CLINICAL TRIAL DESIGNS FOR RARE DISEASES: CROSSOVER AND N-OF-1 TRIALS

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CROSS-OVER TRIALS

- Basic concept
  - Every subject is exposed to both treatments in different time intervals
  - Subjects are randomized to order in which they receive treatment or control
  - Don’t have to worry about imbalance on prognostic factors; primary comparison is within subject
  - Attractive to study candidates, since assured of getting active treatment at some point
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Basic concept

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- Subjects are randomized to order in which they receive treatment or control
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- Attractive to study candidates, since assured of getting active treatment at some point
- Since each subject serves as own control, need fewer subjects
ADDITIONAL ISSUES

❖ Has to be a treatment taken regularly over time
  — Wouldn’t apply to acute treatments, like antibiotics for infections, or treatment of asthmatic attack

❖ Need to randomize order of treatment
  — Treatment given first may tend to show better (or worse) outcome

❖ Subjects may be treated for more than 2 periods
EXAMPLE

- Two treatments to be compared
- Treatment interval of 2 weeks
- Required washout period of 1 week

<table>
<thead>
<tr>
<th>Subject</th>
<th>Interval 1</th>
<th>Wash</th>
<th>Interval 2</th>
<th>Wash</th>
<th>Interval 3</th>
<th>Wash</th>
<th>Interval 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>A</td>
<td></td>
<td>B</td>
<td></td>
<td>B</td>
<td></td>
<td>A</td>
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<tr>
<td>002</td>
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<td>Wash</td>
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<td>003</td>
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POTENTIAL PROBLEM

- Possibility of **carryover effects** from one treatment phase to the next
- Dealt with by including a “washout” period during which no treatment is given
- Washout period must be long enough to ensure that prior treatment is not contributing to effect in next phase
- Hard to be sure how long washout period needs to be
EVALUATING CARRYOVER EFFECTS

- Statistical models can be developed to permit estimation of carryover effects, and testing for their presence.
- If trial is powered to detect main effect, on assumption of zero carryover effect, the power to detect carryover effect will be low.
- Dilemma: if we size trial to have good power to test for carryover effects, we lose the efficiency of the cross-over design.
USE OF CROSS-OVER DESIGNS

- Bioequivalence trials
  - Trials in healthy volunteers to assess comparability of pharmacokinetic parameters of generic to marketed drug
- Medical areas requiring chronic administration of treatment
  - Epilepsy
  - Diabetes
  - Pain relief
  - Asthma
N-OF-1 DESIGNS

- Developed as a rigorous way to assess optimal treatment for an individual patient
- Works like a cross-over trial
  - Patient alternates between active treatment and placebo, or between alternative active treatment regimens
  - More than 2 periods usually necessary
  - To be informative, must see rapid improvement with one regimen, rapid decline when that regimen is withdrawn
N-of-1 trial carried out to determine if oral theophylline was effective as part of asthma regimen

Double-blind trial of 10-day treatment periods on either treatment or placebo

Outcomes assessed by patient self-report on 7-point scale (1 worst)

- Shortness of breath
- Need for albuterol for acute symptoms
- Sleep disturbance
## EXAMPLE: RESULTS

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>DRUG</th>
<th>PLACEBO</th>
<th>DRUG</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Need for inhaler</td>
<td>3</td>
<td>5.5</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>5</td>
<td>5.5</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
EXTENSION TO POPULATION STUDIES

- N-of-1 trials could be used in early stage of drug development to facilitate design and conduct of definitive trials
  - Estimate proportion of responders
  - Study dosage

- Statistical model for combining n-of-1 trials to estimate effects in population has been developed (Zucker et al, J Clin Epid, 1997)
LIMITS OF N-OF-1 STUDIES

- As with cross-over studies, issue is interference over treatment periods
- Washout period required; need to know required length to avoid carryover effect
- Most applicable to chronic conditions where alleviation of symptoms is treatment goal
- Could also be used to assess biomarker changes if carefully monitored to keep subjects out of danger zone