

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

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Rare Diseases Clinical Research Network  
September 21, 2010



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

Bertrand Russell  
Ernest Rutherford



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**Resources**



*Small Clinical Trials: Issues and Challenges*  
Institute of Medicine,  
National Academy Press,  
Washington, DC, 2001).

The Science of Small Clinical Trials  
<http://videocast.nih.gov>

select past events



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**Conducting Clinical Trials Rare Diseases\***

Jeffrey Krischer, Ph.D.  
Data and Technology Coordinating Center  
Rare Diseases Clinical Research Network  
April 17, 2009

\*Griggs RC, et al; Rare Diseases Clinical Research Network.:  
Clinical research for rare disease: opportunities, challenges, and solutions..  
*Mol Genet Metab* 96(1):20-6, 2009.



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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



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**2009:**

Key word:  
**Controls**

No controls  
Historical Controls  
Concurrent Controls  
Self Controls



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**2010:**

Key word:  
**Outcomes**

Categorical  
Continuous  
Longitudinal



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**Categorical Outcomes**

- Response vs. no response
- Analysis is a difference in proportions

**Continuous Outcomes**

- Measured response
- Analysis is a difference in means




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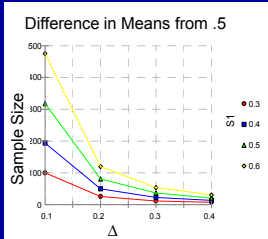
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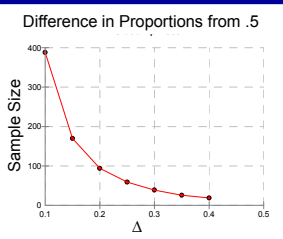
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**Categorical or continuous measure of effect?**

**Difference in Means from .5**



**Difference in Proportions from .5**






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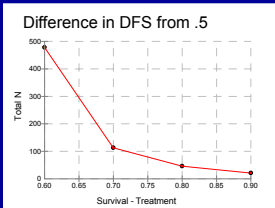
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**Longitudinal Outcomes**

- Time until response
- Analysis is a difference in rate
- Sample Size:

**Difference in DFS from .5**






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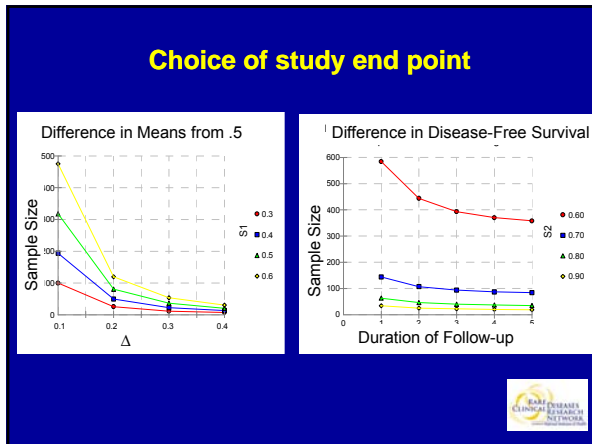
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### Power

Categorical < Continuous < Longitudinal



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### Power

Categorical < Continuous < Longitudinal

Sample Size

Categorical > Continuous > Longitudinal



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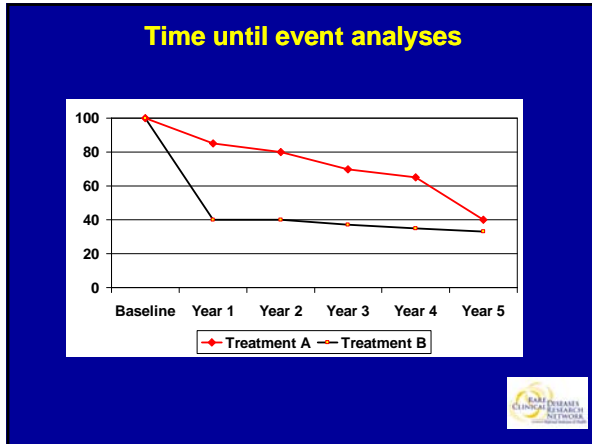
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### Continuous: Parametric vs. Nonparametric

- **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



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### Continuous: Parametric vs. Nonparametric

- **What do we mean?**
  - Parametric statistical procedures: a comparison of means
  - Nonparametric statistical procedures: a comparison of medians



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**Continuous:  
Parametric vs. Nonparametric**

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



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**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.**



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**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.



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



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### Examples of Tests to Use

Parametric Test	Nonparametric Test
T-test (unpaired)	Wilcoxon rank sum test
Paired T-test	Wilcoxon signed rank test
ANOVA	Kruskal-Wallis test
Repeated measures ANOVA	Friedman test
Pearson coefficient of correlation	Spearman's rank correlation



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Outcomes  
+ Controls  
Design



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**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?



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**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.



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**Size of the treatment effect**

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- Patient's perception of benefit.
- Consideration of cost or side effects.
- Change in management



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- Patient's perception of benefit.
- Consideration of cost or side effects.
- Change in management.
  
- Individual benefit vs. population benefit.



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**...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



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### 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)



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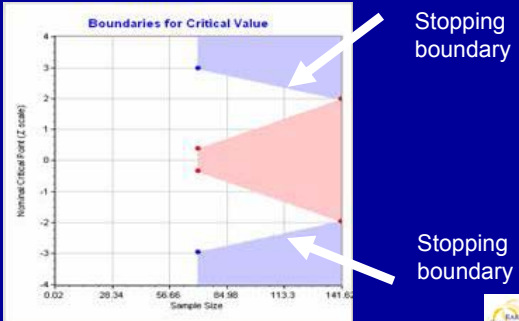
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### Monitoring for Early Emerging Differences



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### Futility Monitoring



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### Adaptive Designs

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



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### 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.



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### 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.



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"By a small sample,  
we may judge of the whole piece."  
Miguel de Cervantes from Don Quixote



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**Questions?**



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