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On Adaptive Designs with Dependent Stages Based on Fisher's Combination Test

Workshop "Adaptive Designs and Multiple Testing Procedures"
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medizinische fakultät
Westfälische Wilhelms-Universität Münster

UKM Universitätsklinikum Münster

ZKS Zentrum für Klinische Studien Münster

Trial Structure with Dependent p-values

- Trial with several primary time-to-event endpoints:
  - E.g.: Event free survival (EFS) and overall survival (OS)
- This implies performance of several significance tests:
  - Multiplicity due to interim analyses (from adaptive design)
  - Multiplicity due to multiple endpoints.
- Doing several significance tests increases the overall chance of a type I error.
- Adjustment for multiple testing: Adaptive closed testing procedure (Hommel, 2001).

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Adaptive Modifications of Hypotheses After an Interim Analysis

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Trial Structure with Dependent p-values

- Treat several time-to-event outcomes as key in an adaptive setting:
  - E.g.: Event free survival (EFS) and overall survival (OS)
- This implies performance of several significance tests:
  - Multiplicity due to interim analyses (from adaptive design)
  - Multiplicity due to multiple endpoints.
- Doing several significance tests increases the overall chance of a type I error.
- Adjustment for multiple testing: Adaptive closed testing procedure (Hommel, 2001).
- May result in dependent p-values!

Example

Hierarchical Testing with Change of Order of Hypotheses in Any Case

	Stage 1	Stage 2
H_1	$p_{1,1} \leftrightarrow T_1(t_{1,1})$	$p_{1,2} \leftrightarrow T_1(t_{1,2}) - T_1(t_{1,1})$

- H_1: Null hypothesis of no difference between two treatment arms with respect to EFS.
- Stage-wise p-values based on independent increment structure of the two-sample log-rank statistic (T_1: associated Brownian motion).

714 Biometrical Journal **48** (2006) 4, 714–729 DOI: 10.1002/bimj.200510190

Planning and Analyzing Adaptive Group Sequential Survival Trials

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Example

Hierarchical Testing with Change of Order of Hypotheses in Any Case

	Stage 1	Stage 2
H_1	$p_{1,1} \leftrightarrow T_1(t_{1,1})$	$p_{1,2} \leftrightarrow T_1(t_{1,2}) - T_1(t_{1,1})$

- Then:
  - P-values are marginally uniformly distributed $P_{1,1}, P_{1,2} \sim U(0,1)$
- Analogously for H_2: Null hypothesis of no difference between two treatment arms with respect to OS.

Example

Hierarchical Testing with Change of Order of Hypotheses in Any Case

	Stage 1	Stage 2
H_1	$p_{1,1} \leftrightarrow T_1(t_{1,1})$	$p_{1,2} \leftrightarrow T_1(t_{1,2}) - T_1(t_{1,1})$
H_2	$p_{2,1} \leftrightarrow T_2(t_{2,1})$	$p_{2,2} \leftrightarrow T_2(t_{2,2}) - T_2(t_{2,1})$

- Attention!
  - Use of information on EFS (H_1) from interim analysis for adaptation of H_2 (OS) is not readily possible.
  - Otherwise p-values might no longer be marginally uniformly distributed, that is, $P_{i,j} \sim U(0,1)$ might be violated.

STATISTICS IN MEDICINE
Statist. Med. 2004; **23**:1333–1335 (DOI: 10.1002/sim.1759)

LETTER TO THE EDITOR

Modification of the sample size and the schedule of interim analyses in survival trials based on data inspections

by H. Schäfer and H.-H. Müller, *Statistics in Medicine* 2001; **20**:3741–3751

From: *P. Bauer and M. Posch*
Department of Medical Statistics
University of Vienna

Example

Hierarchical Testing with Change of Order of Hypotheses in Any Case

	Stage 1	Stage 2
H_1	$p_{1,1} \leftrightarrow T_1(t_{1,1})$	$p_{1,2} \leftrightarrow T_1(t_{1,2}) - T_1(t_{1,1})$
H_2	$p_{2,1} \leftrightarrow T_2(t_{2,1})$	$p_{2,2} \leftrightarrow T_2(t_{2,2}) - T_2(t_{2,1})$

- Therefore, we assume in the sequel:
  - Design modification of H_1 are only based on $p_{1,1}$.
  - Design modification of H_2 are only based on $p_{2,1}$.
- Then, p-values are marginally uniformly distributed: $P_{i,j} \sim U(0,1)$
- $P_{1,1}$ and $P_{2,2}$: Still dependent with unknown dependence structure.
- Even if we refrain from adaptations of H_1, H_2.

Example

Hierarchical Testing with Change of Order of Hypotheses in Any Case

	Stage 1	Stage 2
H_1	$p_{1,1} \leftrightarrow T_1(t_{1,1})$	$p_{1,2} \leftrightarrow T_1(t_{1,2}) - T_1(t_{1,1})$
H_2	$p_{2,1} \leftrightarrow T_2(t_{2,1})$	$p_{2,2} \leftrightarrow T_2(t_{2,2}) - T_2(t_{2,1})$
$H_1 \cap H_2$	$p_{1\cap 2,1} = p_{1,1}$	$p_{1\cap 2,2} = p_{2,2}$

- Properties of the above p-values:
  - $P_{i,j} \sim U(0,1)$
  - $P_{1,1}$ and $P_{2,2}$: Dependent with unknown dependence structure.
  - Even if we refrain from adaptations of H_1, H_2.
- P-clud condition $P_{H_0}(P_{2,2} \leq \alpha | P_{1,1}) \leq \alpha$ might not be fulfilled!

Rationale

- In order to guarantee control of type I error rate, we need adaptive designs with . . .
  - marginally uniformly distributed, but . . .
  - arbitrarily dependent p-values.

Two-Stage Adaptive Designs

- Type I error rate in two-stage adaptive designs:

$$P_{H_0}(P_1 \leq \alpha_1) + P_{H_0}(P_2 \leq \alpha(P_1), \alpha_1 < P_1 \leq \alpha_0)$$

- Depends on:
  - α_0, α_1 and $\alpha(p_1)$.
  - Joint distribution of P_1, P_2, that is, the copula C of P_1, P_2.
  - Write $P_{H_0}^C$ instead of P_{H_0} in sequel to indicate dependence structure.

Adaptive Designs with Arbitrary Dependence Structure

- True type I error rate: $P_{H_0}^{C}(Reject\ H_0).$

- Type I error rate α_{ind} in case of independent p-values:

$$\alpha_{ind} = P_{H_0}^{\Pi}(Reject\ H_0)$$

$\Pi(\mathrm{x}, \mathrm{y}) = \mathrm{x} \cdot y$ independence copula.

- Type I error rate α_W in the worst case:

$$\alpha_W = \sup_C P_{H_0}^{C}(Reject\ H_0)$$

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Adaptive designs with arbitrary dependence structure

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Example: Fisher Combination Test

- $\alpha(p_1) = \begin{cases} 1 & , p_1 \leq \alpha_1 \\ \frac{c_{BK}}{p_1} & , p_1 > \alpha_1 \end{cases}$
- $P_1, P_2 \sim U(0,1)$ under H_0.

BIOMETRICS 50, 1029–1041
December 1994

Evaluation of Experiments with Adaptive Interim Analyses

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Example: Fisher Combination Test

- $\alpha(p_1) = \begin{cases} 1 & , p_1 \leq \alpha_1 \\ \frac{c_{BK}}{p_1} & , p_1 > \alpha_1 \end{cases}$
- $P_1, P_2 \sim U(0,1)$ under H_0.
- Type I error rate for independent und uniformly distr. p-values:

$$\alpha_{ind} = \psi - \log(\psi) c_{BK}, \qquad \psi := \max\{\alpha_1, c_{BK}\}$$

Example: Fisher Combination Test

- $\alpha(p_1) = \begin{cases} 1 & , p_1 \leq \alpha_1 \\ \frac{c_{BK}}{p_1} & , p_1 > \alpha_1 \end{cases}$
- $P_1, P_2 \sim U(0,1)$ under H_0.
- Type I error rate for independent und uniformly distr. p-values:
  - $\alpha_{ind} = \alpha_1 + c_{BK}[\log(\alpha_0) - \log(\alpha_1)]$,
  - if $c_{BK} \leq \alpha_1, \alpha_0 = 1$.

Example: Fisher Combination Test

- $\alpha(p_1) = \begin{cases} 1 & , p_1 \leq \alpha_1 \\ \frac{c_{BK}}{p_1} & , p_1 > \alpha_1 \end{cases}$
- $P_1, P_2 \sim U(0,1)$ under H_0.
- Type I error rate for independent und uniformly distr. p-values:

$$\alpha_{ind} = \psi - \log(\psi) c_{BK}, \qquad \psi := \max\{\alpha_1, c_{BK}\}$$

- Worst case type I error rate α_W:

$$c_{BK} = \begin{cases} \frac{\alpha_W^2}{4} & , if \;\; 2\alpha_1 \leq \alpha_W \\ \alpha_1(\alpha_W - \alpha_1) & , if \;\; 2\alpha_1 > \alpha_W \end{cases}$$

Example: Worst Case Inverse Normal Designs

- Worst case type I error rate α_W in terms of α_{ind} and α_1:

$$\alpha_{ind} = \begin{cases} \frac{\alpha_W^2}{4}\left[1 - \log\left(\frac{\alpha_W^2}{4}\right)\right] & ,if \quad 0 < \alpha_1 \leq \frac{\alpha_W^2}{4} \\ \alpha_1 - \log(\alpha_1)\frac{\alpha_W^2}{4} & ,if \ \frac{\alpha_W^2}{4} < \alpha_1 \leq \frac{\alpha_W}{2} \\ \alpha_1 - \log(\alpha_1)\,\alpha_1(\alpha_W - \alpha_1) & ,if \quad \frac{\alpha_W}{2} < \alpha_1 \end{cases}$$

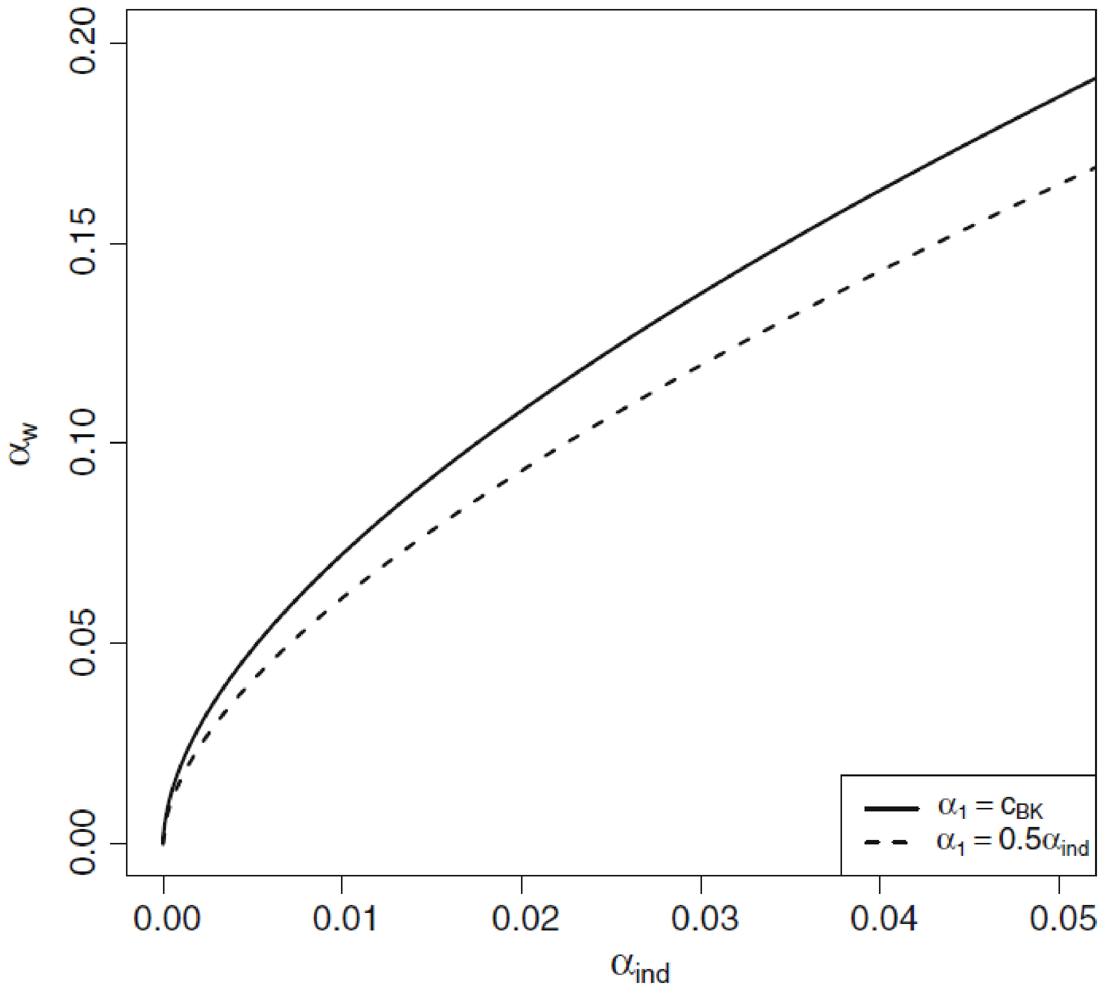
α_W in terms of α_{ind} and α_1 if $\alpha_1 = 0.5\,\alpha_{ind}$

$\alpha_1 = 0.5\alpha_{ind}$		$\alpha_1 = 0.5\alpha_{ind}$	
α_{ind} (%)	α_w (%)	α_{ind} (%)	α_w (%)
0.012	0.5	0.5	4.1
0.042	1.0	1.0	6.1
0.087	1.5	1.5	7.8
0.145	2.0	2.0	9.3
0.214	2.5	2.5	10.7
0.294	3.0	3.0	12.0
0.482	4.0	4.0	14.3
0.706	5.0	5.0	16.5
1.396	7.5	7.5	21.3
2.245	10.0	10.0	25.8

α_W in terms of α_{ind} and α_1 if $\alpha_1 = c_{BK}$

$\alpha_1 = c_{BK}$		$\alpha_1 = c_{BK}$	
α_{ind} (%)	α_w (%)	α_{ind} (%)	α_w (%)
0.008	0.5	0.5	4.9
0.029	1.0	1.0	7.2
0.061	1.5	1.5	9.1
0.102	2.0	2.0	10.8
0.153	2.5	2.5	12.3
0.211	3.0	3.0	13.7
0.353	4.0	4.0	16.3
0.524	5.0	5.0	18.7
1.064	7.5	7.5	23.9
1.748	10.0	10.0	28.6

α_W in terms of α_{ind} and α_1



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Adaptive designs with arbitrary dependence structure based on Fisher's combination test

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Summary

- General concept for adaptive designs with arbitrary dependence structure.
- Application to designs based on Fisher's combination test.
- Motivation: Adaptive Change of Hypotheses in trial with multiple time-to-event endpoints (e.g. in pediatric oncology)
- This example was chosen for illustrative reasons.
- Considerable inflation of the type I error rate can occur, if the dependence structure is not taken into account adequately.
- Controlling the worst case appears practically unfeasible.
- Problem arose from: Patients without event at interim analysis.
- Potential solution, e.g.:
  - Study more specific dependence structures.
  - Forgetting information from patients censored at interim.

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Thank you for your attention!

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