A group sequential method using Hochberg procedure for clinical trials with multiple primary endpoints

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Multiple primary endpoints

- Endpoints in oncology clinical trials

Overall Survival (OS)	Progression Free Survival (PFS)
- the direct measure of clinical benefit for regular approval	- the surrogate for accelerated approval or regular approval

- Choice of the endpoints

Frequently	Recently
- PFS as the primary endpoint - OS as the secondary endpoint	- **Both OS and PFS as the primary endpoints**

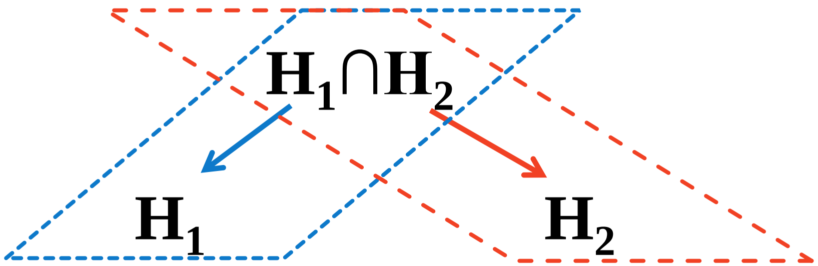
  - In some studies, benefits have demonstrated about OS, but not about PFS.

Group sequential methods for multiple primary endpoints

- Interim analyses
  - Benefit
    - Flexibility to stop early because of overwhelming evidence of efficacy, harm, or futility
  - Problem: multiplicity
    - Multiple looks (interim and final analyses)
    - Multiple endpoints
- Procedure for adjusting the multiplicity
  - **A group sequential Holm procedure** (Ye et al. 2012)
    - Simple stepwise procedure at each interim analysis
    - Group sequential methods are used in the closed testing procedure

Group sequential Holm procedure

- Closed testing procedure (CTP)



- **H_1**: null hypothesis about **OS**
- **H_2**: null hypothesis about **PFS**
- **$H_1 \cap H_2$**: global null hypothesis

  - H. is rejected if all intersection hypothesis are rejected

- Test of each hypothesis

Hypothesis	Test (group sequential method)
$H_1 \cap H_2$	**H_1 at $\alpha/2$ or H_2 at $\alpha/2$**
H_1	H_1 at α
H_2	H_2 at α

Bonferroni's adjustment (applies to the $H_1 \cap H_2$ row)

α: nominal significance level

Aims of study

- Propose a method improving power
  - Bonferroni' adjustment is conservative
    - A group sequential Holm procedure is conservative
  - **Simes' inequality is used** for the test of the global null hypothesis in the proposed method
    - Power can be improved regardless of any structure of correlation of test statistics
- Propose a simple stepwise procedure
  - **Use the idea of Hochberg procedure**
    - Procedure like a group sequential Holm procedure

Setting and notation

- **Setting**
  - one interim analysis and final analysis
  - Two primary endpoints
- **Notation**
  - $P_j(H_i)$: p-value (test statistic)
    - i = 1, 2: hypothesis, j = 1, 2: timing of analysis
      - Uniformly distributed under the null hypothesis
  - O_{jk}: hypothesis ordered by P_j
    - k = 1, 2: order of p-value
      - **O_{21}: hypothesis with smallest p-value at final analysis**
  - α_j: alpha spent at each analysis
    - $\alpha_1 + \alpha_2 = \alpha$ (α: nominal type I error rate)

Boundary of group sequential procedure (in the case of **single endpoint**)

- Rejection probability of $\mathbf{H_1}$ under the null hypothesis

$$\underbrace{\Pr(P_1(H_1) \le c_1)}_{\alpha_1} + \underbrace{\Pr(P_1(H_1) > c_1 \cap P_2(H_1) \le c_2)}_{\alpha_2} \quad \ldots(1)$$

$$\underbrace{\Pr(P_1(H_1) \le c_1)}_{\alpha_1} + \underbrace{\underbrace{\Pr(P_2(H_1) \le c_2)}_{\text{Marginal probability}} - \underbrace{\Pr(P_1(H_1) \le c_1 \cap P_2(H_1) \le c_2)}_{\text{Correction term}}}_{\alpha_2} \quad \ldots(2)$$

  - Dashed line: interim analysis
    - c_1: boundary of p-value at interim analysis
  - Dotted line: final analysis
    - c_2: boundary of p-value at interim analysis

- **c_2 is defined** to satisfy the condition
  - **the value of the dotted frame in (2) is equal to α_2**

Boundary of group sequential Holm procedure (in the case of two endpoints)

- Rejection probability of $\mathbf{H_{12}}$ under the null hypothesis

$$\underbrace{\Pr\{(P_1(H_1) \le c_{11} \cup P_1(H_2) \le c_{12})}_{\le \alpha_1} + \underbrace{(P_2(H_1) \le c_{21} \cup P_2(H_2) \le c_{22})\}}_{\text{Marginal probability}} - \underbrace{\Pr\{(P_1(H_1) \le c_{11} \cup P_1(H_2) \le c_{12}) \cap (P_2(H_1) \le c_{21} \cup P_2(H_2) \le c_{22})\}}_{\text{Correction term}} \quad \ldots(3)$$

The second and third terms together are $\le \alpha_2$.

⇩

$$\underbrace{\Pr(P_1(H_1) \le c_{11}) + \Pr(P_1(H_2) \le c_{12})}_{\alpha_1} + \underbrace{\Pr\{(P_1(H_1) > c_{11} \cap P_2(H_1) \le c_{21}) + \Pr\{(P_1(H_2) > c_{12} \cap P_2(H_2) \le c_{22})}_{\alpha_2} \quad \ldots(4)$$

  - c_{ji}: boundary of p-value

- Group sequential Holm is conservative because of using Bonferroni's inequality for calculation of boundary.

Boundary using Simes' inequality

- Rejection probability of $\mathbf{H_{12}}$ under the null hypothesis

$$\underbrace{\Pr(P_1(O_{11}) \le d_{11} \cup P_1(O_{12}) \le d_{12})}_{\text{Simes' inequality}} + \underbrace{\Pr(P_2(O_{21}) \le d_{21} \cup P_2(O_{22}) \le d_{22})}_{\text{Marginal probability; Simes' inequality}} - \underbrace{\Pr((P_1(O_{11}) \le d_{11} \cup P_1(O_{12}) \le d_{12}) \cap (P_2(O_{21}) \le d_{21} \cup P_2(O_{22}) \le d_{22}))}_{\text{Correction term}} \quad \ldots(5)$$

  - $\mathbf{d_{jk}}$, boundary for $P_j(O_{jk})$, **is defined** to satisfy the condition
    - **the value of the dotted frame in (5) is equal to α_2**

- Use right side in (6) for correction term

$$\Pr((P_1(O_{11}) \le d_{11} \cup P_1(O_{12}) \le d_{12}) \cap (P_2(O_{21}) \le d_{21} \cup P_2(O_{22}) \le d_{22}))$$
$$> \Pr(P_1(H_1) \le d_{11} \cap P_2(H_1) \le d_{21}) + \Pr(P_1(H_2) \le d_{11} \cap P_2(H_2) \le d_{21}) \quad \ldots(6)$$

  - Calculation is simple, but a procedure may be conservative.

e.g. Information fraction = 50%

- Boundary in testing H_{12}

	Simes' ineqality		Group sequential Holm	
	Pocock	O'brien Fleming	Pocock	O'brien Fleming
$P_1(O_{11})$	0.72%	0.07%	0.72%	0.07%
$P_1(O_{12})$	**1.43%**	**0.15%**	0.72%	0.07%
$P_2(O_{21})$	0.72%	1.22%	0.72%	1.22%
$P_2(O_{22})$	**1.43%**	**2.44%**	0.72%	1.22%

- Boundary in testing H_1 (H_2)

	Group sequential methods	
	Pocock	O'brien Fleming
$P_1(H.)$	1.47%	0.258%
$P_2(H.)$	1.47%	2.40%

A group sequential method using Hochberg procedure

Step	Boundary		
		Pocock	O'brien Fleming
Interim analysis			
Step1. If $P_1(O_{12}) \le c_{12}$, reject H_1 and H_2.	c_{12}	1.43%	0.15%
Step2. If $P_1(O_{11}) \le c_{11}$, reject O_{11}.	c_{11}	0.72%	0.07%
Final analysis (**no hypothesis** is rejected at interim analysis)			
Step1. If $P_2(O_{22}) \le c_{22}$, reject H_1 and H_2.	c_{22}	1.43%	2.40%
Step2. If $P_2(O_{21}) \le c_{21}$, reject O_{21}.	c_{21}	0.72%	1.22%
Final analysis (**O_{11}** is rejected at interim analysis)			
Step1. If $P_2(O_{12}) \le c_2$, reject O_{12}.	c_2	1.47%	2.40%

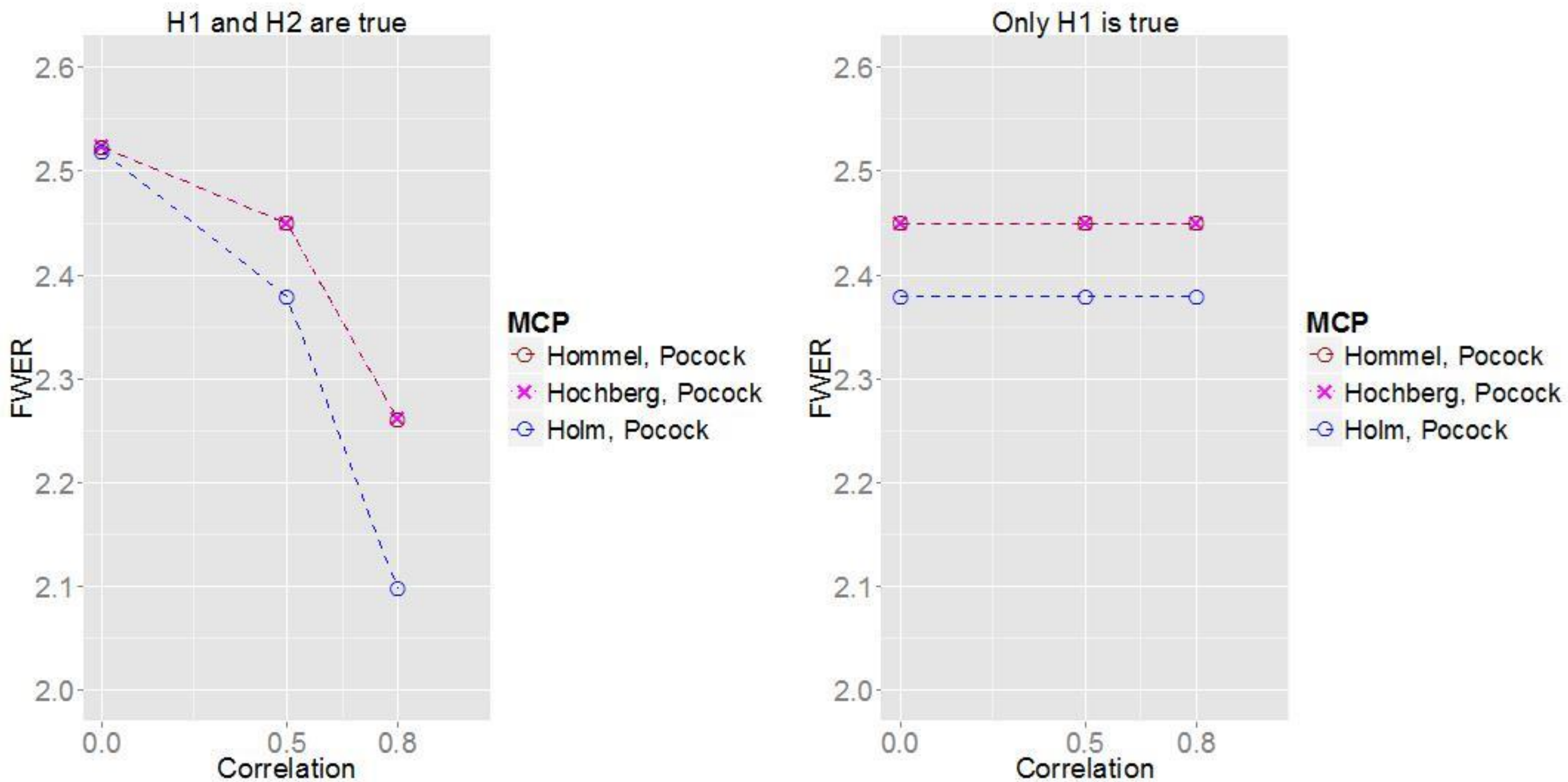
- Stepwise procedure is derived from the CTP using the idea of Hochberg procedure.
  - The procedure is convenient, but slightly conservative.

Simulation

- Setting
  - Comparison among 2 treatments with 2 primary endpoints
    - 1000 subjects in each group
    - **2-variate normal (correlation coefficient: 0, 0.5, 0.8)**
  - Interim and final analysis
    - Interim analysis at information fraction = 50%
    - Pocock, O'brien and Fleming (OF) boundaries are used

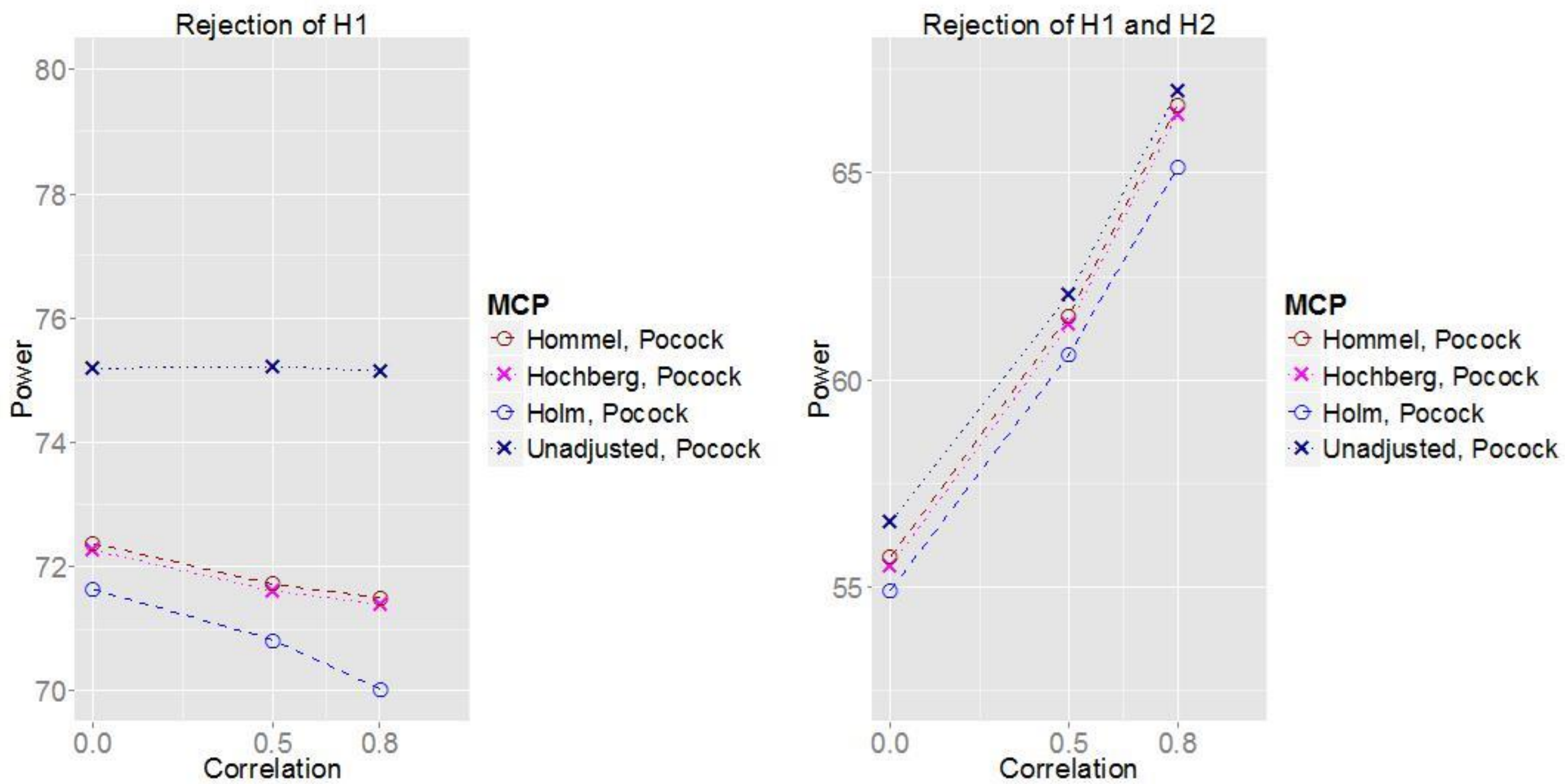
- Comparison
  - methods
    - Group sequential method using Hochberg procedure (**Hochberg**)
    - Simes inequality with the CTP (**Hommel**)
    - Group sequential Holm procedure (**Holm**)
    - Unadjusted multiplicity about multiple endpoints (**Unadjusted**)
  - measures
    - Familywise error rate (FWER) and power

FWER



- Similar results are given in using OF boundary

Power



- Similar results are given in using OF boundary

Discussion and conclusion

- Discussion
  - Results
    - Similarity of “Hochberg” and “Hommel” cannot be guaranteed because boundaries of “Hochberg” depend on the timing of interim analysis.
  - More research
    - Confirm the feature of “Hochberg” in other setting
    - Use weighted Simes’ method for H_{12}
- Conclusion
  - Group sequential methods using Sime’s inequality
    - More powerful than the group sequential Holm procedure
  - Group sequential method with Hochberg procedure
    - Simple stepwise procedure and can be more powerful than the group sequential Holm procedure

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