Clinical trial design issues and options for the study of rare diseases

November 19, 2018

Jeffrey Krischer, PhD
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:

  1. the study should examine valuable and important biomedical research questions;
  2. the study must be based on a rigorous methodology that can answer a specific research question being asked; and
  3. the study must be based on a set of ethical considerations, adherence to which minimizes risks to individuals.
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.
Sample Size Considerations

1. The type 1 error $\alpha$
2. The type 2 error $\beta$
3. One sided vs. two sided hypothesis
4. The study group mean under the null hypothesis $\mu$
5. The minimum increase in the experimentally treated group that we desire to detect $\mu_1 - \mu_2$
6. The variation in the study population (i.e., standard deviation). $\sigma$
Type 1 and Type 2 errors

Blue = Probability of observing a result $m^*$ or larger given $H_0$
Orange = Probability of observing a result $m^*$ or less given $H_1$
Type 1 error: 1 vs. 2-sided
1-sided vs. 2-sided

20-30% more subjects needed for a 2-sided test as compared to a 1-sided test of significance.
Sample Size Considerations

• The type 1 error \( \alpha \)
• The type 2 error \( \beta \)
• One sided vs. two sided hypothesis
• The study group mean under the null hypothesis \( \mu \)
• The minimum increase in the experimentally treated group that we desire to detect \( \mu_1 - \mu_2 \)
• The variation in the study population (i.e., standard deviation). \( \sigma \)
The statistics of comparing 2 means
$T = \text{Treatment}$

$C = \text{Control}$

$\mu_T - \mu_C$

$\sqrt{\frac{\text{var}_T}{n_T} + \frac{\text{var}_C}{n_C}}$

$\text{var} = \sigma^2$
T statistic

\[ T = \text{Treatment} \]
\[ C = \text{Control} \]

\[ t\text{-value} = \frac{\text{difference between group means}}{\text{variability of groups}} \]
\[ T = \text{Treatment} \]
\[ C = \text{Control} \]

\[ \mu_T - \mu_C = \sqrt{\frac{\text{var}_T}{n_T} + \frac{\text{var}_C}{n_C}} \]

\[ \text{var} = \sigma^2 \]
Sample size is directly proportional to the variance, inversely proportional to the detectable difference.
Variance
Power as a function of $\sigma$
Take home message

• When designing a trial:
  – Decide whether it is a 2-sided or 1-sided question.
  – Consider the magnitude of the “minimally clinically significant difference” the study is designed to detect.
  – Imagine ways that can reduce the variability of the treatment response.
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>Design Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard Deviation</td>
</tr>
<tr>
<td><strong>Rituximab (TN05)</strong></td>
<td>0.179</td>
</tr>
<tr>
<td><strong>GAD (TN08)</strong></td>
<td>0.179</td>
</tr>
<tr>
<td><strong>Abatacept (TN09)</strong></td>
<td>0.179</td>
</tr>
<tr>
<td><strong>Canakinamab (TN14)</strong></td>
<td>0.179</td>
</tr>
<tr>
<td><strong>Studies Combined</strong></td>
<td>--</td>
</tr>
</tbody>
</table>
The Model

A linear model adjusted for baseline C-peptide, and age.

\[
\log(Cp_{12} + 1) = \hat{\beta}_0 + \hat{\beta}_{Cp} \log(Cp_0 + 1) + \hat{\beta}_{Age} X_{Age} + \epsilon
\]

\( Cp_y \) = c-peptide level at time "y"

\( X_{Age} \) = Age at trial entry

\( \hat{\beta}_0, \hat{\beta}_{Cp0}, \hat{\beta}_{Age} \) = coefficients to be estimated from the model fit

\( \epsilon \) = measurement error (normally distributed)
### C-Peptide Levels at 1 Year from the TrialNet New Onset T1D Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Model Based†</th>
<th>Design Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SRMSE*</td>
<td>Control Group Mean</td>
</tr>
<tr>
<td>Rituximab (TN05)</td>
<td>0.1489</td>
<td>0.3562</td>
</tr>
<tr>
<td>GAD (TN08)</td>
<td>0.1522</td>
<td>0.3467</td>
</tr>
<tr>
<td>Abatacept (TN09)</td>
<td>0.1462</td>
<td>0.3338</td>
</tr>
<tr>
<td>Canakinamab (TN14)</td>
<td>0.1548</td>
<td>0.3306</td>
</tr>
<tr>
<td>Studies Combined</td>
<td>0.1513</td>
<td>0.3446</td>
</tr>
</tbody>
</table>

†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.
## Comparative Study Design

<table>
<thead>
<tr>
<th>Trial</th>
<th>Actual Planned Sample Size</th>
<th>Model Based Sample Size</th>
</tr>
</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.
Study Designs

Double-blinded placebo controlled clinical trial
Study 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
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 + A2 vs. B1 + B2
Factorial Designs

Compare A to B

A

Compare C to D

C
D
B

D

Time
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

Randomize

1. Active Treatment
   - Responder
   - Non Responder

2. Placebo
   - Responder
   - Non Responder

3. Randomize
   - Active Treatment
   - Placebo

Treatment Phase 1

Results

Treatment Phase 2
Double Enhanced Design

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

2. Treatment Phase 2
   - Responder
   - Non Responder

3. Treatment Phase 2
   - Responder
   - Non Responder

4. Treatment Phase 2
   - Responder
   - Non Responder

5. Treatment Phase 2
   - Responder
   - Non Responder

6. Treatment Phase 2
   - Responder
   - Non Responder
Comparison of Sample sizes between Parallel and enhanced designs for three scenarios with low placebo response rate.

<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>Drug</th>
<th>Pbo</th>
<th>Stage 2</th>
<th>Drug</th>
<th>Pbo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.40</td>
<td>0.20</td>
<td></td>
<td>0.30</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>0.30</td>
<td>0.15</td>
<td></td>
<td>0.20</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.10</td>
<td></td>
<td>0.20</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parallel n</th>
<th>Enhanced n</th>
</tr>
</thead>
<tbody>
<tr>
<td>164</td>
<td>101</td>
</tr>
<tr>
<td>242</td>
<td>134</td>
</tr>
<tr>
<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

![Diagram showing the process of sequential multiple assignment randomized trials](image-url)
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).
Conclusions

• Journal editors often prefer 2-sided testing designs.
• Looking for larger differences requires fewer study participants.
• Reducing the variance through adjusting for confounders has the same proportional effect on sample size as does looking for larger differences.
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


Orphanet Journal of Rare Diseases

Position Statement

Recommendations for the design of small population clinical trials

Simon Day1, Anneliene Hechtelt Jonker2, Lilian Pek Lian Lau3, Ralf-Dieter Hilgers3, Ilan Irony4, Kristina Larsson5, Kit CB Roes5 and Nigel Stallard7