Testing a secondary endpoint after a group sequential test

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Outline of talk

1. A group sequential test for a primary endpoint
2. How should one test a secondary endpoint after a positive outcome for the primary endpoint?
3. Multiple testing procedures
4. Combining multiple testing and group sequential designs
5. Testing a secondary endpoint after a group sequential test

1. Group sequential tests

Suppose a new treatment (Treatment A) is to be compared to a placebo or positive control (Treatment B) in a Phase III trial.

The treatment effect θ for the **primary endpoint** represents the advantage of Treatment A over Treatment B.

If $\theta > 0$, Treatment A is more effective.

We wish to test the null hypothesis H_0: $\theta \leq 0$ against $\theta > 0$ with

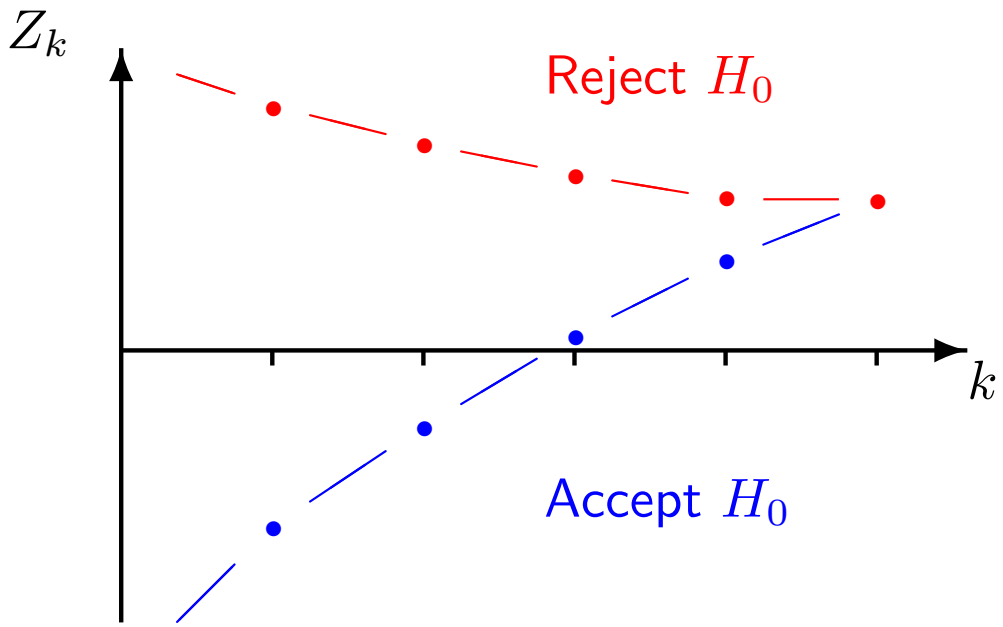
$$P_{\theta=0}\{\text{Reject } H_0\} = \alpha,$$

$$P_{\theta=\delta}\{\text{Reject } H_0\} = 1 - \beta.$$

In a group sequential trial, data are examined on a number of occasions to see if an early decision may be possible.

Group sequential tests

A typical boundary for a one-sided test has the form:



Crossing the upper boundary leads to early stopping for a positive outcome, rejecting H_0 in favour of $\theta > 0$.

Crossing the lower boundary implies stopping for "futility" with acceptance of H_0.

Benefits of group sequential tests

Earlier decisions

Group sequential testing can speed up the process to introduce an effective new treatment.

Fewer patients recruited

Expected sample sizes for group sequential designs are, typically, around 70% of the fixed sample size for a trial with the same type I error rate and power.

2. Testing a secondary endpoint

In a trial of two treatments, A and B, a group sequential test is carried out on the primary endpoint, which has treatment effect θ_1.

Suppose H_1: $\theta_1 \leq 0$ is rejected in favour of $\theta_1 > 0$.

The investigators wish to test whether Treatment A is also superior for a secondary endpoint, with treatment effect denoted by θ_2.

Some familiarity with "gatekeeping" procedures for testing multiple hypotheses suggests it may be legitimate to pass on the type I error $\alpha = 0.025$ to a second hypothesis test.

As this test will be only conducted once, the investigators plan to carry out a fixed sample size, level α test of H_2: $\theta_2 \leq 0$ vs $\theta_2 > 0$ using the available data on the secondary endpoint.

Is this approach to testing the two endpoints valid?

Testing a secondary endpoint: Example

Suppose the primary endpoint is tested using a Pampallona & Tsiatis group sequential design with shape parameter $\Delta = 0$.

There are 4 analyses, type I error probability is $\alpha = 0.025$ and power is 0.8 at $\theta_1 = 1$.

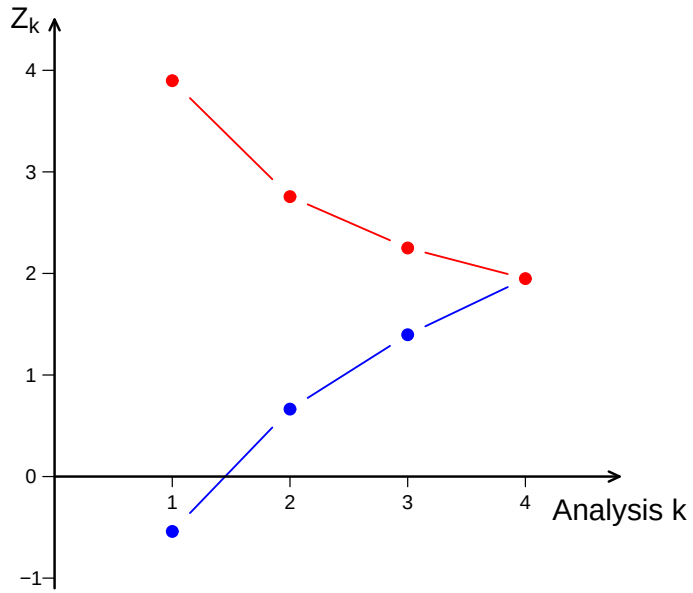
This test has upper boundary:

$$Z_k = 3.90/\sqrt{k}$$

and lower boundary

$$Z_k = 1.48\sqrt{k} - 2.02/\sqrt{k},$$

where $k = 1, \ldots, 4$.

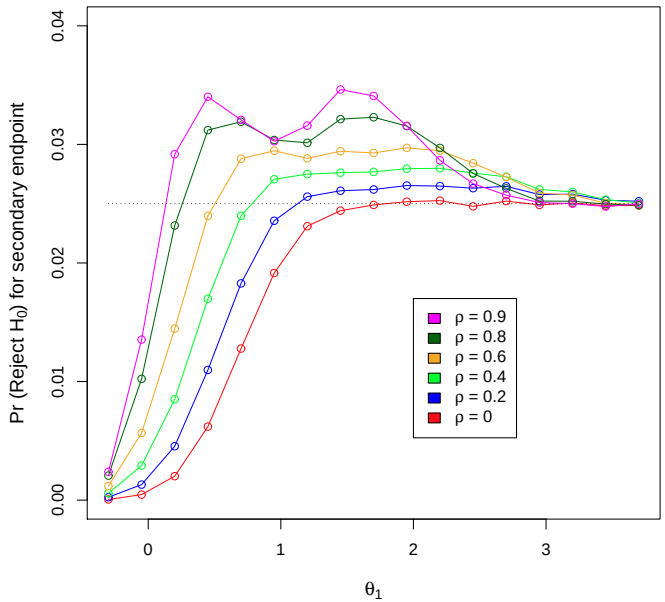


If the upper boundary is crossed, the secondary endpoint is tested in a level α, fixed sample size test, using current data.

Testing a secondary endpoint: Example

The plot shows the probability of rejecting H_2: $\theta_2 \leq 0$, under $\theta_2 = 0$, when the secondary endpoint is tested as described above.

The two endpoints have correlation ρ. For modest values of ρ, the type I error rate for testing H_2 exceeds the nominal 0.025.



Hung, Wang and O'Neill (*J. Biopharm. Statis.*, 2007) have noted this approach to testing a secondary endpoint is not valid.

So, how should the secondary endpoint be tested?

3. Multiple testing procedures

Our example had one primary and one secondary endpoint.

More generally, a clinical trial may involve

- Co-primary endpoints
  - *Positive outcomes required for at least one endpoint*
  - *Positive outcomes required on all endpoints*
- Secondary endpoints, tertiary endpoints, ...

The trial may have

- Multiple treatments,
- Pre-defined sub-populations of patients.

If the trial is group sequential, each hypothesis may be tested on several occasions.

The familywise error rate

Suppose we have h null hypotheses, H_i: $\theta_i \leq 0$ for $i = 1, \ldots, h$.
After our analysis, we accept or reject each of these h hypotheses.

A testing procedure's **familywise error rate** under a set of values $\theta = (\theta_1, \ldots, \theta_h)$ is

$$Pr_\theta\{\text{Reject } H_i \text{ for some } i \text{ with } \theta_i \leq 0\}$$

$$= Pr_\theta\{\text{Reject at least one true } H_i\}.$$

The familywise error rate is controlled **strongly** at level α if this error rate is at most α for all possible combinations of θ_i values.

Then

$$Pr\{\text{Reject any true } H_i\} \leq \alpha \quad \text{for all } (\theta_1, \ldots, \theta_h).$$

Bonferroni adjustment (Carlo Bonferroni, 1892–1960)

Suppose we test h null hypotheses, each at significance level α/h.

If all h null hypotheses are true,

$$Pr\{\text{Reject at least one of } H_1 \ldots H_h\}$$

$$\leq Pr\{\text{Reject } H_1\} + \ldots + Pr\{\text{Reject } H_h\} = h\,\frac{\alpha}{h} = \alpha.$$

If only some of the h null hypotheses are true,

$$Pr\{\text{Reject at least one true } H_i\} < \alpha.$$

So we have **strong control** of the **familywise error rate**.

We start by considering applications in fixed sample size study designs ...

Example: A Bonferroni test with co-primary endpoints

A trial compares a new treatment against control with respect to:

Endpoint 1, Core MACE (*Major Adverse Cardiac Event* — CV-related death, nonfatal stroke, or nonfatal MI)

Endpoint 2, Expanded MACE (Core MACE plus hospitalization for unstable angina or coronary revascularization).

Type I error probability $\alpha = 0.025$ is divided between the endpoints.

With Z-statistics Z_1 and Z_2 for endpoints 1 and 2,

An effect on Core MACE is declared if

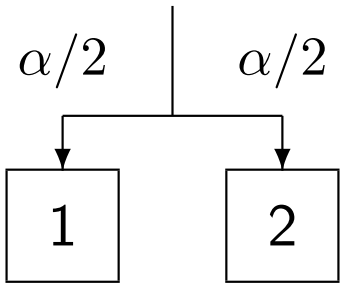
$$Z_1 > \Phi^{-1}(1 - \alpha/2) = 2.24,$$

An effect on Expanded MACE is declared if

$$Z_2 > \Phi^{-1}(1 - \alpha/2) = 2.24.$$

Example: Co-primary endpoints

This Bonferroni procedure can be represented graphically as:



There is a positive correlation between the two tests, due to the common aspects of the two endpoints.

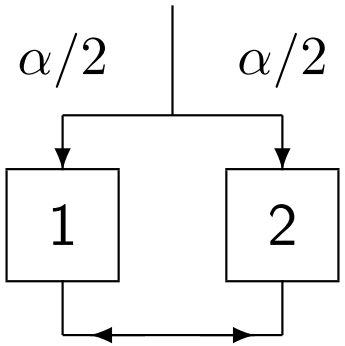
Hence, familywise type I error is protected conservatively.

Power when H_1 and H_2 are false can be increased by "recycling" type I error after one or other hypothesis is rejected.

Bonferroni procedure with recycling (the Holm procedure)

The Holm procedure is a version of the Bonferroni procedure that "recycles" error probability after rejecting H_1 or H_2.

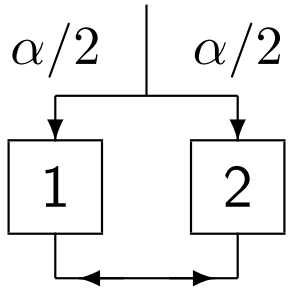
This method can be represented as:



If H_1 is rejected at level $\alpha/2$, we pass that error probability to H_2 and test this hypothesis at level α.

If H_2 is rejected at level $\alpha/2$, we pass that error probability to H_1 and test this hypothesis at level α.

Proof that FWER is protected



If H_1 and H_2 are both true,

$$\begin{aligned}
\text{FWER} &= Pr\{\text{Reject } H_1 \text{ or } H_2\} \\
&\leq Pr\{Z_1 > \Phi^{-1}(1-\alpha/2)\} + Pr\{Z_2 > \Phi^{-1}(1-\alpha/2)\} \\
&\leq \alpha/2 + \alpha/2 = \alpha.
\end{aligned}$$

If H_1 is true and H_2 is false,

$$\text{FWER} = Pr\{\text{Reject } H_1\} \leq Pr\{Z_1 > \Phi^{-1}(1-\alpha)\} = \alpha.$$

H_2 is true and H_1 false: Similar to H_1 true and H_2 false.

H_1 and H_2 both false: A type I error cannot be made.

Example: Primary and secondary endpoints

A hierarchical testing or "gatekeeping" procedure

Consider a trial where

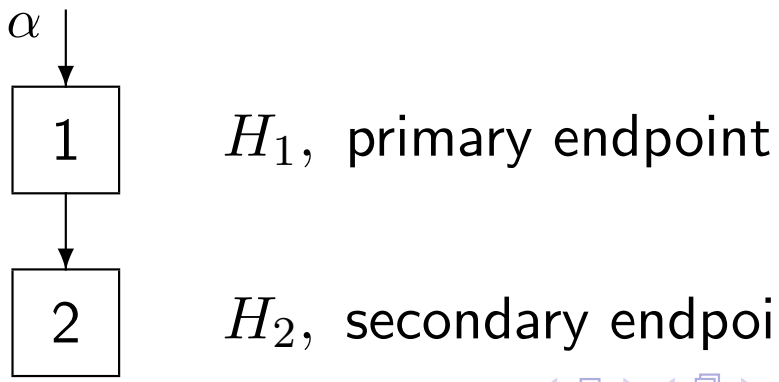
The null hypothesis H_1 concerns the primary endpoint,

The null hypothesis H_2 relates to a secondary endpoint,

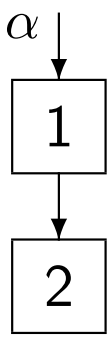
and H_2 will only be tested if H_1 has already been rejected.

First, we test H_1 at significance level α.

If H_1 is rejected, we continue and test H_2 at significance level α.



Proof that FWER is protected



H_1, primary endpoint

H_2, secondary endpoint

Suppose H_1 is true.

A family-wise error occurs if H_1 is rejected (whether or not H_2 is also rejected). So

$$\text{FWER} = Pr\{\text{Reject } H_1\} = Pr\{Z_1 > \Phi^{-1}(1-\alpha)\} = \alpha.$$

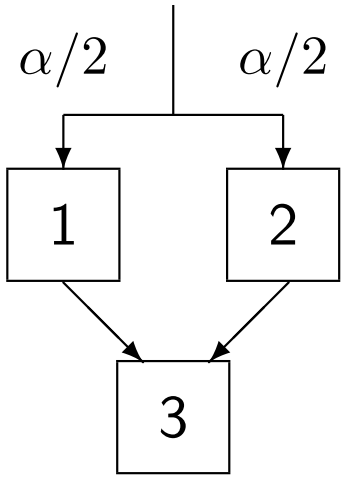
If H_1 is false and H_2 is true,

$$\begin{aligned} \text{FWER} &= Pr\{\text{Reject } H_1 \text{ and then reject } H_2\} \\ &\leq Pr\{Z_2 > \Phi^{-1}(1-\alpha)\} = \alpha. \end{aligned}$$

If H_1 and H_2 are both false, a type I error cannot be made.

Testing co-primary and secondary endpoints

The figure below represents a testing procedure that starts with a Bonferroni test of H_1 and H_2.



H_1, H_2: co-primary endpoints

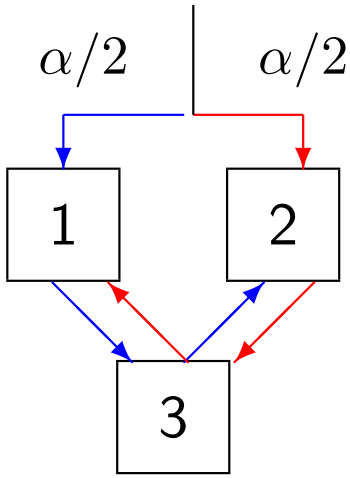
H_3: secondary endpoint

Then, if either H_1 or H_2 is rejected, the associated type I error is passed on to the test of H_3.

We can prove there is strong control of FWER at level α by considering all combinations of H_1, H_2 and H_3 being True or False.

Testing co-primary and secondary endpoints

We can add more "recycling" to the previous testing procedure.



H_1, H_2: co-primary endpoints

H_3: secondary endpoint

The additional lines in the graph indicate that

If $P_1 \leq \alpha/2$ and $P_3 \leq \alpha/2$, then H_2 is tested at level α,

If $P_2 \leq \alpha/2$ and $P_3 \leq \alpha/2$, then H_1 is tested at level α.

Testing co-primary and secondary endpoints

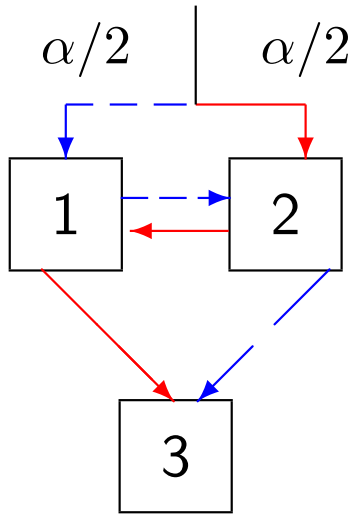
We may prefer to gain maximum power for tests of co-primary endpoints before testing a secondary endpoint.

To do this, we recycle type I error probability between H_1 and H_2 before allocating any error probability to H_3.

A graphical representation is:

H_1, H_2: co-primary endpoints

H_3: secondary endpoint



Half of the type I error probability is cycled through H_1, H_2 and on to H_3.

The other half is cycled through H_2, H_1 and on to H_3.

More complex procedures: General methodology

As we add more options, and get more creative, we can produce some quite complex procedures.

Two papers, published simultaneously, describe an elegant way to describe complex multiple testing procedures.

> *"A recycling framework for the construction of Bonferroni-based multiple tests" by Burman, Sonesson and Guilbaud,* Statistics in Medicine, *2009.*

> *"A graphical approach to sequentially rejective multiple test procedures" by Bretz, Maurer, Brannath and Posch,* Statistics in Medicine, *2009.*

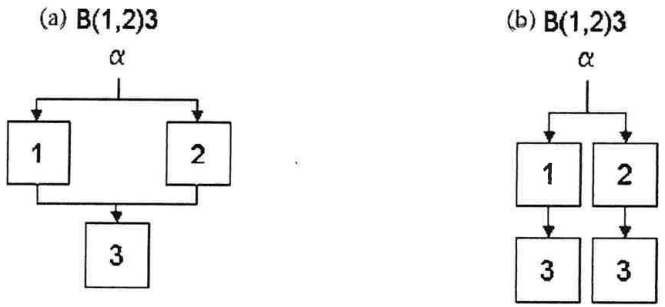
These procedures are closed testing procedures in which the tests of intersection hypotheses are weighted Bonferroni tests.

It is implicit in their method of construction that these procedures provide strong control of the FWER.

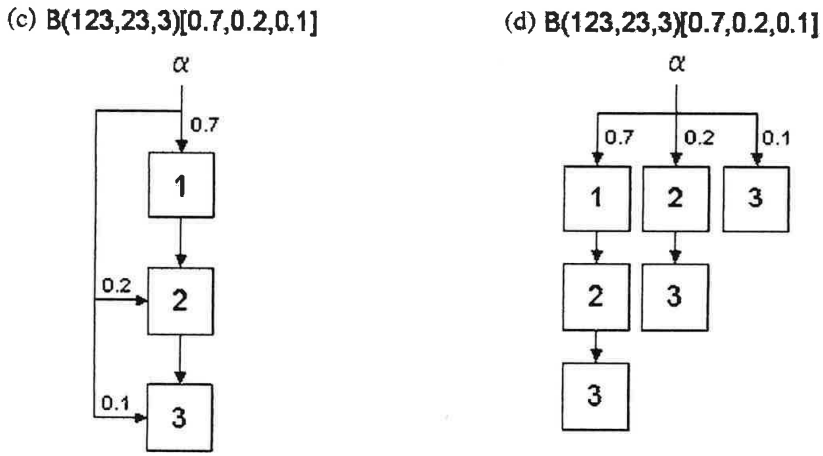
A figure from Burman et al. (2009)

The following diagrams illustrate the graphical representations of multiple testing procedures used by Burman et al.

(a) and (b) A parallel gatekeeping procedure



(c) and (d) A fallback procedure



A figure from Bretz et al. (2009)

And here is an example of a graphical representation of a procedure as defined by Bretz et al.

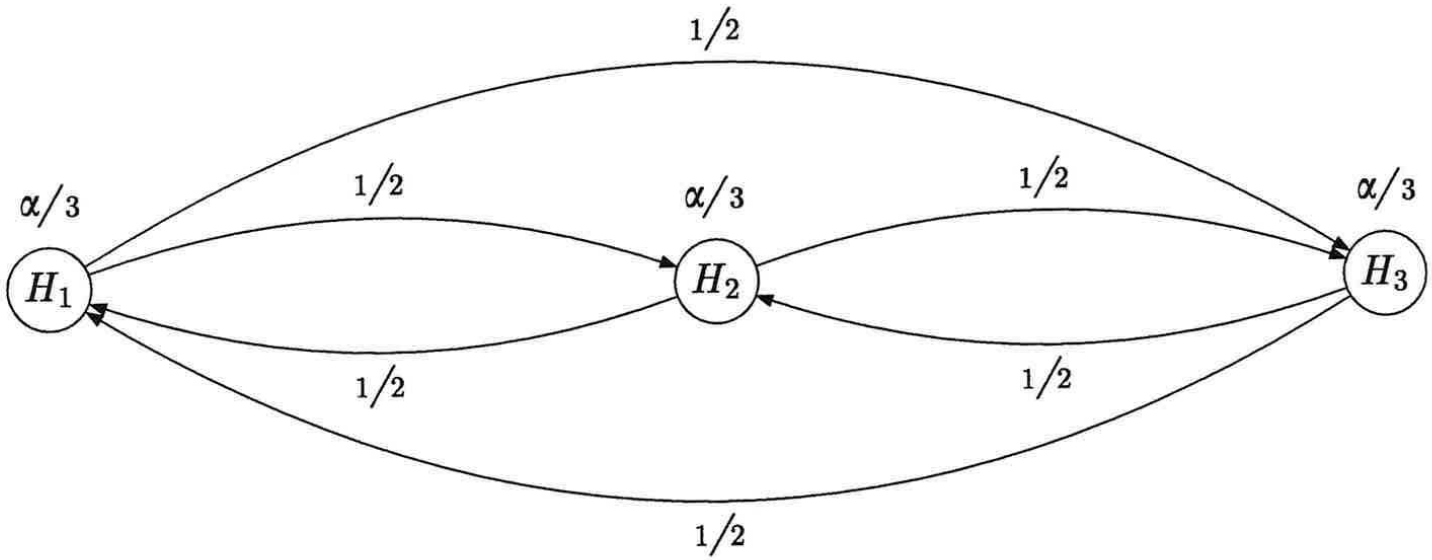


Figure 3. Graphical illustration of the Bonferroni–Holm procedure with $m = 3$ hypotheses and initial allocation $\boldsymbol{\alpha} = (\alpha/3, \alpha/3, \alpha/3)$.

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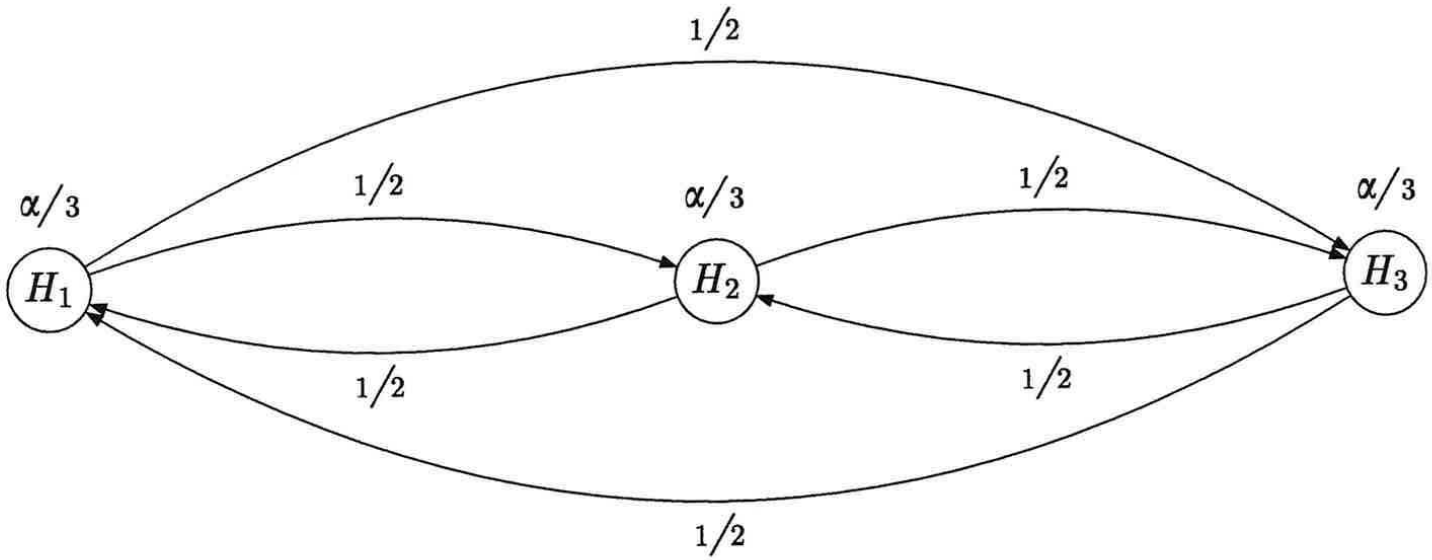


Figure 3. Graphical illustration of the Bonferroni–Holm procedure with $m = 3$ hypotheses and initial allocation $\boldsymbol{\alpha} = (\alpha/3, \alpha/3, \alpha/3)$.

Question: How can we apply such a procedure in a group sequential trial?

4. Multiple testing procedures and group sequential designs

Maurer & Bretz (*Statist. in Biopharm. Research*, 2013) explain how to carry out tests of multiple hypothesis in a group sequential trial with strong control of FWER.

Consider a multiple testing procedure for hypotheses $H_1, \ldots, H_h$ that involves testing $H_1, \ldots, H_h$ at different significance levels, possibly increasing these levels after other hypotheses are rejected.

Define group sequential tests of each hypothesis with type I error rates equal to the various significance levels that may be applied.

At each analysis, conduct tests of $H_1, \ldots, H_h$ using the boundary points of their group sequential tests for the current analysis.

In doing this, follow the testing hierarchy and "re-cycling rules" to determine the type I error rate of each hypothesis testing boundary.

Stop the study when key conclusions have been reached.

Combining multiple testing and group sequential design

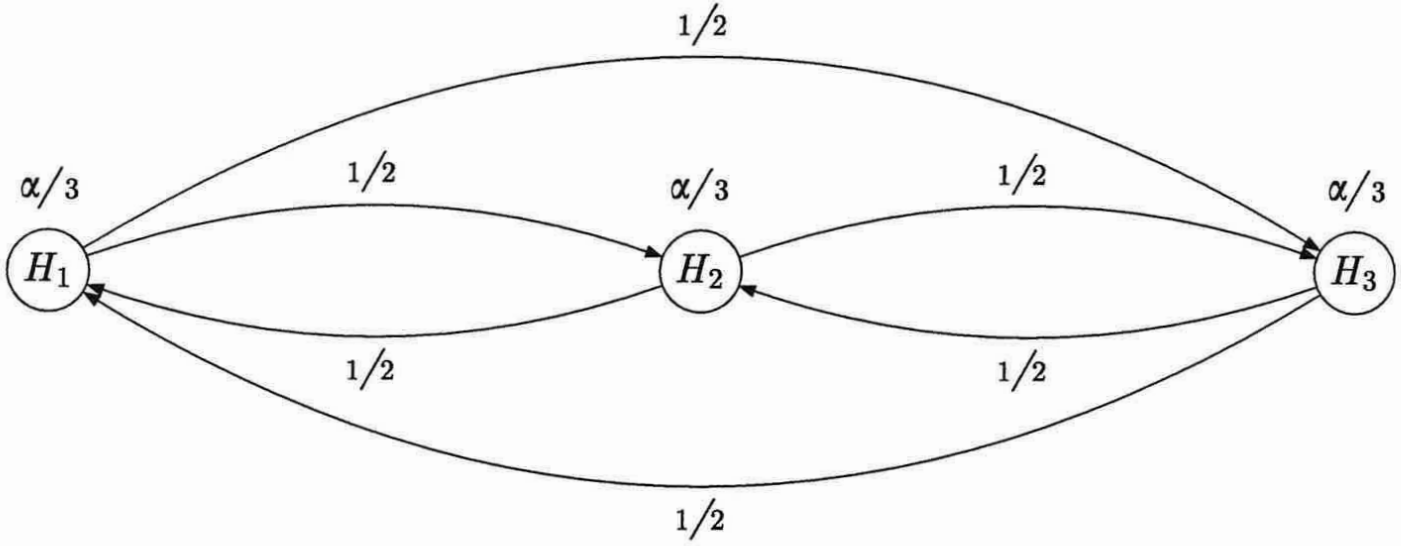


Figure 3. Graphical illustration of the Bonferroni–Holm procedure with $m=3$ hypotheses and initial allocation $\boldsymbol{\alpha}=(\alpha/3, \alpha/3, \alpha/3)$.

For group sequential implementation of the above multiple testing procedure, we need

GSTs at levels $\alpha/3$, $\alpha/2$ and α

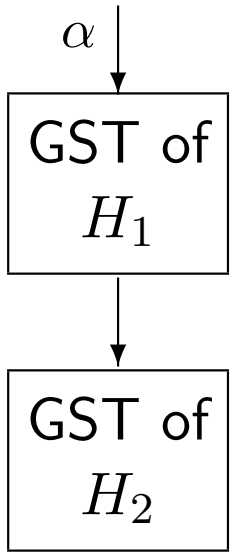
for each of the hypotheses, H_1, H_2 and H_3.

5. Testing a secondary endpoint after a sequential test

A correct gatekeeping procedure

We discussed a group sequential trial comparing the effects of two treatments with on a primary endpoint. Then, if a positive result is obtained, a secondary endpoint is tested.

In Maurer & Bretz's scheme, we need to specify a level α group sequential test for the secondary endpoint: this test of H_2 will be applied whenever the trial terminates.



The group sequential test of H_1 determines the stopping time for the trial

The group sequential test of H_2 is used for the secondary analysis if and when H_1 is rejected

A correct gatekeeping procedure

Let $Z_{1,1}, \ldots, Z_{1,K}$ be Z-statistics for testing H_1: $\theta_1 \leq 0$ at analyses $1, \ldots, K$.

The group sequential test of H_1 stops at analysis k to

$$\text{Reject } H_1 \quad \text{if } Z_{1,k} \geq b_k,$$

$$\text{Accept } H_1 \quad \text{if } Z_{1,k} < a_k.$$

Boundary values for the test of H_1 control the type I error rate at level α under $\theta_1 = 0$, i.e.,

$$\sum_{k=1}^{K} Pr\{Z_{1,1} \in (a_1, b_1), \ldots, Z_{1,k-1} \in (a_{k-1}, b_{k-1}), Z_{1,k} > b_k\} = \alpha.$$

Suppose this GST stops to reject H_1 at analysis k^* ...

A correct gatekeeping procedure

Let $Z_{2,1}, \ldots, Z_{2,K}$ be Z-statistics for testing H_2: $\theta_2 \leq 0$.

The level α group sequential test of H_2 rejects H_2 at analysis k if $Z_{2,k} \geq c_k$, where under $\theta_2 = 0$

$$\sum_{k=1}^{K} Pr\{Z_{2,1} < c_1, \ldots, Z_{2,k-1} < c_{k-1}, Z_{2,k} > c_k\} = \alpha. \quad (1)$$

(The trial's stopping rule is based on the primary endpoint, so we do not need a lower boundary for early acceptance of H_2.)

When the GST of H_1 has rejected H_1 at analysis k^*, we reject H_2 if $Z_{2,k^*} \geq c_{k^*}$.

A gatekeeping procedure *could* reject H_2 if

$$Z_{2,k} \geq c_k \quad \text{for any } k \in \{1, \ldots, K\},$$

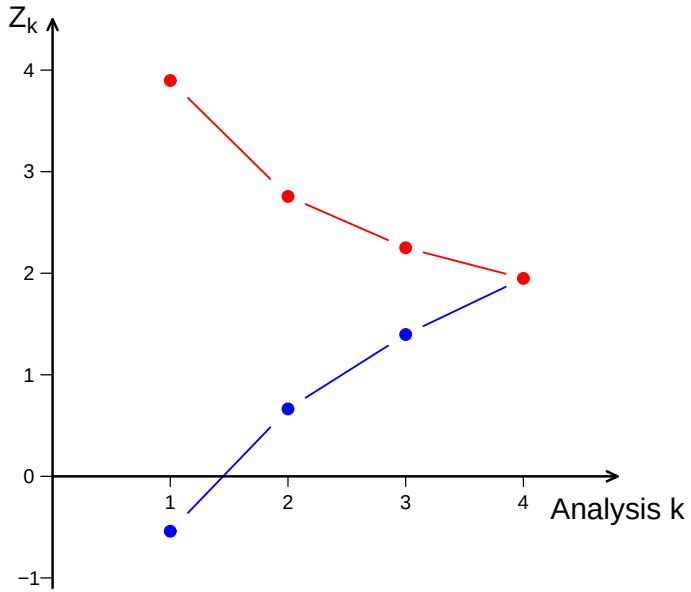
so the FWER is protected conservatively.

Example: Testing primary and secondary endpoints

In a trial comparing two treatments, denote the treatment effects on the primary and secondary endpoints by θ_1 and θ_2.

Suppose the trial is conducted group sequentially, using a Pampallona & Tsiatis test with $\Delta = 0$ for the primary endpoint.

There are 4 analyses, $\alpha = 0.025$ and power is 0.8 at $\theta_1 = 1$.



If H_1: $\theta_1 \leq 0$ is rejected for the primary endpoint at analysis k^*, we test the secondary endpoint: we reject H_2: $\theta_2 \leq 0$ if

$$Z_{2,k^*} \geq c_{k^*}.$$

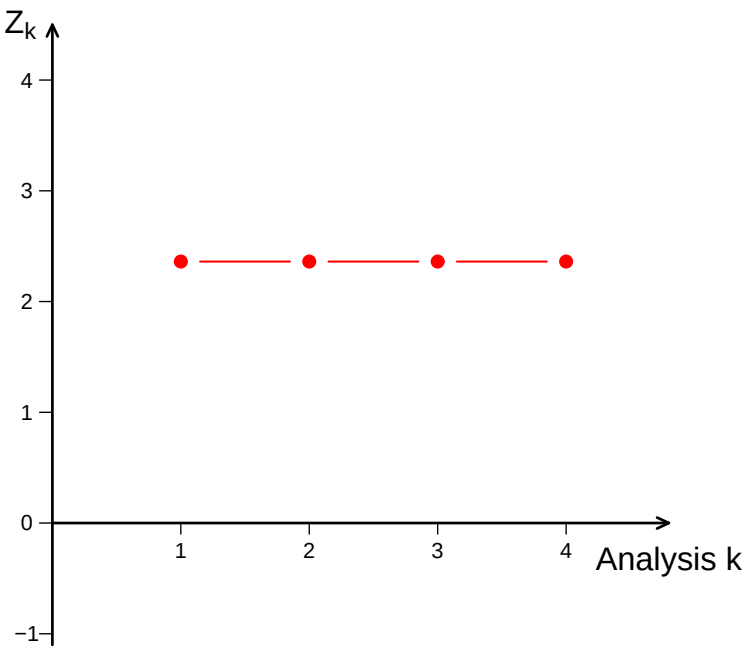
We consider two options for this test of H_2.

Example: Testing primary and secondary endpoints

We consider two options for the group sequential test of H_2.

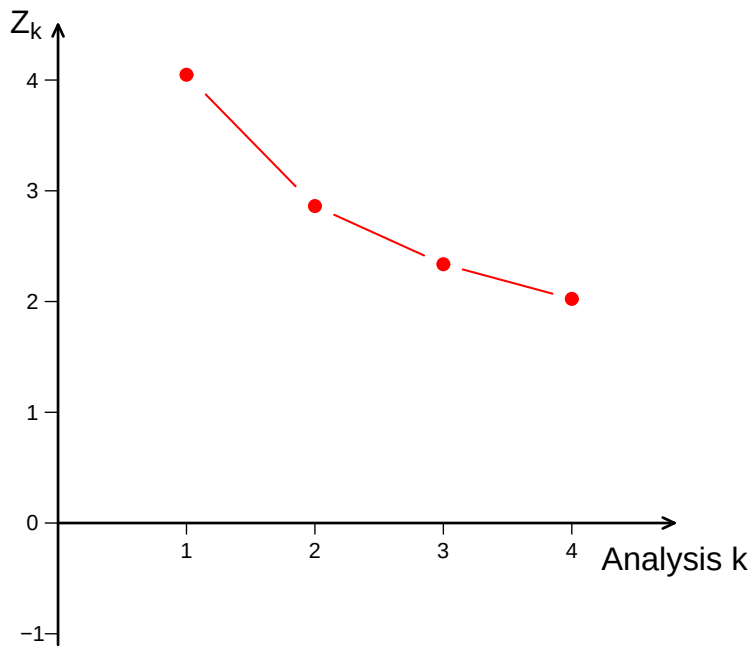
A: Pocock boundary for H_2

$$c_k = 2.361, \quad k = 1, \ldots, 4.$$



B: OBF boundary for H_2

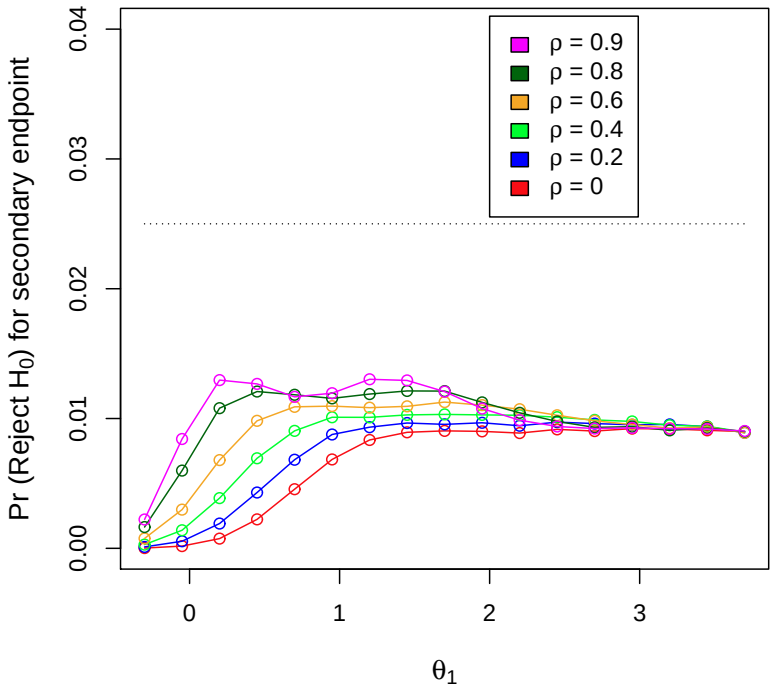
$$c_k = 2.024\sqrt{4/k}, \quad k = 1, \ldots, 4.$$



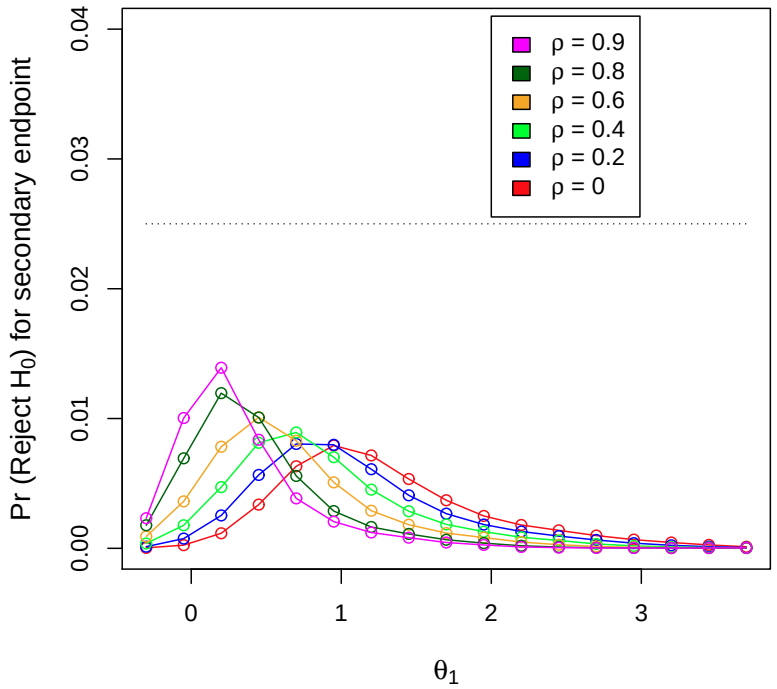
Note: The O'Brien & Fleming boundary requires a very high value of Z_{2,k^*} to reject H_2 if the GST of H_1 stops at the first analysis.

Type I error probability for testing H_2

A: Pocock boundary for H_2



B: OBF boundary for H_2

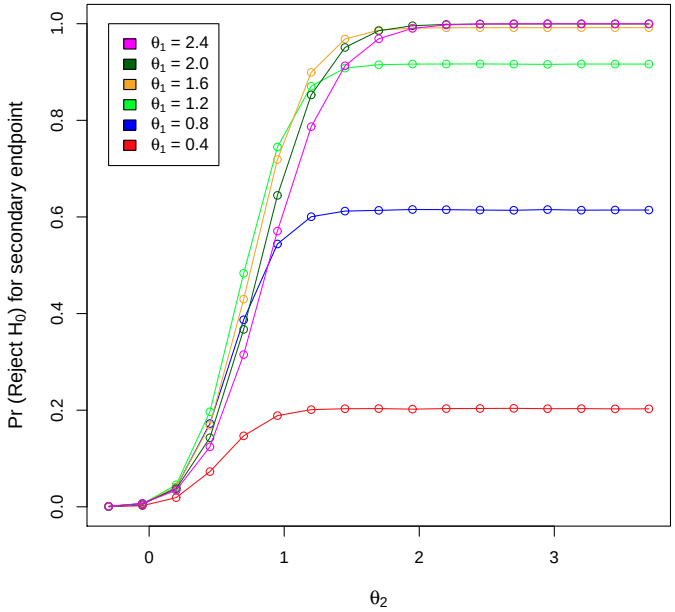


Type I error probabilities are calculated under $\theta_2 = 0$, but they also depend on θ_1 and the correlation, ρ, between the primary and secondary endpoints.

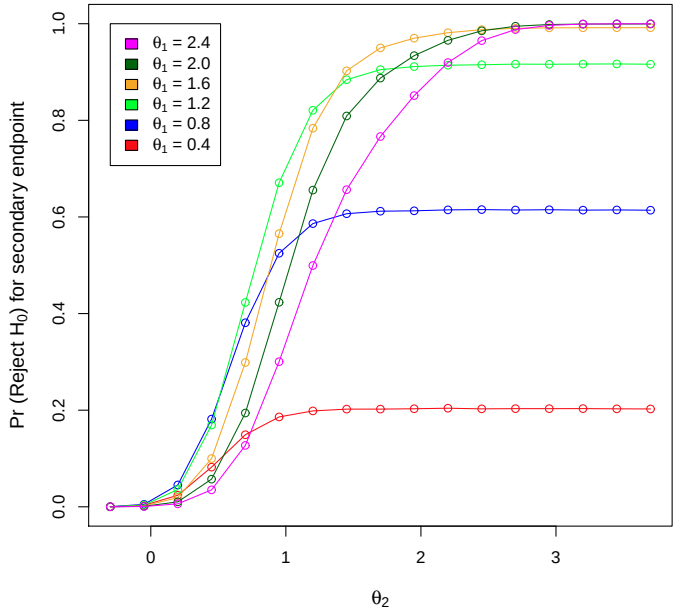
The OBF test of H_2 is particularly conservative when θ_1 is large.

Power for testing H_2, $\rho = 0.25$

A: Pocock boundary for H_2



B: OBF boundary for H_2



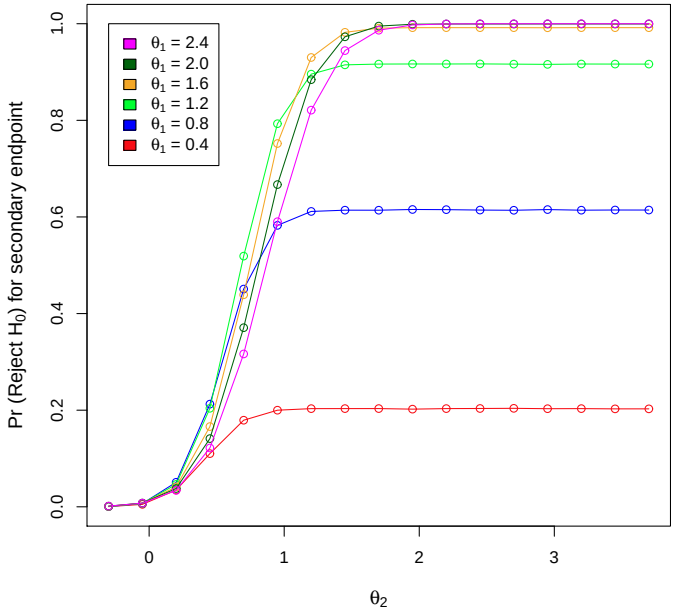
Results are shown for the case that the variance of the secondary response is 0.5 times that for the primary response.

Power is shown as a function of θ_2 for selected values of θ_1.

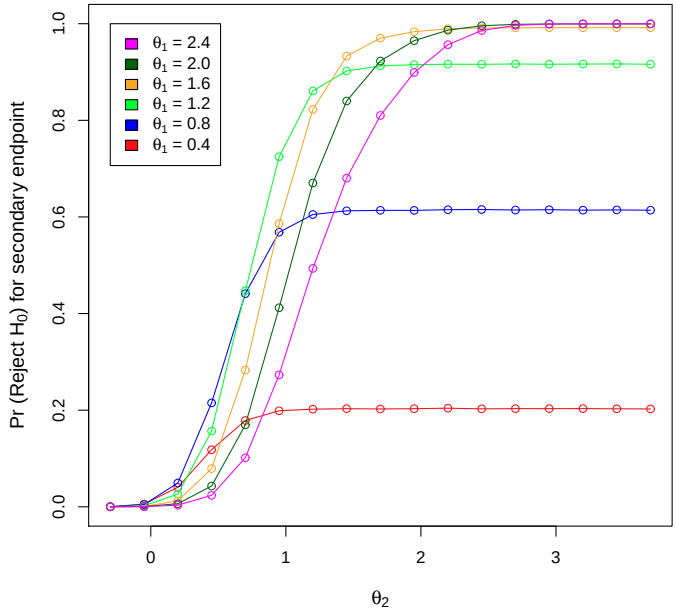
The Pocock boundary for H_2 deals better with the trial's uncertain termination time — which depends significantly on the value of θ_1.

Power for testing H_2, $\rho = 0.5$

A: Pocock boundary for H_2



B: OBF boundary for H_2



Results are shown for the case that the variance of the secondary response is 0.5 times that for the primary response.

Power is shown as a function of θ_2 for selected values of θ_1.

Again, the Pocock boundary for H_2 deals better with the trial's uncertain termination time — which depends significantly on θ_1.

Testing a secondary endpoint: Further options

Conservatism in the overall procedure arises because the test of H_1 may stop at analysis k^* when $Z_{2,k^*} < c_{k^*}$, but

$$Z_{2,k} \geq c_k \quad \text{for some } k < k^* \text{ or } k > k^*.$$

There are options for reducing conservatism and increasing power:

1. Reject H_2 if $Z_{2,k} \geq c_k$ for some $k < k^*$, even though $Z_{2,k^*} < c_{k^*}$.

   However, ignoring more recent data (and not using the sufficient statistic for θ_2) may detract from the credibility of this decision.

2. Continue the trial to see if $Z_{2,k} \geq c_k$ at a future analysis.

   However, if the primary endpoint is observed for future subjects, the positive result on the primary endpoint could be "lost".

Several authors have considered option (2), retaining a positive outcome for H_1, whatever the additional information about θ_1.

GSTs and multiple hypothesis testing: Conclusions

1. There are methods available to test multiple hypotheses in a group sequential design AND control the overall type I error probability.

2. Graphical representations (SiM papers, 2009) can help investigators to select — and understand — an appropriate multiple testing procedure.

3. There are many multiple testing schemes to choose from. The most suitable choice will depend on the importance to investigators of rejecting each null hypothesis and the likelihood of each null hypothesis being true or false.

4. When testing multiple hypotheses in a group sequential trial design, the key point is to use GSTs as the "testing rules" in the multiple testing scheme: if this is not done correctly, FWER may be inflated.

Testing a secondary endpoint: Further options

3. If the worst case scenario, in which a procedure's maximum FWER occurs, can be identified then, the procedure may be calibrated so the FWER is equal to the specified level α in this scenario. See:

Glimm, Maurer & Bretz (Stat. in Med., 2010) Hierarchical testing of multiple endpoints in group-sequential trials.

Tamhane, Mehta & Liu (Biometrics, 2010) Testing a primary and a secondary endpoint in a group sequential design.

Tamhane, Wu & Mehta (Stat. in Med., 2012) Adaptive extensions of a two-stage group sequential procedure for testing primary and secondary endpoints (I) unknown correlation between endpoints.

Tamhane, Gou, Jennison, Mehta & Curto (Biometrics, 2018) A gatekeeping procedure to test a primary and a secondary endpoint in a group sequential design with multiple interim looks.

GSTs and multiple hypothesis testing: further reading

Tang & Geller (Biometrics, 1999) Closed testing procedures for group sequential clinical trials with multiple endpoints.

Ye, Liu & Yao (Statist. in Med., 2012) A group sequential Holm procedure with multiple primary endpoints.

Maurer & Bretz (Statist. in Biopharm. Research, 2013) Multiple testing in group sequential trials using graphical approaches.

Li, Wang, Luo, Grechko & Jennison (Biometrical Journal, 2018) Improved two-stage group sequential procedures for testing a secondary endpoint after the primary endpoint achieves significance.