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

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“If your experiment needs statistics, you ought to have done a better experiment.”

Bertrand Russell
Ernest Rutherford

Resources

Small Clinical Trials: Issues and Challenges
Institute of Medicine,
National Academy Press,

The Science of Small Clinical Trials
http://videocast.nih.gov
select past events
Conducting Clinical Trials Rare Diseases*

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Hierarchy of Designs

- Meta-analyses of “good quality” RCT’s
- Individual RCT’s
- Meta-analyses of observational studies
- Individual observational studies
- Published case reports
- Anecdotal case reports
- Opinion of experts

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Alternative Designs for Clinical Trials
- 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

Key word: 2009: Controls
- No controls
- Historical Controls
- Concurrent Controls
- Self Controls

Key word: 2010: Outcomes
- Categorical
- Continuous
- Longitudinal
**Categorical Outcomes**
- Response vs. no response
- Analysis is a difference in proportions

**Continuous Outcomes**
- Measured response
- Analysis is a difference in means

**Categorical or continuous measure of effect?**

**Longitudinal Outcomes**
- Time until response
- Analysis is a difference in rate
- Sample Size:
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Choice of study end point

Power
Categorical < Continuous < Longitudinal

Sample Size
Categorical > Continuous > Longitudinal
Continuous: Parametric vs. Nonparametric

What do we mean?

- Parametric statistical procedures rely on assumptions about the shape of the distribution in the underlying population.
- Nonparametric statistical procedures make no or few assumptions about the shape or parameters of the population distribution from which the sample was drawn.

Ref: Haskin, T: Parametric and Nonparametric: Demystifying the Terms
Continuous: Parametric vs. Nonparametric

- When to use nonparametric tests?
  - When the sample size is small.
  - When the response distribution is not normal.

**Conundrum**

- For very small sample sizes, nonparametric tests cannot achieve statistical significance, no matter the response.
- This is not true for parametric tests.

**Recommendation**

- Make fewest possible assumptions about the data.
- In designing trial, make use of what is known about the parameter of interest.

... use parametric tests because they are slightly more powerful when data are normally distributed.
Recommendation

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  ...use parametric tests because they are slightly more powerful when data are normally distributed.

- Otherwise, run both. If answers disagree, trust the nonparametric test results.

Examples of Tests to Use

<table>
<thead>
<tr>
<th>Parametric Test</th>
<th>Nonparametric Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-test (unpaired)</td>
<td>Wilcoxon rank sum test</td>
</tr>
<tr>
<td>Paired T-test</td>
<td>Wilcoxon signed rank test</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Kruskal-Wallis test</td>
</tr>
<tr>
<td>Repeated measures ANOVA</td>
<td>Friedman test</td>
</tr>
<tr>
<td>Pearson coefficient of correlation</td>
<td>Spearman's rank correlation</td>
</tr>
</tbody>
</table>

Outcomes

+ Controls

Design
There are options that can help make studies in rare diseases more feasible.

- Choose the study question carefully.
  - What is the size of the treatment effect that the study is designed to detect?
- Choose the study end point carefully.
  - Attaining a fixed result at a single point in time or looking for changes over time?
- Choose the design that is most feasible.
  - Is it possible to accrue the target sample size?

Size of the treatment effect

- Minimally Clinically Important Difference:

  The smallest difference in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management.
• Patient’s perception of benefit.
• Consideration of cost or side effects.
• Change in management

• Patient’s perception of benefit.
• Consideration of cost or side effects.
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• Individual benefit vs. population benefit.

…but we are not quite done
• There are decisions that can be made during the course of a trial that can reduce its duration (or required sample size).

• Interim analyses
• Adaptive study designs
Early Differences or a Lack of Difference

- The determination of significant early emerging differences. (Type 1 error)
- The lack of observed differences which might make the continuation of the trial unnecessary. (Type 2 error)

Monitoring for Early Emerging Differences

Stopping boundary

Futility Monitoring

Stopping boundary
Adaptive Designs

- Re-evaluate baseline assumptions:
  - Control arm outcomes.
- Revise randomization algorithm:
  - Unbalanced randomization.
- Drop a poorly performing arm:
  - Phase II/III designs.

Recommendation

- Use interim monitoring when outcomes are observed faster than subjects will be accrued.
  - YES – planned 3 years of accrual for a study evaluating 1-year disease free survival.
  - NO – planned 3 years of accrual for a study evaluating 5-year disease free survival.
- Consider Phase II/III trials in which the subjects utilized in the Phase II portion of the study can be used in the Phase III portion of the study.
- Specify the interim analysis plan before the study starts.

Summary

- The study of rare diseases is more challenging due to the limited number of subjects to study.
- The nature of rare diseases (often chronic or episodic) lends itself to alternative study designs (factorial, N-of-1).
- The prudent choice of outcome measures of rare diseases trials can lead to answering study questions with fewer subjects.
- Monitoring trials during their conduct can lead to answering study questions with fewer subjects.
"By a small sample, we may judge of the whole piece."

Miguel de Cervantes from Don Quixote

Questions?