MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Adaptive Methods in Clinical Research

Lecture 8: Fully adaptive designs

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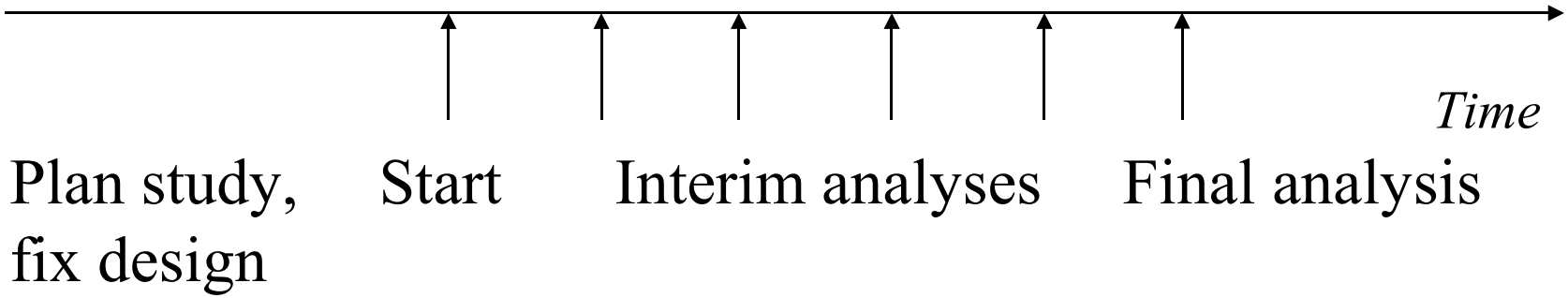
Adaptive Designs



At each interim

- decide whether or not to stop
- change sample size
- drop or add a dose
- change the endpoint
- change the question

Fisher's combination method

	First stage	Second stage
Observations	n_1	n_2
one-sided p-value	p_1	p_2

- p-values need to be independent
- Combine the evidence from the two stages via taking product of p-values from both stages
- Under H_0, $-2\log(p_1 \times p_2) \sim \chi^2_4$ (Fisher, 1932)

The null distribution of a p-value

Consider a test of $H_0 : \theta = 0$ vs $H_1 : \theta > 0$, based on a continuously distributed test statistic $T(\boldsymbol{x})$ computed from data $\boldsymbol{x}$.

Let p denote the resulting one-sided p-value

$$p = \mathbb{P}(T \geq t | \theta = 0)$$

where T denotes the random value and t the observed value of the test statistic.

p itself is an observed value of a random variable P, and the probability $\mathbb{P}(P \leq p | \theta = 0) = p$.

That is, under H_0, P is uniformly distributed on (0, 1).

Proof

under H_0

$$p_1 \sim U(0,1) \quad \text{and independently} \quad p_2 \sim U(0,1)$$

Hence

$$-\log(p_1) \sim Exp(1) \quad \text{and} \quad -\log(p_2) \sim Exp(1)$$

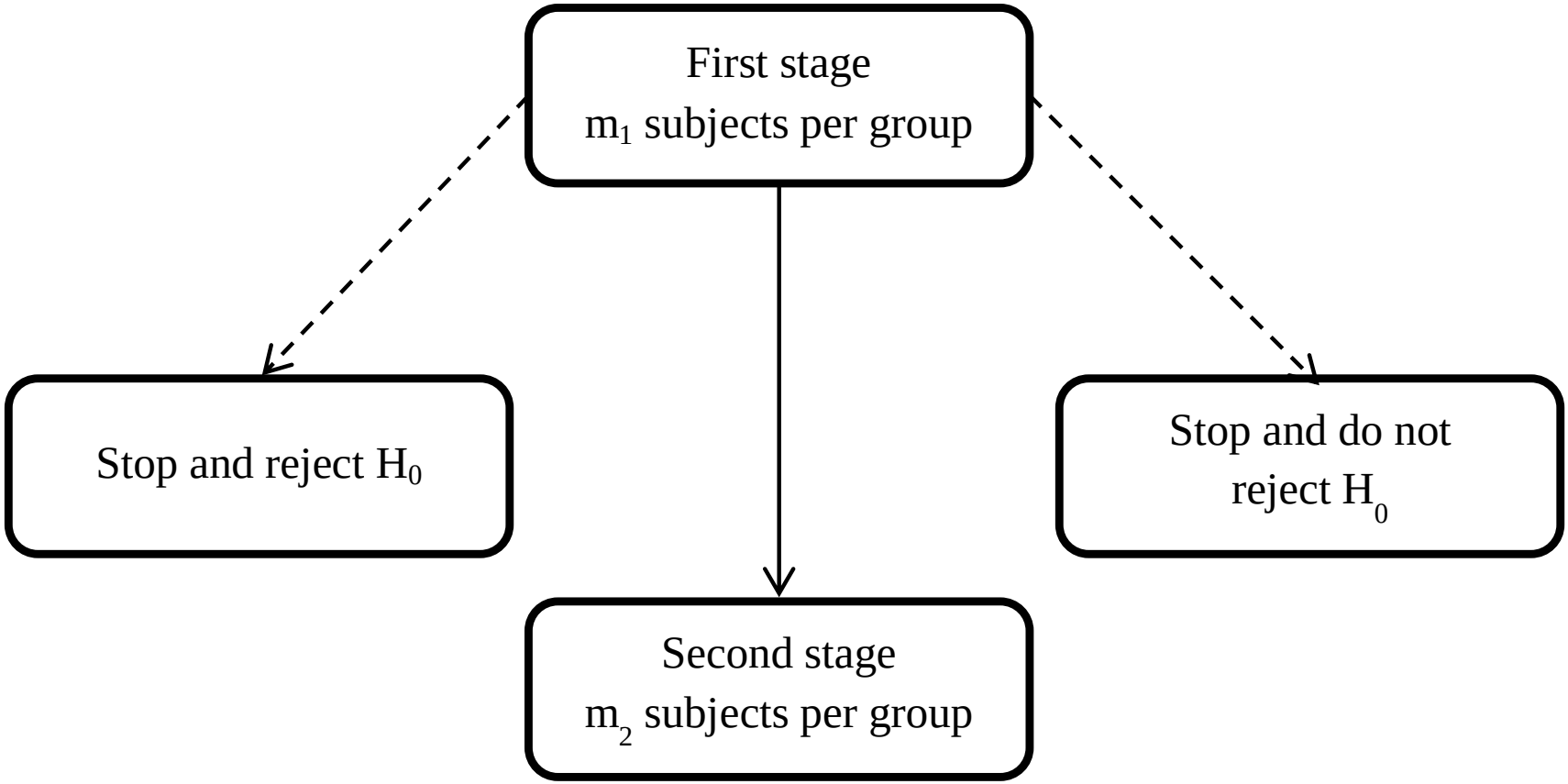
and so

$$-\log(p_1 p_2) = -\log(p_1) - \log(p_2) \sim Ga(2,1)$$

and therefore

$$-2\log(p_1 p_2) \sim Ga\left(\frac{4}{2}, \frac{1}{2}\right) = \chi^2_4$$

Two-stage design with early stopping



- Proposed by Bauer & Köhne (1994)
- Stage 1 and Stage 2 need to be independent

Two-stage design with early stopping

The upper 0.975 point of the χ^2_4 distribution is 11.14. Setting $\alpha = 0.025$ (one-sided), we will PROCEED to claim that E $>$ C if

$$-2\log(p_1 p_2) \geq 11.14$$

or equivalently if

$$p_1 p_2 \leq 0.0038$$

If after the first stage, we already know that

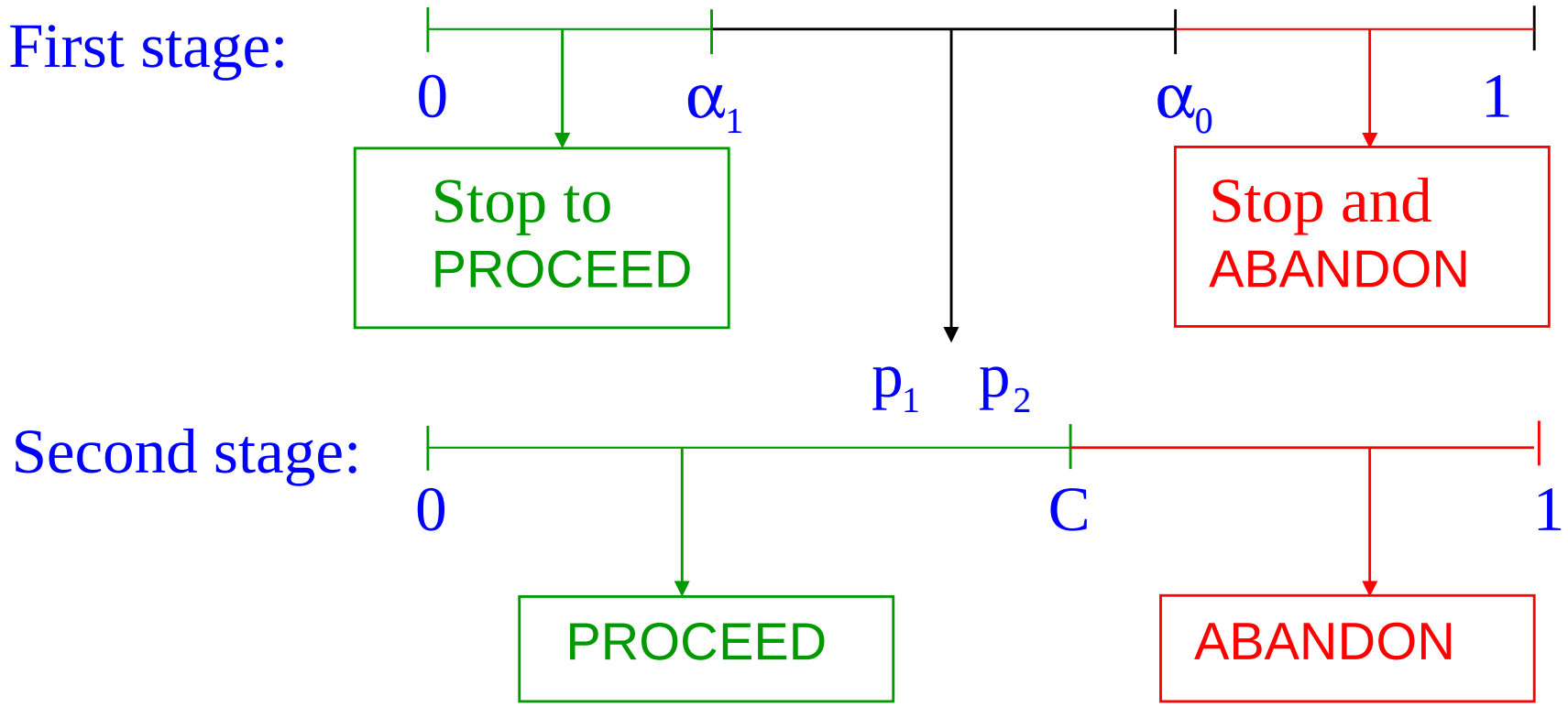
$$p_1 \leq 0.0038$$

then there is no need to conduct the second stage: we will PROCEED to claim that E $>$ C
$-$ curtailed sampling

Two-stage design with early stopping

The full procedure is as shown:

– for $\alpha = 0.025$, $\alpha_1 = 0.0038$

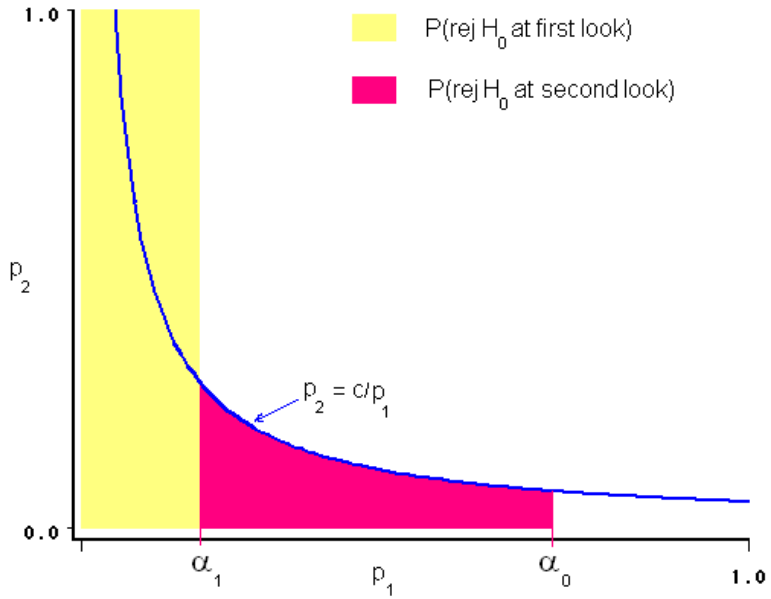


Two-stage design with early stopping

If the early PROCEED boundary is set at α_1 and the early ABANDON boundary is set at α_0, then in order to achieve an overall one-sided type I error rate of α,

$$c = \frac{\alpha - \alpha_1}{\log(\alpha_0) - \log(\alpha_1)}$$

found by integration



Two-stage design with early stopping

Hence

$$\begin{aligned}
\alpha &= \alpha_1 + \int_{\alpha_1}^{\alpha_0} \frac{c}{p_1} dp_1 \\
&= \alpha_1 + c\Big[\log(p_1)\Big]_{\alpha_1}^{\alpha_0} \\
&= \alpha_1 + c\Big[\log(\alpha_0) - \log(\alpha_1)\Big]
\end{aligned}$$

so that

$$c = \frac{\alpha - \alpha_1}{\log(\alpha_0) - \log(\alpha_1)}$$

Beyond 2 stages

- Wassmer (1999) extended this approach to any number of stages
- At the i^{th} interim analysis calculate the product of p-values
  1. Stop and PROCEED if $p_1 \times \cdots \times p_i \leq c_i$
  2. Stop and ABANDON if $p_i \geq \alpha_{0i}$
  3. Use a recursive method to find $c_1, \ldots, c_k$ and $\alpha_{01}, \ldots, \alpha_{0k}$ satisfying some chosen constraints
- Calculations become more complex as number of stages increases
- All stages equally weighted

Inverse normal method

For group sequential trials we need test statistics B_i and V_i which, under the null hypothesis, satisfy

- $B_i \sim N(0, V_i)$
- increments $(B_i - B_{i-1})$ between interims are independent

Regardless of where these statistics come from

Note:

$$Z = \frac{B}{\sqrt{V}}$$

where B is the score statistic and V is the Fisher information.

Transforming the p-value

Let

$$Z = \Phi^{-1}(1 - P)$$

where Φ denotes the $N(0, 1)$ distribution function

Then

$$\begin{aligned}
\mathbb{P}(Z \leq z|\theta = 0) &= \mathbb{P}(\Phi^{-1}(1 - P) \leq z|\theta = 0) \\
&= \mathbb{P}((1 - P) \leq \Phi(z)|\theta = 0) \\
&= \mathbb{P}(P \geq 1 - \Phi(z)|\theta = 0) \\
&= \Phi(z)
\end{aligned}$$

so that $Z \sim N(0, 1)$.

Combining the p-values

Consider tests of $H_{i0}: \theta_i = 0$ vs $H_{i1}: \theta_i > 0$, based on independent, sequentially available data sets $\boldsymbol{x}_i$, with corresponding one-sided p-values, $p_i,\ i = 1, \ldots, k$

Then

$$Z_i = \Phi^{-1}(1 - P_i),\ i = 1, \ldots, k$$

are independent $N(0, 1)$ random variables, and

$$Y_i = W_i \Phi^{-1}(1 - P_i),\ i = 1, \ldots, k$$

are independent $N(0, W_i^2)$ random variables.

Now put

$$B_i = Y_1 + \cdots + Y_i \qquad V_i = W_1^2 + \cdots + W_i^2$$

Then if all null hypotheses $H_{i0} : \theta_i = 0$ are true,

- $B_i \sim N(0, V_i)$
- increments $(B_i - B_{i-1})$ between interims are independent

So, if these statistics are plotted and compared with sequential stopping boundaries, then the required type I error will be achieved.

Applications

1. Hypotheses H_{i0} could all be the same: $\theta = 0$, based on independent data $\mathbf{x}_i$, each comprising the new data only observed between the ith and the (i-1)th interim analyses

   $\Rightarrow$ the sample size, allocation ratio or other design features concerning the ith dataset can depend on previous data

2. The hypotheses H_{i0} could concern different endpoints (mortality, time to progression, tumour shrinkage), or different test statistics (logrank, Wilcoxon, binary) based on independent groups of patients

   $\Rightarrow$ the endpoint or test statistic could be changed between interim analyses, provided that H_0: "the treatments are identical" is to be tested

Example: Group sequential trials

Suppose that H_0: $\theta = 0$ is tested against $H_1 : \theta > 0$ at the i$^{\text{th}}$ interim, based on the group sequential statistic $(B_i - B_{i-1})$.

Corresponding one-sided p-values, P_i, are

$$P_i = 1 - \Phi\left(\frac{B_i - B_{i-1}}{\sqrt{V_i - V_{i-1}}}\right)$$

Put $W_i^2 = (V_i - V_{i-1})$, so that

$$\begin{aligned} Y_i &= W_i \Phi^{-1}(1 - P_i) \\ &= \sqrt{V_i - V_{i-1}}\,\Phi^{-1}\left(\Phi\left(\frac{B_i - B_{i-1}}{\sqrt{V_i - V_{i-1}}}\right)\right) \\ &= (B_i - B_{i-1}) \end{aligned}$$

It follows that

$$B_i = Y_1 + \cdots + Y_i = B_i \quad \text{and} \quad V_i = W_1^2 + \cdots + W_i^2 = V_i$$

so that the inverse normal approach and the group sequential approach are identical in this case.

This is a good thing!

It means that the approach is built on solid foundations

Closed testing

Treatments: k experimentals $T_1, \ldots, T_k$
one control T_0

Adaptive designs tend to use pairwise comparisons i.e. individually test each $H_{0,i}$: $\theta_i = 0$

To strongly control the type I error rate for testing multiple hypotheses closed testing procedures are used (Marcus et al., 1976)

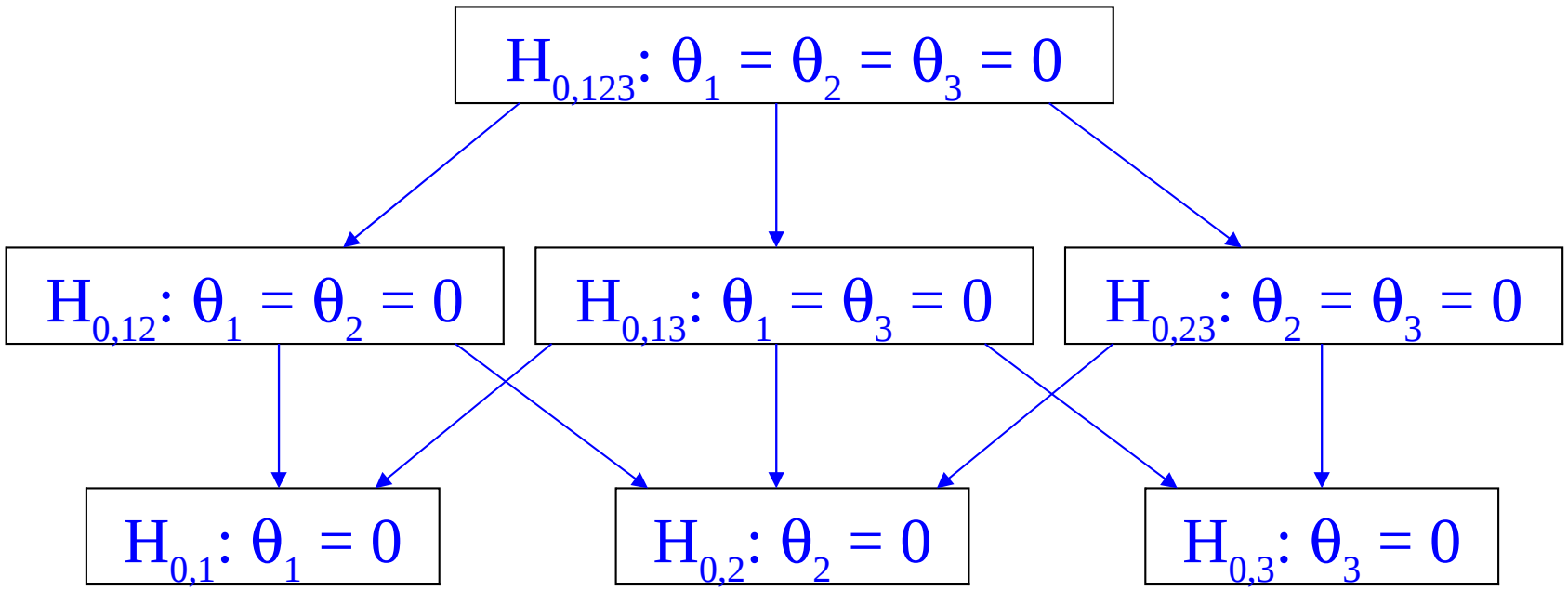
Consider one stage only

Closed testing procedure

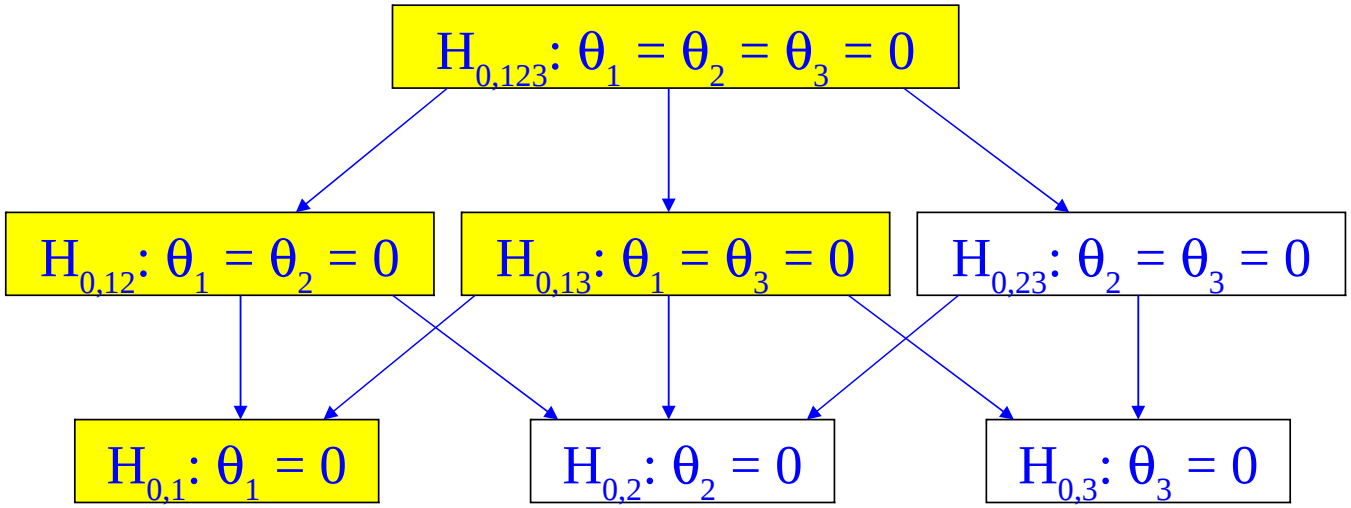
Form a family of H_0's from all possible intersections of $H_{0,i}$'s

Reject $H_{0,i}$ at level α, iff all H_0's that imply $H_{0,i}$ are rejected at level α.

e.g. 3 experimental treatments



Reject $H_{0,1}: \theta_1 = 0$, iff we reject



Let I be a set of m individual hypotheses from k ($m \leq k$)
$H_{0,I}$ denote the intersection hypothesis

$$H_{0,I} = \bigcap_{i \in I} H_{0,i}$$

e.g. if $I = \{1, 2\}$ then $H_{0,I} = H_{0,12}$

p-values for intersection hypotheses

We need to calculate p-value p_I to test $H_{0,I}$

Suppose we calculate a p-value, p_i, for each $H_{0,i}: \ \theta_i = 0$

Bonferroni correction

$$p_I = m \times \min(p_i)$$

where m is the number of indices in I

e.g. $k = 3, \ p_1 = 0.2, \ p_2 = 0.05, \ p_3 = 0.03$
then for $I = \{2, 3\}$ we find $m = 2, \ p_I = 0.03 \times 2 = 0.06$

p-values for intersection hypotheses (Dunnett, 1955)

Dunnett p-values are valid for multiple comparisons against a common control.

Compute a standardised test statistic Z_i for each $H_{0,i} : \theta_i = 0$. Let $z^\star$ be the maximum of the observed z values for $H_{0,i}$, $i \in I$.

Then the Dunnett p-value is

$$\mathbb{P}\{\max_{i \in I} Z_i > z^\star\}$$

calculated assuming that $\{Z_i\}_{i \in I}$ follow a multivariate normal joint distribution with each $Z_i \sim N(0, 1)$ and $cov(Z_i, Z_j) = 0.5$ for $i \neq j$.

p-values for intersection hypotheses (Dunnett, 1955)

Recall our previous example:

$k = 3,\ p_1 = 0.2,\ p_2 = 0.05,\ p_3 = 0.03.$
which correspond to $z_1 = 0.842$, $z_2 = 1.645$, $z_3 = 1.881$.

For $I = \{2, 3\}$ we find $z^\star = 1.881,\ p_I = 0.054$.

Multi-arm multi-stage (Bauer & Kieser 1999; Bretz et al, 2006)

Using closed testing procedure we therefore need to conduct tests for $(2^k - 1)$ hypotheses.

For each hypothesis, $H_{0,I}$ calculate a p-value from data collected at stage j, $p_{I,j}$

Take p-values for $H_{0,I}$ convert into a test statistic
e.g. using the inverse normal method as

$$Y_{I,j} = \frac{1}{\sqrt{j}} \sum_{i=1}^{j} \Phi^{-1}\left(1 - p_{I,j}\right)$$

Compare test statistic for $H_{0,I}$ using the **same boundaries** calculated as for the two treatments (T_1 and T_0) case, as

adaptive approach adjusts for the multiple treatments via the p-values, not via the boundaries.

Stopping rules

Stop for efficacy

When conclude at least one T_i is superior to T_0 via the closed testing procedure
i.e when all test statistics for those H_0's that imply $H_{0,i}$ crosses the upper boundary, u_j

Stop for futility

When test statistic for global H_0 crosses the lower boundary, l_j or when maximum number of looks is reached

Comments

- Sample size calculations
  - difficult under complex rules
  - larger then specialised methods
- Can do other adaptations, e.g.
  - select populations
  - Changing the primary endpoint
  - Changing the trial objective (such as switching from non-inferiority to superiority)
  - sample size re-estimation
- Ordering in treatment effects could be incorporated into closed testing procedure