A Multiple Comparison Procedure for Hypotheses with Gatekeeping Structures

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Outline

- A clinical trial example
- Problem Set-up
- Proposed procedure
- Comparison with alternative procedures
- Application to the clinical trial
- Conclusions

A Clinical Trial*

- **Population: Patients with psoriasis**
- **Treatments: 1:1:1:1 randomization**
  - **Placebo (P)**
  - **Low dose regimen (L)**
  - **Medium dose regimen (M)**
  - **High dose regimen (H)**
- **Endpoints**
  1. **PASI change from baseline at week 24**
  2. **sPGA change from baseline at week 24**
- **Objectives with strong control of FWER**
  1. **Claim significant improvement in PASI change for one or more dose groups**
  2. **Claim significant improvement in sPGA change for significant dose group(s)**
- **Sample size: 280 = 4 x 70**

* Some design features and data are modified for illustrative purpose.

Statistical Problem

Endpoint	Mean Difference		
	L-P	M-P	H-P
PASI	π_{11}	π_{12}	π_{13}
sPGA	π_{21}	π_{22}	π_{23}

- **Data**
- **$H_{\gamma l}$: $\pi_{\gamma l} = 0$**
- **Individual Z-scores**
- **Which of {$H_{\gamma l}$: γ=1,2; l=1,2,3} can be rejected with a strong control at one-sided 2.5% significant level?**
- **No normality assumption for PASI and sPGA changes**

$$Y_\nu^l = \sum_{j=1}^{n_l} Y_{\nu,j}^l, l = 0,1,\ldots, K; \nu = 1,2,\ldots, p$$

$$Z_\nu^l = \sqrt{\frac{K+1}{N}}(Y_\nu^l - Y_\nu^0), l = 1,\ldots, K; \nu = 1,2,\ldots, p$$

$$Z_\nu^l \prec n\left(\sqrt{\frac{N}{K+1}}\pi_{\nu l}, \hat{\sigma}_{\nu l}^2 + \hat{\sigma}_{\nu 0}^2\right)$$

$$p_{\nu l} = P\left(\sqrt{\frac{1}{\hat{\sigma}_{\nu l}^2 + \hat{\sigma}_{\nu 0}^2}} Z_\nu^l > z_{\nu l}\right)$$

Some Available MCPs

- For the combined family of F_1 and F_2 , use weighted bonferroni procedures (or graphical representation)
  - Bretz, Maurer, and Hommel 2011 SIM
- Use Bonferroni for F_1 and F_2 individually, and then mix them for the combined family with a bonferroni mixing function
  - Dmitrienko and Tamhane (2011) SIM
- Use truncated Hommel test for F_1 and F_2 individually, and then mix them for the combined family with a bonferroni mixing function
  - Brechenmacher, Xu, Dmitrienko, Tamhane, A.C. (2011) JPS

Points for Consideration

- Many MCPs are implemented based on marginal p-values $\{p_{\gamma l} : \gamma=1,2, l=1,2,3\}$
  - Can they be improved by considering the correlation among individual test statistics?
- Some assume individual test statistics are positively correlated
  - May not be easily verified in some cases
- How do we choose initial local alpha?
- Power assessment of a MCP

Joint asymptotic distribution

Endpoint	Mean Difference		
	L-P	M-P	H-P
PASI	$\pi_{11}=\pi_1$	$\pi_{12}=\pi_3$	$\pi_{13}=\pi_5$
sPGA	$\pi_{21}=\pi_2$	$\pi_{22}=\pi_4$	$\pi_{23}=\pi_6$

$$(\gamma, l) \equiv \gamma + p(l-1), \gamma = 1,2, l = 1,2,3$$

$$Z_{\nu}^{l} \prec n\left(\sqrt{\frac{N}{K+1}}\pi_{\nu l}, \hat{\sigma}_{\nu l}^{2} + \hat{\sigma}_{\nu 0}^{2}\right)$$

$$(Z_1, \ldots, Z_{pK}) \prec n\left(\sqrt{\frac{N}{K+1}}(\pi_1, \ldots, \pi_{pK})', \hat{V}\right)$$

$$\hat{V} = \begin{pmatrix} C^0 + C^1 & C^0 & C^0 \\ C^0 & C^0 + C^2 & C^0 \\ C^0 & C^0 & C^0 + C^3 \end{pmatrix}$$

C^{l} = sample covariance matrix of random vector $(Y_1^{l}, \ldots, Y_p^{l})$

Proposed Procedure: Overview

- For any intersection of $H_1,\ldots,H_6$, $H(e)$ with $e=(e_1,\ldots,e_6)$, define an α level test
  - Truncated Dunnett type for F_1 family
  - Union test to maintain gatekeeping structure
  - Joint distribution to compute local type I error
- Use Maucus' closed test principle to derive a strongly controlled MCP

Some Notations

$$(Z_1,\ldots, Z_{pK}) \prec n\left(\sqrt{\frac{N}{K+1}}(\pi_1,\ldots, \pi_{pK})', \hat{V}\right)$$

$$(W_1,\ldots, W_{pK}) \prec n((0,\ldots, 0)', \hat{V})$$

$$U_{e,\hat{V}(e)}(u) = P(\max\{W_j : e_j = 1\} \le u)$$

$$p(e) = 1 - U_{e,\hat{V}(e)}(\max\{Z_j : e_j = 1\})$$

α level test for H(e) :

$$\max\{Z_j : e_j = 1\} \ge U_{e,\hat{V}(e)}(1-\alpha)$$

$$c(1,\alpha) = U_{e^M,\hat{V}(e^M)}(1-\alpha),\ e^M = (1,0,1,0,1,0)$$

$$f(\nu_1, e, \alpha) = \nu_1 U_{e,\hat{V}(e)}(1-\alpha) + (1-\nu_1)c(1,\alpha)$$
$$\ge U_{e,\hat{V}(e)}(1-\alpha)$$

Dunnett-type test for F_1 and for F_2

For any e within F_1, construct a truncated α level test for H(e):

$$\max\{Z_j : e_j = 1\} \geq f(\nu_1, e, \alpha)$$

For any e within F_2, construct an un-truncated α level test for H(e):

$$\max\{Z_j : e_j = 1\} \geq U_{e,\hat{V}(e)}(1-\alpha)$$

Union Test for Mixed Intersections

$$e = e^1 + e^2, e^1 \in F_1, e^2 \in F_2$$

$$H(e) = H(e^1) \cap H(e^2)$$

$$C(e) = \{\max\{Z_j : e_j^1 = 1\} \geq f(v_1, e^1, \alpha)\} \bigcup \{\max\{Z_j : e_j^2 = 1\} \geq g(v_1, e, \alpha)\}$$

$$P(C(e) \mid H(e)) = \alpha \text{ for finding } g(v_1, e, \alpha)$$

Special case for $e^1 = e^M$:

$$C(e) = \{\max\{Z_j : e_j^1 = 1\} \geq f(v_1, e^1, \alpha)\}$$

Modification with Logical Constraint

$e = (0,1,1,0,1,1)$ with common treatment H(3)

$e^1 = (0,0,1,0,1,0)$ for endpoint 1 and treatment M and H

$e^2 = (0,1,0,0,0,1)_2$ for endpoint 2 and treatment L and H

$H(e) = H(e^1) \cap H(e^2)$

$C(e) = \{\max\{Z_j : e_j^1 = 1\} \geq f(\nu_1, e^1, \alpha)\}$

$e = (0,1,1,0,1,0)$ without common treatment

$e^1 = (0,0,1,0,1,0)$ for endpoint 1 and treatment M and H

$e^2 = (0,1,0,0,0,0)_2$ for endpoint 2 and treatment L

$H(e) = H(e^1) \cap H(e^2)$

$C(e) = \{\max\{Z_j : e_j^1 = 1\} \geq f(\nu_1, e^1, \alpha)\} \bigcup \{\max\{Z_j : e_j^2 = 1\} \geq g(\nu_1, e, \alpha)\}$

Simulation Model

Endpoint	Mean Difference		
	L-P	M-P	
1	$\pi_{11}=\pi_1$	$\pi_{12}=\pi_3$	
2	$\pi_{21}=\pi_2$	$\pi_{22}=\pi_4$	

Random sample from $(Y_1^l, Y_2^l) \prec n((m_1^l, m_2^l)', \Sigma^l), l = 0,1,2$

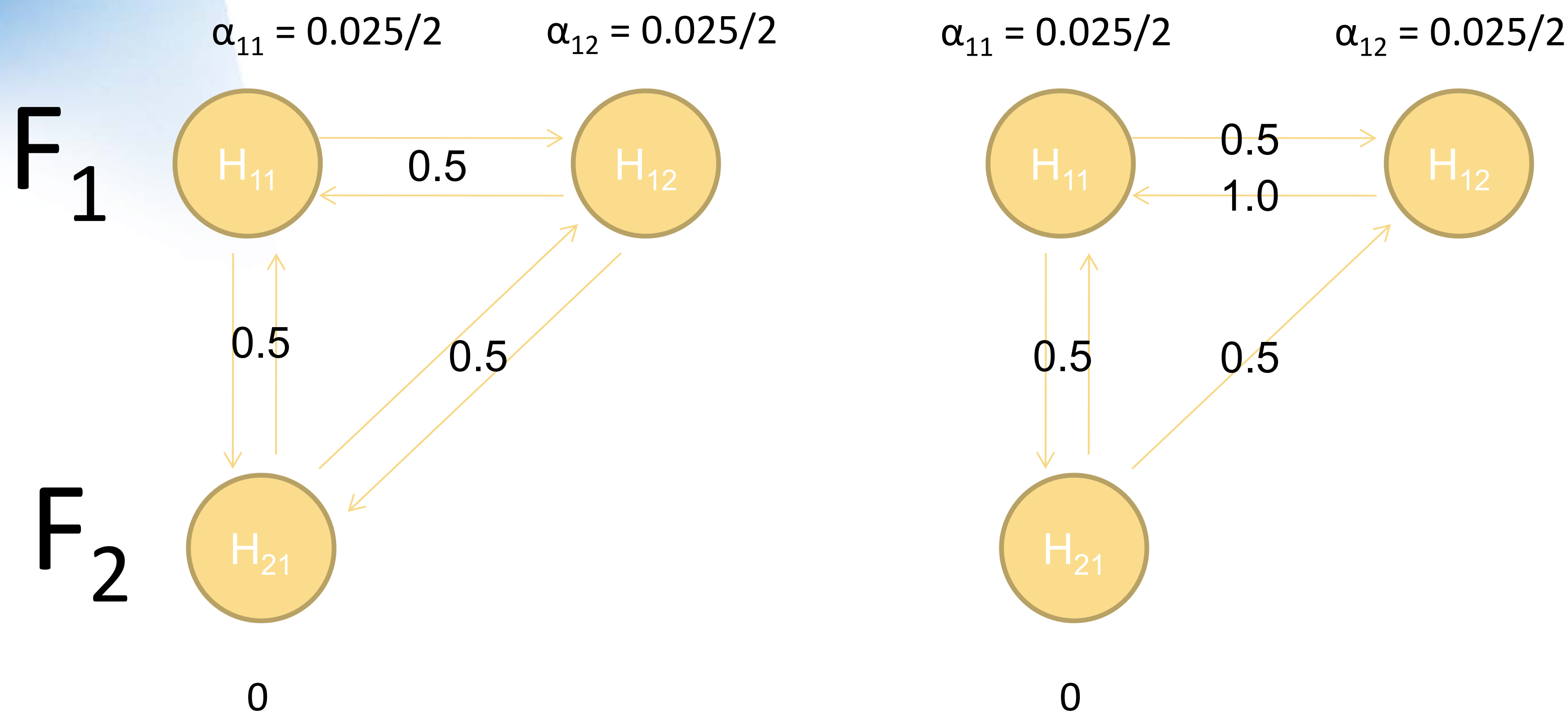
$$V = \begin{pmatrix} 2.0 & -0.7 & 1.0 & 0 \\ -0.7 & 2.0 & 0 & 1.0 \\ 1.0 & 0 & 2.0 & -0.8 \\ 0 & 1.0 & -0.8 & 2.0 \end{pmatrix}$$

$$Y_\nu^l = \sum_{j=1}^{n_l} Y_{\nu,j}^l, l = 0,1,2; \nu = 1,2, \ p_{\nu l} = P\left(\sqrt{\frac{1}{\hat{\sigma}_{\nu l}^2 + \hat{\sigma}_{\nu 0}^2}} Z_\nu^l > z_{\nu l}\right)$$

$$H_i : \pi_i = 0, i = 1,2,3; F_1 = \{H_1, H_3\}, F_2 = \{H_2\}$$

simulation runs : 10,000

Graphical Representation of a Gatekeeping Structure



Bonferroni Mixing

$$\text{Reject } H(I) \text{ if } \begin{cases} p_i(I_i) \leqslant \alpha & \text{if } I = I_i \ (i = 1, 2), \\ \phi_I(p_1(I_1), p_2(I_2)) \leqslant \alpha & \text{if } I = I_1 \cup I_2, I_1 \text{ and } I_2 \text{ are nonempty.} \end{cases}$$

$$\phi_I(p_1(I_1), p_2(I_2)) = \min\left(p_1(I_1), \frac{p_2(I_2)}{1 - e_1(I_1|\alpha)/\alpha}\right)$$

- **Error function for Bonferroni test**
  - **Dmitrienko and Tamhane (2011) SIM**
- **Error function for truncated Hommel test**
  - **Brechenmacher, Xu, Dmitrienko, Tamhane, A.C. (2011) JPS**

$$e_1(I_1|\alpha) = |I_1|\alpha/n_1 \qquad e(I|\alpha,\gamma) = (\gamma + (1-\gamma)|I|/n)\alpha \text{ if } |I| > 0$$

Simulation Results

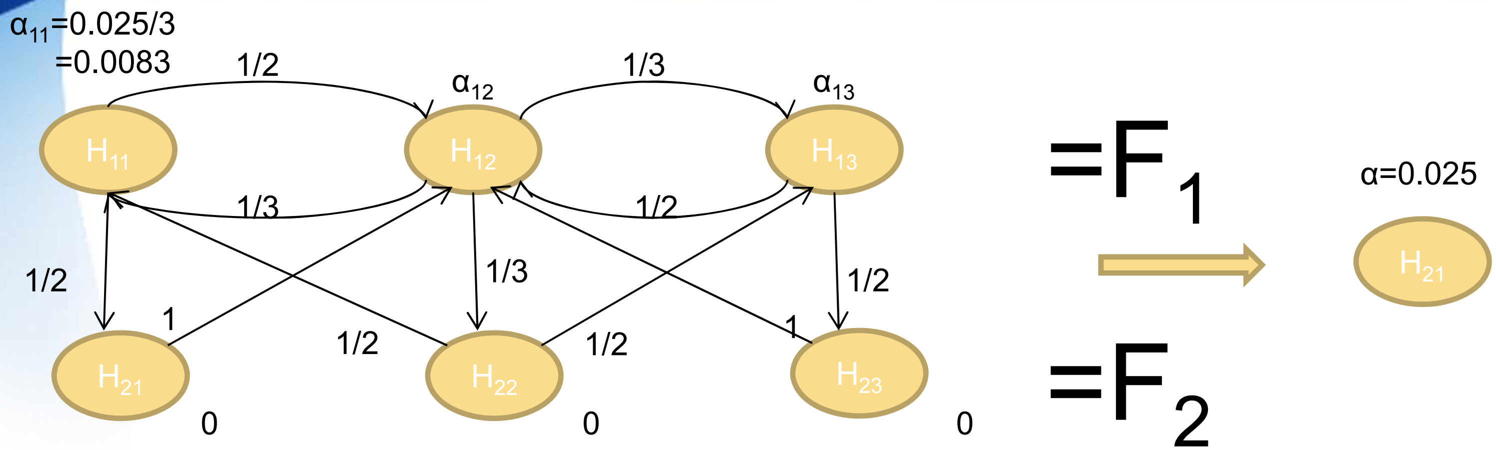
pi	B	BC	H	HC	FB	FBC	D	DC
0	0%	0%	2%	2%	1%	1%	2%	2%
0	0%	0%	0%	0%	0%	0%	0%	0%
0	0%	0%	1%	1%	1%	1%	2%	2%
0.45	1%	1%	83%	83%	83%	83%	83%	83%
0	0%	0%	0%	0%	0%	0%	2%	0%
0	1%	1%	2%	2%	2%	2%	2%	2%
0	2%	2%	3%	3%	2%	3%	2%	2%
0	0%	0%	1%	0%	1%	0%	2%	0%
0.45	2%	2%	82%	82%	82%	82%	83%	83%
0	0%	0%	1%	1%	1%	1%	1%	1%
0.45	0%	0%	1%	0%	1%	1%	2%	1%
0	0%	0%	2%	2%	2%	2%	2%	2%
0.45	1%	1%	82%	82%	82%	82%	83%	83%
0.45	1%	1%	60%	47%	60%	60%	72%	61%
0	1%	1%	2%	2%	2%	2%	2%	2%
0.45	72%	72%	86%	86%	85%	86%	85%	85%
0	1%	1%	2%	2%	2%	2%	2%	1%
0.45	72%	72%	87%	87%	85%	85%	85%	85%
0	1%	1%	3%	3%	2%	2%	2%	2%
0.45	1%	1%	64%	2%	64%	2%	75%	1%
0.45	1%	1%	83%	83%	83%	83%	84%	84%
0.45	73%	73%	88%	88%	88%	88%	86%	86%
0.45	64%	64%	81%	74%	81%	76%	83%	74%
0.45	73%	73%	88%	88%	87%	87%	86%	86%

Application to the Clinical Trial*

- **Population: Patients with psoriasis**
- **Placebo (P): n=79; Low dose regimen (L): n=66; Medium dose regimen (M): n=70; High dose regimen (H): n=72**
- **Standardized PASI and sPGA changes adjusted by P group**
  - **Z=(24.32 , 2.36, 38.25, 5.67, 52.77, 7.32)**
  - **V=(78.22 7.68 42.91 3.96 42.91 3.96**
    7.68 1.62 3.96 0.72 3.96 0.72
    42.91 3.96 92.30 9.28 42.91 3.96
    3.96 0.72 9.28 1.82 3.96 0.72
    42.91 3.96 42.91 3.96 96.00 7.66
    3.96 0.72 3.96 0.72 7.66 1.64)
- **C(1,0.025)=22.43 and compute f(1,0.025,e), all of which are smaller than 23. Thus, L, M, H are better than P in PASI**
- **Compute g bounds and decision rules**
  - **Gatekeeping: M and H are better than P (L cannot be concluded)**
  - **Gatekeeping with constraint: same result in this case**

* Some design features and data are modified for illustrative purpose.

Graphical Approach to the trial data



updated graph after sequentially rejecting H11, H12, H13, H22 and H23

	Endpoint 1			Endpoint 2		
	H11	H12	H13	H21	H22	H23
raw P-value	0.003	3E-05	<1E-05	0.032	1.4E-05	<1E-05
alpha by step						
0	0.00833	0.00833	0.00833	0	0	0
1	0	0.012495	0.00833	0.004165	0	0
2	0	0	0.013322	0.006661	0.004992	0
3	0	0	0	0.008324	0.008318	0.008324
4	0	0	0	0.012478	0	0.012478
5	0	0	0	0.024907	0	0
NULL Rejected	1	1	1	0	1	1

Conclusions

- **Propose a MCP based on jointly asymptotic multivariate distribution**
  - Utilize internal correlation among marginal tests statistics
  - Avoid assumption of normal distribution
  - Avoid assumption of positive correlation among individual test statistics
  - Show to have improvement over graphical procedure and bonferroni mixing for gatekeeping procedure in numerical examples under study
- **Apply the procedure to a real clinical trial data**
  - Easy implementation with computational package of multivariate normal distribution
- **Application to group sequential design with multiple endpoints could be extended**