A fallback test for three co-primary endpoints

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joint work with
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Examples for co-primary endpoints

In complex diseases, more than one primary endpoint may be required for characterization of treatment effects.

- Alzheimer's disease:
  Cognitive functions and functions of daily living as co-primary, global assessment as secondary (EMA guideline)
- Duchenne and Becker muscular dystrophy:
  Motor functioning and muscle strength (EMA guideline)
- Lennox-Gastaut epilepsy syndrome (rare disease):
  Total seizure frequency, tonic/atonic seizure frequency and global improvement in seizure severity were used as three co-primary endpoints (Glauser et al., 2008)

Concepts in hypothesis testing

- Elementary null hypothesis H_i
  - H_i is true means "No effect in endpoint i"
- Level α Test for a single H_i
  - Reject H_i if the test statistic $T_i > c$
  - Choose c so that $P(T_i > c|H_i) = \alpha$
  - E.g. $T_i|H_i \sim N(0,1)$, one sided level $\alpha = 0.025$, $c = 1.96$
- Intersection null hypothesis $H_i \cap H_j$
  - H_i and H_j are true
  - Alternative: Effect in endpoint i or endpoint j or both
  - Multiple testing problem:
  - E.g. Uncorrelated endpoints i and j, $\alpha = 0.025$
  - Probability to individually reject H_i or H_j is $1 - (1 - 0.025)^2 = 0.049 \approx 2\alpha$

Regulatory position and reverse multiplicity problem

- Regulators: All co-primary endpoints must be significant at local level α (one-sided $\alpha = 0.025$)
- This means: Reject all H_i if all $T_i > c$. Othwerwise do not reject any null hypothesis.
- This may require increased sample sizes compared to single-endpoint-problems
- E.g.: Three uncorrelated co-primary endpoints with similar effects
- Power for each single-endpoint test is 80%
- Power to reject all three endpoints is $0.8^3 = 0.512$
- What to do in rare disease situation?

What to do if 2 of 3 co-primary endpoints are significant?

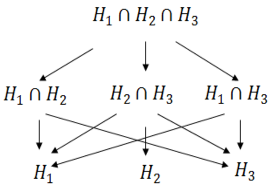
- Consider a trial with three co-primary endpoints.
- Can we perform some inference with level α control, in case that only two of three endpoints were signficant?
- All information is valuable, especially in rare diesease settings.
- Is there a "fallback" strategy to draw confirmative conclusions from a trial, that would otherwise be considered failed?

"A fallback test for three co-primary endpoints", R. Ristl, F. Frommlet, A. Koch, M. Posch, submitted

Fallback test for three co-primary endpoints

- Reject all H_i if all $T_i > c, i \in \{1, 2, 3\}$
- Reject $H_i \cap H_j$ if $T_i > c$ and $T_j > c$, for some $i \neq j$

Closed test scheme



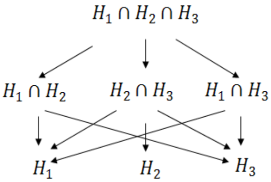
Intersection hypotheses	Reject if	Upper bound for local Level
$H_1 \cap H_2 \cap H_3$	At least 2 of 3 $T_i > c$	α, trivariate normal test statistics $3\alpha/2$, arbitrary distribution (Rüger)
$H_1 \cap H_2$, $H_2 \cap H_3$, $H_1 \cap H_3$	$T_i > c$ and $T_j > c$	α
H_1, H_2, H_3	$T_i > c$	α

Under normality assumption the family wise type I error rate (FWER) is bounded by α.

A liberal Fallback test for three co-primary endpoints

- Reject a pair H_i and H_j if both $T_i > c$ and $T_j > c$

Closed test scheme



Intersection hypotheses	Reject if	Upper bound for local Level
$H_1 \cap H_2 \cap H_3$	At least 2 of 3 $T_i > c$	α, trivariate normal test statistics 3α/2, arbitrary distribution (Rüger)
$H_1 \cap H_2$, $H_2 \cap H_3$, $H_1 \cap H_3$	$T_i > c$ or $T_j > c$	2α
H_1, H_2, H_3	$T_i > c$	α

Under global intersection null hypothesis $H = H_1 \cap H_2 \cap H_3$ the FWER is bounded by α.
Else, the FWER is bounded by 2α.

Application to diagnostic trials

- Study design: Three readers, individually rating each of n patients as healthy or diseased
- Aim: Show that a prespecified sensitivity AND specificity can be reached.

Hypotheses and test statistics for reader i:

Hypothesis	Test statistic	Reject if
$H_{se,i} : sensitivity_i = sens_0$	$Z_{se,i}$	
$H_{sp,i} : specificity_i = spec_0$	$Z_{sp,i}$	
$H_i = H_{se,i} \cup H_{sp,i}$	$T_i = min(Z_{se,i}, Z_{sp,i})$	$T_i > z_{1-\alpha}$

- The fallback test can be applied to $T = (T_1, T_2, T_3)$
- FWER controlled, because there is an asymptotically multivariate normal vector $(Z_{s_1,1}, Z_{s_2,2}, Z_{s_3,3})$, $s_i \in \{se, sp\}$ so that $(T_1, T_2, T_3) \leq Z$

Power (%) to reject $H_1 \cap H_2 \cap H_3$ for standardized effects δ

δ_1	δ_2	δ_3	Correlation	Fallback	Bonferroni-Holm
3	0	0	0	4.2	73.2
			0.5	4.5	72.8
			0.85	3.7	72.8
3	3	0	0	73.0	92.6
			0.5	75.9	86.4
			0.85	80.0	80.1
3	3	3	0	94.0	98.0
			0.5	88.9	91.5
			0.85	86.1	83.3

Compare: Power for one primary endpoint (or hierarchical test) is 85.1 %.

Power (%) to reject all three H_i for standardized effects δ

δ_1	δ_2	δ_3	Correlation	Fallback	Bonferroni-Holm
3	0	0	0	0.1	0.1
			0.5	0.5	0.4
			0.85	1.3	1.1
3	3	0	0	1.8	1.6
			0.5	2.5	2.5
			0.85	2.5	2.5
3	3	3	0	61.6	59.8
			0.5	69.4	67.7
			0.85	77.0	73.7

Larger power for Fallback test.

Theorem

Assumptions:

- Trivariate normal random vector $Z \sim N_3(0, \Sigma)$
- $var(Z_i) = 1, i = 1, 2, 3$
- $\alpha \leq 1/2$
- $c = \Phi^{-1}(1 - \alpha)$

Theorem

Under the assupmtions, The probability π that at least two of the three random variables take values larger than c does not exceed α.

Remark

For $c \geq 0 : \pi \leq \alpha \Leftrightarrow$
$P(Z_1 > c, Z_2 < c, Z_3 < c) \geq P(Z_1 > c, Z_2 > c, Z_3 < c)$

Outline of proof

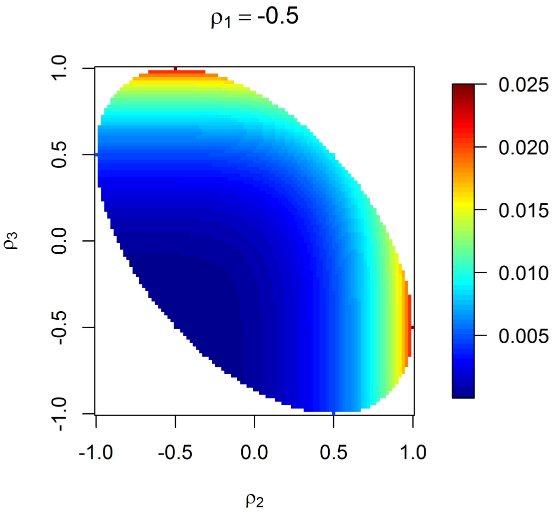
Special cases:

- Z uncorrelated, $\alpha \in [0; 0.5]$: $\pi = 3\alpha^2 - 2\alpha^3 < \alpha$
- Perfect correlation of any pair $(Z_i, Z_j), i \neq j$: $\pi = \alpha$

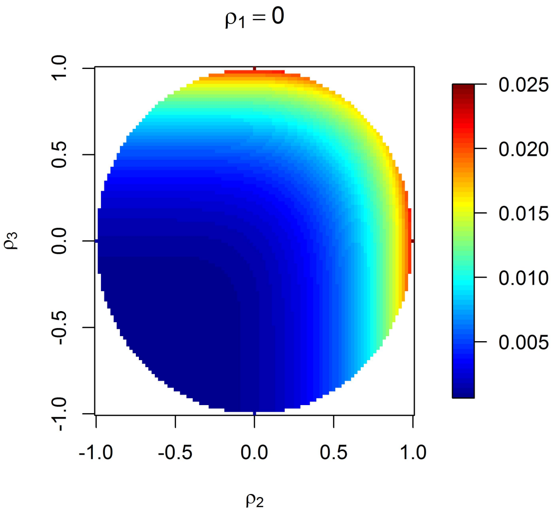
Arbitrary correlation structure:

- Study the gradient of π with respect to $\rho_{ij} = cor(Z_i, Z_j), i \neq j$
- Show that there is no local extreme value of π in the parameter space of $\{\rho_{ij}\}$, such that $det(\Sigma) > 0$
- At the boundary ($det(\Sigma) = 0$) the problem can be transformed to two dimensions.
- Geometric arguments show $\pi \leq \alpha$ on the boundary.

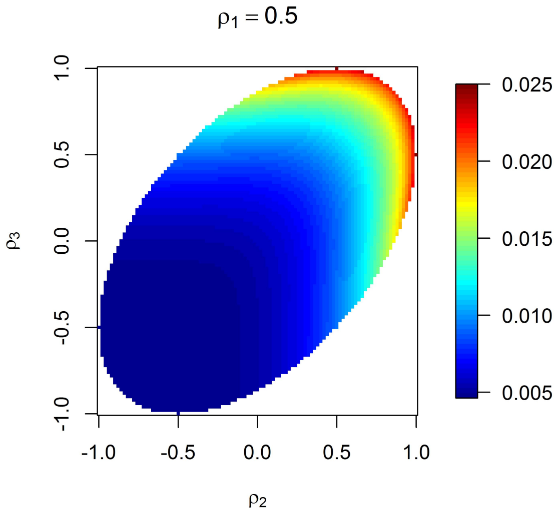
Numeric solution: Fallback test FWER, $\rho_1 = -0.5$



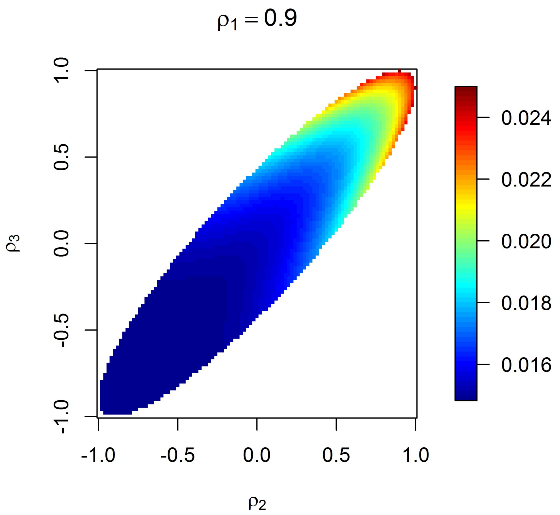
Numeric solution: Fallback test FWER, $\rho_1 = 0$



Numeric solution: Fallback test FWER, $\rho_1 = 0.5$



Numeric solution: Fallback test FWER, $\rho_1 = 0.9$



Summary fallback test

- Allows for proof of principle when two of three H_i are rejected at level α
- Reject $H_i \cap H_j$ with level α control
- Allows to reject significant elementary H_i and H_j with global level 2α
- Uniformly improvement of Rüger test under normality assumption
- Potentially useful in regulatory decision making
- Adds possibility for conclusion, which is especially desirable in the rare disease setting

Literature

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Thank you for your attention!
Any questions and discussion are welcome!