Presenter Disclosure
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The following relationships exist related to this presentation:

Statistics Collaborative, Inc. has an ongoing contract with BioMarin Pharmaceutical, Inc.
Special considerations in gene transfer: small populations – orphan diseases

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ASGCT Clinical Trials Training Course
May 18, 2010
Overview

∑ Introduction
∑ Design considerations
∑ Analysis considerations
   θ Example and analysis options
∑ Additional issues
MPS I
(mucopolysaccharidosis I)

- Enzyme deficiency which causes buildup of glycosaminoglycans (GAGs)

- GAG accumulation leads to irreversible organ damage

- Progressive, debilitating, possibly life-threatening disease
Rare Disease

small population
Rare Disease

small population
↓
small sample size
Rare Disease

- small population
  - small sample size
  - variability
Rare Disease

cost

small population

↓

small sample size

↓

variability
Rare Disease

- small population
  - small sample size
  - variability

$\rightarrow$

feasibility and logistics

$\downarrow$

cost
Rare Disease

- small population $\rightarrow$ feasibility and logistics
  - small sample size $\rightarrow$ multi-center
    - variability $\rightarrow$ multi-national

- cost
Rare Disease

small population → feasibility and logistics
  ↓ multi-center
  ↓ multi-national

small sample size → variability

cost → feasibility and logistics
  ↓ multi-center
  ↓ multi-national

variability
Rare Disease

- Small population → cost
- Small sample size → feasibility and logistics
- Variability → multi-center
- Power → multi-national
Potential issues in design

- Selection criteria and generalizability
Potential issues in design

- Selection criteria and generalizability
- Recruitment timing
Potential issues in design

- Selection criteria and generalizability
- Recruitment timing
- Criteria for choosing the length of study
Potential issues in design

- Selection criteria and generalizability
- Recruitment timing
- Criteria for choosing the length of study
  - Time to observe clinically significant effect
Potential issues in design

Σ Selection criteria and generalizability

Σ Recruitment timing

Σ Criteria for choosing the length of study
  θ Time to observe clinically significant effect
  θ Feasibility
Potential issues in design

∑ Selection criteria and generalizability
∑ Recruitment timing
∑ Criteria for choosing the length of study
  θ Time to observe clinically significant effect
  θ Feasibility
∑ Endpoint exploration
Potential issues in design

∑ Selection criteria and generalizability
∑ Recruitment timing
∑ Criteria for choosing the length of study
  θ Time to observe clinically significant effect
  θ Feasibility
∑ Endpoint exploration
∑ Randomization
Potential issues in analysis

\[ \sum \text{Baseline (imbalance)} \]
Potential issues in analysis

∑ Baseline (imbalance)

∑ Distributional assumptions (not met)
Potential issues in analysis

∑ Baseline (imbalance)

∑ Distributional assumptions (not met)

∑ Variability (higher)
Potential issues in analysis

- Baseline (imbalance)
- Distributional assumptions (not met)
- Variability (higher)
- Power (lower)
The sample: n=45

- Phase 3 trial, ERT treatment
- Two treatment groups: active ($n_a=22$) and placebo ($n_p=23$)
- Measurements at baseline and Weeks 4, 8, 12, 16, 20, and 26
- Outcome is a continuous measure of response
- Endpoint: evaluate improvement of response between groups at Week 26
Analytic method should address:

- Baseline (possible adjustment)
- Distributional assumptions (robust)
- Variability (minimize)
- Power (maximize)
Analysis: what are our options?

1. Ignore baseline
Analysis: what are our options?

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1. Ignore baseline
2. Continuous outcome: change (W26-BL)
Analysis: what are our options?

1. Ignore baseline
2. Continuous outcome: change (W26-BL)
   - T-test on change
Analysis: what are our options?

1. Ignore baseline
2. Continuous outcome: change (W26-BL)
   - T-test on change
   - Wilcoxon
Analysis: what are our options?

1. Ignore baseline

2. Continuous outcome: change (W26-BL)
   - T-test on change
   - Wilcoxon
   - ANOVA
Analysis: what are our options?

1. Ignore baseline
2. Continuous outcome: change (W26-BL)
3. Responder analysis on change
Analysis: what are our options?

1. Ignore baseline
2. Continuous outcome: change (W26-BL)
3. Responder analysis on change
4. Use all timepoints in longitudinal model
Analysis: what are our options?

1. Ignore baseline
2. Continuous outcome: change (W26-BL)
3. Responder analysis on change
4. Use all timepoints in longitudinal model
   - Repeated measures to model data
   - Use a contrast to find original comparison of interest
Analysis: what are our options?

1. Ignore baseline
2. Continuous outcome: change (W26-BL)
3. Responder analysis on change
4. Use all timepoints in longitudinal model
5. Use a randomization test
Analysis: what are our options?

1. Ignore baseline
2. Continuous outcome: change (W26-BL)
3. Responder analysis on change
4. Use all timepoints in longitudinal model
5. Use a randomization test
   - Often as in conjunction with primary analysis, as a sensitivity analysis
5. Use a randomization test

\[ \sum \text{ Randomize allocation of treatment label to patient} \]
5. Use a randomization test

- Randomize allocation of treatment label to patient
- For large number of replications, calculate test statistic from model
5. Use a randomization test

- Randomize allocation of treatment label to patient
- For large number of replications, calculate test statistic from model
- \( p\text{-value} = \text{proportion of } p\text{-values as or more extreme than observed in actual dataset} \)
Issues in small, but not larger studies

∑ Degrees of freedom

Example: Drug to decrease blood pressure. Include people not meeting blood pressure entry criteria.

- Large study: doesn't help, but doesn't really hurt.
- Small study: doesn't help: population, variability, power, effect dilution.
Issues in small, but not larger studies

∑ Degrees of freedom

∑ Larger n \(\neq\) decrease in variability

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Issues in large, but not smaller studies

Σ Manageability
Issues in large, but not smaller studies

∑ Manageability
∑ “Getting into” the data
Issues in large, but not smaller studies

∑ Manageability
∑ “Getting into” the data
∑ Auditing and quality control
Special considerations in gene transfer:
small populations – orphan diseases

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