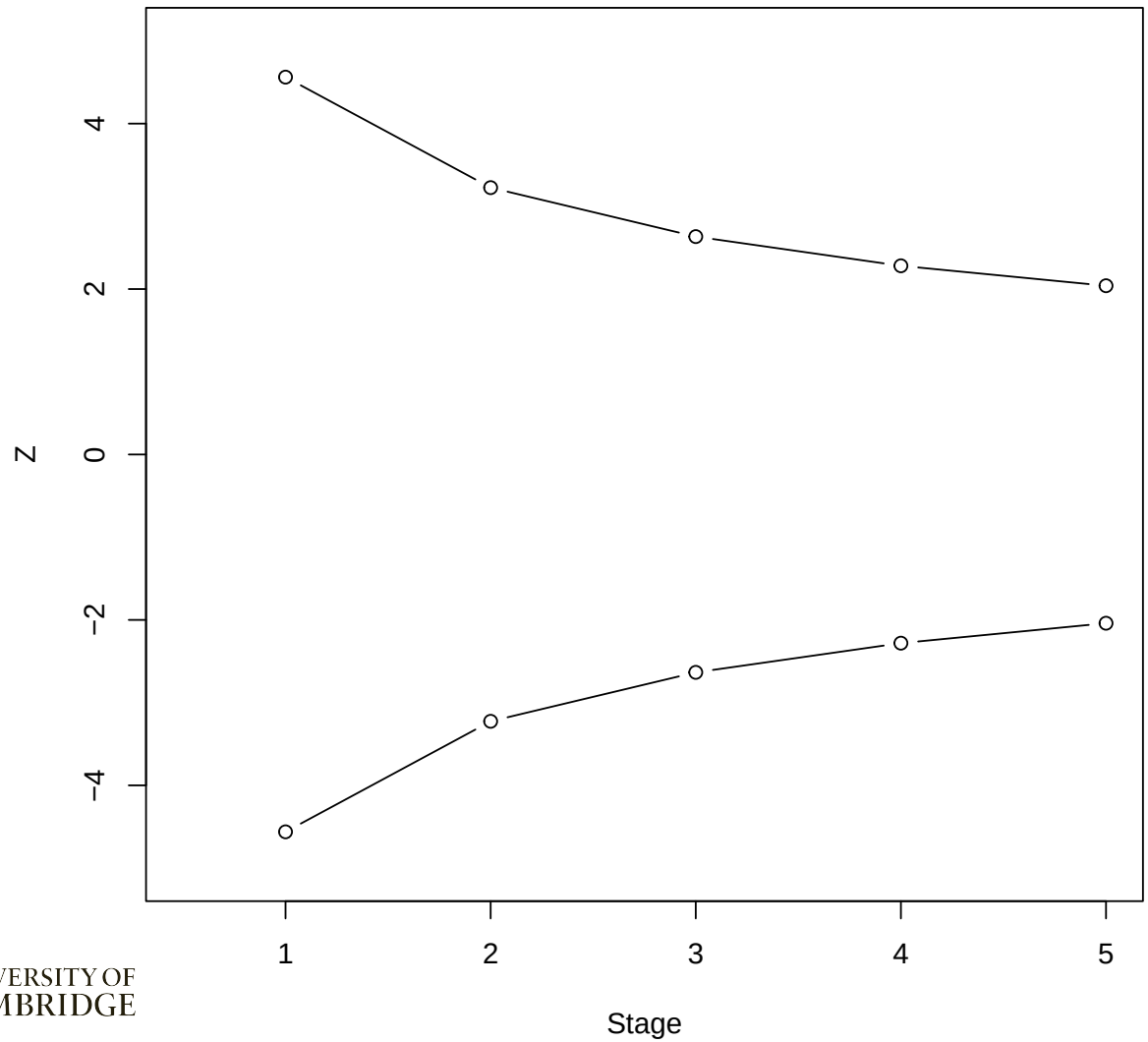
Pocock

- $l_i = -a;$ $\quad u_i = a$



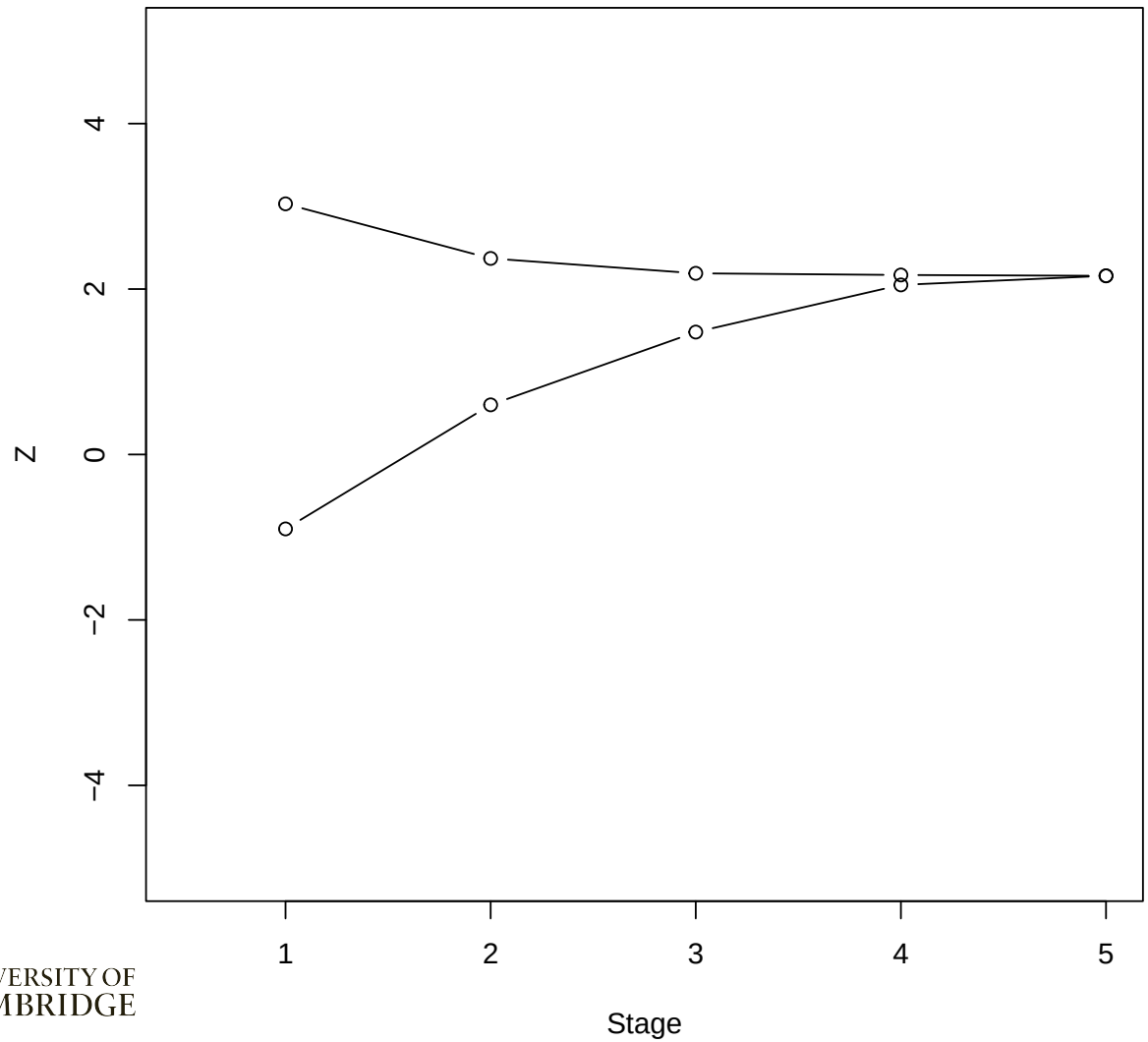
O'Brien & Fleming

- $l_i = -a/\sqrt{r_i}; u_i = a/\sqrt{r_i}$



Triangular Test

- $l_i = -a\{1 - 3(r_i/r_k)\}/\sqrt{r_i}; u_i = a\{1 + (r_i/r_k)\}/\sqrt{r_i}$



Choice of Design

- **Symmetric design:** $-l_i = u_i$
  - Pocock and O'Brien & Fleming:
    $\mathbb{P}\{\text{E worse then C} \mid -\theta_R\} = 1 - \beta$
  - Use when important to prove either harm or establish benefit
  - Compare two existing treatments
  - Fixed sample size designs are symmetric
- **Asymmetric designs:** $-l_i \neq u_i$
  - Triangular:
    $\mathbb{P}\{\text{E worse than C} \mid -\theta_R\} \neq 1 - \beta$
  - Not important to prove harm, lack of benefit will lead to abandon E
  - Compare a new/expensive/hazardous treatment with placebo/standard

Example

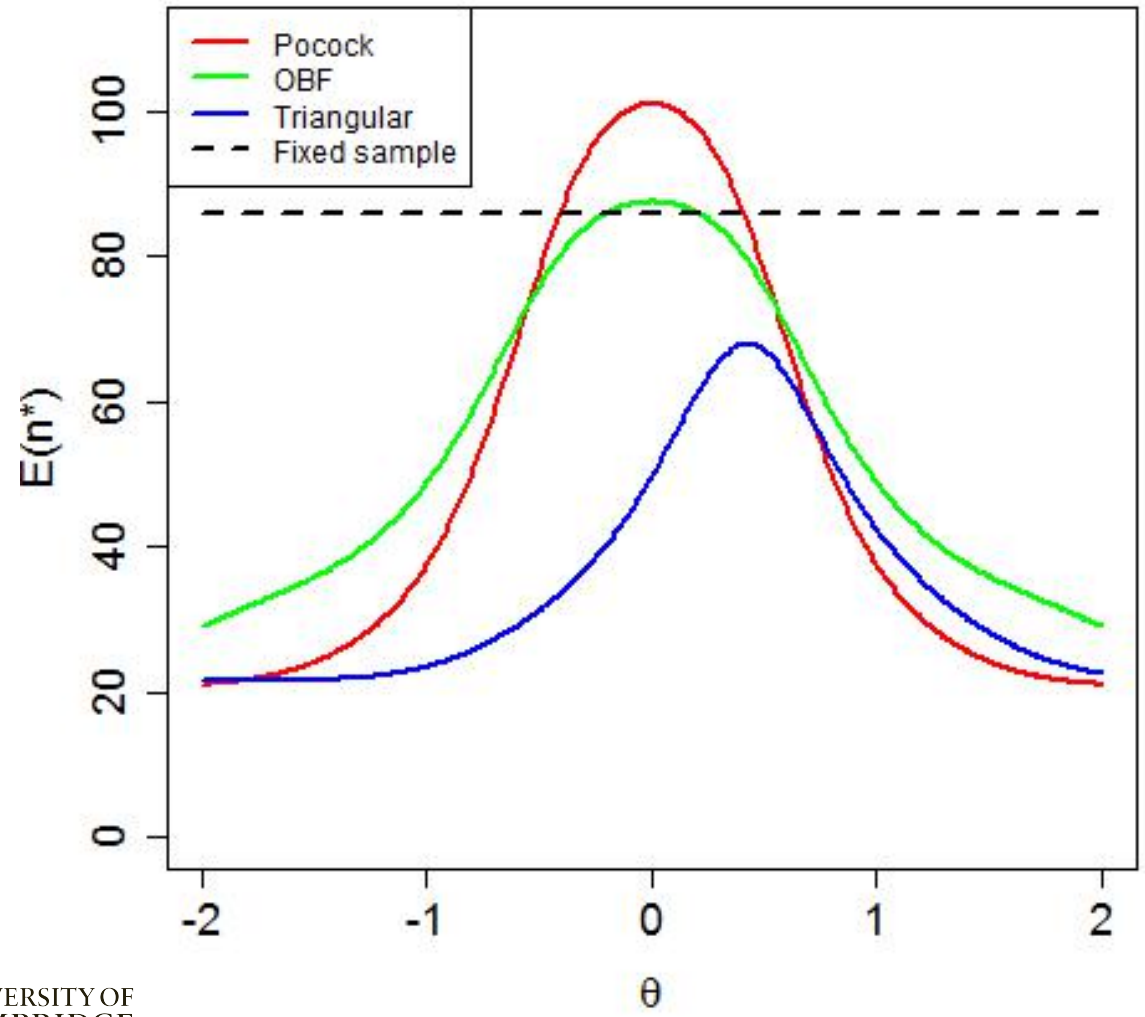
Design 5-stage trial with $\alpha = 0.025$, $1 - \beta = 0.9$, $\theta_R = 0.7$, $\sigma^2 = 1$. Assume equally spaced interim analyses and 1:1 allocation between treatments.

Design	a	n_1	n_5
Pocock	2.413	20.7	103.5
O'Brien & Fleming	4.4	17.6	88.0
Triangular	2.16	21.5	107.6

Fixed sample test requires a total of 85.8 patients.

Example (continued)

Expected sample size curves for our five-stage designs:



References

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