Group sequential designs for Clinical Trials with multiple treatment arms

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Objectives of multi-arm multi-stage trials

Aim: Comparison of several treatments to a common control

Advantages:

- less patients needed than for separate controlled clinical trials
- especially important for limited set of patients (rare diseases, children)
- larger number of patients are randomised to experimental treatments
- allows changes to be made during the trial using the trial data so far, e.g. stopping for efficacy or futility

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

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

$\rightarrow$ **different kind of stopping rules!!**

Design setup: group sequential Dunnett test

- control of the FamilyWise Error Rate (FWER) $= 0.025$
- comparison of two treatments to a control
- normal endpoints, variance known
- one sided tests: $H_A : \mu_A - \mu_C \leq 0$ and $H_B : \mu_B - \mu_C \leq 0$
- two stage group sequential trial: one interim analysis at $\frac{N_{max}}{2}$
- power to reject at least one hypothesis $= 0.8$
- $Z_{A,i}$, $Z_{B,i}$ are the cumulative z-statistics at stage i=1,2

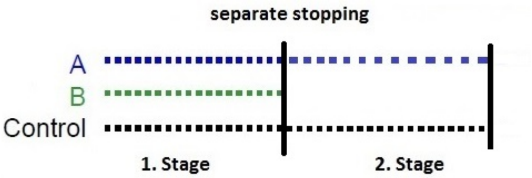
Classical group sequential Dunnett tests with “separate stopping”

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.:

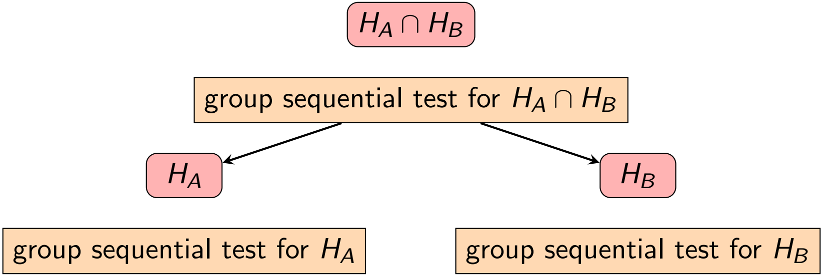


→ H_B is rejected at interim
→ A can go on and is tested again at the end

Magirr, Jaki, Whitehead (2012)

Closed testing - sequentially rejective tests

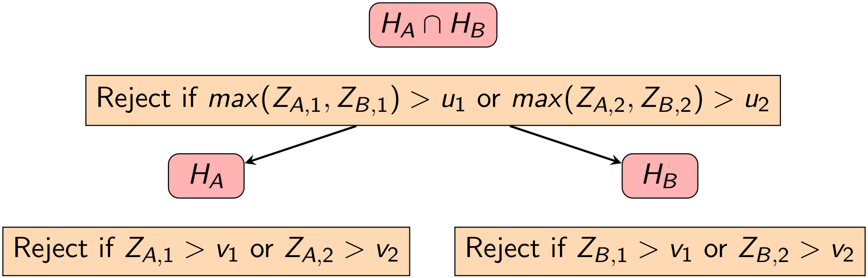
Local group sequential tests for $H_A \cap H_B$ and H_A, H_B are needed!!!



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

Xi, Tamhane (2015)
Maurer, Bretz (2013)

Closed testing - sequentially rejective tests



u_1, u_2...global boundaries

v_1, v_2...elementary boundaries

Koenig, Brannath, Bretz and Posch (2008)

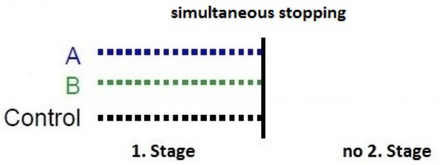
Group sequential Dunnett tests with “simultaneous stopping”

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

E.g.: H_B is rejected at interim



$\rightarrow$ There is no second stage!

Simultaneous versus Separate stopping

- **FWER** is controlled using the separate stopping design boundaries.
- **Lower expected sample size** 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.

Example: O'Brien Flemming boundaries

What changes when stopping simultaneously?

$H_A \cap H_B$

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 $Z_{A,2} > v_2$

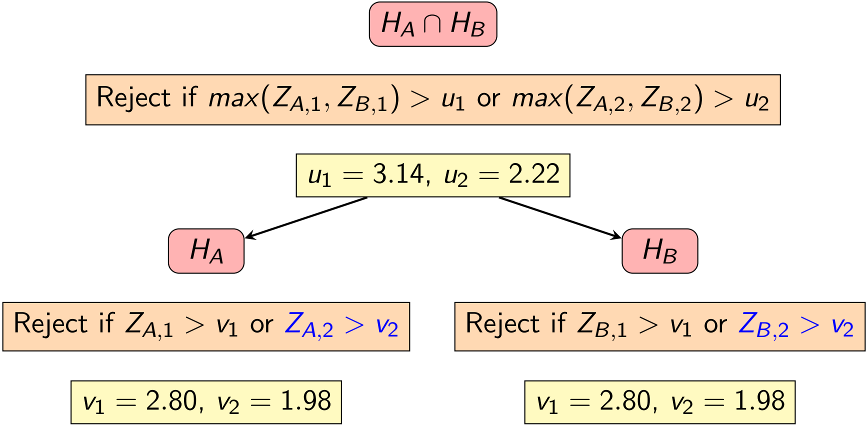
$v_1 = 2.80,\ v_2 = 1.98$

H_B

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

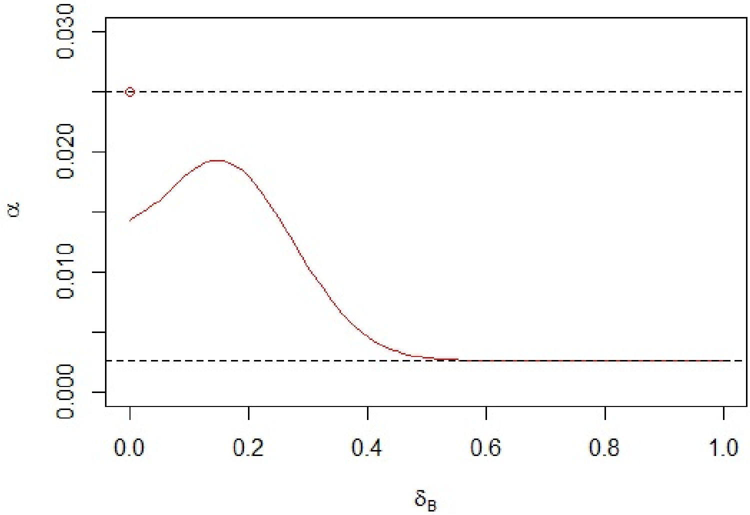
$v_1 = 2.80,\ v_2 = 1.98$

Example: O'Brien Flemming boundaries



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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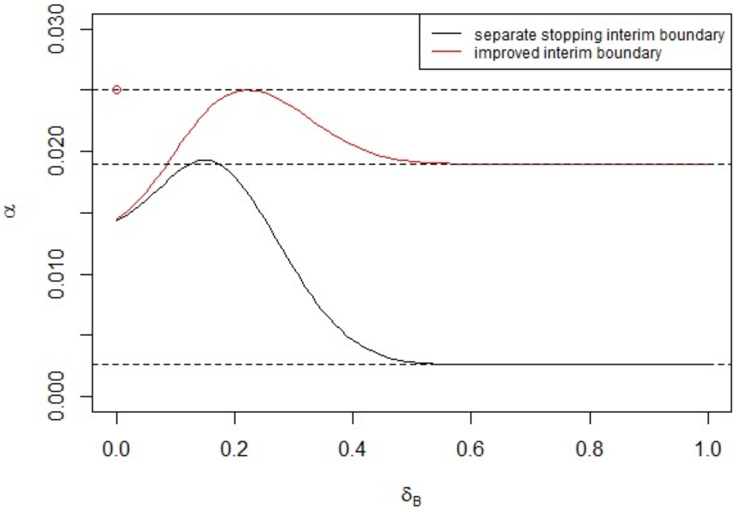

Example: O'Brien Flemming form of rejection boundaries

Improved boundary at interim for simultaneous stopping:

$H_A \cap H_B$

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 $Z_{A,2} > v_2$

$v_1' = 2.08,\ v_2 = 1.98$

H_B

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

$v_1' = 2.08,\ v_2 = 1.98$

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

Question 2: Impact on ESS and power?

global boundaries	$u_1 = 3.14,\ u_2 = 2.22$		
local α for test of $H_A \cap H_B$	$\alpha = 0.025$		
	separate stopping rule	simultaneous stopping rule	improved simultan.
local α for test of H_j	0.025	0.019	0.025
interim boundary v_1	2.80	2.80	2.08
final boundary v_2	1.98	1.98	1.98

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interim boundary v_1	2.80	2.80	2.08
final boundary v_2	1.98	1.98	1.98
disj. power	0.8	0.8	0.8
N	162	162	162

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interim boundary v_1	2.80	2.80	2.08
final boundary v_2	1.98	1.98	1.98
disj. power	0.8	0.8	0.8
N for $\delta_A = \delta_B = 0.5$	162	162	162
ESS for $\delta_A = \delta_B = 0.5$	154	149	149
conj. power for $\delta_A = \delta_B = 0.5$	0.59	0.50	0.56

Optimized multi-arm multi-stage designs

Optimal designs

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

Optimal designs

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Stopping rule	separate stopping rule	simultaneous stopping rule	simultaneous stopping rule
N_{max}	chosen to achieve disjunctive power of 0.8		
Obj. function optimize u_1, u_2	minimize ESS under certain parameter configuration		

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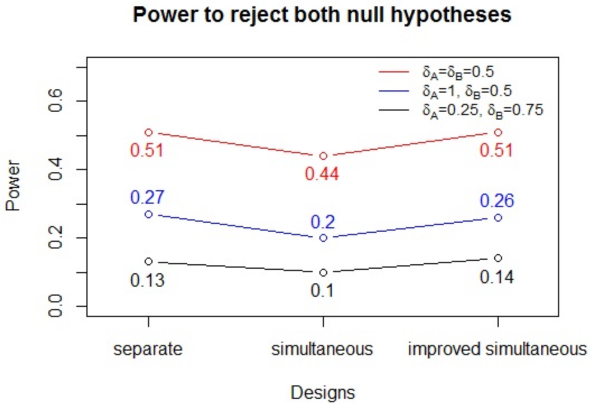
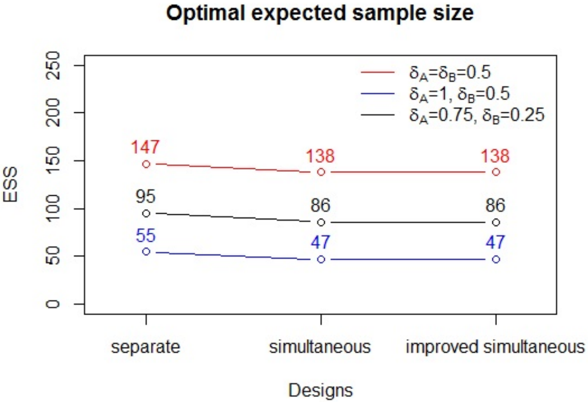
Stopping rule	separate stopping rule	simultaneous stopping rule	simultaneous stopping rule
N_{max}	chosen to achieve disjunctive power of 0.8		
Obj. function optimize u_1, u_2	minimize ESS under certain parameter configuration		
Obj. function optimize v_1, v_2	minimize ESS	maximize conjunctive power	

Power to reject both null hypotheses

Power to reject at least one hypothesis = 0.8



Optimal expected sample size (ESS)



Remarks: Percentual reduction gets bigger, but stays between 5 and 12%

Summary

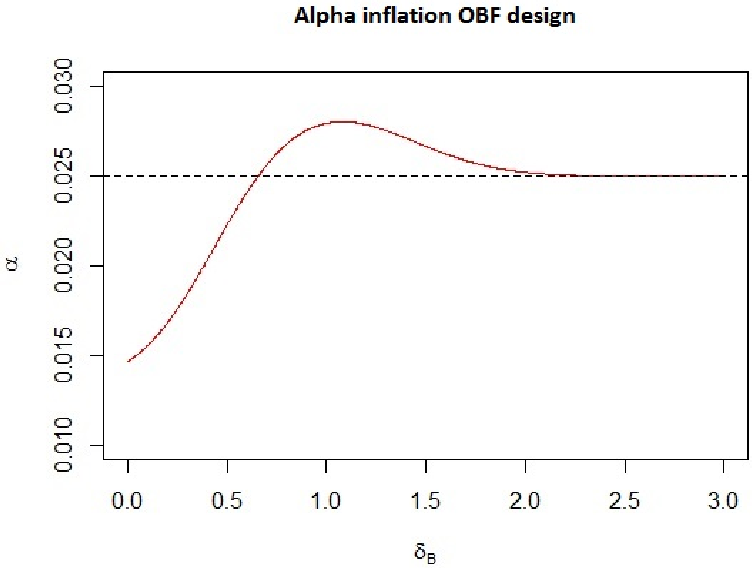
- The **optimal design** depends on the objective:
  - Reject **all** hypotheses
  - Reject **at least one** hypothesis
- **Simultaneous stopping compared to separate stopping** leads to
  - lower expected sample size
  - the same power to reject any hypothesis
  - lower power to reject both hypotheses

  Improved boundaries can be used to rescue some of the power to reject both null hypotheses.
- **Limitation:** If improved boundaries are used, the simultaneous stopping rule must be adhered to!
- **Extensions:**
  - unknown variance: t-test: p-value approach
  - more treatment arms, stopping for futility
  - optimal choice of first stage sample size/allocation ratio

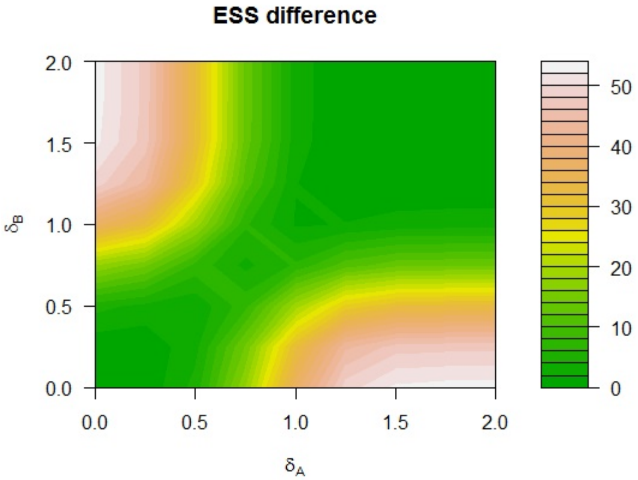
References

- 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

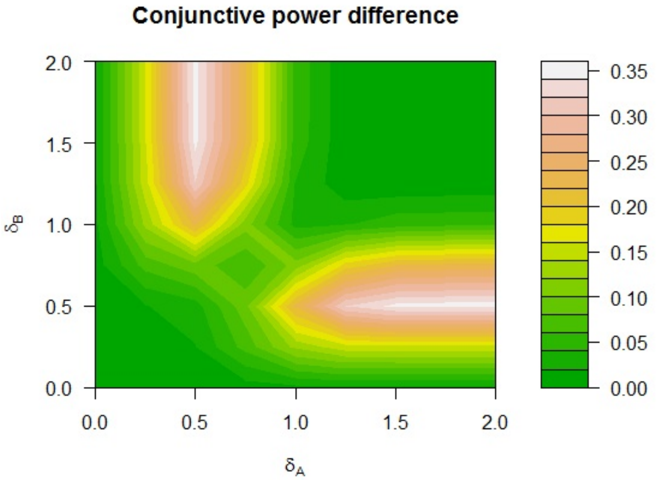
FWER inflation when $u_1^* = z_{1-\alpha}$=1.96



Difference in expected sample size: OBF design



Difference in conjunctive power: OBF design



Unknown variance: Extension to the t test

- **p-value approach = quantile substitution (Pocock (1977)):** z-score boundaries are converted to p-value boundaries and then converted to t-score boundaries:

$$u_i' = T_{2n_i-2}(\Phi^{-1}(u_i))$$

- **for known variance:** sample size per arm per stage n of **8** for a power to reject at least one of 0.8 at $\delta_A = \delta_B = 1$

(separate: ESS=32/power=0.61; improved simultaneous: ESS=30/power=0.51)

Simulation of t-statistics for p-value approach ($\delta_A = \delta_B = 1$)					
Design	n	α	power at least one	power both	ESS
separate	8	0.0260	0.80	0.56	34
separate	10	0.0258	0.89	0.70	43
imp. sim.	8	0.0260	0.79	0.49	32
imp. sim.	10	0.0258	0.88	0.61	39

Optimal boundaries

$\delta_A = 0.5,\ \delta_B = 0.5$			
Design	separate	simultaneous	improved simult.
u_1	2.64	2.48	2.48
u_2	2.29	2.37	2.37
v_1	2.09	2.16	2.05
v_2	2.29	2.20	1.97
conj. power	0.51	0.44	0.51
ESS	147	138	138