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Homogeneity of Stages in Adaptive Designs

Dr. Andreas Faldum

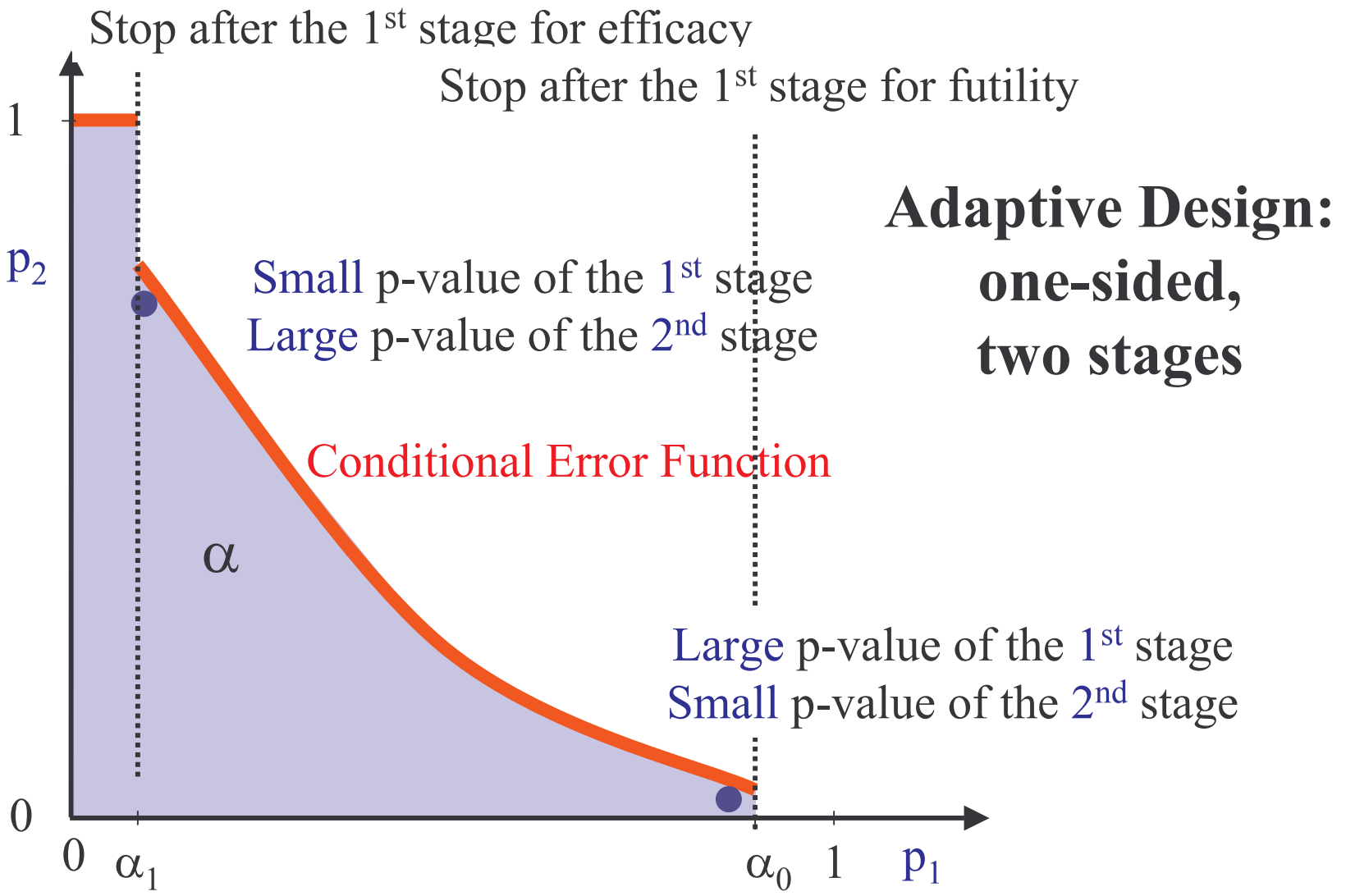
Institute of Medical Biostatistics, Epidemiology and Informatics

JOHANNES GUTENBERG UNIVERSITÄT MAINZ

Dr. Andreas Faldum
Mathematician and Physician

Institute of Medical Biostatistics,
Epidemiology and Informatics
Johannes Gutenberg-University
Langenbeckstraße 1 - D-55101 Mainz

Tel.: +49-6131-17-3938
Fax +49-6131-17473938
faldum@imbei.uni-mainz.de


Stop after the 1st stage for efficacy
Stop after the 1st stage for futility
1
p2
0
0
α1
α0
1
p1
Small p-value of the 1st stage
Large p-value of the 2nd stage
Conditional Error Function
α
Large p-value of the 1st stage
Small p-value of the 2nd stage
Adaptive Design:
one-sided,
two stages

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London, 23 March 2006
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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS WITH FLEXIBLE DESIGN AND ANALYSIS PLAN

DRAFT AGREED BY THE EFFICACY WORKING PARTY	11 January 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	23 March 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 September 2006

EMEA: Reflection Paper on Flexible Designs

- Request for comparable results of interim and end analysis
- Difficulties to interpret conclusions from discrepant stages
- Suspicion of dissemination of interim results
- Bias of the results of forthcoming stages
- Rejection of the global null hypothesis across all stages is not sufficient
- Discrepant stages cause problems with regulatory authorities

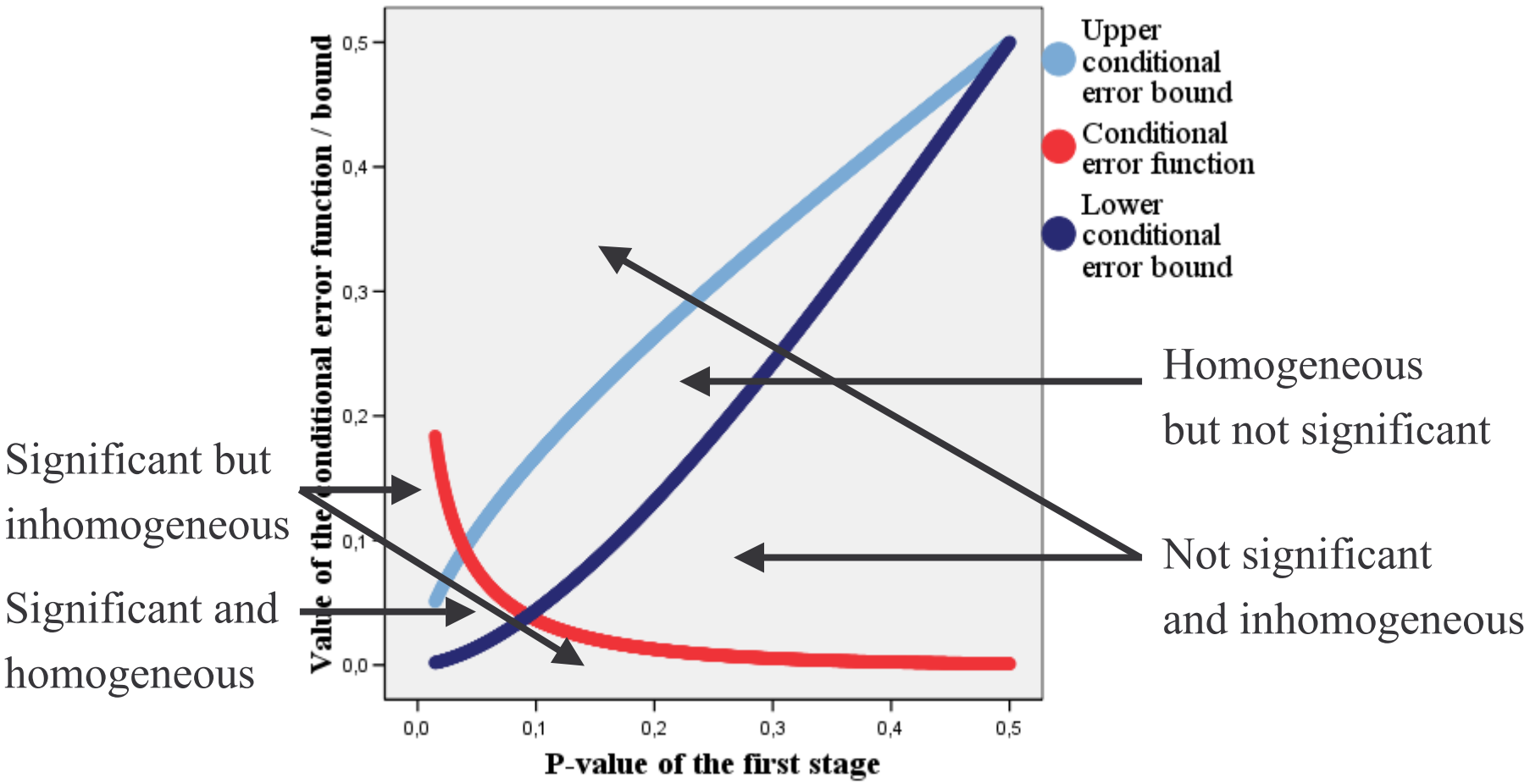
Homogeneity of Treatment Effect Estimates

- Two-sample Gauss test for difference of means
- Sample size for each group in stage i = n_i
- Treatment effect estimate observed in the i^{th} stage:
  Standardised difference = $\delta_i = \sqrt{\{2/n_i\}} \cdot \Phi^{-1}(1-p_i)$
- Choose homogeneity bound $C > 1$
- Idea: Homogeneity of stages $\Leftrightarrow \delta_1/C \le \delta_2 \le \delta_1 \cdot C$
- Lower and upper conditional error bounds:
  - $\alpha_{low}(p_1) \le p_2 \le \alpha_{up}(p_1) \Leftrightarrow \delta_1/C \le \delta_2 \le \delta_1 \cdot C$
- Requirement: $\alpha(p_1) \in [\alpha_{low}(p_1), \alpha_{up}(p_1)]$

Example 1: Group Sequential Design

- Pocock group sequential design with:
  $n_2 = n_1$, $\alpha = 0.025$, $\alpha_1 = 0.015$, $\alpha_0 = 0.50$
- Homogeneity bound: $C = 1.33$

Example 1: Group Sequential Design



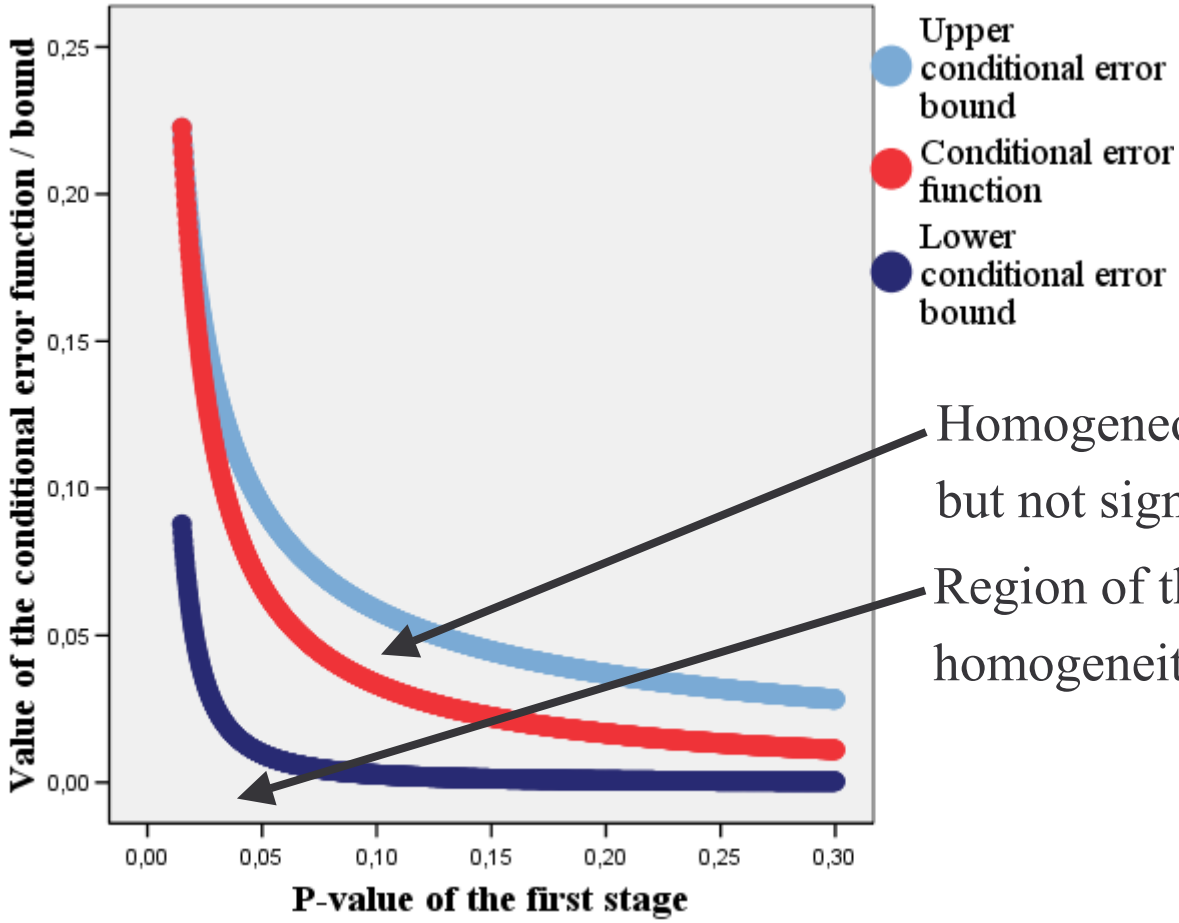
Adaptive Design

- Power: $1- \beta_1, 1 - \beta_2 > ½$
- Futility bound: $\alpha_0 < ½$
- Conditional error function: $\alpha(+\alpha_1) := \lim_{p_1 \to +\alpha_1} \alpha(p_1) < ½$
- Sample size calculation:
  - $n_1 = 2 \cdot ([\Phi^{-1}(1 - \alpha_1) + \Phi^{-1}(1 - \beta_1)] / \delta_{a1})^2$
  - $\delta_{a2} = \delta_1$
- Homogeneity bound:
  $C \geq C_{min}$ increasing in $\alpha(+\alpha_1)$
- Proposition: $C \geq C_{min} \Leftrightarrow \alpha_{low}(p_1) \leq \alpha(p_1) \leq \alpha_{up}(p_1)$
- For significant results: $p_2 \leq \alpha(p_1) \Rightarrow \delta_1/C \leq \delta_2$
- Question: $P_\delta(\delta_1 \cdot C < \delta_2) = ?$

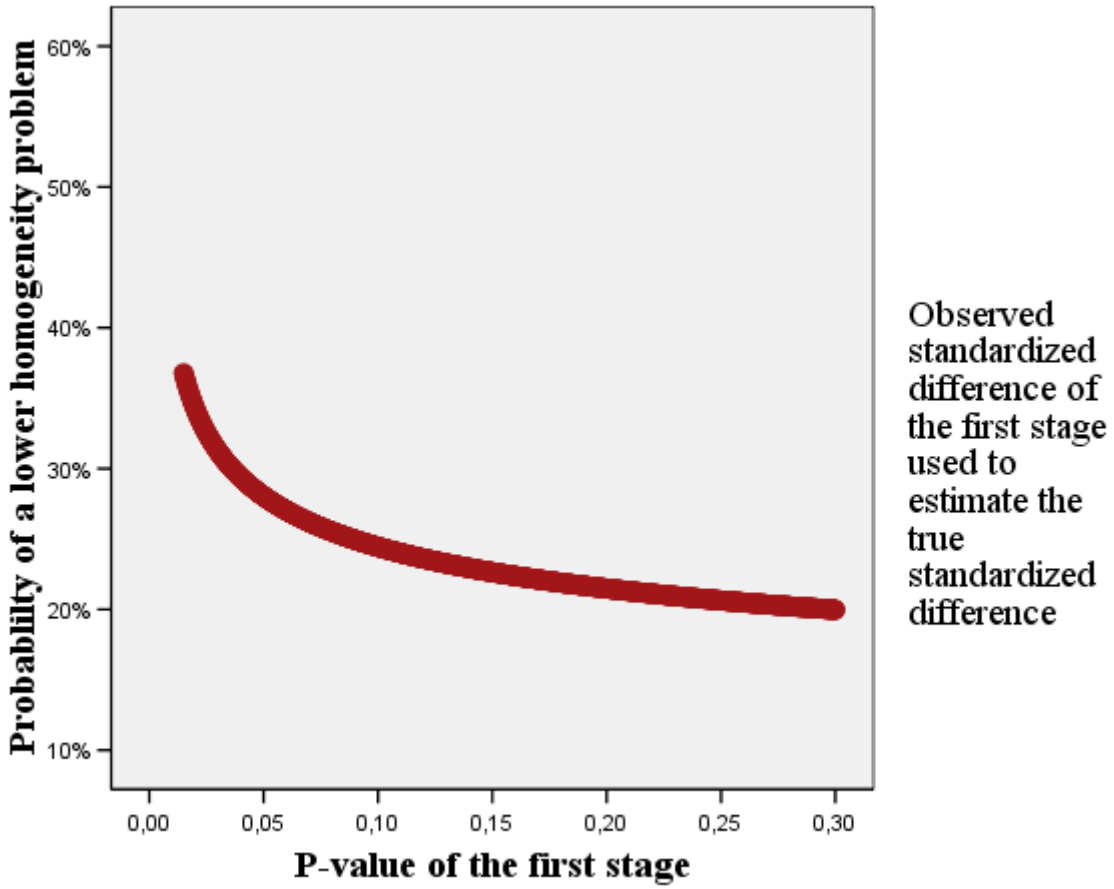
Example 2: Bauer & Köhne Design

- Adaptive design with two stages and one-sided test problem
  - $\alpha = 0.025$, $\alpha_1 = 0.015$, $\alpha_0 = 0.30$
  - $\alpha(p_1) = 0.00334 / p_1 \quad \forall p_1 \in]\alpha_1, \alpha_0]$
- Two-sample Gauss test for difference of means
- Sample size calculation for the 1st stage:
  - $1\text{-}\beta_1 = 60\%$
- Sample size calculation for the 2nd stage:
  - $1\text{-}\beta_2 = 60\%$
  - Standardized difference estimate = $\delta_{a2} = \delta_1$
- Homogeneity bound:
  $C = C_{min} = 1.33$

Example 2: Conditional Error Bounds



Example 2: Lower Homogeneity Problem



Alternative Methods

- Confidence interval:
  - $(1- \alpha)$-CI $= [\delta_1 - \delta_2 \pm \Phi^{-1}(1- \alpha)\ (2/n_1 + 2/n_2)]$
  - Homogeneity $\Leftrightarrow 0 \in (1- \alpha)$-CI
  - Homogeneity $\Rightarrow$ small n_1 and n_2 needed
- Test of equivalence:

  Power for proof of homogeneity $\Rightarrow$ large n_1 and n_2 needed
- Sample size vs. homogeneity:
  - n_1 and n_2 are chosen to prove efficacy.
  - n_1 and n_2 usually don't satisfy a test for homogeneity.

Conclusion

- Group sequential designs:
  Protection against inhomogeneous stages is rarely possible.
- Adaptive designs:
  - Choose homogeneity bound C for effect estimate.
  - $C \geq C_{min}$ may restrict the choice of β_2 and $\alpha(+\alpha_1)$.
  - Otherwise: free choice of $\alpha(\cdot)$; unchanged ASN and max. n_2
  - Upper homogeneity problem can be avoided.
  - Lower homogeneity problem are unavoidable.
  - The probability of lower homogeneity problem can be calculated in advance.
- Finally: Further discussions and practical experience are needed.