Clinical trial design issues and options for study of rare diseases

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Rare Diseases Clinical Research Network
Conflicts of Interest

None
Clinical Trial Design Principles

- The design and conduct of any type of clinical trial requires three considerations:
  - the study should examine valuable and important biomedical research questions;
  - the study must be based on a rigorous methodology that can answer a specific research question being asked; and
  - the study must be based on a set of ethical considerations, adherence to which minimizes risks to individuals.

http://www.nap.edu/catalog/10078.html
A study design that is considered appropriate should include sufficient sample size (n, statistical power, and proper control of bias to allow meaningful interpretation of) the results.*

– Enrolling the planned number of subjects is often a major barrier in orphan diseases.

– **Some designs are better than others for rare diseases**

*Small Clinical Trials: Issues and Challenges
http://www.nap.edu/catalog/10078.html
Alternative Designs

- 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
Randomized clinical trial:
- Assign participants as they are enrolled to an experimental treatment or a standard treatment (control).
- Treat and assess the outcome.
- When the outcome for the last participant enrolled has been observed, compare the experimental and control arms on their average response.
The Standard Design

1 Participant = 1 Treatment

1 Participant = 1 Outcome
The Standard Design

1 Participant = 1 Treatment

1 Participant = 1 Outcome
Modeling source of variance in endpoints

Premise that sample size calculations should utilize the same statistical approach as will be used in the analysis.

- Accounting for covariates at enrollment in predicting outcomes.
- Using the modeled or “adjusted” estimates of means and variances in sample size calculations.
- Incorporating adaptive designs with sample size re-estimation.
C-Peptide Levels* at 1 Year from the TrialNet New Onset T1D Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Model Based†</th>
<th>Observed</th>
<th>Design Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab (TN05)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GAD (TN08)</td>
<td></td>
<td></td>
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<tr>
<td>Abatacept (TN09)</td>
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<tr>
<td>Canakinamab (TN14)</td>
<td></td>
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<tr>
<td>Studies Combined</td>
<td></td>
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</tbody>
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*\( \log[X_{Cpep} + 1] \)  
†The linear model is adjusted for baseline C-peptide, and age. The estimated mean is evaluated at the mean baseline C-peptide level, and the mean age.
C-Peptide Levels* at 1 Year from the TrialNet New Onset T1D Trials

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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard Deviation</td>
<td>Control Group Mean</td>
</tr>
<tr>
<td>Rituximab (TN05)</td>
<td></td>
<td>0.2578</td>
<td>0.3405</td>
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<td>GAD (TN08)</td>
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<td>0.2111</td>
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<tr>
<td>Abatacept (TN09)</td>
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<td>0.2557</td>
<td>0.3251</td>
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<tr>
<td>Canakinamab (TN14)</td>
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<td>0.2592</td>
<td>0.3155</td>
</tr>
<tr>
<td>Studies Combined</td>
<td></td>
<td>0.2409</td>
<td>0.3235</td>
</tr>
</tbody>
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*\log[X_{\text{Cpep}} + 1])

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</thead>
<tbody>
<tr>
<td></td>
<td>SRMSE*</td>
<td>Control Group Mean</td>
<td>Standard Deviation</td>
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<tr>
<td>Rituximab (TN05)</td>
<td>0.1489</td>
<td>0.3562</td>
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<tr>
<td>GAD (TN08)</td>
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<td>Abatacept (TN09)</td>
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<tr>
<td>Canakinamab (TN14)</td>
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<td>Studies Combined</td>
<td>0.1513</td>
<td>0.3446</td>
<td>0.2409</td>
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</tbody>
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## Comparative Study Design

<table>
<thead>
<tr>
<th>Trial</th>
<th>Actual Planned Sample Size</th>
<th>Model Based Sample Size</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>including 10% inflation factor</td>
<td>including 10% inflation factor</td>
</tr>
<tr>
<td>TN-05 (Rituximab)</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>TN-08 (GAD)</td>
<td>126</td>
<td>66</td>
</tr>
<tr>
<td>TN-09 (Abatacept)</td>
<td>108</td>
<td>55</td>
</tr>
<tr>
<td>TN-14 (Canakinumab)</td>
<td>66</td>
<td>34</td>
</tr>
</tbody>
</table>

Modelled design requires 52% the number of subjects
The Enhanced Design

1 Participant = 1 Treatment

1 Participant = 1 Outcome
The Enhanced Design

1 Participant > 1 Treatment

1 Participant > 1 Outcome
The Enhanced Design

- Cross over designs
- Factorial Designs
- Single and Dual Enhanced Designs
- Sequential Multiple Assignment Randomized Trials
- N=1 Designs
Crossover Designs

A1

B1

A2

B2

washout

Time
Crossover Designs

A1
\[ \text{A1} + \text{A2} \quad \text{vs.} \quad \text{B1} + \text{B2} \]
A2

B1

B2
Factorial Designs

Diagram:

- A
- B
- C
- D

Timeline: Time
Factorial Design Analysis

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

and

C+A + C+B  vs. D+A + D+B
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 active & placebo treatment arms.
Single Enhanced Design

1. **Active Treatment**
   - **Responder**
   - **Non Responder**

2. **Placebo**
   - **Responder**
   - **Non Responder**

3. **Randomize**
   - **Active Treatment**
   - **Placebo**

4. **Treatment Phase 2**
   - **Responder**
   - **Non Responder**

**Results**
Double Enhanced Design

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

2. Randomize
   - Treatment Phase 2
     - Active Treatment
     - Placebo
Comparison of Sample sizes between Parallel and enhanced 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</th>
<th>Enhanced</th>
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<tbody>
<tr>
<td></td>
<td>Drug</td>
<td>Pbo</td>
<td>Drug</td>
<td>Pbo</td>
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<tr>
<td>Scenario 1</td>
<td>.40</td>
<td>.20</td>
<td>.30</td>
<td>.10</td>
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<td>164</td>
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<tr>
<td>Scenario 2</td>
<td>.30</td>
<td>.15</td>
<td>.20</td>
<td>.05</td>
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<td>242</td>
<td>134</td>
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<tr>
<td>Scenario 3</td>
<td>.25</td>
<td>.10</td>
<td>.20</td>
<td>.05</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>200</td>
<td>116</td>
</tr>
</tbody>
</table>

All calculations are based on two-tailed alpha = 0.05, 80% power. For the enhanced, 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.
Sequential Multiple Assignment Randomized Trials

Stage 1

Enrollment randomization

A

non-responders
randomized

B

non-responders
randomized

C

responders

Stage 2

A

responders

B

non-responders
randomized

C

responders

non-responders
randomized

A

B
N=1 Randomized Trial Design

Drug and placebo administered sequentially in a random sequence, generally 3 or more drug-placebo pairs.
Concept

• Can be thought of as multiple cross-over designs in the same participant.
• The successful N=1 design requires commitments on the part of the clinician and the participant.
• Suitable for chronic or slowly progressive disorders.
• When participants experience the different treatments being studied, then their outcomes can inform clinical decision making at the level of the individual (i.e., personalized medicine).

• The data across individuals can also be aggregated according to treatment groups for comparative effectiveness outcomes.
N=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=1 Randomized Trial

- Disorder should be chronic, i.e. relatively unchanging.
- 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).
Summary

Pros

• Each individual receives all treatments, so the best treatment for that individual is known.
• Multiple treatments in the same individuals give rise to more outcomes, so a smaller N is required.

Cons

• Study takes longer.
• Issues regarding changes in disease status (or patient’s health status) over time.
• Possible carry-over effects.
• Autocorrelation limits amount gained.
• Limited numbers of patients may raise concerns re generalizability.
Conclusions

• 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.
Thank you

Reference: Small Populations Clinical Trials Task Force Workshop Report and Recommendation, July 2106
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM (IRDiRC)