Introduction to Crossover Trials

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What Are Crossover Trials?

- Study is divided into periods and each subject receives a different treatment in each period
- Sequence of treatments is randomized
  – May be more than 2 treatments and periods
  – Subjects may each receive only subset of treatments
- Subjects “serve as own controls”
Simplest Crossover Design

- 2 treatments (A and B), 2 periods
- random assignment of subjects to AB or BA

Study Population

Randomization

Wash out period
Advantages of Crossover Designs

• Each subject “serving as own control” implies less concern for baseline imbalance

• Can be much more efficient, if practical
  – Suppose treatment effect is difference in means
  – Variance for a parallel group trial, assuming equal variances, is \((2 / N) \sigma^2\)
  – Variance for a crossover trial is \((2 / N) \sigma^2 (1 – \rho)\)
    • \(\rho\) is correlation between responses from same subject
  – Ratio of 2 variances (design effect) is \((1 – \rho)\)
  – Example: if \(\rho = 0.75\), crossover design requires \(\frac{1}{4}\) number of observations to attain equal precision
Potential Problems and Limitations

• Carryover!!
  – Treatments received in earlier periods may affect responses in later periods
  – Goal: avoid it through design
• Blinding – subjects able to compare drugs
• Assessing adverse events – which drug may have caused an event observed in period 2?
• Loss of subjects can cause problems, as usual
• Behavioral/educational interventions – how would you wash those out?
Avoiding carryover “best done by selective and careful use of the design on the basis of adequate knowledge of both disease area and new medication."

ICH E9

*Statistical Principles for Clinical Trials*
Practicalities

• Condition should be chronic and stable (period 1 treatment should not “cure” disease)
• The washout periods should be sufficiently long for complete reversibility of drug effects
• Treatment effects should be quickly observable
• Cross-over designs often used in phase I and II bioequivalence studies
  – pharmacokinetic studies in healthy volunteers
Example

- 2-period crossover with 3 headache treatments (2 active drugs, A and B, and placebo, P)
  - Primary goal is to compare A and B
- Each subject randomized to one of 6 sequences: AB, BA, AP, PA, BP, PB
- Note that design is “incomplete” – each subject is “missing” one treatment
### Observed Data

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Response Profiles</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FF</td>
<td>FU</td>
</tr>
<tr>
<td>A : B</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>B : A</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>A : P</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>P : A</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>B : P</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>P : B</td>
<td>13</td>
<td>5</td>
</tr>
</tbody>
</table>

F = favorable response; U = unfavorable response
Analysis Method?

• Response in each period is binary: F or U
• Each person provides 2 responses
  – Do we expect responses to be independent?
• What are our analysis options?
  – Remember, primary concern is comparing A and B
How About GEE?

• Consider this model:

$$\text{logit}(\theta) = \beta_0 + \beta_1 \cdot \text{DRUGA} + \beta_2 \cdot \text{DRUGB} + \beta_3 \cdot \text{PERIOD1} + \beta_4 \cdot \text{CARRYA} + \beta_5 \cdot \text{CARRYB}$$

where $\theta = \Pr\{F | \text{drug, period, carry-over}\}$

DRUGA = 1 for A, 0 otherwise
DRUGB = 1 for B, 0 otherwise
PERIOD1 = 1 for period 1, 0 otherwise
CARRYA = 1 if period 2 AND drug in period 1 was A
CARRYB = 1 if period 2 AND drug in period 1 was B
Carryover Effects

• We hope that there are none!
  – Makes interpretation very difficult

• But, it’s a good idea to at least explore them
  – Test of carryover effects typically has low power
  – Remember, not finding them does not mean they are not there

• So, it’s important to make them implausible by design using an appropriate washout period
## Data in “Long” Form!

<table>
<thead>
<tr>
<th>id</th>
<th>seq</th>
<th>response</th>
<th>drugA</th>
<th>drugB</th>
<th>period1</th>
<th>carryA</th>
<th>carryB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AB</td>
<td>F</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>AB</td>
<td>F</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>BA</td>
<td>F</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>BA</td>
<td>U</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>PA</td>
<td>U</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PA</td>
<td>F</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Let’s Fit the Model!

- link = logit (for logistic regression)
- distribution or family = binomial
- corrtype or corr = exchangeable
# Model Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>95% Confidence Limits</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>$\beta_0 =$ -0.28</td>
<td>0.30</td>
<td>-0.87</td>
<td>0.30</td>
</tr>
<tr>
<td>drugA</td>
<td>$\beta_1 =$ 1.18</td>
<td>0.21</td>
<td>0.77</td>
<td>1.59</td>
</tr>
<tr>
<td>drugB</td>
<td>$\beta_2 =$ 0.33</td>
<td>0.22</td>
<td>-0.09</td>
<td>0.76</td>
</tr>
<tr>
<td>period1</td>
<td>$\beta_3 =$ -0.71</td>
<td>0.25</td>
<td>-1.21</td>
<td>-0.21</td>
</tr>
<tr>
<td>carryA</td>
<td>$\beta_4 =$ 0.07</td>
<td>0.33</td>
<td>-0.57</td>
<td>0.72</td>
</tr>
<tr>
<td>carryB</td>
<td>$\beta_5 =$ 0.04</td>
<td>0.33</td>
<td>-0.61</td>
<td>0.69</td>
</tr>
</tbody>
</table>
Reduced Model

• With individual p-values of 0.823 and 0.908, no evidence of carryover effects (good!)
  – Would be better to test parameters simultaneously using a 2 df test (p-value for this test is 0.975)

• So, we can fit reduced model
  \[
  \text{logit}(\theta) = \beta_0 + \beta_1 \cdot \text{DRUGA} + \beta_2 \cdot \text{DRUGB} + \beta_3 \cdot \text{PERIOD1}
  \]
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<th>Standard Error</th>
<th>95% Confidence Limits</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>$\beta_0 = -0.23$</td>
<td>0.15</td>
<td>-0.53</td>
<td>0.06</td>
</tr>
<tr>
<td>drugA</td>
<td>$\beta_1 = 1.16$</td>
<td>0.19</td>
<td>0.79</td>
<td>1.53</td>
</tr>
<tr>
<td>drugB</td>
<td>$\beta_2 = 0.32$</td>
<td>0.19</td>
<td>-0.05</td>
<td>0.69</td>
</tr>
<tr>
<td>period1</td>
<td>$\beta_3 = -0.74$</td>
<td>0.15</td>
<td>-1.03</td>
<td>-0.45</td>
</tr>
</tbody>
</table>

- Pretty clear evidence that Drug A is better than placebo
- Drug B, not so much
- But primary concern is A vs. B…
Answering the Primary Question

• How do drugs A and B compare?
• $H_0: \beta_1 - \beta_2 = 0$
• Estimated OR = $\exp\{1.16 - 0.32\} = \exp\{0.84\} = 2.31$
• The odds of favorable response doubled with A
• 95% CI = (1.58, 3.37)
• p-value < 0.001
“Only if there is substantial evidence that the therapy has no carryover effects, and the scientific community is convinced by that evidence, should a cross-over design be considered.”

Friedman, Furberg, and DeMets