Multi-arm Group Sequential Designs with a Simultaneous Stopping Rule

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Objectives of multi-arm multi-stage trials

Aim: Comparison of several treatments to a common control

Compared to separate, fixed sample two-armed trials

- less patients needed than for separate controlled clinical trials
- larger number of patients are randomised to experimental treatments
- possibility to stop early for efficacy or futility

Objective: Identify **all** treatments that are superior to control

Objective: Identify **at least one** treatment that is superior to control

Which stopping rule?

Design setup: group sequential Dunnett test

- Comparison of two treatments to a control
- Normal endpoints, variance known
- One sided tests: $H_A : \mu_A - \mu_C \leq 0$ and $H_B : \mu_B - \mu_C \leq 0$
- Control of the FamilyWise Error Rate (FWER) $= 0.025$
- Two stage group sequential trial: one interim analysis at $\frac{N_{max}}{2}$
- $Z_{A,i}$, $Z_{B,i}$ are the cumulative z-statistics at stage i=1,2

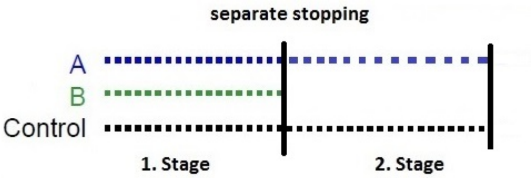
Classical group sequential Dunnett tests with “separate stopping”

Classical group sequential Dunnett tests

Objective: Identify all treatments that are superior to control

"separate stopping rule":
Treatment arms, for which a stopping boundary is crossed, stop.

E.g.:

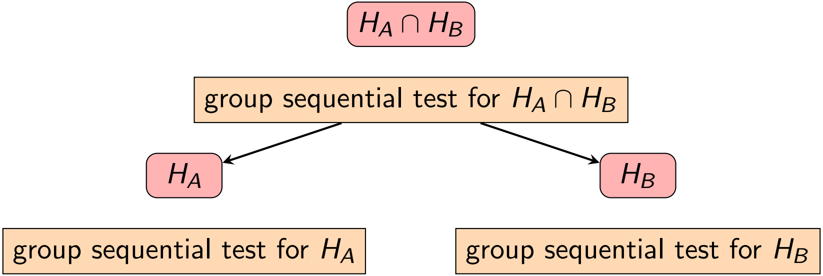


→ H_B is rejected at interim
→ A can go on and is tested again at the end

Magirr, Jaki, Whitehead (2012)

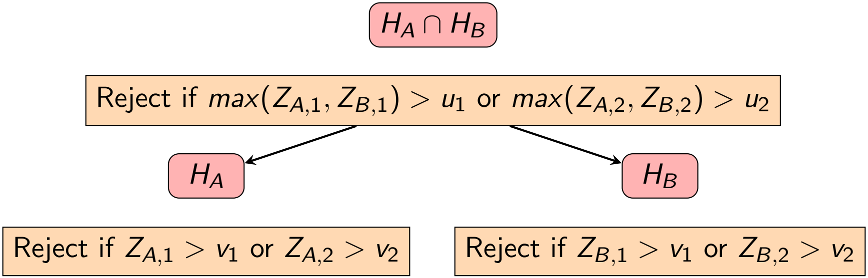
Closed group sequential tests

Local group sequential tests for $H_A \cap H_B$ and H_A, H_B are needed!!!



A hypothesis is rejected with FWER α if the intersection hypothesis and the corresponding elementary hypothesis are rejected locally at level α.

Closed group sequential tests



u_1, u_2...global boundaries

v_1, v_2...elementary boundaries

Koenig, Brannath, Bretz and Posch (2008)
Xi, Tamhane (2015)
Maurer, Bretz (2013)

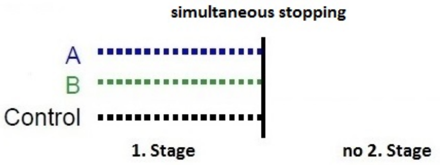
Group sequential Dunnett tests with “simultaneous stopping”

Group sequential simultaneous stopping designs

"simultaneous stopping rule":
If at least one rejection boundary is crossed, the whole trial stops.

Objective: Identify at least one treatment that is superior to control

If, e.g., H_B is rejected at interim then the trial is stopped:



Simultaneous versus Separate Stopping

- The **FWER** is controlled when using the boundaries of the separate stopping design.
- The **expected sample size (ESS)** is lower compared to separate stopping designs.
- The **power to reject**
  - **any** null hypothesis is the **same** as for separate stopping designs.
  - **both** null hypotheses is **lower** than for separate stopping designs.

$\rightarrow$ **Trade-off between ESS and conjunctive power**

Construction of efficient simultaneous stopping designs

1. Can one **relax the interim boundaries** when stopping simultaneously?
2. How large is the impact on **ESS and power** when stopping simultaneously or separately?
3. How to **optimize** the critical boundaries for either stopping rule?

Question 1: Relaxation of interim boundaries?

For simultaneous stopping:

- The boundaries u_1, u_2 for the local test of $H_A \cap H_B$ cannot be relaxed.
- The boundaries v_1, v_2 for the local test of H_j can be relaxed.

Intuitive explanation

If, e.g., H_B is rejected at interim, but H_A not, H_A is no longer tested at the final analysis and not all α is spent.

It's possible to choose improved boundaries for the elementary tests.

(similar as for group sequential multiple endpoint tests in Tamhane, Metha, Liu 2010).

What changes when stopping simultaneously?

Example: O'Brien Fleming boundaries

$H_A \cap H_B$

Reject if $max(Z_{A,1}, Z_{B,1}) > u_1$ or $max(Z_{A,2}, Z_{B,2}) > u_2$

$u_1 = 3.14, \; u_2 = 2.22$

H_A

Reject if $Z_{A,1} > v_1$ or $Z_{A,2} > v_2$

$v_1 = 2.80, \; v_2 = 1.98$

H_B

Reject if $Z_{B,1} > v_1$ or $Z_{B,2} > v_2$

$v_1 = 2.80, \; v_2 = 1.98$

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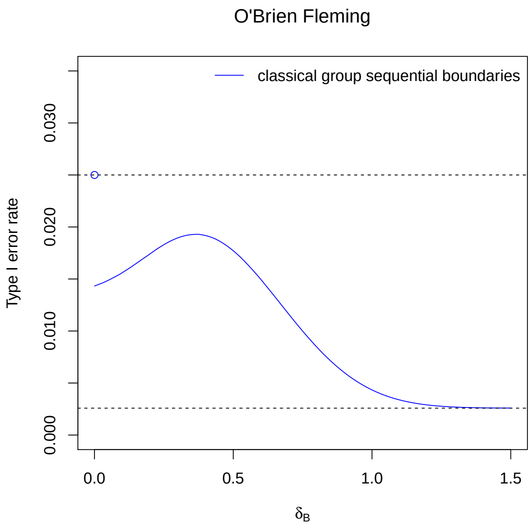
H_B

Reject if $Z_{B,1} > v_1$ or $Z_{B,2} > v_2$

$v_1 = 2.80, \ v_2 = 1.98$

For simultaneous stopping there is no second stage test if one of the null hypotheses can already be rejected at interim.

FWER for simultaneous stopping if only H_A holds ($\delta_A = 0$)



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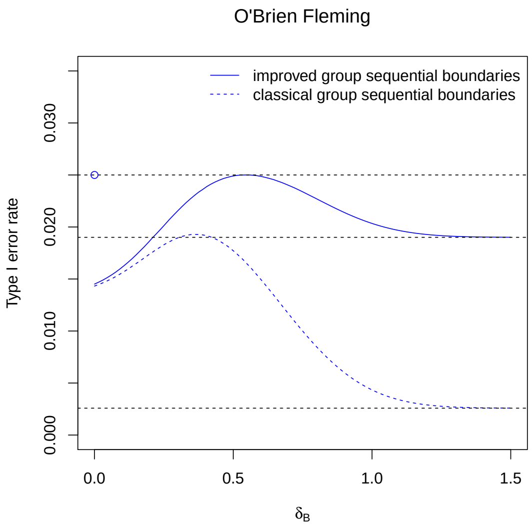

Question 2: Impact on ESS and power?

For $\alpha = 0.025$ and $\delta_A = \delta_B = 0.5$

Conjunctive Power = Power to reject both false hypotheses
Disjunctive Power = Power to reject at least one false hypothesis

	separate stopping rule	simultaneous stopping rule	improved simultan.
Boundaries u_i for $H_1 \cap H_2$	$u_1 = 3.14,\ u_2 = 2.22$		
Interim boundary v_1	2.80	2.80	2.08
Final boundary v_2	1.98	1.98	1.98
Maximum α for test of H_j	0.025	0.019	0.025
Disj. power	0.97	0.97	0.97
N	324	324	324
ESS	230	205	205
Conj. power	0.89	0.69	0.76

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Optimized multi-arm multi-stage designs

Optimized designs

For $\alpha = 0.025$ and $\delta_A = \delta_B = 0.5$.

Design	**"Separate stopping"**	**"Simultaneous stopping"**	**"Improved simult. stopping"**
Boundaries	group sequential	group sequential	improved group sequential
Stopping rule	separate stopping rule	simultaneous stopping rule	simultaneous stopping rule

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N_{max}	chosen to achieve disjunctive power of 0.9		
Obj. function to optimize u_1, u_2	expected sample size		

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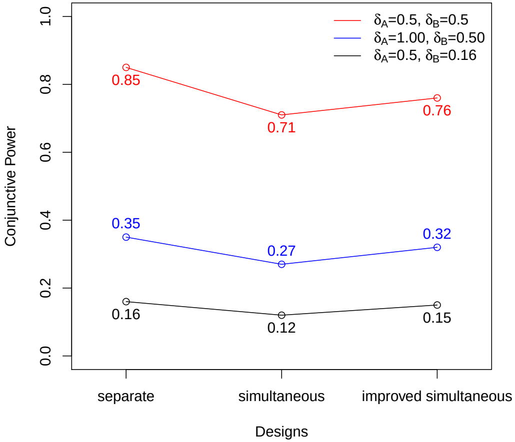
Obj. function to optimize u_1, u_2	expected sample size		
Obj. function to optimize v_1, v_2	expected sample size	conjunctive power	

Optimized boundaries $\delta_A = 0.5$, $\delta_B = 0.5$

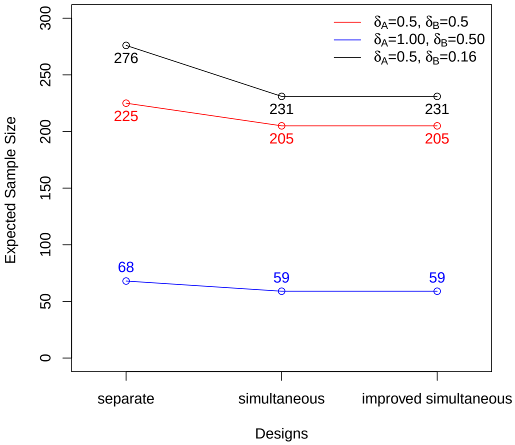
	separate	simultaneous	improved simult.
u_1	2.47	2.41	2.41
u_2	2.38	2.43	2.43
v_1	2.05	2.06	2.00
v_2	2.38	2.37	2.06
conj. power	0.85	0.71	0.76
ESS	225	205	205
N_{max}	318	324	324

Power to reject both null hypotheses



Power to reject at least one false hypothesis = 90% for all designs.

Optimal expected sample size (ESS)



ESS reduction between 8% and 16%.

Unknown variance: Extension to the t test

- P-value approach: z-score boundaries are converted to p-value boundaries and then applied to t-test p-values
- Simulation of t-statistics for p-value approach (optimized for $\delta_A = \delta_B = 1$) for $\sigma = 1$.

Design	N	α
separate	8	0.0259
	12	0.0257
	100	0.0251
improved	8	0.0261
	12	0.0258
	100	0.0250

Summary

- The **optimal design** depends on the type of objective:
  - Reject **all** hypotheses
  - Reject **at least one** hypothesis

- **Simultaneous stopping compared to separate stopping** leads to
  - lower expected sample size
  - the same power to reject any hypothesis
  - lower power to reject both hypotheses

  Improved boundaries can be used to regain some of the power to reject both null hypotheses.

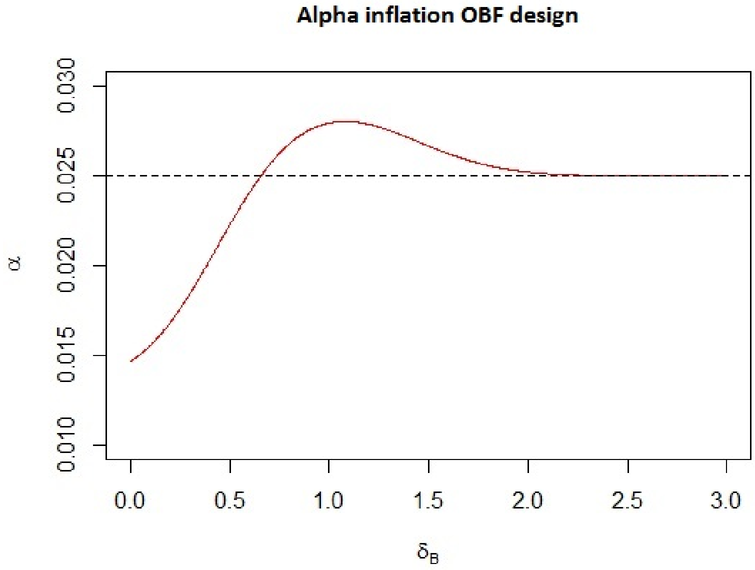
- **Limitation:** If improved boundaries are used, the simultaneous stopping rule must be adhered to!

- **Extensions:**
  - more treatment arms, stopping for futility
  - optimal choice of first stage sample size/allocation ratio

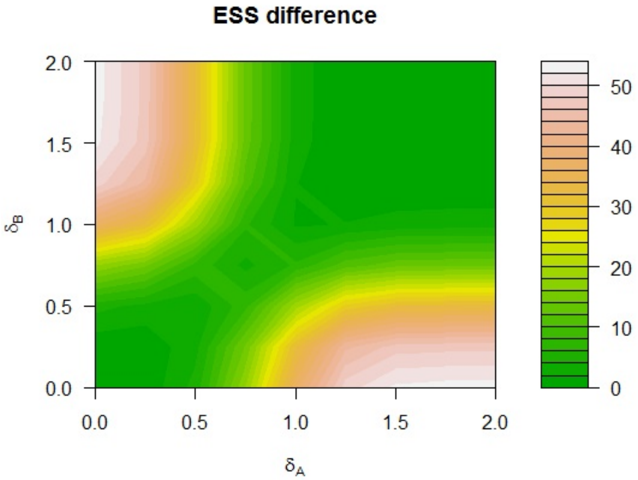
References

- Thall et al. (1989): one treatment continues, futility stopping, two stages, power comparisons under LFC
- Follmann et al. (1994): Pocock and OBF MAMS designs, Dunnett and Tukey generalisations, several stages
- Stallard & Todd (2003): only one treatment is taken forward, several stages, power comparisons
- Stallard & Friede (2008): stagewise prespecified number of treatments
- **Magirr, Jaki, Whitehead (2012)**: FWER of generalised Dunnett
- Koenig, Brannath, Bretz (2008): closure principle for Dunnett test, adaptive Dunnett test
- **Magirr, Stallard, Jaki (2014)**: Flexible sequential designs
- Di Scala & Glimm (2011): Time to event endpoints
- **Wason & Jaki (2012)**: Optimal MAMS designs
- **Tamhane & Xi (2013)**: multiple hypotheses and closure principle
- Maurer & Bretz (2013): Multiple testing using graphical approaches

FWER inflation when $u_1^* = z_{1-\alpha}$=1.96



Difference in expected sample size: OBF design



Difference in conjunctive power: OBF design