Branching tests in clinical trials with multiple objectives

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Outline

Gatekeeping procedures
Serial and parallel testing

Branching procedures
Multiple tests for clinical trials with hierarchically ordered objectives
Extension of gatekeeping methods

Clinical trial examples
Trial with multiple endpoints and objectives
Dose-finding trial with multiple endpoints
Mickey Mouse problem
Multiple endpoints
Two co-primaries/one secondary

Primary endpoint 1
$p \leq 0.025$

Primary endpoint 2
$p \leq 0.025$

Secondary endpoint
$p \leq 0.05$
Multiple endpoints
Two co-primaries/one secondary

Family 1: Bonferroni test

Primary endpoint 1
\[ p \leq 0.025 \]

Primary endpoint 2
\[ p \leq 0.025 \]

Secondary endpoint
\[ p \leq 0.05 \]
Multiple endpoints
Two co-primaries/one secondary

Family 2: Test if at least one primary endpoint is significant
Multiple endpoints
Two co-primaries/one secondary

Primary endpoint 1
\( p \leq 0.025 \)

Primary endpoint 2
\( p \leq 0.025 \)

Secondary endpoint
\( p \leq 0.05 \)

Type I error rate is inflated
\( 0.025 + 0.05 > 0.05 \)
Gatekeeping methods

Gatekeeping procedures
Multiple testing procedures for sequential families of null hypotheses
Serial gatekeeping methods, Westfall and Krishen (2001)
Parallel gatekeeping methods, Dmitrienko, Offen and Westfall (2003)
Parallel gatekeeping methods with logical restrictions, Chen, Luo and Capizzi (2005)

General overview
Dmitrienko et al (2005, Chapter 2)
Gatekeeping methods
Serial versus parallel strategies

Serial strategy
(Rheum arthritis)

- Endpoint 1: Signs and symptoms
- Endpoint 2: Disease progression
- Endpoint 3: Physical function/disability

Parallel strategy
(Acute lung injury)

- Endpoint 1: Lung function
- Endpoint 2: Mortality rate
- Endpoint 3: Quality of life
- Endpoint 4: ICU-free days
**Branching methods**

Trial designs are becoming increasingly more complex

Clinical researchers explore complex testing strategies

**Examples**

- Two- or three-dimensional rather than simple sequential strategies
- Logical restrictions

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**Serial strategy**

- Rheumatoid arthritis
  - Endpoint 1: Signs and symptoms
  - Endpoint 2: Disease progression
  - Endpoint 3: Physical function/disability

**Parallel strategy**

- Acute lung injury
  - Endpoint 1: Lung function
  - Endpoint 2: Mortality rate
  - Endpoint 3: Quality of life
  - Endpoint 4: ICU-free days
Clinical trial examples

Hypertension trial

Design
Experimental drug versus active control

Four endpoints
Primary (P): Systolic blood pressure
Secondary (S1 and S2): Diastolic blood pressure and proportion of patients with controlled systolic/diastolic blood pressure
Tertiary (T): Average blood pressure based on ambulatory blood pressure monitoring

Noninferiority vs superiority
Hypertension trial
Decision tree

P = Primary, S1 and S2 = Secondary, T = Tertiary endpoints
Clinical trial examples
Type II diabetes trial

Design
Three doses (L, M and H) versus placebo (P)

Three endpoints
Primary (P): Hemoglobin A1c
Secondary (S1 and S2): Fasting serum glucose and HDL cholesterol

Logical restrictions
Diabetes trial
Decision tree

P = Primary, S1 and S2 = Secondary endpoints
Closed testing principle
Marcus, Peritz and Gabriel (1976)
Define a branching procedure based on Bonferroni test
Compute multiplicity-adjusted p-values
Gatekeeping sets

Gatekeepers specific to each null hypothesis

Parallel gatekeeping and serial gatekeeping sets for each null hypothesis
Serial gatekeeping set

Null hypothesis H
Serial gatekeeping set:
All null hypotheses must be rejected in this set to test H
Parallel gatekeeping set for H:
At least one null hypothesis must be rejected in this set to test H
Hypertension trial

Decision tree

H11
P, Noninf

H21
S1, Noninf

H31
S1, Super

H23
P, Super

H33
T, Noninf

H22
S2, Noninf

H32
S2, Super

H41
T, Super
## Hypertension trial

### Parallel gatekeeping sets

<table>
<thead>
<tr>
<th>Null hypothesis</th>
<th>Parallel set</th>
</tr>
</thead>
<tbody>
<tr>
<td>H11 (P, Noninf)</td>
<td>NA</td>
</tr>
<tr>
<td>H21 (S1, Noninf)</td>
<td>H11</td>
</tr>
<tr>
<td>H22 (S2, Noninf)</td>
<td>H11</td>
</tr>
<tr>
<td>H23 (P, Super)</td>
<td>H11</td>
</tr>
<tr>
<td>H31 (S1, Super)</td>
<td>H21</td>
</tr>
<tr>
<td>H32 (S2, Super)</td>
<td>H22</td>
</tr>
<tr>
<td>H33 (T, Noninf)</td>
<td>H21, H22</td>
</tr>
<tr>
<td>H41 (T, Super)</td>
<td>H33</td>
</tr>
</tbody>
</table>

Serial gatekeeping sets are empty

[Slide 20]
Hypertension trial

Multiplicity-adjusted p-values

<table>
<thead>
<tr>
<th></th>
<th>Raw p-values</th>
<th>Multiplicity-adjusted p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>P, Noninf</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>P, Super</td>
<td>0.003</td>
<td>0.009</td>
</tr>
<tr>
<td>S2, Noninf</td>
<td>0.026</td>
<td>0.078</td>
</tr>
<tr>
<td>S1, Super</td>
<td>0.208</td>
<td>0.624</td>
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<tr>
<td>T, Noninf</td>
<td>0.010</td>
<td>0.045</td>
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<tr>
<td>T, Super</td>
<td>0.578</td>
<td>0.906</td>
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<tr>
<td>S1, Noninf</td>
<td>0.026</td>
<td>0.078</td>
</tr>
</tbody>
</table>
Diabetes trial
Decision tree

Endpoint P
- H11
- H12
- H13

Endpoint S1
- H21
- H22
- H23

Endpoint S2
- H31
- H32
- H33
## Diabetes trial

### Serial gatekeeping sets

<table>
<thead>
<tr>
<th>Null hypothesis</th>
<th>Serial set</th>
</tr>
</thead>
<tbody>
<tr>
<td>H11 (P, L vs P)</td>
<td>NA</td>
</tr>
<tr>
<td>H12 (P, M vs P)</td>
<td>NA</td>
</tr>
<tr>
<td>H13 (P, H vs P)</td>
<td>NA</td>
</tr>
<tr>
<td>H21 (S1, L vs P)</td>
<td>H11</td>
</tr>
<tr>
<td>H22 (S1, M vs P)</td>
<td>H12</td>
</tr>
<tr>
<td>H23 (S1, H vs P)</td>
<td>H13</td>
</tr>
<tr>
<td>H31 (S2, L vs P)</td>
<td>H11, H21</td>
</tr>
<tr>
<td>H32 (S2, M vs P)</td>
<td>H12, H22</td>
</tr>
<tr>
<td>H33 (S2, H vs P)</td>
<td>H13, H23</td>
</tr>
</tbody>
</table>

Parallel gatekeeping sets are empty

[Slide 23]
Diabetes trial
Branching strategy

Logical restrictions

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>L vs P</th>
<th>M vs P</th>
<th>H vs P</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>0.018</td>
<td>0.011</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>0.054</td>
<td>0.033</td>
<td>0.015</td>
</tr>
<tr>
<td>S1</td>
<td>0.013</td>
<td>0.007</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>0.054</td>
<td>0.033</td>
<td>0.041</td>
</tr>
<tr>
<td>S2</td>
<td>0.051</td>
<td>0.012</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>0.054</td>
<td>0.033</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Raw p-values  Multiplicity-adjusted p-values
Diabetes trial
Parallel gatekeeping strategy

No logical restrictions

L vs P  M vs P  H vs P

Endpoint P
0.018  0.054
0.011  0.033
0.005  0.015

Endpoint S1
0.013  0.054
0.007  0.033
0.009  0.041

Endpoint S2
0.051  0.054
0.012  0.054
0.010  0.054

Raw p-values  Multiplicity-adjusted p-values
Extensions

Basic branching framework
Based on Bonferroni test

**Account for correlation**
Correlation among multiple endpoints
Correlation among multiple dose-control comparisons
Account for correlation via resampling
(Westfall and Young, 1993)
Summary

Branching procedures
Efficient way to account for hierarchically ordered multiple objectives in clinical trials
Extend serial and parallel gatekeeping methods
Simple software implementation (SAS macro)

Closed testing principle
Control the familywise error rate in the strong sense
References


References
