Clinical Trial Design
Issues and Options
for the Study of Rare Diseases

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Financial Disclosure

• None
<table>
<thead>
<tr>
<th>The Issue</th>
<th>The Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Few patients.</td>
<td>• Multi-site studies.</td>
</tr>
<tr>
<td>• Few patients.</td>
<td>• Difficulty getting drugs for limited indications.</td>
</tr>
<tr>
<td>• Few patients.</td>
<td>• Longer studies.</td>
</tr>
<tr>
<td>• Few patients.</td>
<td>• Limited design options for clinical trials.</td>
</tr>
</tbody>
</table>
The Basic Issue

• To test efficacy, need a control group.
  • Choices: literature control, historical controls, concurrent controls, patients as own controls.

• Typical design is to recruit/assign to a treatment group/observe each group and compare outcomes.
  • But what if you could design a study using the same patient more than once?
Possible Design Options

- Parallel group design
- Cross-over design
- Factorial design
- Historical controls design
- Randomized withdrawal design
- Early escape design
- n-of-1 design
- Group sequential design
- Case-Control design
- Prospective cohort design
- Decision analysis-based design
- Ranking and selection design
- Adaptive design
- Risk-based allocation design
- Bayesian designs
- Enhanced designs

Reduce the number of study subjects needed by using enrolled subjects more than once.
Crossover Designs

Difficulty getting drugs for limited indications.

A1

B1

A2

B2

washout

Time
Crossover Designs

Difficulty getting drugs for limited indications.

A1
B1
A2
B2

A1+A2 vs. B1+B2
Crossover Design Analysis

Model: \( Y_{ijk} = \mu + b_{ij} + \pi_k + \phi_m + \lambda_m + \varepsilon_{ijk} \)
Where \( i = \text{sequence}, \ j = \text{patient}, \ k = \text{period} \) and \( m = \text{treatment} \)

<table>
<thead>
<tr>
<th></th>
<th>Period 1</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seq. 1</td>
<td>( \mu + \pi_1 + \phi_1 ) (( \bar{Y}_{1.1} ))</td>
<td>( \mu + \pi_2 + \phi_2 + \lambda_1 ) (( \bar{Y}_{2.1} ))</td>
</tr>
<tr>
<td>Seq. 2</td>
<td>( \mu + \pi_1 + \phi_2 ) (( \bar{Y}_{1.2} ))</td>
<td>( \mu + \pi_2 + \phi_1 + \lambda_2 ) (( \bar{Y}_{2.2} ))</td>
</tr>
</tbody>
</table>

Where (sequence, patient, period)
Treatment Effects

Estimation of Treatment Effect

\[ \phi_1 - \phi_2 = \bar{Y}_{1,1} - \bar{Y}_{1,2} \]
using first period data

\[ \phi_1 - \phi_2 = \frac{((\bar{Y}_{1,1} - \bar{Y}_{2,1}) - (\bar{Y}_{1,2} - \bar{Y}_{2,2}))}{2} \]
Carryover Effects

Estimation of Carryover Effects

\[ \lambda_1 - \lambda_2 = (\bar{Y}_{11} + \bar{Y}_{21}) - (\bar{Y}_{12} + \bar{Y}_{22}) \]

Seq. AB  Seq. BA
Using Crossover Designs

• Chronic condition.
• Relatively short study period.
• No carryover effect expected.
Advantages and Limitations

• Advantages:
  • Doubles the effective sample size.

• Limitations:
  • Study takes twice as long.
  • Refusal bias.
  • Carryover effects make interpreting study very complex.
Factorial Designs

Difficulty getting drugs for limited indications.
Factorial Design Analysis

A+C + A+D  vs.  B+C + B+D

and

C+A + C+B  vs.  D+A + D+B
Factorial Design Analysis

\[ y_i = \beta_0 + \beta_1 Z_{1i} + \beta_2 Z_{2i} + \beta_3 Z_{1i}Z_{2i} + e_i \]

where:

- \( y_i \) = outcome score for the \( i^{th} \) unit
- \( \beta_0 \) = coefficient for the intercept
- \( \beta_1 \) = mean difference on factor 1
- \( \beta_2 \) = mean difference on factor 2
- \( \beta_3 \) = interaction of factor 1 and factor 2
- \( Z_{1i} \) = dummy variable for factor 1 (0 = 1 hr/wk, 1=4 hrs/wk)
- \( Z_{2i} \) = dummy variable for factor 2 (0 = in class, 1= pull-out)
- \( e_i \) = residual for the \( i^{th} \) unit
### Example of an Interaction

<table>
<thead>
<tr>
<th>Combination</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{active}, B_{active}$</td>
<td>60%</td>
</tr>
<tr>
<td>$A_{active}, B_{placebo}$</td>
<td>30%</td>
</tr>
<tr>
<td>$A_{placebo}, B_{active}$</td>
<td>30%</td>
</tr>
<tr>
<td>$A_{placebo}, B_{placebo}$</td>
<td>30%</td>
</tr>
</tbody>
</table>
Interactions
Placebo Controlled Experiments
(B and D are placebo)

If both questions are placebo controlled, then

A     C     A+C     Placebo

Secondary comparison of combined effects
Advantages and Limitations

• Advantages:
  • Doubles the effective sample size, and it is possible for the treatments to run concurrently.

• Limitations:
  • Study could take twice as long.
  • Refusal bias.
  • Interaction effects make interpreting study very complex.
N-of-1 Randomized Trial Design

Drug and placebo administered sequentially in a random sequence, generally 3 or more drug-placebo pairs.
N-of-1 Randomized Trial Design

• If patient’s response was poor, that treatment stopped and the next treatment in the sequence begun immediately without breaking the randomized sequence.

• At the end of the study, the mean values for all measures and the mean differences between treatments are computed.
n-of-1 Randomized Trial

- Disorder should be chronic, i.e. relatively unchanged.
- Treatment effect rapid.
- Treatment duration for optimal effect should be well known.
Advantages and Limitations

- **Advantages:**
  - Every patient receives every treatment.
  - Treatment is evaluated in each patient.

- **Limitations:**
  - Study could take very long.
  - Refusal bias.
  - Difficult to know whether design assumptions are met (duration of treatment for optimal effect).
Enhanced Trial Designs

Using patients more than once,

but using the trial itself to select which group to re-use.
Conventional design

Efficacy analysis is based on comparing the results of the two treatment arms.
### Sample Size Required for a Given Power

<table>
<thead>
<tr>
<th></th>
<th>Drug</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Phase Design</td>
<td>60%</td>
<td>45%</td>
<td>15%</td>
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<table>
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<tr>
<th>Power</th>
<th>Total n</th>
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<tbody>
<tr>
<td>70%</td>
<td>274</td>
</tr>
<tr>
<td>80%</td>
<td>346</td>
</tr>
<tr>
<td>90%</td>
<td>462</td>
</tr>
</tbody>
</table>
Single Enhanced Design

Treatment Phase 1

1. Randomize
   - Active Treatment
     - Responder
     - Non Responder
   - Placebo
     - Non Responder
     - Responder

Treatment Phase 2

3. Randomize
   - Active Treatment
   - Placebo
## Comparison of Sample Size Required for a Given Power

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<tr>
<td>Single Phase Design</td>
<td>60%</td>
<td>45%</td>
<td>15%</td>
</tr>
<tr>
<td>or SPCD Phase 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPCD Phase 2</td>
<td>50%</td>
<td>25%</td>
<td>25%</td>
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### Total n

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Comparison of Sample sizes between Parallel and SPD designs for three scenarios with low placebo response rate

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Parallel n</th>
<th>SPD n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug</td>
<td>Pbo</td>
<td>Drug</td>
<td>Pbo</td>
</tr>
<tr>
<td>Scenario 1</td>
<td>.40</td>
<td>.20</td>
<td>.30</td>
<td>.10</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>.30</td>
<td>.15</td>
<td>.20</td>
<td>.05</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>.25</td>
<td>.10</td>
<td>.20</td>
<td>.05</td>
</tr>
</tbody>
</table>

All calculations are based on two-tailed alpha = 0.05, 80% power. For the SPD, the estimates are based on a 2:1 initial allocation of placebo:drug, and assumed retention of placebo patients from Stage 1 to Stage 2 = 90%.
Issues

• 2 chances to receive the active agent.
• Study takes at least twice as long.
• Efficiency depends upon response rate of those receiving placebo (placebo effect)
• Savings in sample size since all patients are used once and some are used twice.
Conventional design

Treatment Phase 1

Randomize

1. Active Treatment
   - Responder
   - Non Responder

2. Placebo
   - Responder
   - Non Responder
Double Enhanced Design

- **Treatment Phase 1**
  - Randomize
    - **Active Treatment**
      - Responder
      - Non Responder
    - **Placebo**
      - Responder
      - Non Responder

- **Results**
  - Randomize
    - **Active Treatment**
      - Placebo
    - **Placebo**

- **Treatment Phase 2**
  - Randomize
    - **Active Treatment**
    - **Placebo**
Summary

- When the number of study subjects is limited, it is possible to design studies that “re-use” the subjects enrolled to increase study power.
- Such designs require a number of assumptions that may or may not be verifiable.
- For some assumptions, it may be possible to test for their effect, but this is done after the study concludes and may complicate reporting and interpretation of results.
- Analyses are more complex and require good statistical advice at the time the study is being designed.
References


Ivanova A., Qaqish B., Schoenfeld D.: Optimality, sample size and power calculations for the sequential parallel comparison design; Statistics in Medicine 2011; 30: 2793-2803.

Tamura R., Xuang X., Boos D.: Estimation of Treatment Effect for the Sequential Parallel Design; Statistics in Medicine 2011; Accepted for publication.

Power calculator for a Sequential Parallel Design | MGH Biostatistics Center
Thank You