# Interim Monitoring of

# Clinical Trials

Christopher Jennison,

Dept of Mathematical Sciences,

University of Bath, UK

http://www.bath.ac.uk/∼mascj

Magdeburg,

16 October 2003

# Plan of talk

1. Why sequential monitoring?
2. 1929, Dodge & Romig: 2-stage sampling
3. 1940s: methods for manufacturing
4. 1950s and 60s: methods for medical studies
5. 1963, Anscombe, Colton: should we be testing hypotheses anyway?
6. 1970s: group sequential tests
7. Types of test, including equivalence
8. Types of stopping rule
9. Sequential theory, including survival data
10. A unified approach for group sequential design and analysis
11. Nuisance parameters: updating a design
12. Survival data example
13. Error spending
14. Response-dependent treatment allocation

# 1. Motivation of interim monitoring

In clinical trials, animal trials and epidemiological studies there are reasons of

*ethics*

*administration* (accrual, compliance, . . . )

*economics*

to monitor progress and accumulating data.

Subjects should not be exposed to unsafe, ineffective or inferior treatments. National and international guidelines call for interim analyses to be performed — and reported.

It is now standard practice for medical studies to have a Data and Safety Monitoring Board to oversee the study and consider the option of early termination.

## The need for special methods

There is a danger that multiple looks at data can lead to over-interpretation of interim results

*Overall Type I error rate applying repeated significance tests at* $\alpha = 5\%$ *to accumulating data*

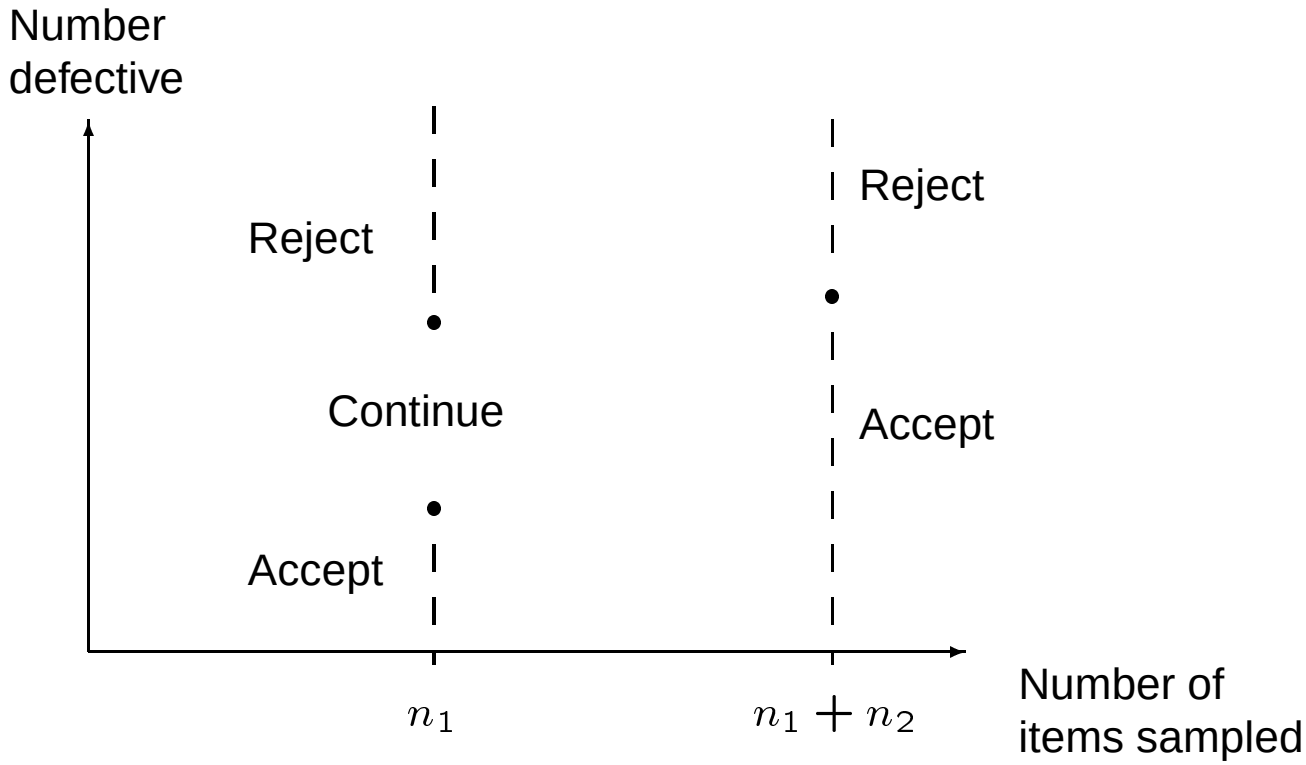
| Number of tests | Error rate |
|---|---|
| 1 | 0.05 |
| 2 | 0.08 |
| 3 | 0.11 |
| 5 | 0.14 |
| 10 | 0.19 |
| 20 | 0.25 |
| 100 | 0.37 |
| $\infty$ | 1.00 |

Pocock (1983) *Clinical Trials* Table 10.1,
Armitage, *et al.* (1969), Table 2.

# 2. Acceptance sampling

Dodge & Romig (1929), *Bell Systems Technical Journal*.

Components are classified as effective or defective. A batch is only accepted if the proportion of defectives in a sample is sufficiently low.

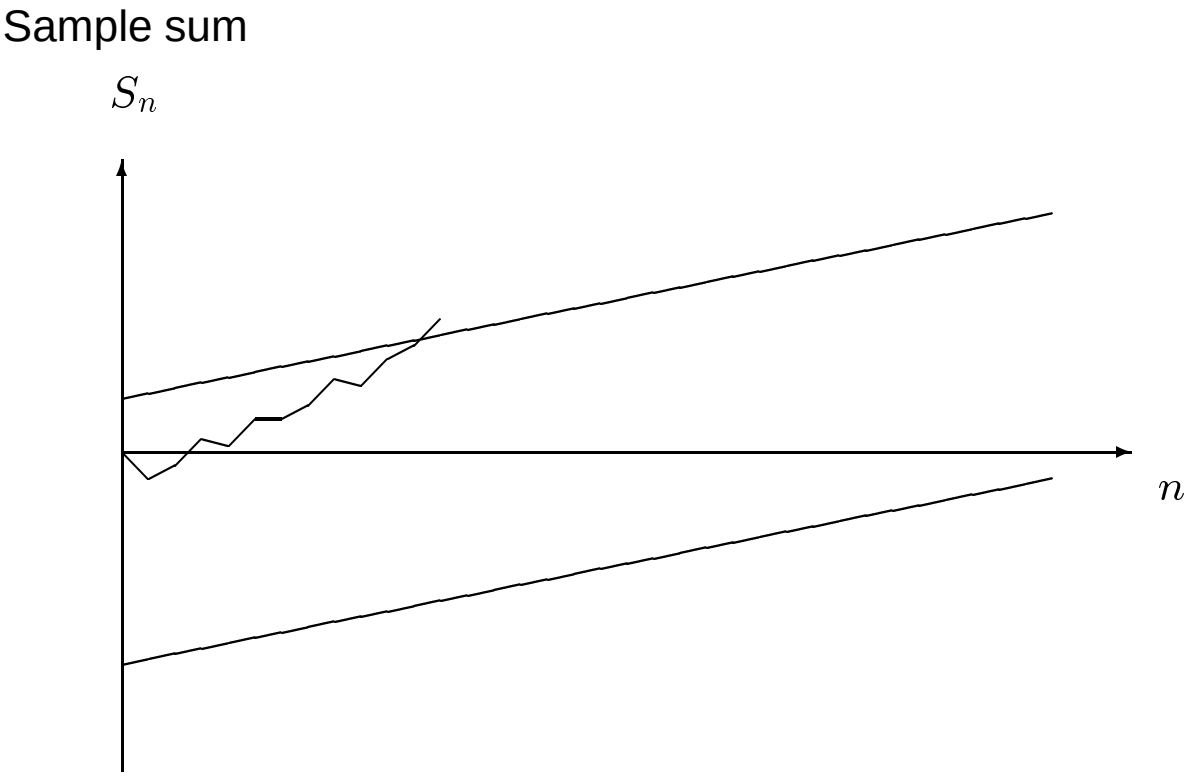


## 3. Manufacturing production

Barnard and Wald developed methods for industrial production and development.

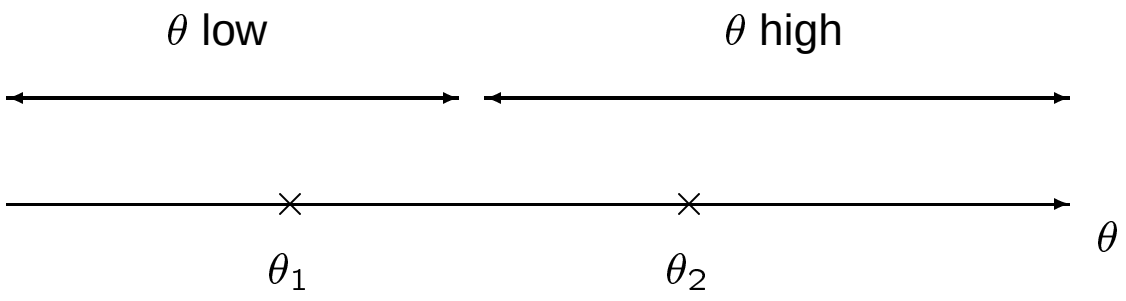
Wald (1947) published his Sequential Probability Ratio Test (SPRT) for testing between two simple hypotheses.

Stopping boundaries and continuation region



# The SPRT

Ostensibly, the SPRT tests between $H_1$: $\theta = \theta_1$ and $H_2$: $\theta = \theta_2$.




In reality, it is usually used to choose between two sets of $\theta$ values.

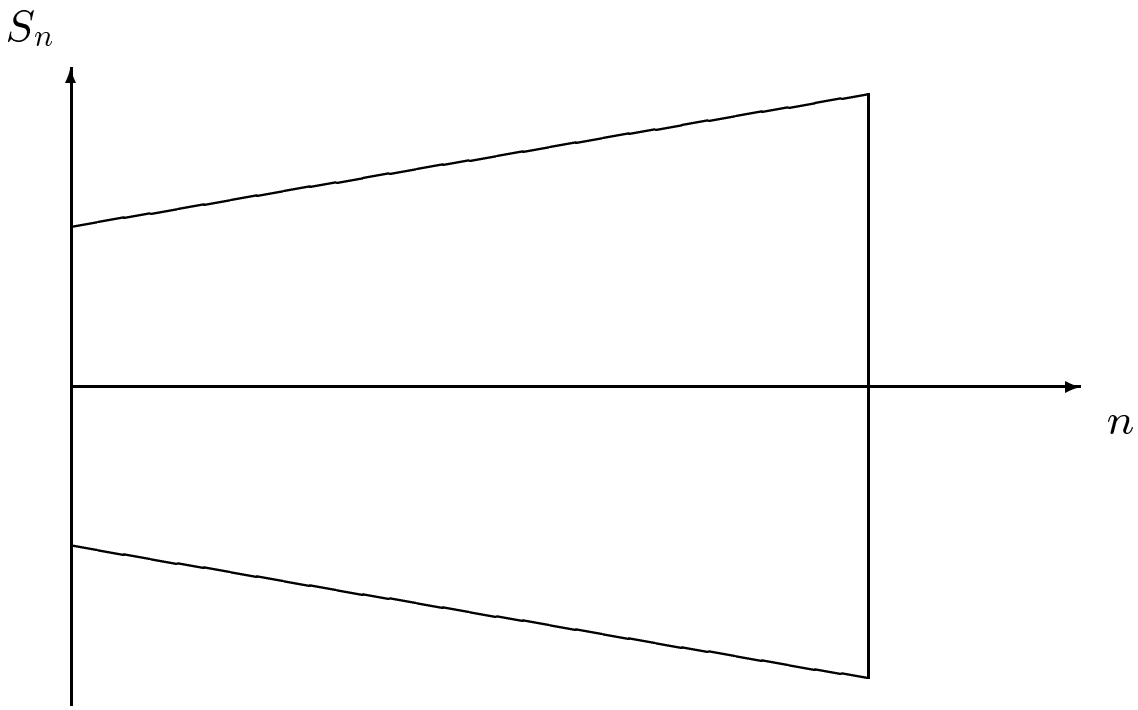
The SPRT has an "optimality" property if only $\theta_1$ and $\theta_2$ need be considered.

However, it assumes *continuous monitoring* of the data and has *no upper bound* on the possible sample size.

# 4. Sequential monitoring of clinical trials

In the 1950s, Armitage and Bross took sequential testing from industrial applications to comparative clinical trials. Their plans were fully sequential but with a bounded maximum sample size.

The “restricted” test, Armitage (1957),

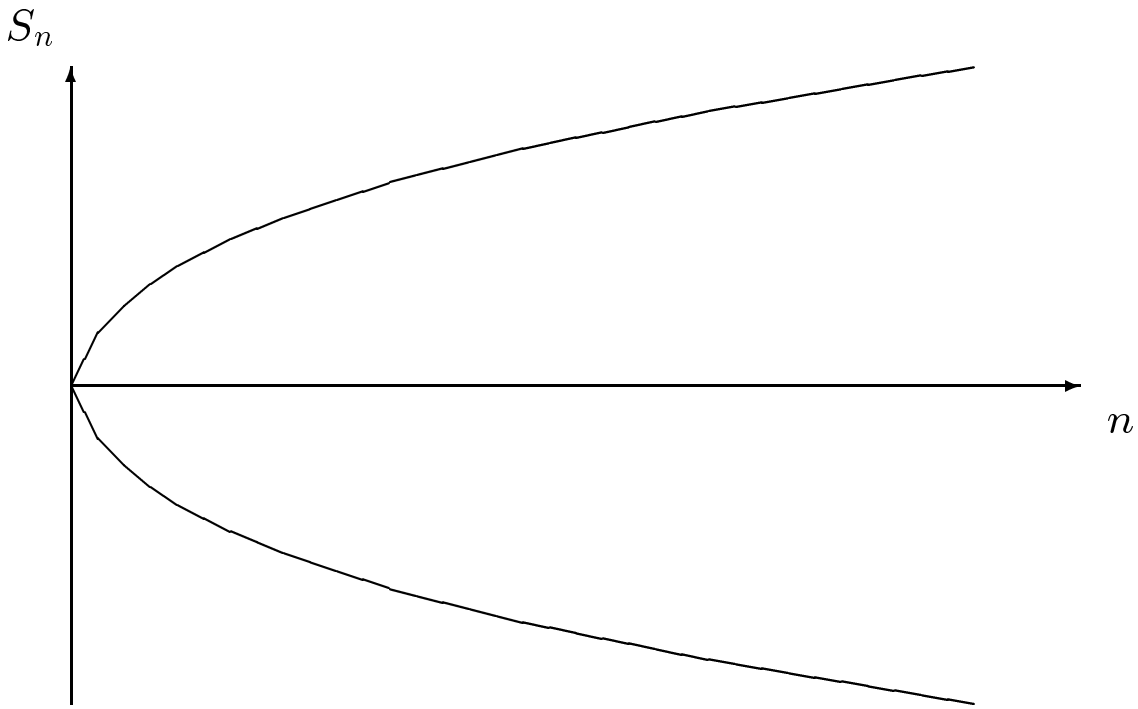



testing $H_0$: $\theta = 0$ against $\theta \neq 0$, where $\theta$ is the treatment difference.

## Armitage's repeated significance test

Armitage, McPherson & Rowe (1969) applied a significance test of $H_0$: $\theta = 0$ after each new pair of observations.

Numerical calculations gave the "nominal" significance level $\alpha'$ to use in each of $N$ repeated significance tests for an overall type I error $\alpha$.



# 5. Horizon problems

In a review of Armitage's book *Sequential Medical Trials*, Anscombe questioned the role of hypothesis testing in medical research, arguing instead for a decision theoretic formulation.

Sampling costs and "loss" for a wrong decision are neatly combined in the "horizon" formulation of Anscombe (1963) and Colton (1963):

> A total of $N$ patients must be treated.
> After an experimental phase, one treatment
> is chosen for all remaining patients.

# 6. Group sequential tests

In practice, one can only analyse a clinical trial on a small number of occasions.

*Shaw (1966):* talked of a “block sequential” analysis.

*Elfring & Schultz (1973):* gave “group sequential” designs to compare two binary responses.

*McPherson (1974):* use of repeated significance tests at a small number of analyses.

*Pocock (1977):* provided clear guidelines for group sequential tests with given type I error and power.

*O’Brien & Fleming (1979):* an alternative to Pocock’s repeated significance tests.

# Pocock's repeated significance test

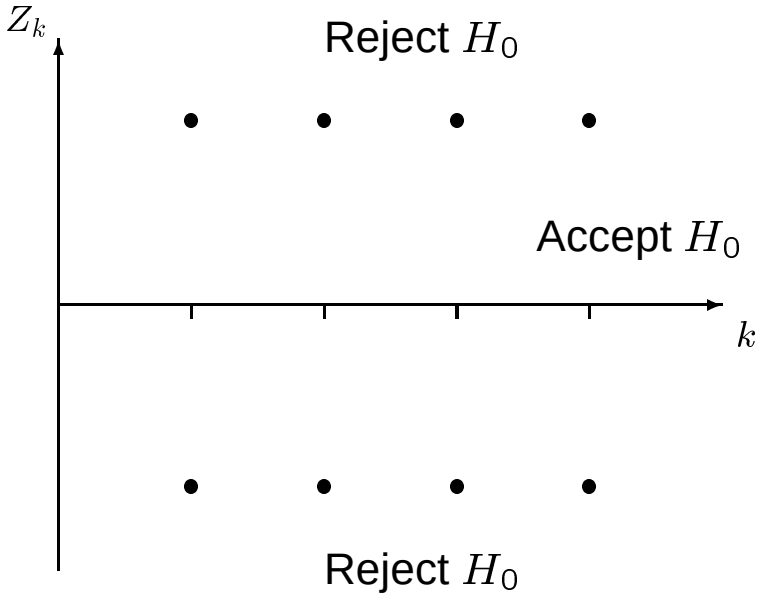
To test $H_0$: $\theta = 0$ against $\theta \neq 0$.

Use standardised test statistics $Z_k$, $k = 1, \ldots, K$.

Stop to reject $H_0$ at analysis $k$ if

$$|Z_k| > c.$$

If $H_0$ has not been rejected by analysis $K$, stop and accept $H_0$.



## 7. Types of hypothesis testing problems

*Two-sided test:*

testing $H_0$: $\theta = 0$ against $\theta \neq 0$.

*One-sided test:*

testing $H_0$: $\theta \leq 0$ against $\theta > 0$.

*Equivalence tests:*

one-sided — to show treatment A is as good (or nearly as good) as treatment B.

two-sided — to show two treatment formulations are equal within an accepted tolerance.

## One-sided tests

If we are only interested in showing that a new treatment is superior to a control, we should test

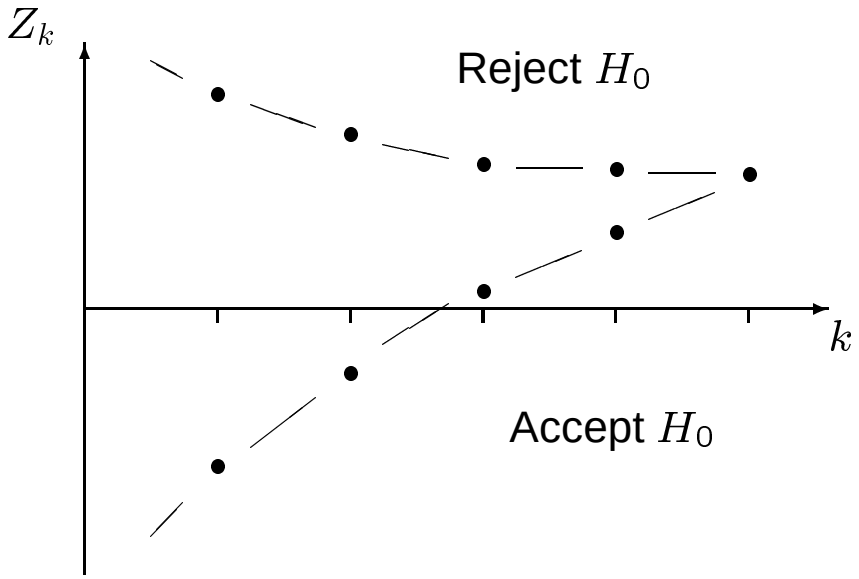
$$H_0\text{: } \theta \leq 0 \quad \text{against} \quad \theta > 0,$$

requiring

$$Pr\{\text{Reject } H_0 \,|\, \theta = 0\} = \alpha,$$

$$Pr\{\text{Reject } H_0 \,|\, \theta = \delta\} = 1 - \beta.$$

A typical boundary is:




E.g., DeMets & Ware (1980), Whitehead (1997).

## Equivalence testing

To show

- treatment A is as good as treatment B, or
- a new formulation of a drug delivers the same bio-chemicals as a standard formulation.

We cannot *prove equality*. So, aim to

- show treatment A is not worse than B by a clinically significant amount $\delta$, or
- show two formulations are equal within an acceptable tolerance.

If we test

$$H_0: \quad \text{treatments are equal},$$

the key issue is the power to reject $H_0$ in specific non-null situations.

## One-sided equivalence testing

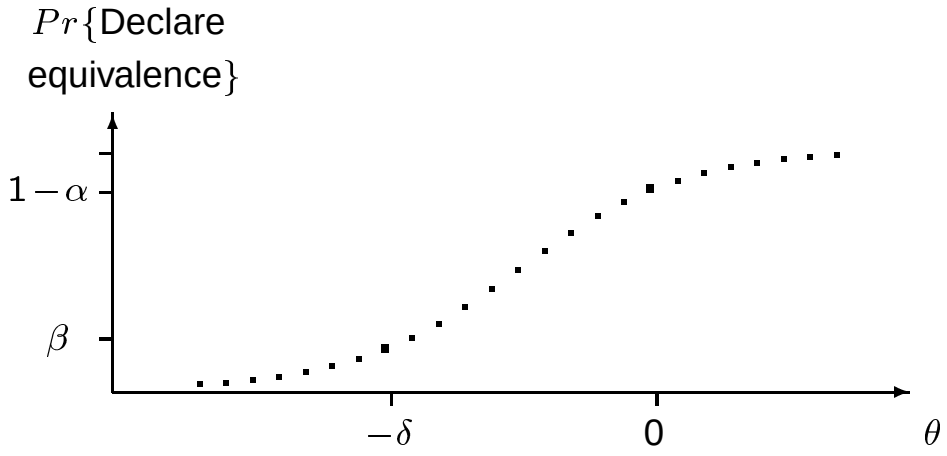
Suppose a new treatment has mean response $\mu_A$, the standard has mean $\mu_B$ and high responses are desirable. We would like to show $\mu_A \geq \mu_B$ — but this is difficult to prove when $\mu_A = \mu_B$.

Let $\theta = \mu_A - \mu_B$. We shall require

$$Pr\{\text{Declare equivalence} \,|\, \theta = -\delta\} \leq \beta.$$

The producer's risk, $\alpha$, is

$$Pr\{\text{Do not declare equivalence} \,|\, \theta = 0\}.$$

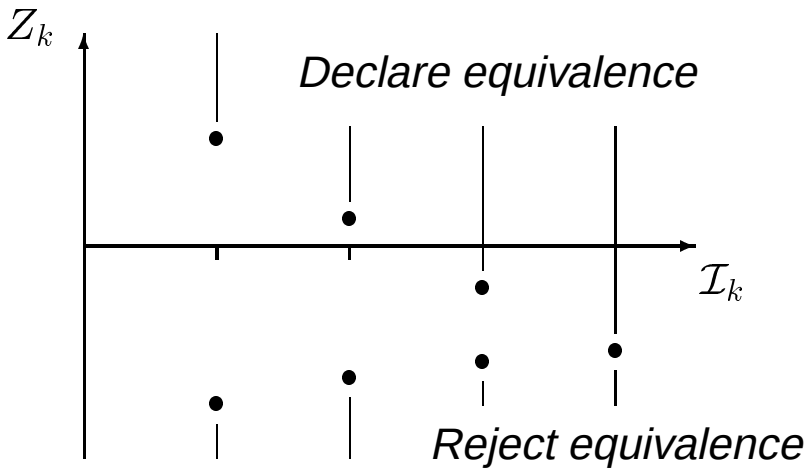


## *One-sided equivalence testing*

Achieve specified error rates by running a test of $H_0$: $\theta \geq 0$ *vs* $\theta < 0$ with

Type I error rate $\alpha$ at $\theta = 0$,

Power $1 - \beta$ at $\theta = -\delta$.




Equate "Accept $H_0$" with "Declare equivalence".

Set $\delta$ and $\beta$ to satisfy the external audience.

In implementing the test, give priority to attaining power $1 - \beta$ at $\theta = -\delta$.

## Two-sided equivalence testing

*Example: Bio-availability (JT, Section 6.3)*

A drug formulation is administered and blood samples drawn over the next 48 hours.


A single summary such as *Peak concentration level* or *Area under the curve* is determined. Suppose formulations A and B are compared in a cross-over design. Let

$$X_i = \ln\left\{\frac{\text{Response on A}}{\text{Response on B}}\right\}, \quad \text{if A given first,}$$

$$Y_i = \ln\left\{\frac{\text{Response on A}}{\text{Response on B}}\right\}, \quad \text{if B given first.}$$

Model

$$X_i \sim N(\theta+\phi, \sigma^2), \quad Y_i \sim N(\theta-\phi, \sigma^2), \quad i = 1, 2, \ldots .$$

Here

$\theta =$ treatment difference,

$\phi =$ period effect.

The two formulations are to be considered equivalent if $|\theta| < \delta$ for a suitably chosen $\delta$.

We require

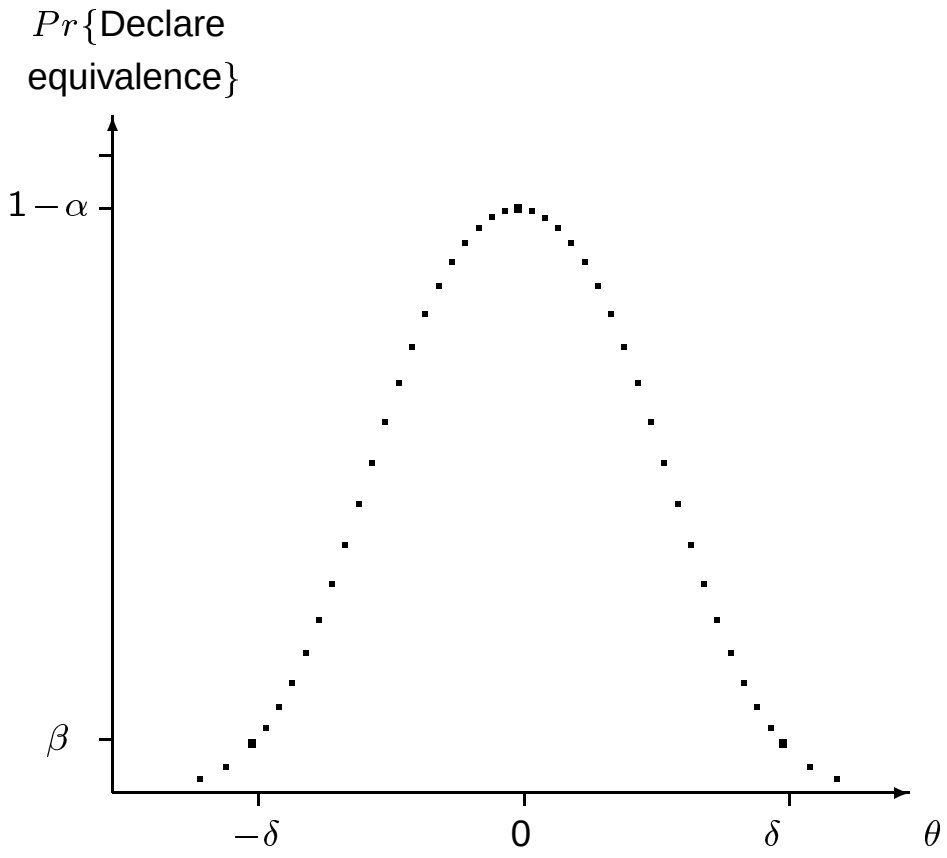
$$Pr\{\text{Declare equivalence} \,|\, \theta = \pm\delta\} \leq \beta,$$

$$Pr\{\text{Do not declare equivalence} \,|\, \theta = 0\} \leq \alpha.$$

A standard choice is $\beta = 0.05$ for $\delta = \ln(1.25)$.

Conduct a test of $H_0$: $\theta = 0$ *vs* $\theta \neq 0$ with type I error rate $\alpha$ and power $1 - \beta$ at $\theta = \pm\delta$.

Declare equivalence if $H_0$ is accepted.

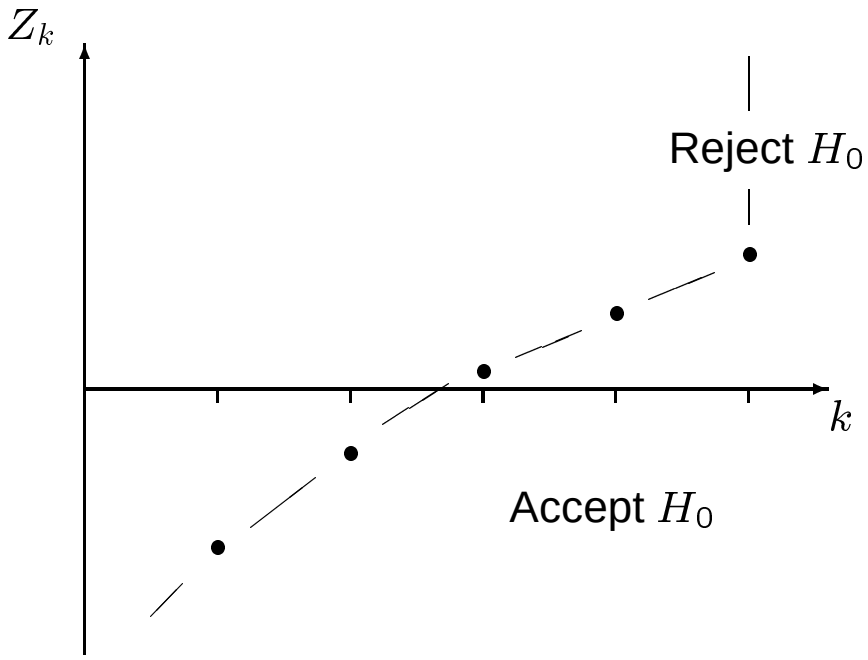



In implementing the test, give priority to attaining power $1 - \beta$ at $\theta = \pm\delta$.

# 8. Types of stopping rule

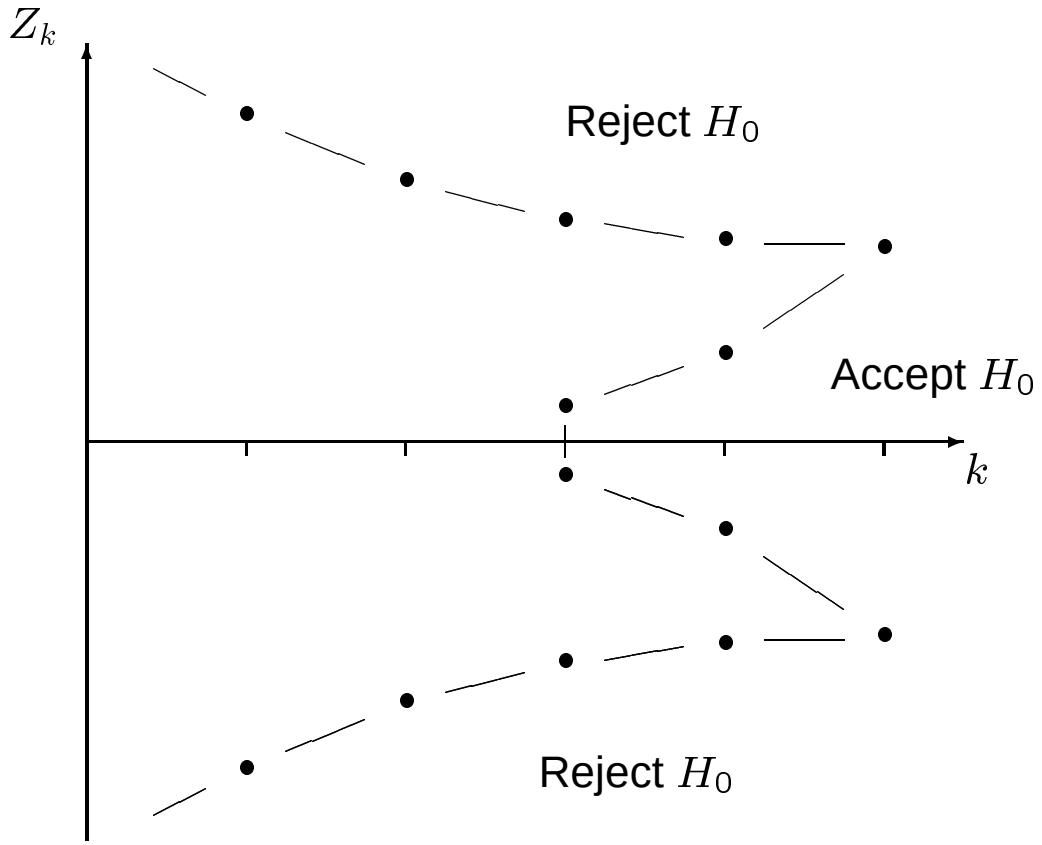
If, in a one-sided test, results on the primary outcome are favourable, it may still be desirable to continue collecting data to check other aspects of the new treatment.

Early stopping “for futility” saves time and effort when a study is unlikely to lead to a positive conclusion.



*When to stop early?*

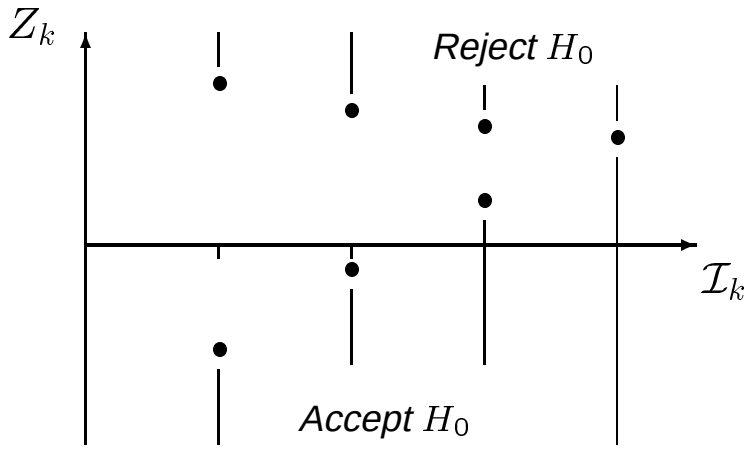
Early stopping in favour of $H_0$ may be included in a two-sided test in order to “abandon a lost cause”.



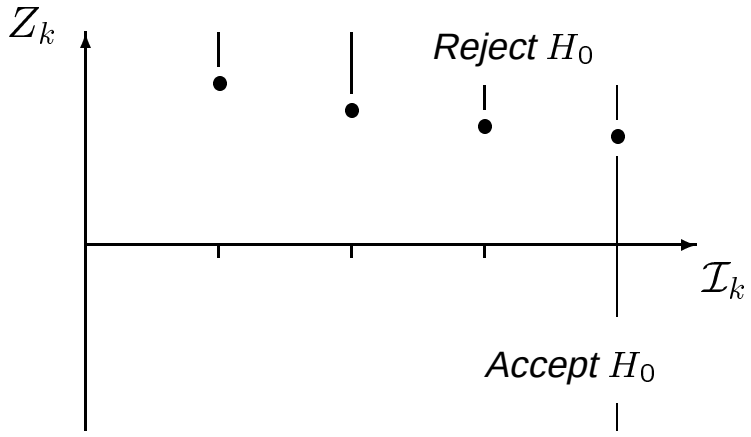

Upper, lower and inner boundaries can be included as investigators deem inappropriate in one-sided and two-sided tests — and also when these are used for equivalence testing problems.

## One-sided tests of $H_0$: $\theta = 0$ vs $\theta > 0$

Early stopping to reject $H_0$ or accept $H_0$

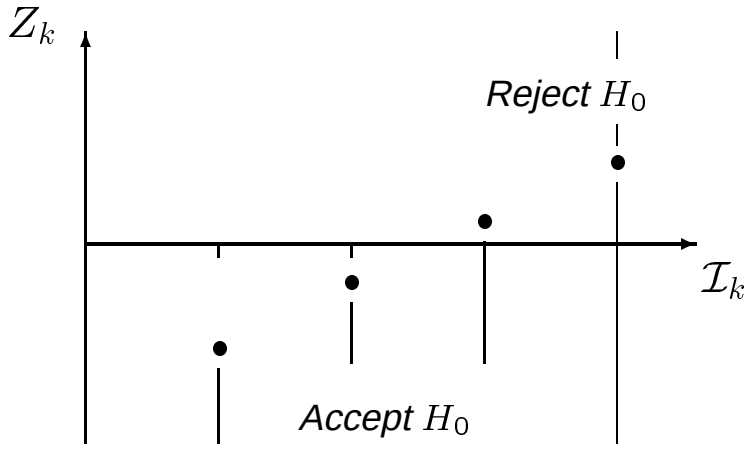



Early stopping only to reject $H_0$



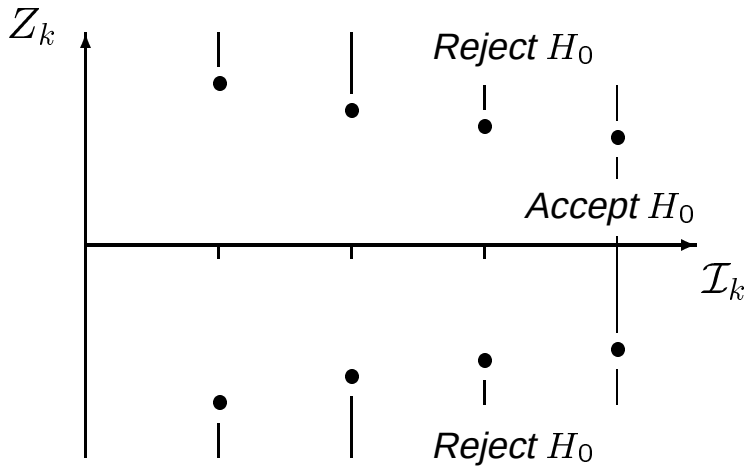

*Abandoning a lost cause:*

Early stopping only to accept $H_0$



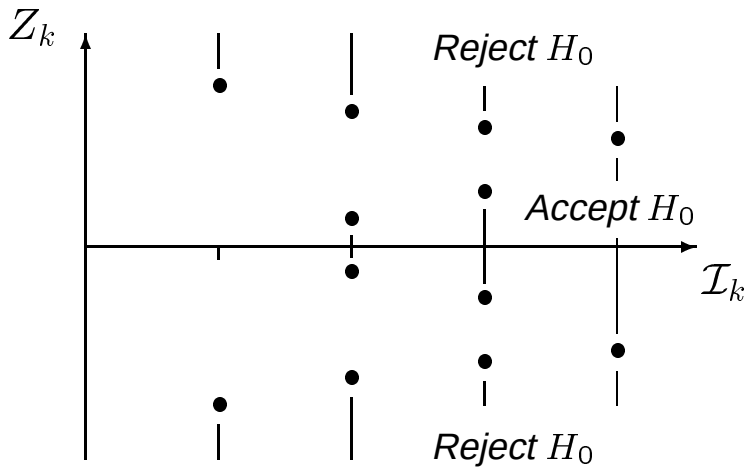
## Two-sided tests of $H_0$: $\theta = 0$ vs $\theta \neq 0$

Early stopping to reject $H_0$



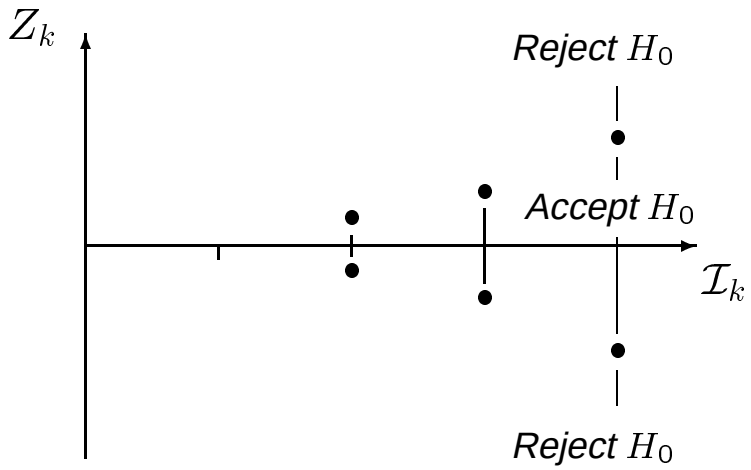

*An inner wedge:*

Early stopping to reject $H_0$ or accept $H_0$




*Abandoning a lost cause:*

Only an inner wedge



# 9. Joint distribution of parameter estimates

Reference: Jennison & Turnbull, Ch. 11

Suppose our main interest is in the parameter $\theta$ and let $\widehat{\theta}_k$ denote the estimate of $\theta$ based on data available at analysis $k$.

The information for $\theta$ at analysis $k$ is

$$\mathcal{I}_k = \{\text{Var}(\widehat{\theta}_k)\}^{-1}, \quad k = 1, \ldots, K.$$

*Canonical joint distribution of* $\widehat{\theta}_1, \ldots, \widehat{\theta}_K$

In many situations, $\widehat{\theta}_1, \ldots, \widehat{\theta}_K$ are approximately multivariate normal,

$$\widehat{\theta}_k \sim N(\theta, \{\mathcal{I}_k\}^{-1}), \quad k = 1, \ldots, K,$$

and

$$\text{Cov}(\widehat{\theta}_{k_1}, \widehat{\theta}_{k_2}) = \text{Var}(\widehat{\theta}_{k_2}) = \{\mathcal{I}_{k_2}\}^{-1} \quad \text{for } k_1 < k_2.$$

The preceding results for the joint distribution of $\widehat{\theta}_1, \ldots, \widehat{\theta}_K$ can be demonstrated directly for:

$\theta$ a single normal mean,

$\theta = \mu_A - \mu_B,$ the effect size in a comparison of two normal means.

The results also apply when $\theta$ is a parameter in:

a general normal linear,

a general model fitted by maximum likelihood (large sample theory).

So, we have the theory necessary for general comparisons, including adjustment for covariates if required.

## Canonical joint distribution of $z$-statistics

In testing $H_0$: $\theta = 0$, the *standardised statistic* at analysis $k$ is

$$Z_k = \frac{\widehat{\theta}_k}{\sqrt{\text{Var}(\widehat{\theta}_k)}} = \widehat{\theta}_k \sqrt{\mathcal{I}_k}.$$

For this,

- $(Z_1, \ldots, Z_K)$ is multivariate normal,
- $Z_k \sim N(\theta\sqrt{\mathcal{I}_k}, 1), \quad k = 1, \ldots, K,$
- $\text{Cov}(Z_{k_1}, Z_{k_2}) = \sqrt{\mathcal{I}_{k_1}/\mathcal{I}_{k_2}}$ for $k_1 < k_2$.

## Canonical joint distribution of score statistics

The *score statistics* $S_k = Z_k\sqrt{\mathcal{I}_k}$, are also multivariate normal with

$$S_k \sim N(\theta\,\mathcal{I}_k,\, \mathcal{I}_k), \quad k = 1, \ldots, K.$$

The score statistics possess the "independent increments" property,

$$\text{Cov}(S_k - S_{k-1},\, S_{k'} - S_{k'-1}) = 0 \quad \text{for } k \neq k'.$$

It can be helpful to know that the score statistics behave as Brownian motion with drift $\theta$ observed at times $\mathcal{I}_1, \ldots, \mathcal{I}_K$.

## Survival data

The canonical joint distributions also arise for

a) the estimates of a parameter in Cox's proportional hazards regression model

b) a sequence of log-rank statistics (score statistics) for comparing two survival curves

— and to $z$-statistics formed from these.

For survival data, observed information is roughly proportional to the number of failures seen.

Special types of group sequential test are needed to handle unpredictable and unevenly spaced information levels: see *error spending tests*.

# 10. Group sequential design and analysis

To have the usual features of a fixed sample study,

- Randomisation, stratification, etc.,
- Adjustment for baseline covariates,
- Appropriate testing formulation,
- Inference on termination,

plus the opportunity for early stopping.

Response distributions:

- Normal, unknown variance
- Binomial
- Cox model or log-rank test for survival data
- Normal linear models
- Generalized linear models

## General approach

Think through a fixed sample version of the study.

Decide on the type of early stopping, number of analyses, and choice of stopping boundary: these will imply increasing the fixed sample size by a certain “inflation factor”.

In interim monitoring, compute the standardised statistic $Z_k$ at each analysis and compare with critical values (calculated specifically in the case of an error spending test).

On termination, one can obtain p-values and confidence intervals possessing the usual frequentist interpretations.

## Example of a two treatment comparison, normal response, 2-sided test

*Cholesterol reduction trial*

Treatment A: new, experimental treatment

Treatment B: current treatment

Primary endpoint: reduction in serum cholesterol level over a four week period

Aim: To test for a treatment difference.

High power should be attained if the mean cholesterol reduction differs between treatments by 0.4 *mmol/l*.

**DESIGN — MONITORING — ANALYSIS**

# DESIGN

## How would we design a fixed-sample study?

Denote responses by

$X_{Ai}$, $i = 1, \ldots, n_A$, on treatment A,

$X_{Bi}$, $i = 1, \ldots, n_B$, on treatment B.

Suppose each

$$X_{Ai} \sim N(\mu_A, \sigma^2) \quad \text{and} \quad X_{Bi} \sim N(\mu_B, \sigma^2).$$

Problem: to test $H_0$: $\mu_A = \mu_B$ with

two-sided type I error probability $\alpha = 0.05$

and power 0.9 at $|\mu_A - \mu_B| = \delta = 0.4$.

We suppose $\sigma^2$ is known to be 0.5.

(Facey, *Controlled Clinical Trials*, 1992)

## Fixed sample design

Standardised test statistic

$$Z = \frac{\bar{X}_A - \bar{X}_B}{\sqrt{\sigma^2/n_A + \sigma^2/n_B}}.$$

Under $H_0$, $Z \sim N(0,1)$ so reject $H_0$ if

$$|Z| > \Phi^{-1}(1-\alpha/2).$$

Let $\mu_A - \mu_B = \theta$. If $n_A = n_B = n$,

$$Z \sim N(\frac{\theta}{\sqrt{2\sigma^2/n}}, 1)$$

so, to attain desired power at $\theta = \delta$, aim for

$$\begin{aligned} n &= \{\Phi^{-1}(1-\alpha/2) + \Phi^{-1}(1-\beta)\}^2 \, 2\sigma^2/\delta^2 \\ &= (1.960 + 1.282)^2 (2 \times 0.5)/0.4^2 = 65.67, \end{aligned}$$

i.e., 66 subjects on each treatment.

## Group sequential design

Specify type of early termination:

*stop early to reject $H_0$*

Number of analyses:

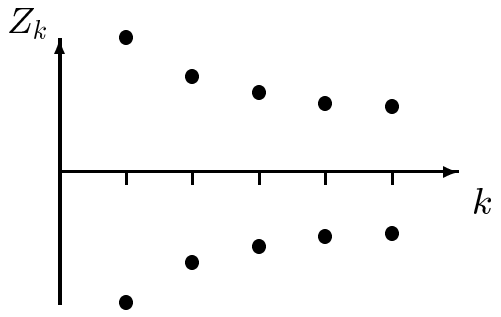
*5 (fewer if we stop early)*

Stopping boundary:

*O'Brien & Fleming*.

Reject $H_0$ at analysis $k$, $k = 1, \ldots, 5$,

if $|Z_k| > c\sqrt{\{5/k\}}$,




where $Z_k$ is the standardised statistic

based on data at analysis $k$.

*Example: cholesterol reduction trial*

**O'Brien & Fleming design**

From tables (JT, Table 2.3) or computer software

$$c = 2.040 \qquad \text{for } \alpha = 0.05$$

so reject $H_0$ at analysis $k$ if

$$|Z_k| > 2.040\sqrt{5/k}.$$

Also, for specified power, inflate the fixed sample size by a factor (JT, Table 2.4)

$$IF = 1.026$$

to get the maximum sample size

$$1.026 \times 65.67 = 68.$$

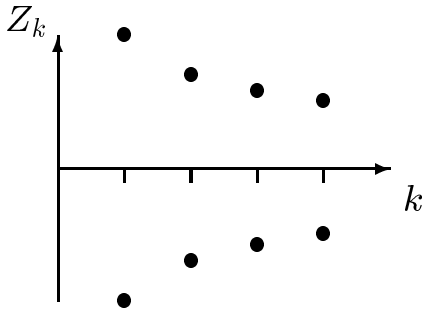
Divide this into 5 groups of 13 or 14 observations per treatment.

## Some designs with $K$ analyses

*O'Brien & Fleming*

Reject $H_0$ at analysis $k$ if

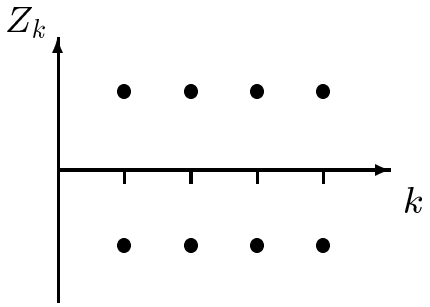
$$|Z_k| > c\sqrt{K/k}.$$




*Pocock*

Reject $H_0$ at analysis $k$ if

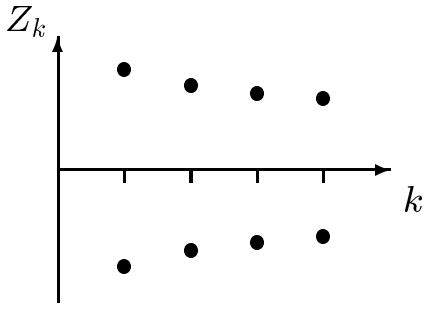
$$|Z_k| > c.$$




*Wang & Tsiatis, shape* $\Delta$

Reject $H_0$ at analysis $k$ if

$$|Z_k| > c\,(k/K)^{\Delta-1/2}.$$




($\Delta = 0$ gives *O'Brien & Fleming*, $\Delta = 0.5$ gives *Pocock*)

## Properties of different designs

Sample sizes are per treatment.

Fixed sample size is 66.

| $K$ | Maximum sample size | Expected sample size $\theta = 0$ | $\theta = 0.2$ | $\theta = 0.4$ |
|---|---|---|---|---|
| *O'Brien & Fleming* | | | | |
| 2 | 67 | 67 | 65 | 56 |
| 5 | 68 | 68 | 64 | 50 |
| 10 | 69 | 68 | 64 | 48 |
| *Wang & Tsiatis,* $\Delta = 0.25$ | | | | |
| 2 | 68 | 67 | 64 | 52 |
| 5 | 71 | 70 | 65 | 47 |
| 10 | 72 | 71 | 64 | 44 |
| *Pocock* | | | | |
| 2 | 73 | 72 | 67 | 51 |
| 5 | 80 | 78 | 70 | 45 |
| 10 | 84 | 82 | 72 | 44 |

## Implementing the OBF test

Divide the total sample size of 68 per treatment into 5 groups of roughly equal size, e.g.,

14 in groups 1 to 3, 13 in groups 4 and 5.

At analysis $k$, define

$$\bar{X}_A^{(k)} = \frac{1}{n_{Ak}} \sum_{i=1}^{n_{Ak}} X_{Ai}, \quad \bar{X}_B^{(k)} = \frac{1}{n_{Bk}} \sum_{i=1}^{n_{Bk}} X_{Bi}$$

and

$$Z_k = \frac{\bar{X}_A^{(k)} - \bar{X}_B^{(k)}}{\sqrt{\sigma^2(1/n_{Ak} + 1/n_{Bk})}}.$$

Stop to reject $H_0$ if

$$|Z_k| > 2.040\sqrt{5/k}, \quad k = 1, \ldots, 5.$$

Accept $H_0$ if $|Z_5| < 2.040$.

*Implementing the 5-analysis OBF test*

The stopping rule gives

type I error rate $\alpha = 0.050$ and

power 0.902 at $\theta = 0.4$

if group sizes are equal to their design values.

Note the minor effects of discrete group sizes.

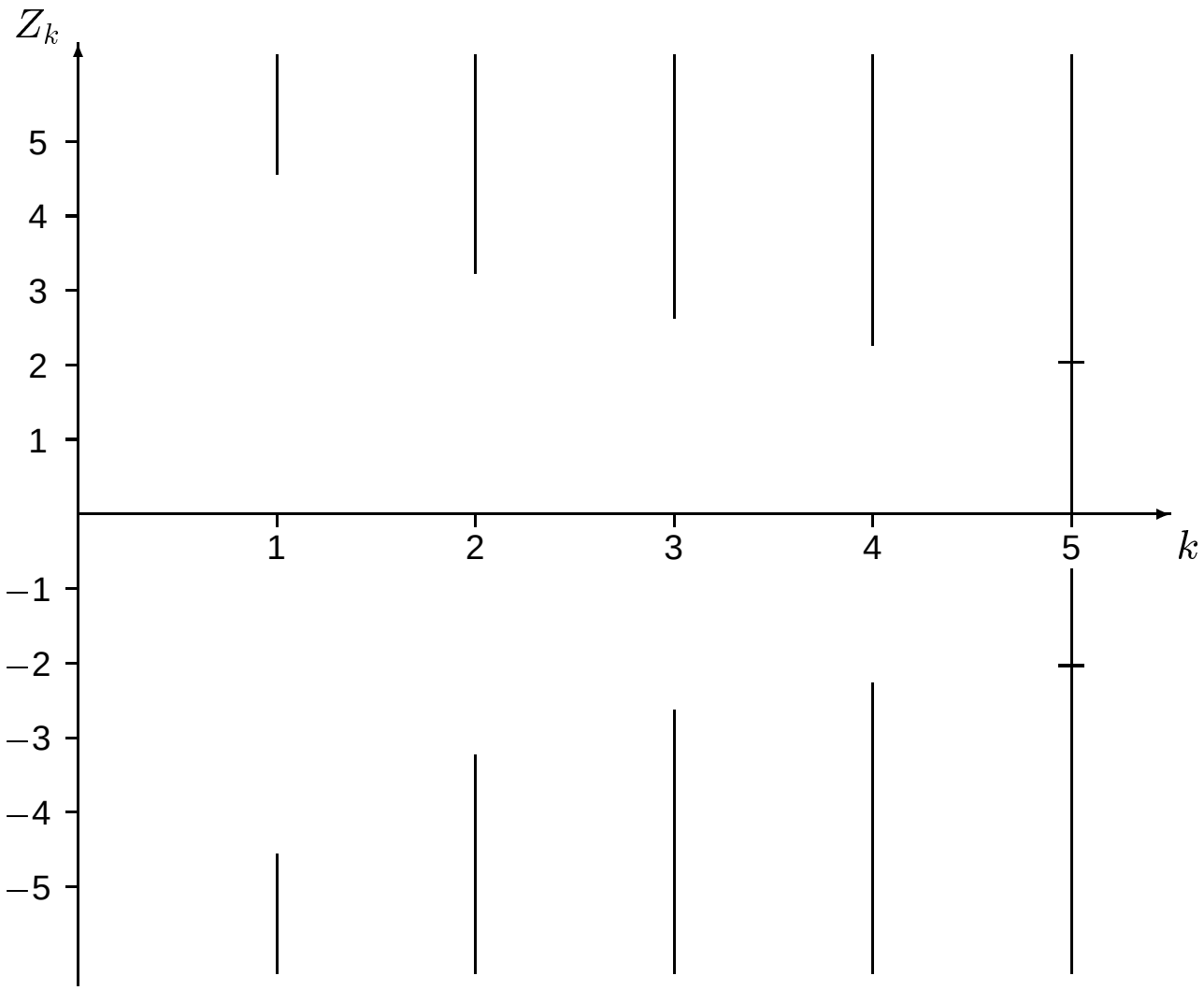
Perturbations in error rates also arise from small variations in the *actual* group sizes.

For major departures from planned group sizes, we should really follow the “error spending” approach — see later.

# ANALYSIS

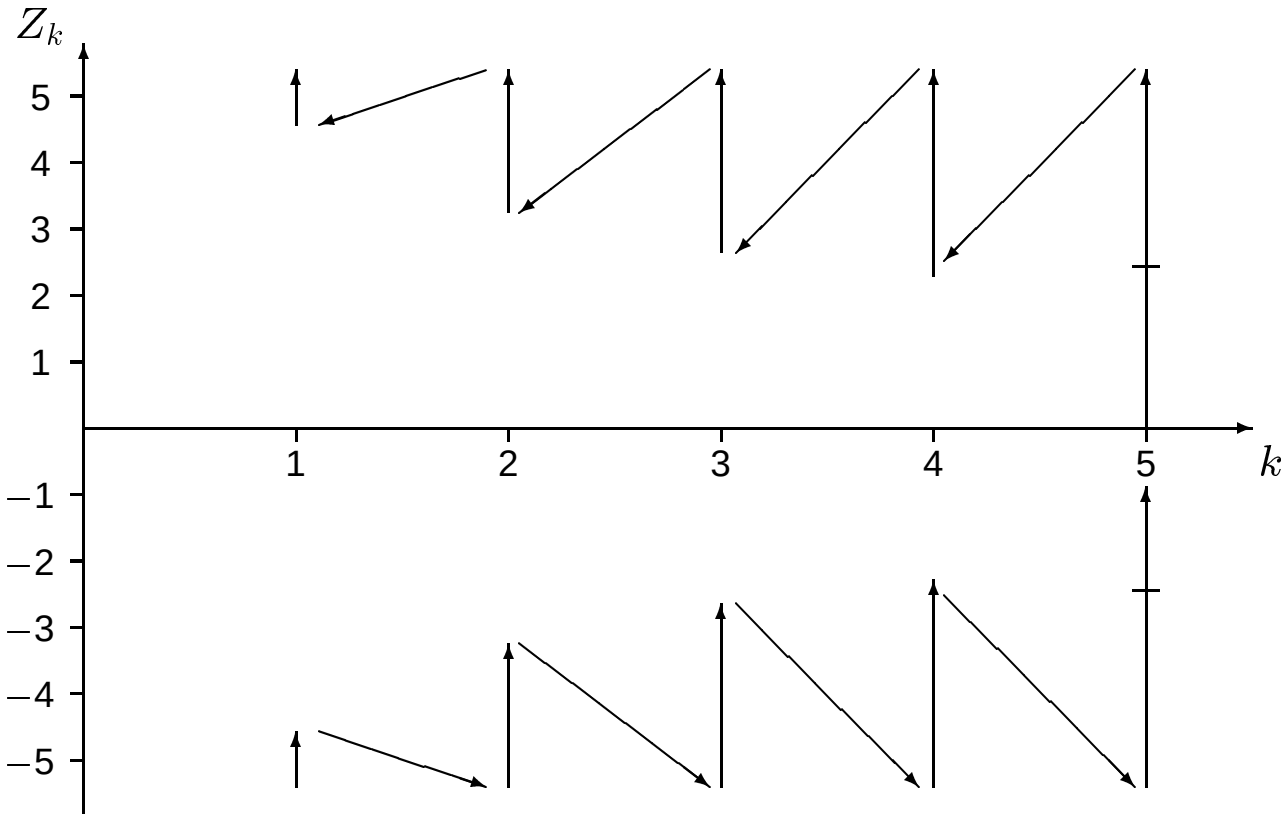
## Analysis on termination

The sample space consists of all possible pairs $(k, Z_k)$ on termination:



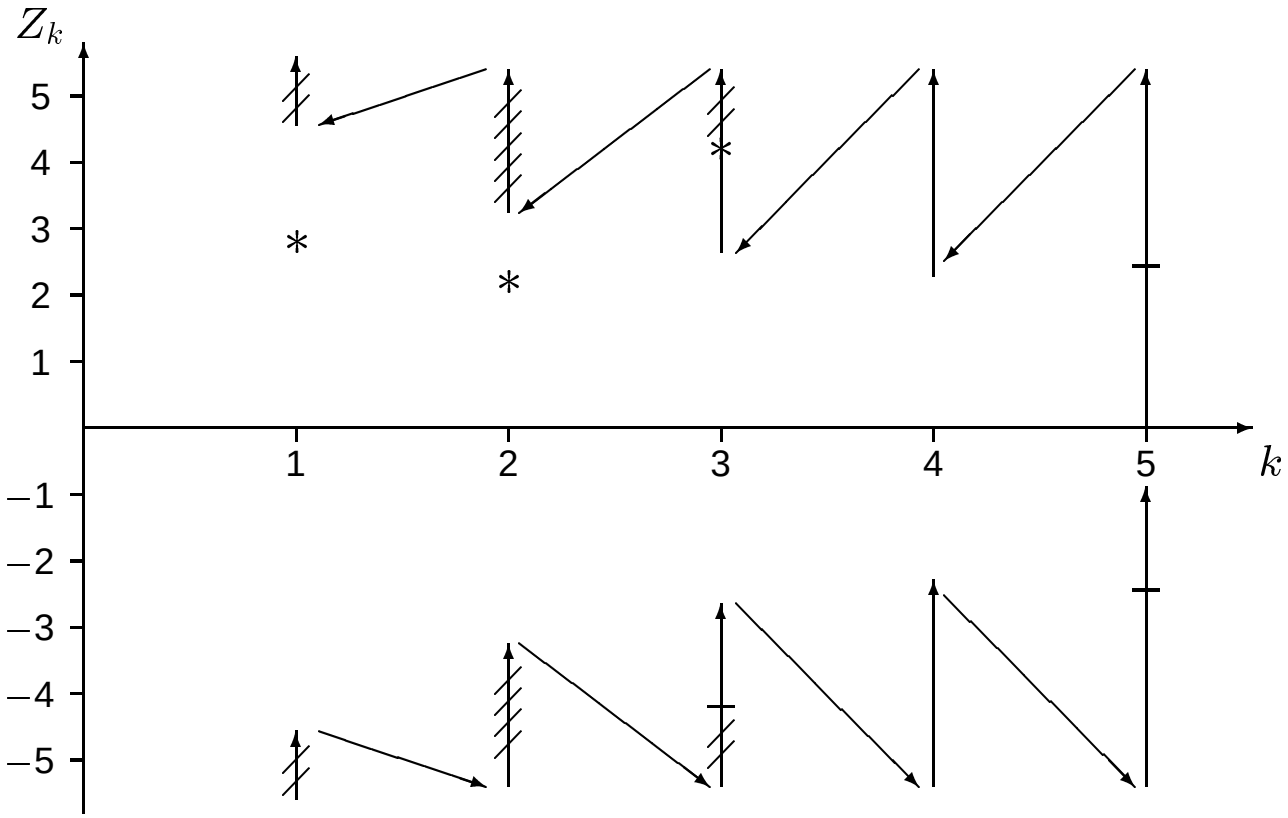
*Analysis on termination*

First, order the sample space.




We define P-values and confidence intervals with respect to this ordering.

**The P-value** for $H_0$: $\mu_A = \mu_B$ is the probability under $H_0$ of observing such an extreme outcome.




E.g., if the test stops at analysis 3 with $Z_3 = 4.2$, the two-sided P-value is

$$Pr_{\theta=0}\{|Z_1| \geq 4.56 \text{ or } |Z_2| \geq 3.23 \text{ or } |Z_3| \geq 4.2\}$$

$$= 0.0013.$$

## A confidence interval on termination

Suppose the test terminates at analysis $k^*$ with $Z_{k^*} = Z^*$.

A $100(1-\alpha)\%$ confidence interval for $\theta = \mu_A - \mu_B$ is the interval $(\theta_1, \theta_2)$ where

$$Pr_{\theta=\theta_1}\{\text{An outcome above } (k^*, Z^*)\} = \alpha/2$$

and

$$Pr_{\theta=\theta_2}\{\text{An outcome below } (k^*, Z^*)\} = \alpha/2.$$

E.g., if the test stops at analysis 3 with $Z_3 = 4.2$, the 95% confidence interval for $\theta$ is

$$(0.24, 0.91),$$

using our specified ordering.

Compare: fixed sample CI would be $(0.35, 0.95)$.

# 11. Updating a design as a nuisance parameter is estimated

## The case of unknown variance

We can design as for the case of known variance but use an *estimate* of $\sigma^2$ initially.

If in doubt, err towards over-estimating $\sigma^2$ in order to safeguard the desired power.

At analysis $k$, estimate $\sigma^2$ by

$$s_k^2 = \frac{\sum(X_{Ai} - \bar{X}_A^{(k)})^2 + \sum(X_{Bi} - \bar{X}_B^{(k)})^2}{n_{Ak} + n_{Bk} - 2}\,.$$

In place of $Z_k$, define $t$-statistics

$$T_k = \frac{\bar{X}_A^{(k)} - \bar{X}_B^{(k)}}{\sqrt{s_k^2(1/n_{Ak} + 1/n_{Bk})}}\,,$$

then test at the *same significance level* used for $Z_k$ when $\sigma^2$ is known.

## Updating the target sample size

Recall, maximum sample size is set to be the fixed sample size multiplied by the Inflation Factor.

In a 5-group O'Brien & Fleming design for the cholesterol example this is

$$1.026 \times \{\Phi^{-1}(1-\alpha/2) + \Phi^{-1}(1-\beta)\}^2 \, 2\sigma^2/\delta^2$$

$$= 134.8 \times \sigma^2.$$

After choosing the first group sizes using an initial estimate of $\sigma^2$, at each analysis $k = 1, 2, \ldots$ we can re-estimate the target for $n_{A5}$ and $n_{B5}$ as

$$134.8 \times s_k^2$$

and modify future group sizes to achieve this.

## Example: updating the sample size

*Initially:*

With initial estimate $\widehat{\sigma}^2 = 0.5$,

aim for $n_{A5} = n_{B5} = 134.8 \times 0.5 = 68$.

Plan 14 observations per treatment group.

*Analysis 1:*

With $n_{A1} = n_{B1} = 14$ and $s_1^2 = 0.80$,

aim for $n_{A5} = n_{B5} = 134.8 \times 0.80 = 108$.

For now, keep to 14 obs. per treatment group.

*Analysis 2:*

With $n_{A2} = n_{B2} = 28$ and $s_2^2 = 0.69$,

aim for $n_{A5} = n_{B5} = 134.8 \times 0.69 = 93$.

Now increase group size to 22 obs. per treatment.

*Example: updating the sample size*

*Analysis 3:*

With $n_{A3} = n_{B3} = 50$ and $s_3^2 = 0.65$,

aim for $n_{A5} = n_{B5} = 134.8 \times 0.65 = 88$.

Set next group size to 19 obs. per treatment.

*Analysis 4:*

With $n_{A4} = n_{B4} = 69$ and $s_4^2 = 0.72$,

aim for $n_{A5} = n_{B5} = 134.8 \times 0.72 = 97$.

Set final group size to 28 obs. per treatment.

*Analysis 5:*

With $n_{A5} = n_{B5} = 97$, suppose $s_5^2 = 0.74$,

so the target is $n_{A5} = n_{B5} = 134.8 \times 0.74 = 100$

— and the test may be slightly under-powered.

## Remarks on “re-estimating” sample size

1. The target information for $\theta = \mu_A - \mu_B$ is

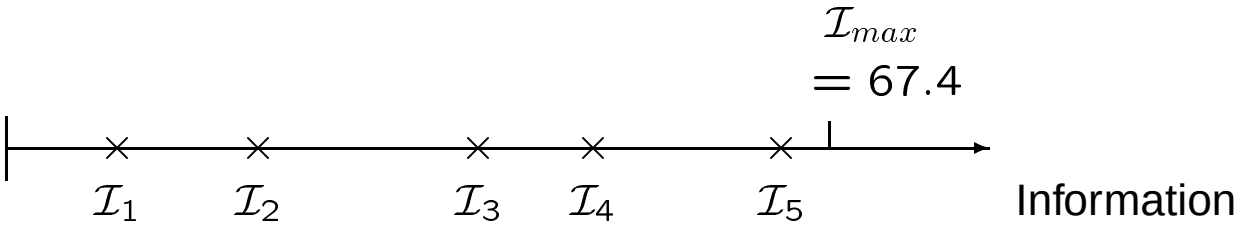
$$\begin{aligned} \mathcal{I}_{max} &= IF \times \{\Phi^{-1}(1-\alpha/2) + \Phi^{-1}(1-\beta)\}^2 / \delta^2 \\ &= 1.026 \times (1.960 + 1.282)^2 / 0.4^2 = 67.4. \end{aligned}$$

The relation between information and sample size

$$\mathcal{I}_k = \left\{ \left( \frac{1}{n_{Ak}} + \frac{1}{n_{Bk}} \right) \sigma^2 \right\}^{-1}$$

involves the *unknown* $\sigma^2$. Hence, the initial uncertainty about the necessary sample size.

In effect, we proceed by monitoring observed information:




NB, state $\mathcal{I}_{max} = 67.4$ in the protocol, not $n = \ldots$

2. The unequal group sizes which arise using this method are best dealt with by the “error spending” approach — see later.

3. Estimation error in $s_1^2$, $s_2^2$, etc. can be allowed for using analogues of Stein’s two-stage method (*Ann. Math, Statist.*, 1944, 16, 243–258).

4. For further justification of this adaptive approach, see Denne & Jennison, *Biometrika*, 2000, 87, 125–134.

## Recapitulation

**Designing** a group sequential test:

- Formulate the testing problem
- Create a fixed sample study design
- Choose number of analyses and boundary shape parameter
- Set maximum sample size equal to fixed sample size times the inflation factor

**Monitoring:**

- Find observed information at each analysis
- Compare $z$-statistics with critical values

**Analysis:**

- P-value and confidence interval on termination

This method can be applied to many response distributions and statistical models.

# 12. A survival data example

## Oropharynx Clinical Trial Data

(Kalbfleisch & Prentice (1980) Appendix 1, Data Set II)

Patient survival was compared on experimental Treatment A and standard Treatment B.

| | | Number entered | | Number of deaths | |
|---|---|---|---|---|---|
| $k$ | Date | Trt A | Trt B | Trt A | Trt B |
| 1 | 12/69 | 38 | 45 | 13 | 14 |
| 2 | 12/70 | 56 | 70 | 30 | 28 |
| 3 | 12/71 | 81 | 93 | 44 | 47 |
| 4 | 12/72 | 95 | 100 | 63 | 66 |
| 5 | 12/73 | 95 | 100 | 69 | 73 |

# The logrank statistic

At stage $k$, observed number of deaths is $d_k$. Elapsed times between study entry and failure are $\tau_{1,k} < \tau_{2,k} < \ldots < \tau_{d_k,k}$ (assuming no ties).

Define

| | |
|---|---|
| $r_{iA,k}$ and $r_{iB,k}$ | numbers at risk on Treatments A and B at $\tau_{i,k}-$ |
| $r_{ik} = r_{iA,k} + r_{iB,k}$ | total number at risk at $\tau_{i,k}-$ |
| $O_k$ | observed number of deaths on Treatment B at stage $k$ |
| $E_k = \sum_{i=1}^{d_k} \frac{r_{iB,k}}{r_{ik}}$ | "expected" number of deaths on Treatment B at stage $k$. |
| $V_k = \sum_{i=1}^{d_k} \frac{r_{iA,k} r_{iB,k}}{r_{ik}^2}$ | "variance" of $O_k$ |

The standardised logrank statistic at stage $k$ is

$$Z_k = \frac{O_k - E_k}{\sqrt{V_k}}.$$

## Proportional hazards model

Assume hazard rates $h_A$ on Treatment A and $h_B$ on Treatment B are related by

$$h_B(t) = \lambda\, h_A(t).$$

The log hazard ratio is $\theta = \ln(\lambda)$.

Then, approximately,

$$Z_k \sim N(\theta\sqrt{\mathcal{I}_k},\, 1)$$

and

$$\text{Cov}(Z_{k_1}, Z_{k_2}) = \sqrt{(\mathcal{I}_{k_1}/\mathcal{I}_{k_2})}, \quad 1 \le k_1 \le k_2 \le K,$$

where $\mathcal{I}_k = V_k$.

For $\lambda \approx 1$, we have $\mathcal{I}_k \approx V_k \approx d_k/4$.

## Design of the Oropharynx trial

One-sided test of $H_0$: $\theta \leq 0$ vs $\theta > 0$. Under the alternative $\lambda > 1$, i.e., Treatment A is better.

Require:

type I error probability $\alpha = 0.05$,

power $1 - \beta = 0.95$ at $\theta = 0.6$, i.e., $\lambda = 1.8$.

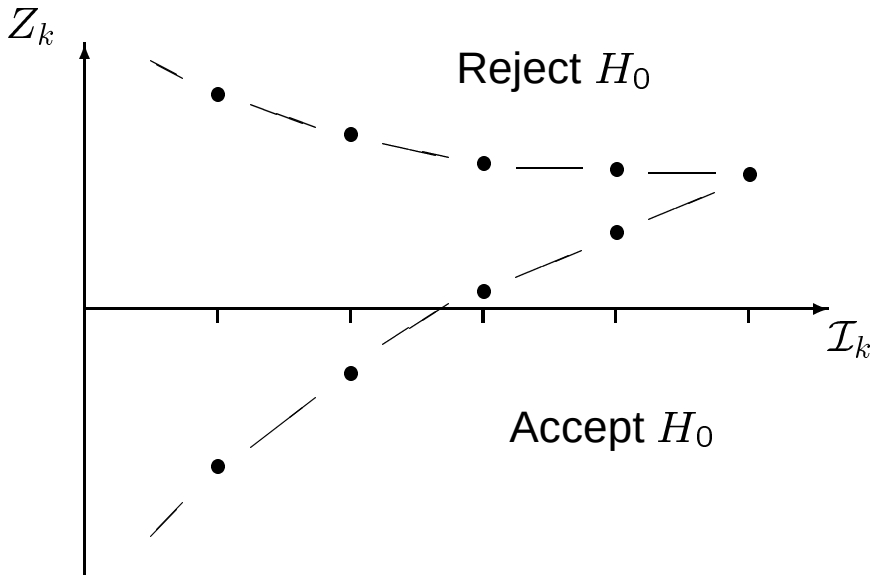
Information needed for a fixed sample study is

$$\mathcal{I}_f = \frac{\{\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)\}^2}{0.6^2} = 30.06$$

Under the approximation $\mathcal{I} \approx d/4$ the total number of failures to be observed is $d_f = 4\,\mathcal{I}_f = 120.2$.

## *Design of the Oropharynx trial*

For a one-sided test with up to 5 analyses, we could use a standard design created for equally spaced information levels.




However, increments in information between analyses will be unequal and unpredictable.

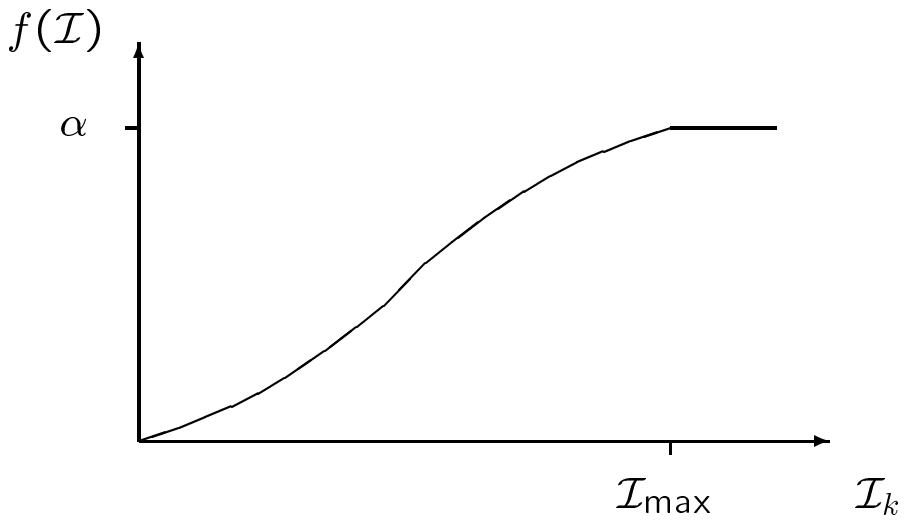
This leads to consideration of an “error spending” design.

# 13. Error spending tests

Lan & DeMets (1983) presented two-sided tests which "spend" type I error as a function of observed information.

*Maximum information design:*

Error spending function $f(\mathcal{I})$




Set the boundary at analysis $k$ to give cumulative Type I error $f(\mathcal{I}_k)$.

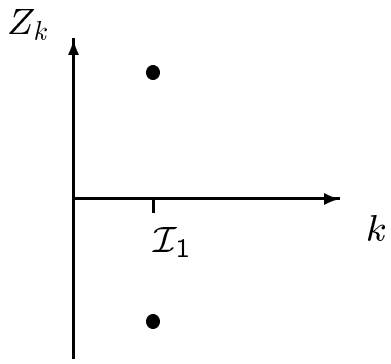
Accept $H_0$ if $\mathcal{I}_{\max}$ is reached without rejecting $H_0$.

*Analysis 1:*

Observed information $\mathcal{I}_1$.

Reject $H_0$ if $|Z_1| > c_1$ where

$$Pr_{\theta=0}\{|Z_1| > c_1\} = f(\mathcal{I}_1).$$

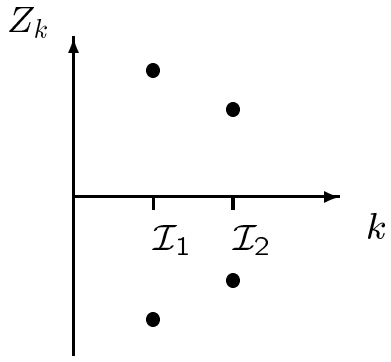



*Analysis 2:*

Cumulative information $\mathcal{I}_2$.

Reject $H_0$ if $|Z_2| > c_2$ where

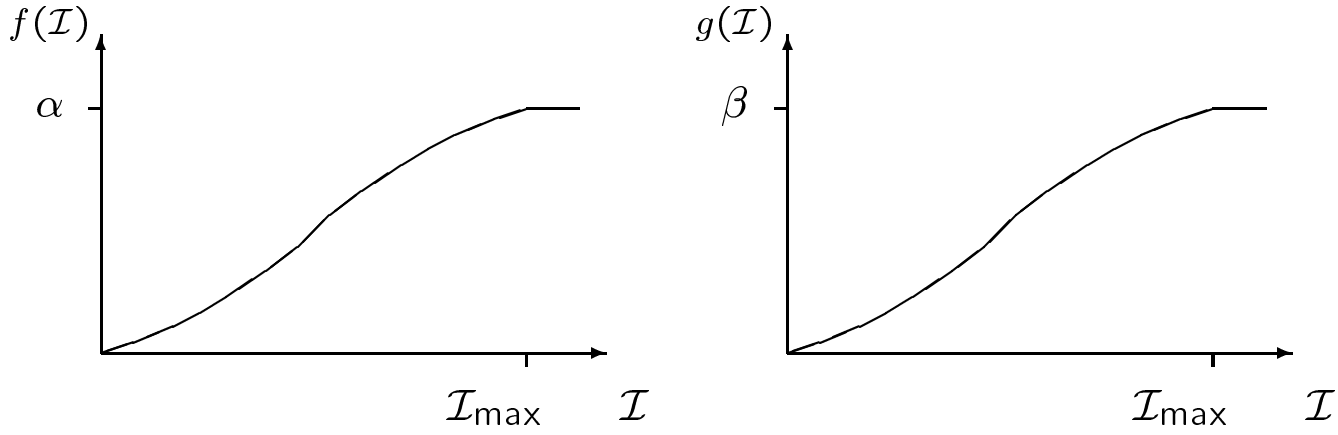
$$Pr_{\theta=0}\{|Z_1| < c_1, |Z_2| > c_2\}$$
$$= f(\mathcal{I}_2) - f(\mathcal{I}_1).$$




etc.

## One-sided error spending tests

For a one-sided test, define $f(\mathcal{I})$ and $g(\mathcal{I})$ to specify how type I and type II error probabilities are spent as a function of observed information.




At analysis $k$, set boundary values $(a_k,\, b_k)$ so that

$$Pr_{\theta=0}\{\text{Reject } H_0 \text{ by analysis } k\} \;=\; f(\mathcal{I}_k),$$

$$Pr_{\theta=\delta}\{\text{Accept } H_0 \text{ by analysis } k\} \;=\; g(\mathcal{I}_k).$$

Power family of error spending tests:

$$f(\mathcal{I}) \text{ and } g(\mathcal{I}) \;\propto\; (\mathcal{I}/\mathcal{I}_{\max})^{\rho}.$$

*One-sided error spending tests*

1. Values $\{a_k, b_k\}$ are easily computed using iterative formulae of McPherson, Armitage & Rowe (1969).

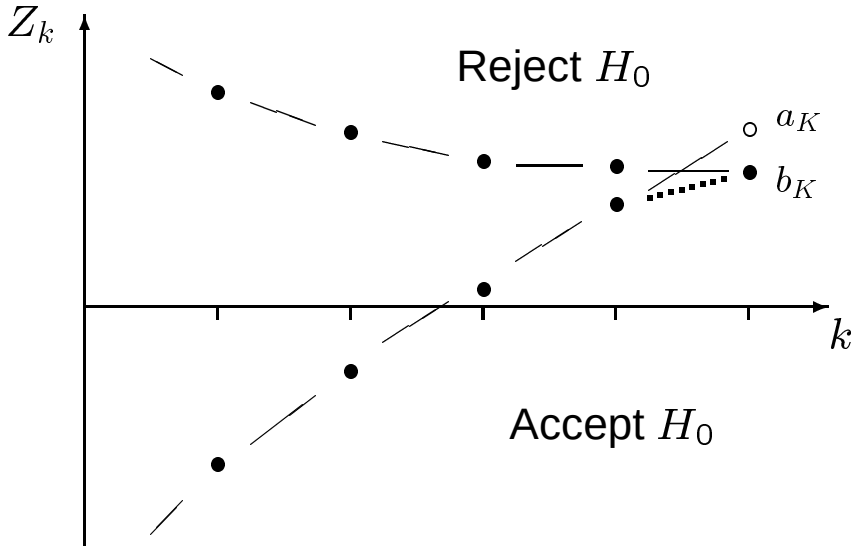
2. Computation of $(a_k,\ b_k)$ does **not** depend on future information levels, $\mathcal{I}_{k+1}, \mathcal{I}_{k+2}, \ldots$.

3. In a "maximum information design", the study continues until the boundary is crossed or an analysis is reached with $\mathcal{I}_k \geq \mathcal{I}_{\mathsf{max}}$.

4. The value of $\mathcal{I}_{\mathsf{max}}$ should be chosen so that boundaries converge at the final analysis under a typical sequence of information levels, e.g., $\mathcal{I}_k = (k/K)\,\mathcal{I}_{\mathsf{max}}, \quad k = 1, \ldots, K.$

## Over-running

If one reaches $\mathcal{I}_K > \mathcal{I}_{\max}$, solving for $a_K$ and $b_K$ is liable to give $a_K > b_K$.



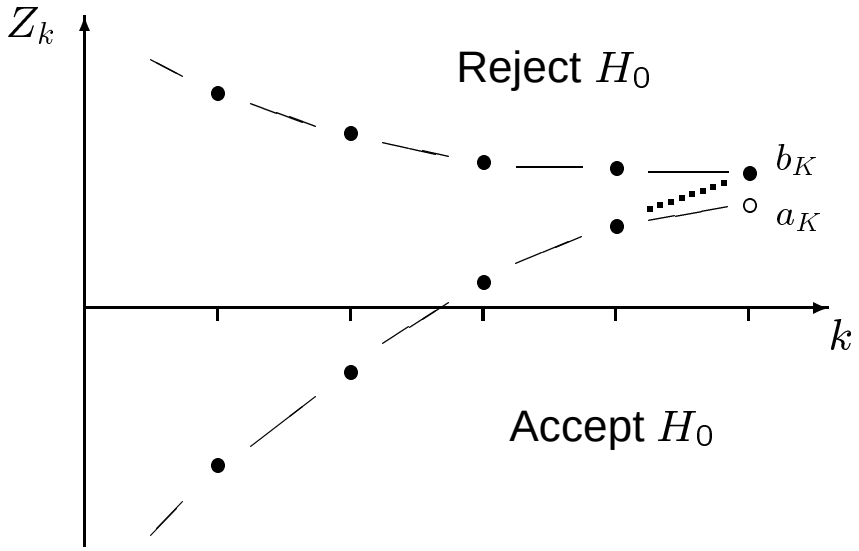

Keeping $b_K$ as calculated guarantees type I error probability of exactly $\alpha$.

So, reduce $a_K$ to $b_K$ — and gain extra power.

Over-running may also occur if $\mathcal{I}_K = \mathcal{I}_{\max}$ but information levels deviate from the equally spaced values (say) used in choosing $\mathcal{I}_{\max}$.

## Under-running

If a final information level $\mathcal{I}_K < \mathcal{I}_{\max}$ is imposed, solving for $a_K$ and $b_K$ is liable to give $a_K < b_K$.




Again, with $b_K$ as calculated, the type I error probability is exactly $\alpha$.

This time, increase $a_K$ to $b_K$ — and attained power will be a little below $1 - \beta$.

## A one-sided error spending design for the Oropharynx trial

Specification:

one-sided test of $H_0$: $\theta \leq 0$ vs $\theta > 0$,

type I error probability $\alpha = 0.05$,

power $1 - \beta = 0.95$ at $\theta = \ln(\lambda) = 0.6$.

At the design stage, assume $K = 5$ equally spaced information levels.

Use a power-family test with $\rho = 2$, i.e., spending error $\propto (\mathcal{I}/\mathcal{I}_{\max})^2$.

Information of a fixed sample test is inflated by a factor $R(K, \alpha, \beta, \rho) = 1.101$ (JT, Table 7.6).

So, we require $\mathcal{I}_{\max} = 1.101 \times 30.06 = 33.10$, which needs a total of $4 \times 33.10 = 132.4$ deaths.

## Summary data and critical values for the Oropharynx trial

We construct error spending boundaries for the information levels actually observed.

This gives boundary values $(a_1, b_1), \ldots, (a_5, b_5)$ for the standardised statistics $Z_1, \ldots, Z_5$.

| $k$ | *Number entered* | *Number of deaths* | $\mathcal{I}_k$ | $a_k$ | $b_k$ | $Z_k$ |
|---|---|---|---|---|---|---|
| 1 | 83 | 27 | 5.43 | $-1.60$ | 3.00 | $-1.04$ |
| 2 | 126 | 58 | 12.58 | $-0.37$ | 2.49 | $-1.00$ |
| 3 | 174 | 91 | 21.11 | 0.63 | 2.13 | $-1.21$ |
| 4 | 195 | 129 | 30.55 | 1.51 | 1.81 | $-0.73$ |
| 5 | 195 | 142 | 33.28 | 1.73 | 1.73 | $-0.87$ |

This stopping rule would have led to termination at the 2nd analysis.

## Covariate adjustment in the Oropharynx trial

Covariate information was recorded for subjects:

gender, initial condition, T-staging, N-staging.

These can be included in a proportional hazards regression model along with treatment effect $\beta_1$. The goal is then to test $H_0$: $\beta_1 = 0$ against the one-sided alternative $\beta_1 > 0$.

At stage $k$ we have the estimate $\hat{\beta}_1^{(k)}$,

$$v_k = \widehat{\mathrm{Var}}(\hat{\beta}_1^{(k)}),\ \mathcal{I}_k = v_k^{-1} \text{ and } Z_k = \hat{\beta}_1^{(k)}/\sqrt{v_k}.$$

All these are available from standard Cox regression software.

The standardised statistics $Z_1, \ldots, Z_5$ have, approximately, the canonical joint distribution.

## Covariate-adjusted group sequential analysis of the Oropharynx trial

Constructing the error spending test gives boundary values $(a_1, b_1), \ldots, (a_5, b_5)$ for $Z_1, \ldots, Z_5$.

| $k$ | $\mathcal{I}_k$ | $a_k$ | $b_k$ | $\widehat{\beta}_1^{(k)}$ | $Z_k$ |
|---|---|---|---|---|---|
| 1 | 4.11 | $-1.95$ | 3.17 | $-0.79$ | $-1.60$ |
| 2 | 10.89 | $-0.61$ | 2.59 | $-0.14$ | $-0.45$ |
| 3 | 19.23 | 0.43 | 2.20 | $-0.08$ | $-0.33$ |
| 4 | 28.10 | 1.28 | 1.90 | 0.04 | 0.20 |
| 5 | 30.96 | 1.86 | 1.86 | 0.01 | 0.04 |

Under this model and stopping rule, the study would have terminated at the 3rd analysis.

# 14. Adaptive treatment allocation

There can be benefits to patients in adapting the proportion randomised to each treatment in the light of previous responses.

Such methods have been much studied in the patient horizon formulation.


Objective: minimise the total number allocated to the inferior treatment.

Robbins & Siegmund (1974) showed how to accommodate adaptive sampling in an SPRT, preserving its type I and II error rates.

## Group sequential adaptive sampling

Jennison & Turnbull, Ch. 17

Consider a group sequential test concerning one parameter, $\theta$, in a normal linear model.

If the sampling rule for stage $k+1$ is allowed to depend on $\widehat{\theta}_k$, then the conditional distribution

$$\widehat{\theta}_{k+1} \mid \widehat{\theta}_1, \ldots, \widehat{\theta}_k \quad \text{and} \quad \mathcal{I}_1, \ldots, \mathcal{I}_{k+1}$$

is still as in the canonical case.

This result allows adaptive sampling to be incorporated in standard group sequential tests.

Strictly speaking, $\mathcal{I}_{k+1}$ should not be affected by $\widehat{\theta}_k$. To avoid such problems, adjust total group sizes so that the information levels stay close to a pre-specified sequence of values.

# Example

Two treatment comparison, $\theta = \mu_A - \mu_B$.

Pampallona & Tsiatis one-sided test, $\Delta = 0$, with 5 analyses,

type I error rate 0.05 at $\theta = 0$,

power $= 0.9$ at $\theta = \delta$.

Adaptive sampling aims for $N_A/N_B = 2^{\theta/(2\delta)}$.

Sample sizes as percentages of fixed sample size:

| | Equal sampling | Adaptive sampling | | | |
|---|---|---|---|---|---|
| $\theta$ | $E(N_A) = E(N_B)$ | $E(N_A)$ | $E(N_B)$ | % drop in ITN | % rise in ASN |
| $-\delta/2$ | 47.0 | 45.6 | 49.3 | 3.0 | 1.0 |
| 0 | 63.8 | 66.0 | 62.5 | — | 0.7 |
| $\delta/2$ | 80.1 | 88.5 | 73.7 | 8.0 | 1.2 |
| $\delta$ | 71.8 | 85.5 | 62.6 | 12.8 | 3.1 |
| $3\delta/2$ | 54.3 | 71.0 | 44.8 | 17.5 | 6.6 |

ITN = Inferior Treatment Number, ASN = Average Sample Number.

# Further topics

Chapters of Jennison & Turnbull,

*Group Sequential Methods with Applications to Clinical Trials:*

Ch 9. Repeated confidence intervals

Ch 10. Stochastic curtailment

Ch 12. Special methods for binary data

Ch 15. Multiple endpoints

Ch 16. Multi-armed trials

Ch 18. Bayesian approaches

Ch 19. Numerical computations for group sequential tests