




AMERICAN SOCIETY OF GENE & CELL THERAPY
13TH ANNUAL MEETING | Washington, DC USA May 19-22, 2010

Presenter Disclosure Zi-Fan Yu, ScD

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

Zi-Fan Yu, ScD

ASGCT Clinical Trials Training Course
May 18, 2010

Overview

- Σ Introduction
- Σ Design considerations
- Σ Analysis considerations
 - ⊖ Example and analysis options
- Σ Additional issues

MPS I

(mucopolysaccharidosis I)

- Σ Enzyme deficiency which causes buildup of glycosaminoglycans (GAGs)
- Σ GAG accumulation leads to irreversible organ damage
- Σ 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

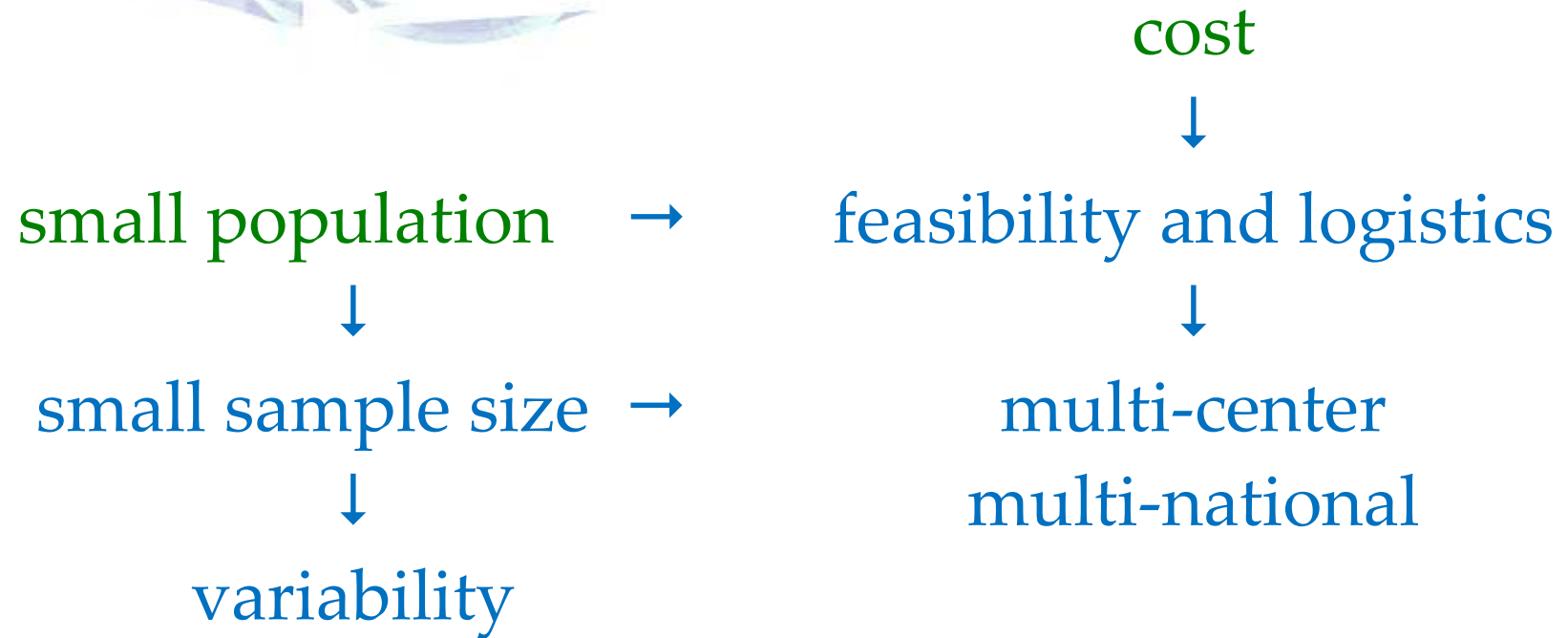


variability

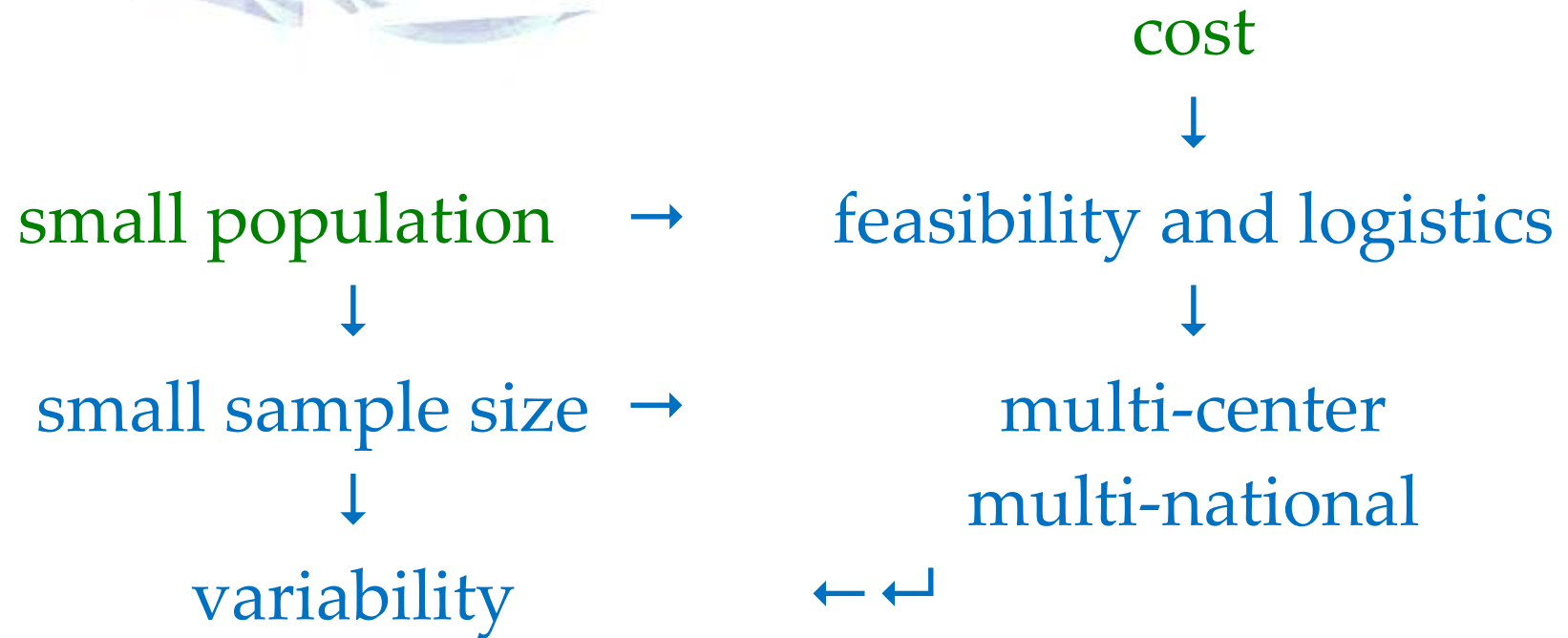
Rare Disease



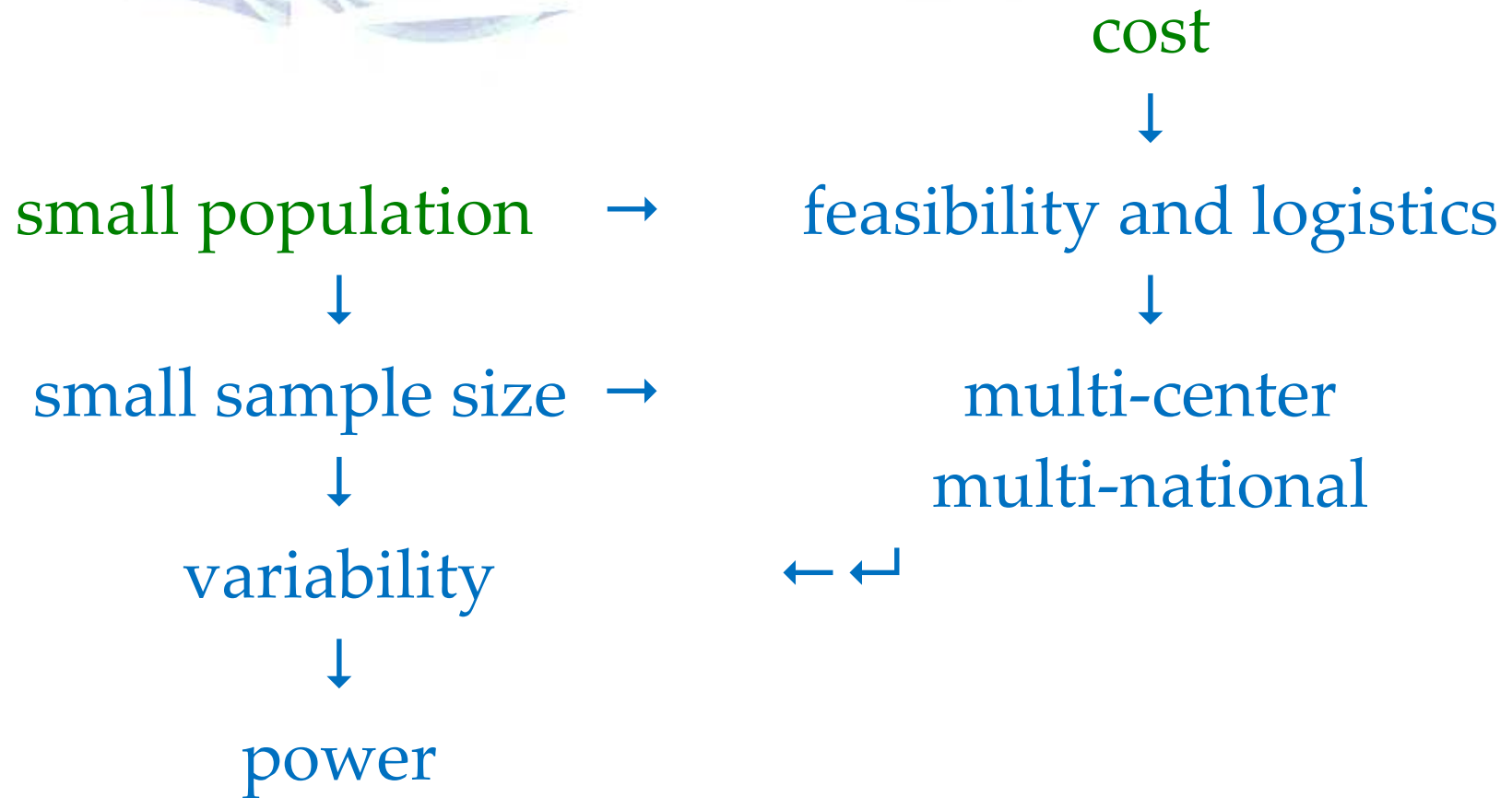
Rare Disease



Rare Disease



Rare Disease



Potential issues in design

- Σ Selection criteria and generalizability

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- Σ Selection criteria and generalizability
- Σ Recruitment timing
- Σ Criteria for choosing the length of study
 - ⊖ Time to observe clinically significant effect
 - ⊖ Feasibility
- Σ Endpoint exploration
- Σ Randomization

Potential issues in analysis

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- Σ Variability (higher)
- Σ Power (lower)

The sample: $n=45$

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

Analytic method should address:

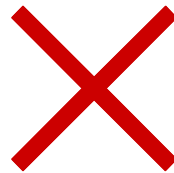
- Σ Baseline (possible adjustment)
- Σ Distributional assumptions (robust)
- Σ Variability (minimize)
- Σ Power (maximize)

Analysis: what are our options?

1. Ignore baseline

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2. Continuous outcome: change (W26-BL)

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⊖ T-test on change

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 - ⊖ Wilcoxon

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2. Continuous outcome: change (W26-BL)
 - ⊖ T-test on change
 - ⊖ Wilcoxon
 - ⊖ ANOVA

Analysis: what are our options?

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2. Continuous outcome: change (W26-BL)
3. Responder analysis on change

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4. Use all timepoints in longitudinal model

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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

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- Σ For large number of replications, calculate test statistic from model

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- Σ Randomize allocation of treatment label to patient
- Σ For large number of replications, calculate test statistic from model
- Σ p -value = proportion of p -values as or more extreme than observed in actual dataset

Issues in small, but not larger studies

Σ Degrees of freedom

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- Large study: doesn't help, but doesn't really hurt.

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- Σ Larger $n \not\Rightarrow$ decrease in variability

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 large, but not smaller studies


Σ Manageability

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Issues in large, but not smaller studies

- Σ Manageability
- Σ “Getting into” the data
- Σ Auditing and quality control



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