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

Kentaro Sakamaki        Yokohama City University
sakamaki@yokohama-cu.ac.jp
Multiple primary endpoints

• Endpoints in oncology clinical trials

<table>
<thead>
<tr>
<th>Overall Survival (OS)</th>
<th>Progression Free Survival (PFS)</th>
</tr>
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<tbody>
<tr>
<td>- the direct measure of clinical benefit for regular approval</td>
<td>- the surrogate for accelerated approval or regular approval</td>
</tr>
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• Choice of the endpoints

<table>
<thead>
<tr>
<th>Frequently</th>
<th>Recently</th>
</tr>
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<tbody>
<tr>
<td>- PFS as the primary endpoint</td>
<td>- Both OS and PFS as the primary endpoints</td>
</tr>
<tr>
<td>- OS as the secondary endpoint</td>
<td></td>
</tr>
</tbody>
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- 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 is rejected if all intersection hypothesis are rejected
  - Test of each hypothesis

\[ H_1 \cap H_2 \]

- \( H_1 \): null hypothesis about OS
- \( H_2 \): null hypothesis about PFS
- \( H_1 \cap H_2 \): global null hypothesis

\[ H_1 \]

\[ H_2 \]

\[ H_1 \text{ at } \alpha/2 \text{ or } H_2 \text{ at } \alpha/2 \]

\[ H_1 \text{ at } \alpha \]

\[ H_2 \text{ at } \alpha \]

α: nominal significance level

Hypothesis | Test (group sequential method) |
---|---|
\( H_1 \cap H_2 \) | \( H_1 \text{ at } \alpha/2 \text{ or } H_2 \text{ at } \alpha/2 \) |
\( H_1 \) | \( H_1 \text{ at } \alpha \) |
\( H_2 \) | \( H_2 \text{ at } \alpha \)
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
- $\alpha_j$: alpha spent at each analysis
  - $\alpha_1 + \alpha_2 = \alpha$ ($\alpha$: nominal type I error rate)
Boundary of group sequential procedure (in the case of single endpoint)

- Rejection probability of \( H_1 \) under the null hypothesis

\[
\Pr(P_1(H_1) \leq c_1)_{\alpha_1} + \Pr(P_1(H_1) > c_1 \cap P_2(H_1) \leq c_2)_{\alpha_2} \quad \ldots (1)
\]

\[
\Pr(P_1(H_1) \leq c_1)_{\alpha_1} + \Pr(P_2(H_1) \leq c_2) - \Pr(P_1(H_1) \leq c_1 \cap P_2(H_1) \leq c_2)_{\alpha_2} \quad \ldots (2)
\]

- 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 \( \alpha_2 \)
Boundary of group sequential Holm procedure (in the case of two endpoints)

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

\[
\Pr\{(P_1(H_1) \leq c_{11} \cup P_1(H_2) \leq c_{12}) \leq \alpha_1\} + \Pr\{(P_2(H_1) \leq c_{21} \cup P_2(H_2) \leq c_{22})\} - \Pr\{(P_1(H_1) \leq c_{11} \cup P_1(H_2) \leq c_{12}) \cap (P_2(H_1) \leq c_{21} \cup P_2(H_2) \leq c_{22})\} \leq \alpha_2 \quad \text{(3)}
\]

Correction term

Marginal probability

\[
\Pr(P_1(H_1) \leq c_{11}) + \Pr(P_1(H_2) \leq c_{12}) + \Pr(P_2(H_1) > c_{11} \cap P_2(H_1) \leq c_{21}) + \Pr(P_1(H_2) > c_{12} \cap P_2(H_2) \leq c_{22}) \leq \alpha_2 \quad \text{(4)}
\]

\quad c_{ji}: \text{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 $H_{12}$ under the null hypothesis

\[ \Pr(P_1(O_{11}) \leq d_{11} \cup P_1(O_{12}) \leq d_{12}) + \frac{\Pr(P_2(O_{21}) \leq d_{21} \cup P_2(O_{22}) \leq d_{22})}{\text{Simes’ inequality}} - \]

\[ \Pr((P_1(O_{11}) \leq d_{11} \cup P_1(O_{12}) \leq d_{12}) \cap (P_2(O_{21}) \leq d_{21} \cup P_2(O_{22}) \leq d_{22})) \quad \text{(5)} \]

- $d_{jk}$, boundary for $P_j(O_{jk})$, is defined to satisfy the condition
  - the value of the dotted frame in (5) is equal to $\alpha_2$

- Use right side in (6) for correction term

\[ \Pr((P_1(O_{11}) \leq d_{11} \cup P_1(O_{12}) \leq d_{12}) \cap (P_2(O_{21}) \leq d_{21} \cup P_2(O_{22}) \leq d_{22})) > \Pr(P_1(H_1) \leq d_{11} \cap P_2(H_1) \leq d_{21}) + \Pr(P_1(H_2) \leq d_{11} \cap P_2(H_2) \leq d_{21}) \quad \text{(6)} \]

- Calculation is simple, but a procedure may be conservative.
e.g. Information fraction = 50%

- Boundary in testing $H_{12}$

<table>
<thead>
<tr>
<th></th>
<th>Simes’ inequality</th>
<th>Group sequential Holm</th>
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<tbody>
<tr>
<td></td>
<td>Pocock</td>
<td>O’brien Fleming</td>
</tr>
<tr>
<td>$P_1(O_{11})$</td>
<td>0.72%</td>
<td>0.07%</td>
</tr>
<tr>
<td>$P_1(O_{12})$</td>
<td><strong>1.43%</strong></td>
<td><strong>0.15%</strong></td>
</tr>
<tr>
<td>$P_2(O_{21})$</td>
<td>0.72%</td>
<td>1.22%</td>
</tr>
<tr>
<td>$P_2(O_{22})$</td>
<td><strong>1.43%</strong></td>
<td><strong>2.44%</strong></td>
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- Boundary in testing $H_1 (H_2)$

<table>
<thead>
<tr>
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<th>Group sequential methods</th>
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<tbody>
<tr>
<td></td>
<td>Pocock</td>
</tr>
<tr>
<td>$P_1(H.)$</td>
<td><strong>1.47%</strong></td>
</tr>
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A group sequential method using Hochberg procedure

<table>
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<tr>
<th>Step</th>
<th>Boundary</th>
</tr>
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<tr>
<td></td>
<td>Pocock</td>
</tr>
<tr>
<td></td>
<td>O’brien Fleming</td>
</tr>
</tbody>
</table>

**Interim analysis**

- Step 1. If $P_1(O_{12}) \leq c_{12}$, reject $H_1$ and $H_2$.  
  - $c_{12}$  
  - 1.43% for Pocock  
  - 0.15% for O’brien Fleming
- Step 2. If $P_1(O_{11}) \leq c_{11}$, reject $O_{11}$.  
  - $c_{11}$  
  - 0.72% for Pocock  
  - 0.07% for O’brien Fleming

**Final analysis (no hypothesis is rejected at interim analysis)**

- Step 1. If $P_2(O_{22}) \leq c_{22}$, reject $H_1$ and $H_2$.  
  - $c_{22}$  
  - 1.43% for Pocock  
  - 2.40% for O’brien Fleming
- Step 2. If $P_2(O_{21}) \leq c_{21}$, reject $O_{21}$.  
  - $c_{21}$  
  - 0.72% for Pocock  
  - 1.22% for O’brien Fleming

**Final analysis (O_{11} is rejected at interim analysis)**

- Step 1. If $P_2(O_{12}) \leq c_{2}$, reject $O_{12}$.  
  - $c_{2}$  
  - 1.47% for Pocock  
  - 2.40% for O’brien Fleming

- 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
• 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
Reference

- Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. *Statistics in Biopharmaceutical Research* 2013; published online.