# Multiple and repeated testing of primary, co-primary and secondary hypotheses

Ekkehard Glimm, Willi Maurer, Novartis

with contributions by Frank Bretz

**BBS Spring Seminar, 7 March 2011, Basel**

NOVARTIS

# Outline

- Analysis of primary and secondary endpoints in multiple treatment arms
  - Importance of primary and secondary variables in regulatory submissions
  - „Consistency“ and separate control of type I error for primary and secondary hypotheses
  - Properties of two consistent strategies

Maurer W, Glimm E, Bretz F. Multiple and repeated testing of primary, co-primary and secondary hypotheses.
*Statistics in Biopharmaceutical Reserach 2010 (published online)*

# Analysis of primary and secondary endpoints

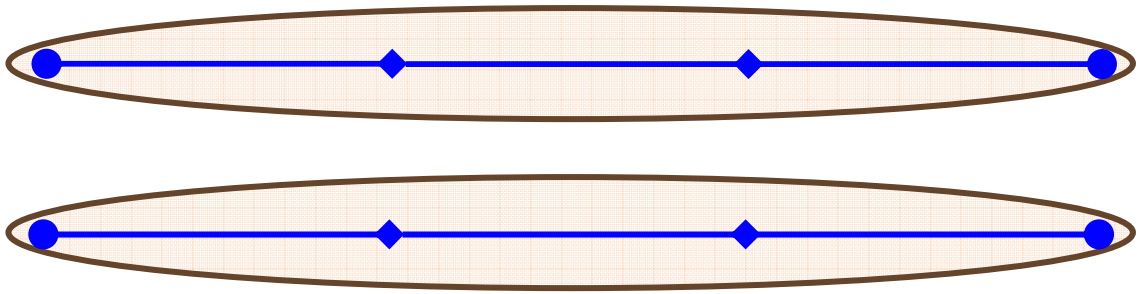
- Case: parallel group trial with
  - 2 treatment arms (e g. high/low dose)
  - a primary and a secondary endpoint (e.g. HBA1C reduc. / weight loss)
- Serial gatekeeping
  - Test primary hypotheses, secondary only if both primary are rejected
- Hung and Wang (2009, J. of Biopharm. Statistics,19:1,1 - 11):
  - does not make „common sense“ to condition the rejection of a secondary endpoint on the rejection of the primary endpoint in another dose group
  - Parallel gatekeeping procedures can help
  - “*Fundamental question is whether the studywise type I error rate needs to be tied in with testing secondary endpoints.*”

# Primary and Secondary hypotheses

- General gatekeeping procedures assume „unrelated blocks“ to be tested hierarchically

***Primary hypotheses***

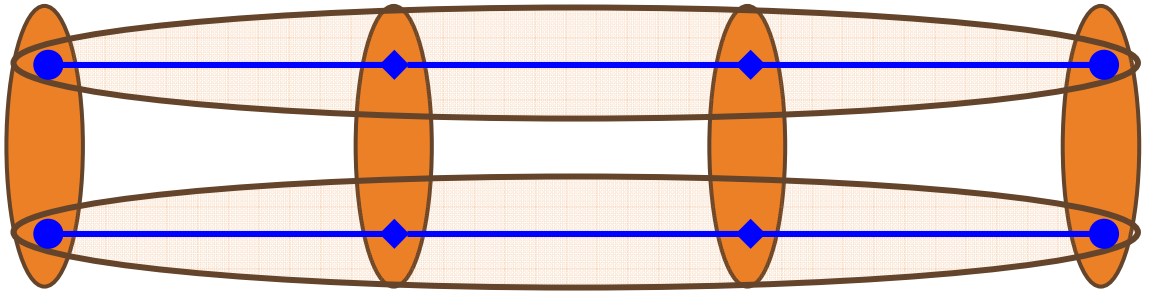
***Secondary hypotheses***



- As just seen, concrete examples often impose more structure („parent-descendant“ relation of primary and a corresponding secondary)

***Primary hypotheses***

***Secondary hypotheses***



# Structured families of primary and secondary hypotheses

- Consider a family of hypotheses that can be partitioned into
  - a primary family and a secondary family
  - for each primary hypothesis there is a set of “descendant” secondary hypotheses.
  - each secondary hypothesis has at least one "parent" primary hypothesis.
- A secondary hypothesis is only of interest (in a confirmatory sense) if one of the respective “parent” primary hypothesis is rejected.

# Importance of primary and secondary variables in regulatory submissions

- Purpose of successful claims on
  - primary variables: usually the basis for regulatory approval
  - secondary variables: often only for the qualification of an established primary effect
    - only of interest if a “related primary” null-hypothesis could be rejected.
- Definition of consistent and successive procedures:
  - Successive: A secondary hypothesis can only be rejected if at least one of its parent primary hypotheses is rejected,
  - Consistent: successive + retention of a secondary hypothesis cannot preclude the rejection of a primary hypothesis.

# Analysis of primary and secondary endpoints

## *Notation*

- primary endpoints *P*, secondary endpoint *S*
  - Primary hypotheses $F_P = \{H_{1,P}, H_{2,P}\}$; rejection of either $H_{1,P}$ or $H_{2,P}$ is a pre-requisite for a positive study
  - Primary type I error to be controlled at level $\alpha_P = \alpha$ (e.g., $\alpha = 0.025$)
  - Descendant secondary hypotheses $F_S = \{H_{1,S}, H_{2,S}\}$; rejection of either $H_{1,S}$ or $H_{2,S}$ is not sufficient for a positive study, but may allow label claims
  - Secondary type I error to be controlled at level $\alpha_S$ (can be larger than $\alpha$)
  - Family of prim. and sec. hypotheses $F_{PS} = F_S \cup F_P$
  - *R(H)* = rejection of a null hypothesis *H*
- *R(F)* = erroneous rejection of at least one true null hypothesis from a family *F* of hypotheses

# Analysis of primary and secondary endpoints

## *Consistent strategies*

- Test $F_P$ with a closed test at multiple level $\alpha_P = \alpha$
  - Let $cF_S$ denote the (consistent) family of secondary hypotheses with rejected parent primary hypothesis
- Strategies:
  - $\boldsymbol{S_1}$ : Test $cF_S$ at multiple level $\alpha_S = \alpha$
  - $\boldsymbol{S_2}$ : Test the members of $cF_S$ individually at level $\alpha_S = \alpha$
- Strategies $S_1$ and $S_2$ are consistent and

1) $P(R(F_P)) \leq \alpha$
2) $P(R(F_S)) \leq 2\alpha$
3) $P(R(F_P) \text{ or } R(F_S)) = P(R(F_{PS})) \leq 2\alpha$
4) Boundaries cannot be tightened in general

# Typical scenarios

„Generators“ of such multiple endpoint scenarios:

1. Two endpoints
   - e.g. Ophthalmology: visual acuity, eye inflammation
2. Two treatments (e.g. doses) with same drug vs control
3. Two subpopulations
   - E.g. Cardiovascular: HBA1C change from baseline in Chinese subpopulation/ all patients
4. Non-inferiority and superiority in an endpoint

- Situation arises whenever 2 of these 4 occur in combination.
- One is strictly „hierarchical“ (primary/secondary), the other may have any preference structure.

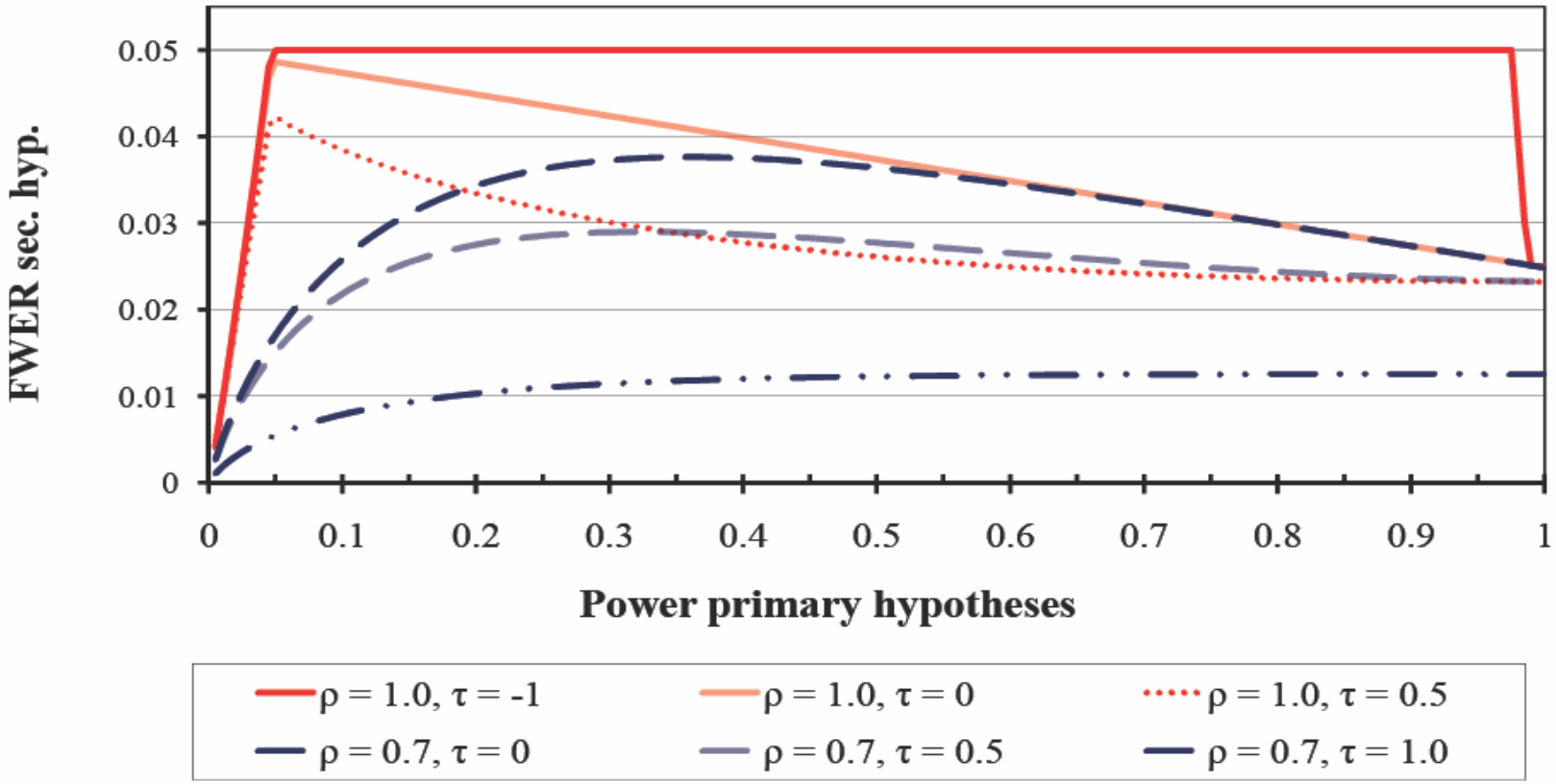
# Typical scenarios

Assume the corresponding test statistics are normally distributed with correlation $\rho$ and $\tau$, respectively.

| Strictly Hierarchical (prim/sec) | Any preference structure | Corr between prim and sec | Corr within prim and within sec |
|---|---|---|---|
| Endpoints | Treatment | $\rho \in (-1,1)$ | $n_{trt}/(n_{trt}+n_{ctrl})$ |
| Endpoints | Subpop | $\rho \in (-1,1)$ | $n_{comm}/(n_1 n_2)^{1/2}$ |
| Endpoints | Endpoints | $\rho_1, \rho_2 \in (-1,1)$ | $\tau_1, \tau_2 \in (-1,1)$ |
| Treatment | Endpoints | $n_{trt}/(n_{trt}+n_{ctrl})$ | $\tau \in (-1,1)$ |
| Subpop | Endpoints | $n_{comm}/(n_1 n_2)^{1/2}$ | $\tau \in (-1,1)$ |
| Non-Inf / Sup | Endpoints | 1 or $(n_{PP}/n_{\text{ITT}})^{1/2}$ | $\tau \in (-1,1)$ |
| Non-Inf / Sup | Subpop | 1 or $(n_{PP}/n_{\text{ITT}})^{1/2}$ | $n_{comm}/(n_1 n_2)^{1/2}$ |
| Non-Inf/ Sup | Treatment | 1 or $(n_{PP}/n_{\text{ITT}})^{1/2}$ | $n_{trt}/(n_{trt}+n_{ctrl})$ |

# FWER for strategy $S_1$

Actual type I error of strategy $S_1$ at nominal $\alpha$=0.025
(when $H_{1,S}$, $H_{2,S}$ are both true, Bonf-Holm test for $F_P$ and c$F_S$)






NOVARTIS

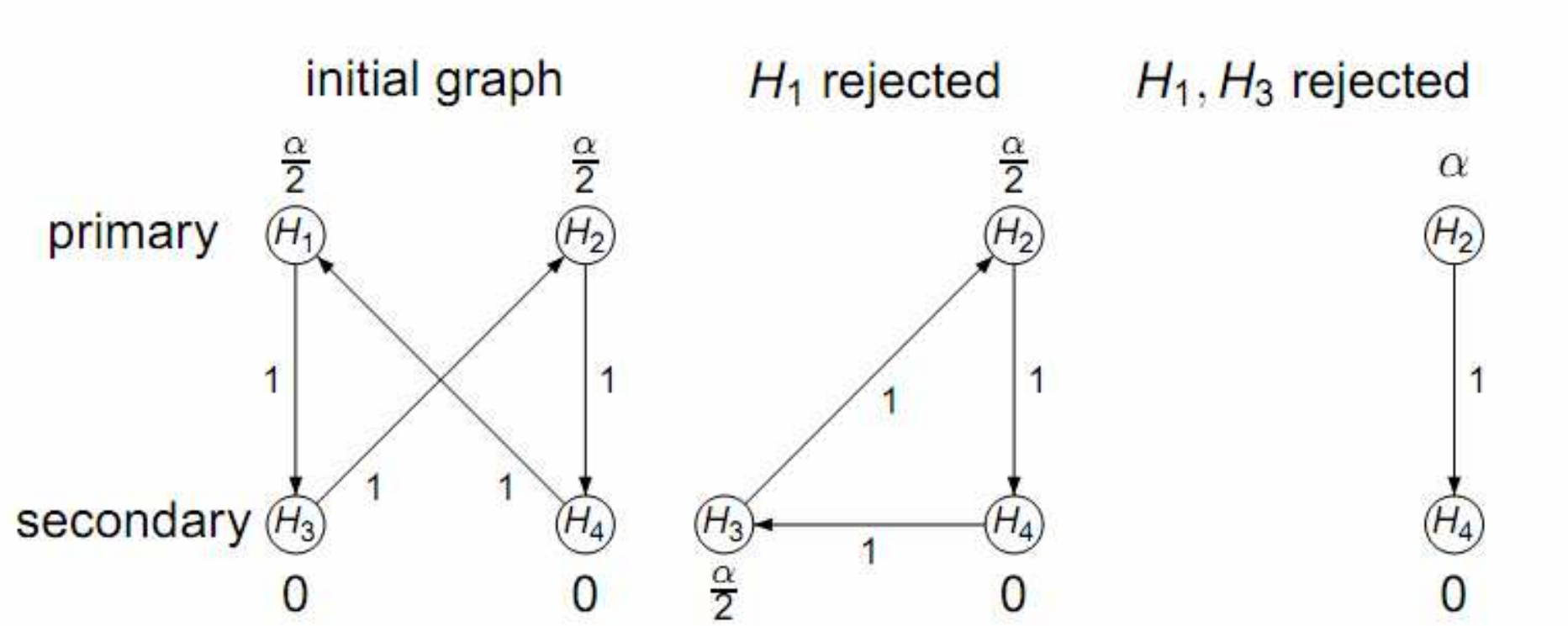
# Multiple primary and secondary hypotheses: Summary

- Separate error control for primary and secondary hypotheses can be sensible
  - Additional consistency property avoids „illogical“ outcomes and reduces overall error rate (primary and secondary hyp. combined)
  - Allows to fully exploit the FWER level for primary hypotheses
  - Generalization to more than 2 treatment arms are possible
  - Buy in by regulators?
  - More on upper type I error bounds for consistent strategies (and on relation with group-sequential tests): Maurer, Glimm and Bretz (2010).

# Graphical methods controlling the FWER for the entire family $F_{PS}$

# Successive and consistent closed test procedures of level α defined by transition graphs

- Graphical representation of structural relation and of a Bonferroni based test procedure






NOVARTIS

# The transition graph test procedure: definition and sequential rejection algorithm

- Vertices and initial levels:
  - hypotheses $H_i$ are represented by vertices of the graph with initial levels $\alpha_i$ summing up to $\alpha$.
  - Hypothesis $H_i$ is rejected if associated p-value $p_i < \alpha_i$ (Bonferroni)
- Update of graph
  - The level $\alpha_i$ of a rejected hypothesis is distributed and added to the levels of the remaining hypotheses according to predefined weights on the directed edges between the vertices (transition weights)
  - The transition weights between the remaining vertices representing candidates for further rejection are updated with a specific algorithm*
  - This process is repeated until no further hypothesis can be rejected.

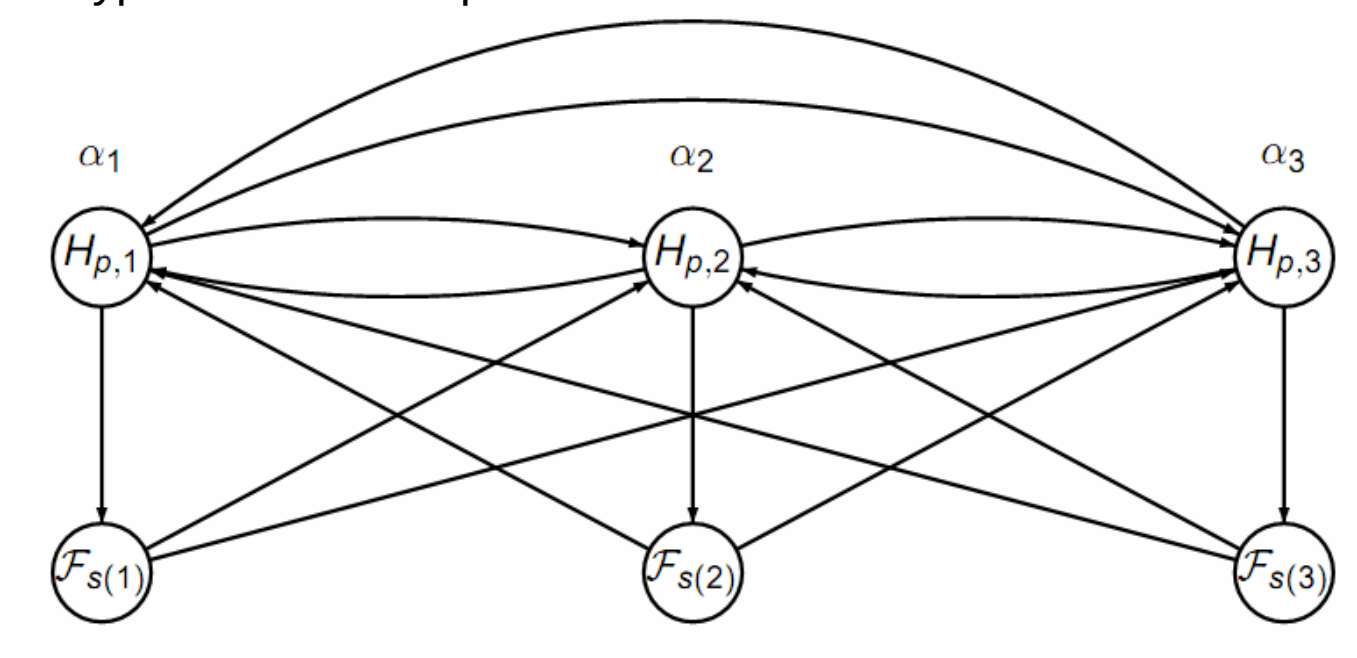
* Bretz, Maurer, Brannath, Posch (Stat. in Med. 2009)

# The transition graph test procedure: Properties

- The transition graph test procedure
  - is equivalent to a unique closed test procedure based on Bonferroni level-α tests on each of the intersection hypotheses,
  - is independent of the rejection sequence and
  - is sequentially rejective;
    - the individual levels of not yet rejected hypotheses cannot decrease after rejection of a hypothesis (consonance of the test)
  - controls strongly the familywise type I error rate at level $\alpha$
    - (i.e. is of multiple level $\alpha$)
  - covers most „classical“ Bonferroni based sequentially rejective procedures

# Successive procedure for multiple primary hypotheses
## …and each with a descendant family of secondary hypotheses

- A graph generates a successive procedure if
  - Initial weights are 0 on all secondary hypotheses
  - the only edges with positive weight leading into a secondary hypothesis are those originating at its parent primary hypotheses
  - no edges from a secondary hypothesis to another secondary hypothesis unless parents are the same.

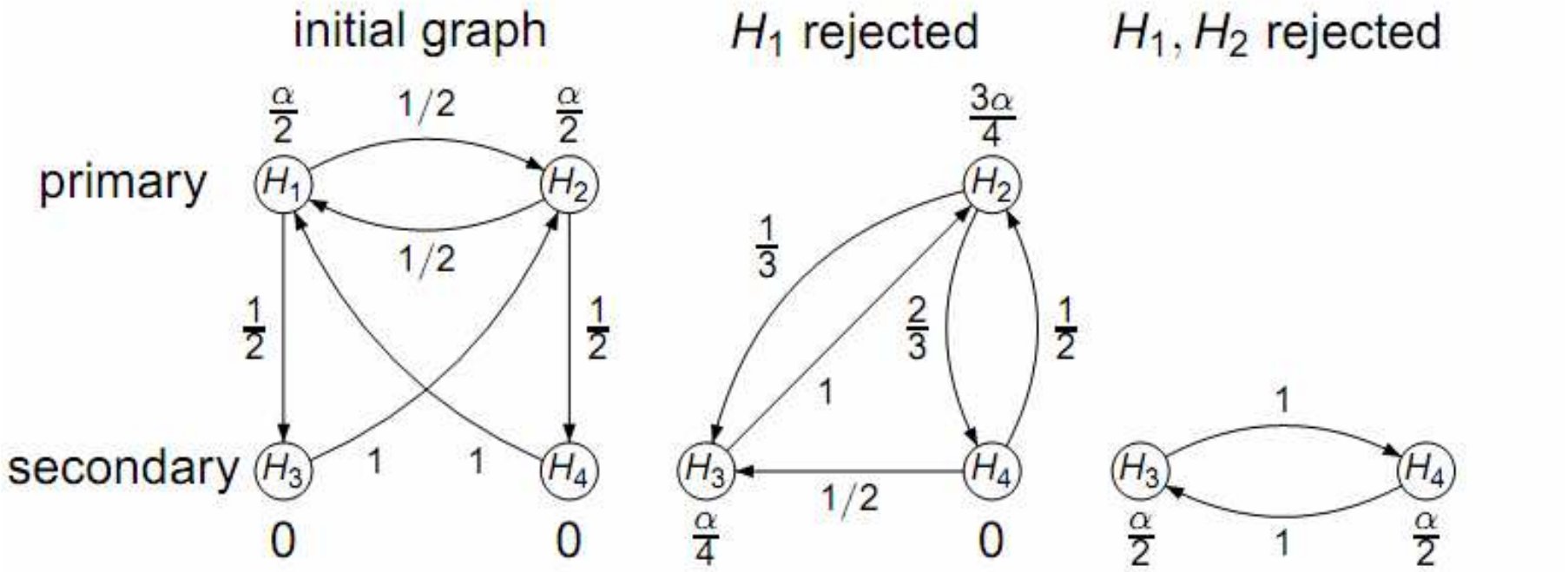





NOVARTIS

# Two primary hypotheses with one secondary descendant each

- An example where after rejection of one of the primary hypotheses its significance level is passed on equally to the other primary and the descendant secondary hypothesis

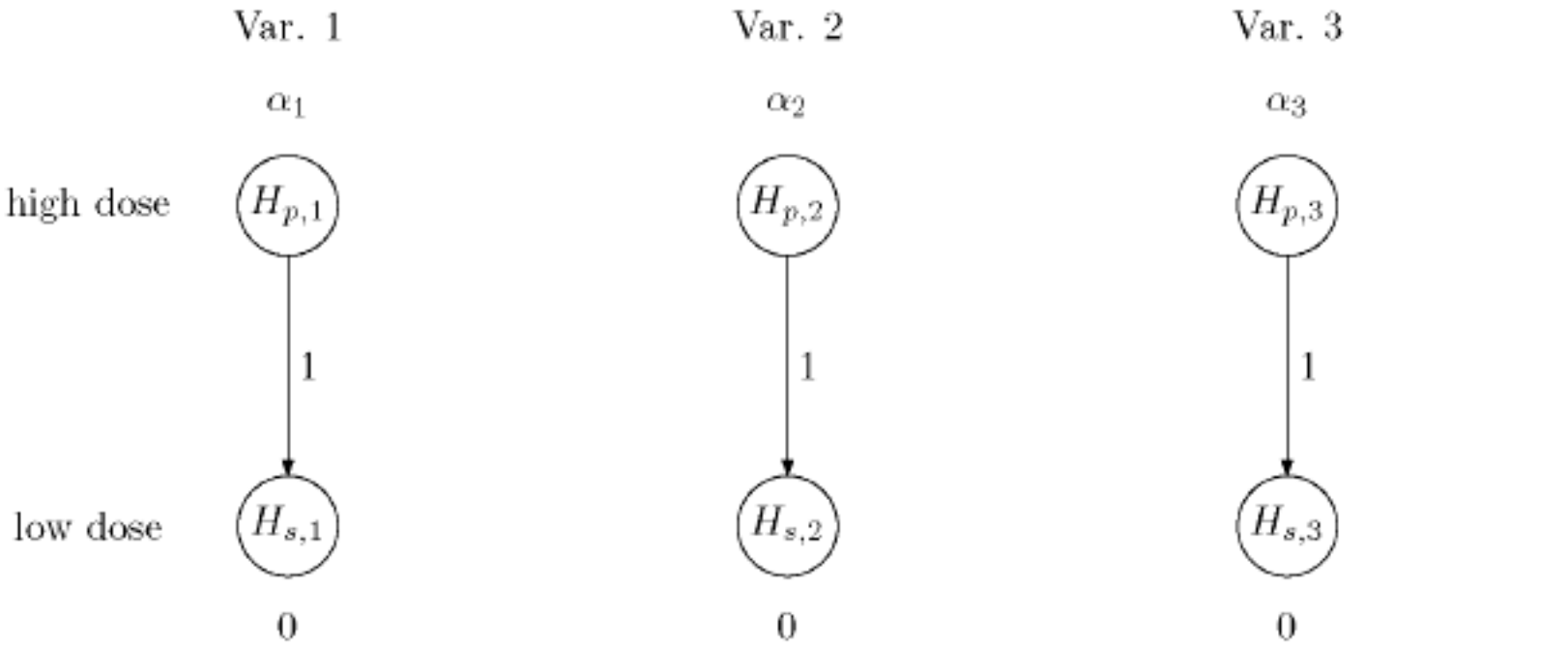





NOVARTIS

# Improving sequentially rejective procedures by weighted Simes Tests

- Graphical representation of a procedure proposed by Quan et al. (2009)
  - In addition to rejections possible by graph, reject **all** primary and secondary hypotheses if **all** are significant at level α






NOVARTIS

# Weighted Simes test

- Quan et al.'s procedure keeps the FWER under positive regression dependence, because it is a conservative simplification of the Weighted Simes procedure (Kling, 2005, has shown that this keeps the FWER).

- In general, the following multiple test protects the FWER at level α (under positive regression dependence):
  - Reject all hypotheses if all are significant at level α.
  - Otherwise, reject those hypotheses that are rejected by a transition graph procedure.

# Trimmed Simes test for two hypotheses

- Trimmed weighted Simes test for two hypotheses
  - $H_A$ and $H_B$ with multivariate normal or t-distributed test statistics and associated univariate p-values $p_A$ and $p_B$
  - Given significance levels $\alpha_A$ and $\alpha_B$, $\alpha_A+\alpha_B= \alpha$,
    - Reject $H_A \cap H_B$ if
    - $p_A < \alpha_A$ and $p_B < 1- \alpha_B$ or
    - $P_B < \alpha_B$ and $p_A < 1- \alpha_A$ or
    - $\max(p_A,p_B) < \alpha$.
  - The trimmed Simes test protects type I error rate at level $\alpha$ for any correlation between the test statistics*

*Brannath, W., Bretz, F., Maurer, W., and Sarkar, S. (2009), "Trimmed Weighted Simes' Test for Two One-Sided Hypotheses With Arbitrarily Correlated Test Statistics," *Biometrical Journal*, 51, 885–898

# Properties of the trimmed 1-sided Simes test

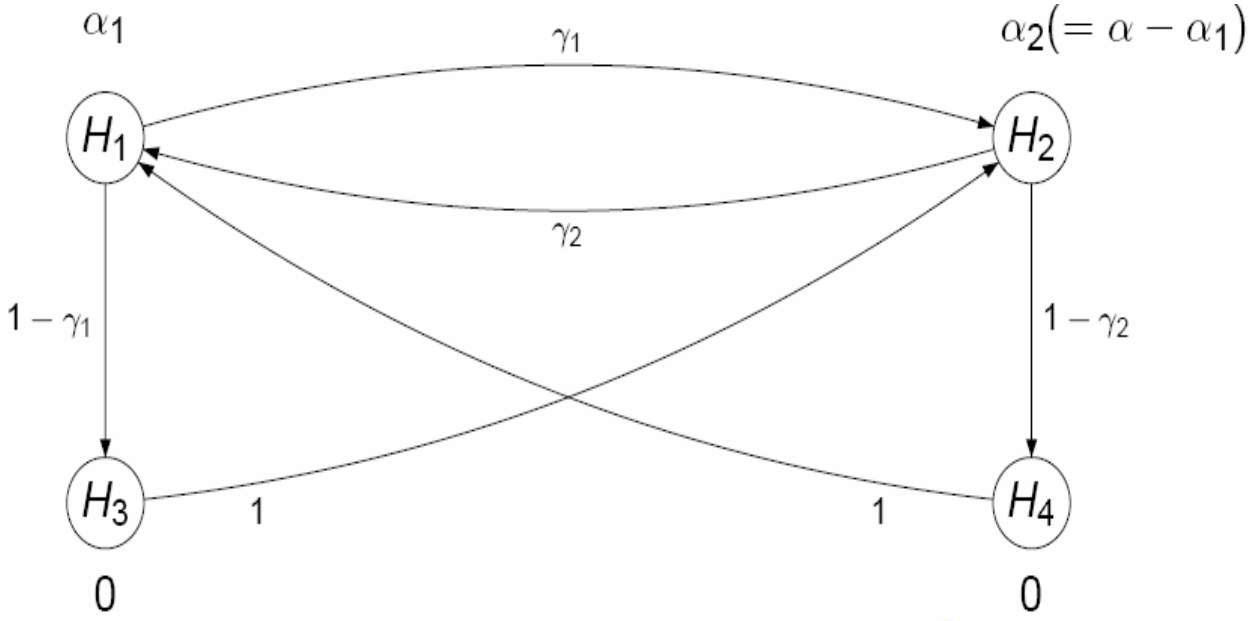
- For multivariate normal tests statistics level α is protected irrespective of the correlation
  - for negatively correlated variables it is very conservative
  - for alternatives with positive effects in both variables and positive correlation, the power gain over Bonferroni is similar to Simes' test
- Test can be used in a closed test
- Strongly contradicting effects in the two test statistics do not result in a rejection of any of the null-hypotheses
  - Trimming is in the same spirit as the consistency requirement by Alosh and Huque*, though somewhat weaker

*Alosh, M. and Huque M. F. (2010), "A consistency-adjusted alpha adaptive strategy for sequential testing," *Statistics in Medicine. 28.*

# Application of trimmed Simes test to successive multiple tests with 2 primary hypotheses

- This multiple test protects the FWER at level α
  - i) **Retain all** four hypotheses if for **any** $p_i > 1-\alpha_i$
  - ii) **reject all** four hypotheses if **all** $p_i < \alpha$
  - iii) **otherwise perform** a closed successive weighted Bonferroni-test, e.g. based on a successive **graphical approach** as below.

Reason: all intersections include never more than 2 hypotheses with positive weight






NOVARTIS

# Conclusions

- Multiple sources of multiplicity often induce partial order(s) of importance on the hypotheses;
- Test procedures consistent with such a partial order can be constructed (i.e. have succession property),
  - but need not control FWER at level α for the combined family of primary and secondary hypotheses, even if they do so separately.
- Full FWER control can transparently be achieved by means of “successive” graphical procedures
- „Simes- and Dunnett-like“ considerations (=knowledge about correlations) can be combined with the graphical methods (Huque and Alosh, J Stat. Plan.& Inf. , 2008; Bretz et al., to appear)

# Backup slides

# Weighted Simes test

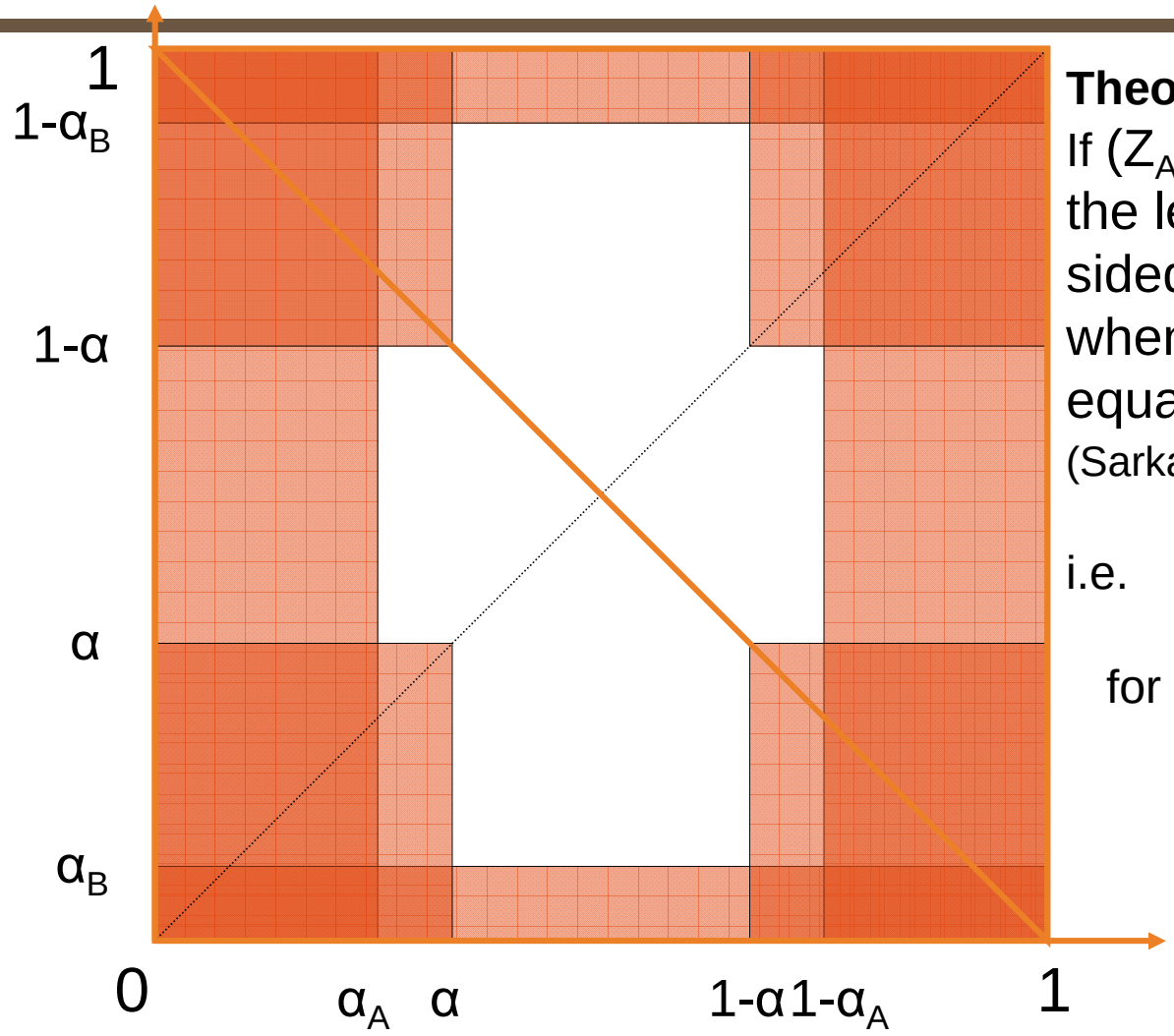
- Weighted Simes: Given hypotheses $H_i$, $i \in M = \{1,\ldots,m\}$, the intersection hypothesis $H_M$ can be rejected if for some $j \in M$

$$p_{(j)} \leq \sum_{i=1}^{j} \alpha_{(i)}$$

  - where $p_{(j)}$ are the ordered p-values and $\alpha_{(j)}$ are the corresponding local significance levels. **Kling (2005) showed that this global test controls the Type I error rate at level α if the test statistics are positive regression dependent.**

- Assuming positive regression dependence one can show that the following multiple test protects the FWER at level α:
- In addition to the hypotheses rejected by a transition graph procedure of level α, all hypotheses can be rejected if all are significant at level α.

# Unequal α-split, 2-sided Simes



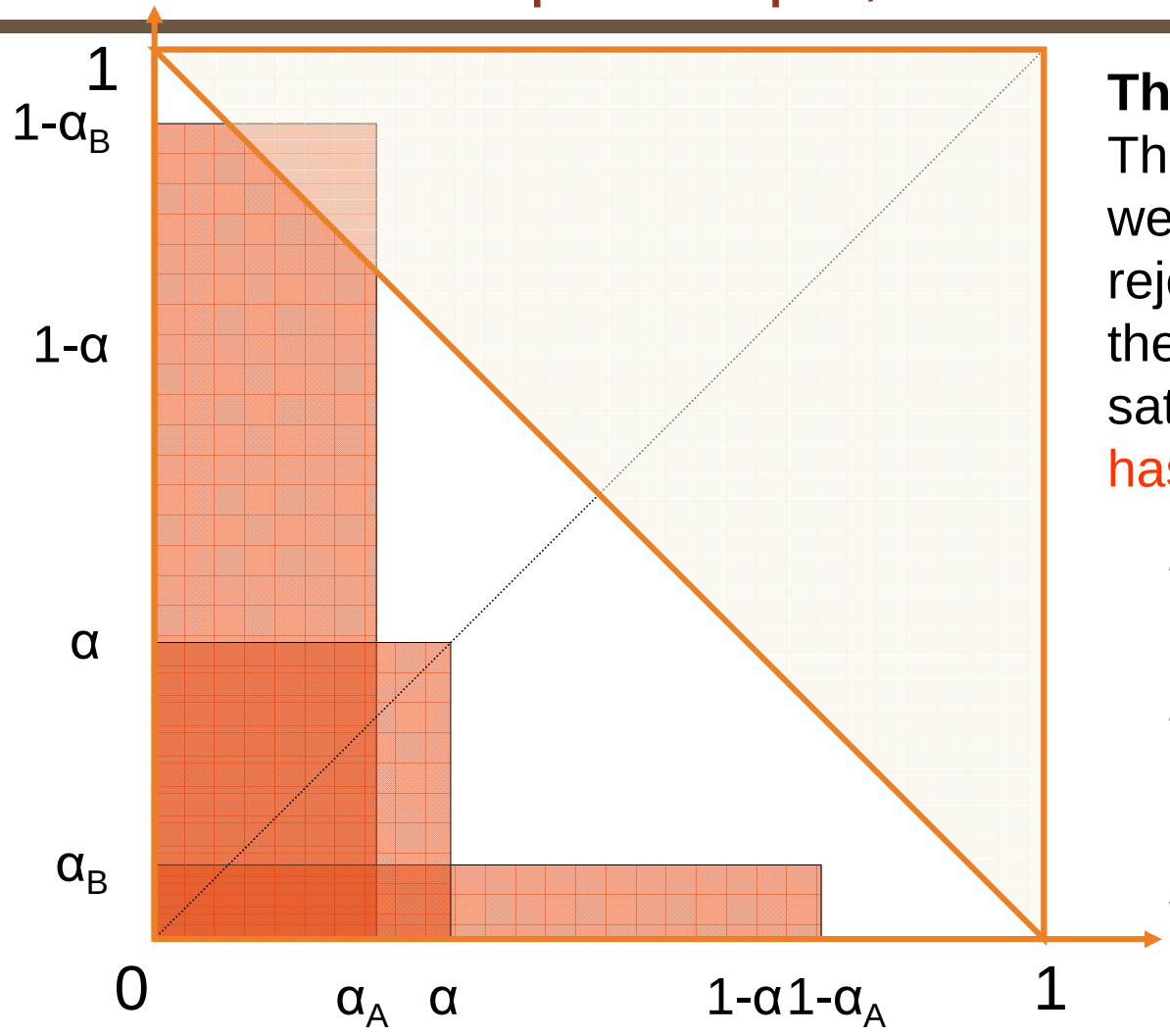

**Theorem 1**:
If $(Z_A, Z_B) \sim BVN(0, 0, \rho)$
the level of the weighted two-sided Simes' test is equal to $2\alpha$ when $\rho = 0$ and less than or equal to $2\alpha$ when $\rho \neq 0$
(Sarkar 2007).

i.e.

$P(\{\text{Reject } H_0\}) \leq 2\alpha$
for the rejection region to the left
for $-1 \leq \rho \leq 1$,
with equality for
$\rho \in \{-1,0,1\}$

NOVARTIS

# Modified unequal α-split, 1-sided Simes




**Theorem 2**

The modified one-sided weighted Simes test, which rejects $H_{AB}$ if either one of the conditions below is satisfied,

has level ≤ α for any ρ.

$P_A \le \alpha$ and $P_B \le \alpha$

or

$P_A \le \alpha_A$ and $P_B \le 1-\alpha_B$

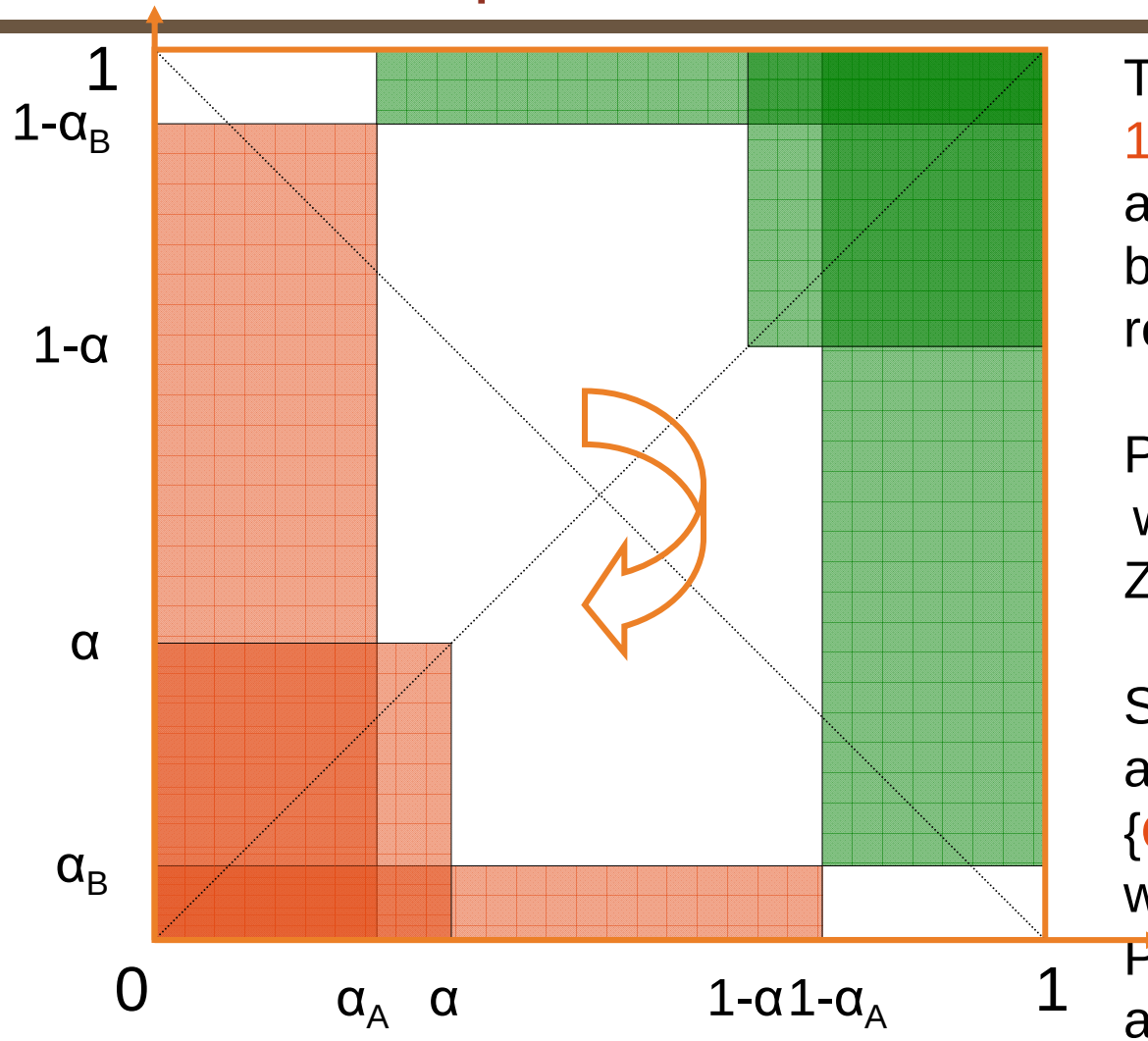
or

$P_B \le \alpha_B$ and $P_A \le 1-\alpha_A$

Why?

NOVARTIS

# Modified unequal α-split, 1-sided Simes
# An intuitive „proof“ of theorem 2




Turning the orange modified 1-sided rejection region {O} around the midpoint (0.5,0.5) by 180° produces the green region {G}.

$P(\{O\}) = P(\{G\})$
when $(Z_A,Z_B) \sim (Z_B,Z_A)$ and $Z_i \sim -Z_i$, i= A,B.

Since {O} and {G} are disjoint and
{O} U {G} ⊂ {Rej. 2-sided},
we have:
$P(\{O\}) + P(\{G\}) \leq 2\alpha$
and hence $P(\{O\}) \leq \alpha$

NOVARTIS