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Thanks to Friends at Genzyme

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L.J. Wei, Harvard University

Pompe Disease

- Metabolic myopathy characterized by cardiac, skeletal and smooth muscle involvement with a continuum of disease severity
 - From early onset → rapid progression to death (infantile onset)
 - To later onset → slower progression, longer survival with marked morbidity (late onset)
- Deficiency of lysosomal enzyme, acid alpha-glucosidase (GAA)
- Glycogen accumulation → muscle tissue damage → functional impairment → permanent disability
- Very rare disease (estimated incidence 1:40,000)

Pompe Disease

- ***Late onset (or juvenile/adult) Pompe disease*** is the result of a partial deficiency of GAA

- *alglucosidase alfa* (Myozyme) is indicated for long-term use in patients with late onset Pompe disease (GAA deficiency). *alglucosidase alfa* has been shown to improve distance walked and stabilize pulmonary function in patients with late onset Pompe disease
- Proposed definition of late onset disease
 - Limited to patients with symptom onset *>24 months* **without** hypertrophic cardiomyopathy

Late Onset Treatment Study (LOTS)

- Rare, clinically heterogeneous disease
 - Challenge to identify an eligible trial population
- Pompe disease is a neuromuscular disease with loss of mobility and respiratory failure
 - Limited number of possible endpoints
- What is the expectation of treatment?
 - Stabilization or improvement?
 - Extent of muscle damage may determine magnitude of response to treatment
- One chance to perform a placebo-controlled clinical trial

- Co-primary endpoints:
- 6 MWT distance walked
- % predicted FVC

- Randomized, double-blind, placebo-controlled
 - 2:1 drug to placebo assignment
 - 20 mg/kg alglucosidase alfa or placebo IV administration qow
- Multi-center, multi-national
 - 90 patients enrolled at 8 sites in 3 countries
- Patients stratified for baseline disease severity
 - 6MWT distance \geq or $<$ 300 m
 - % predicted FVC \geq or $<$ 55%

Inclusion Criteria

- At least 8 years of age
 - Lower age limit for FVC reference standards and an age that ensured test compliance
- Ambulatory
- Not invasively ventilated
- Quantifiable evidence of:
 - Lower extremity muscle weakness
 - Diminished pulmonary function
 - Diaphragmatic weakness

What are questions?

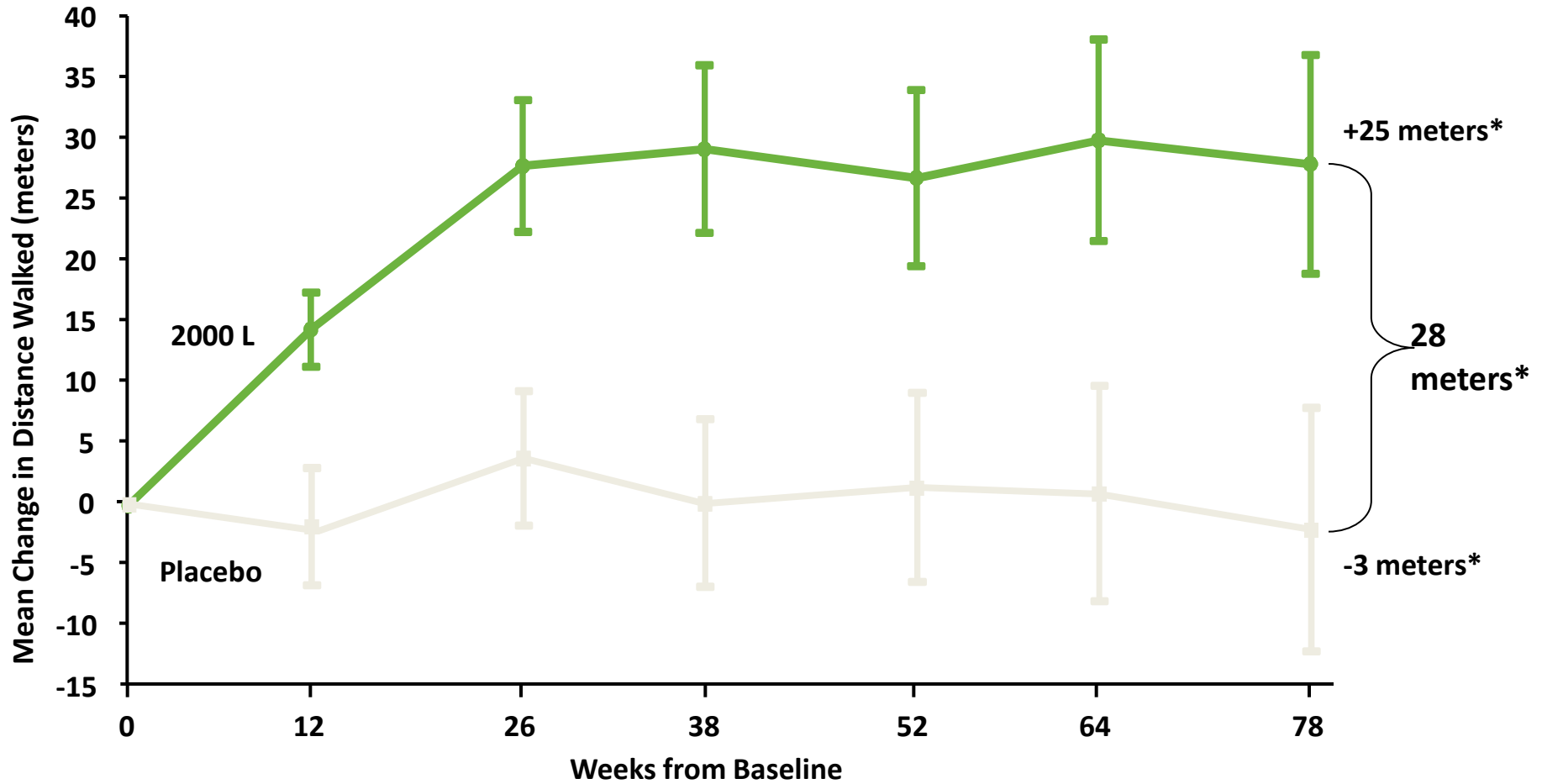
- How to quantify the treatment difference?
- At a specific time point?
- Over the entire study period?
- Data were collected repeatedly over time for each patient.
- How to analyze the data?

Statistical Methods

- Repeated measures analysis using a linear mixed effects (LME) model
 - Robust variance estimation
- ANCOVA analysis of the change from baseline to week 78

- N=90
- 60 were treated; 30 were placebo
- 55 treated and 26 placebo subjects completed the study

2000 L alglucosidase alfa Improves Walking Distance (6MWT)

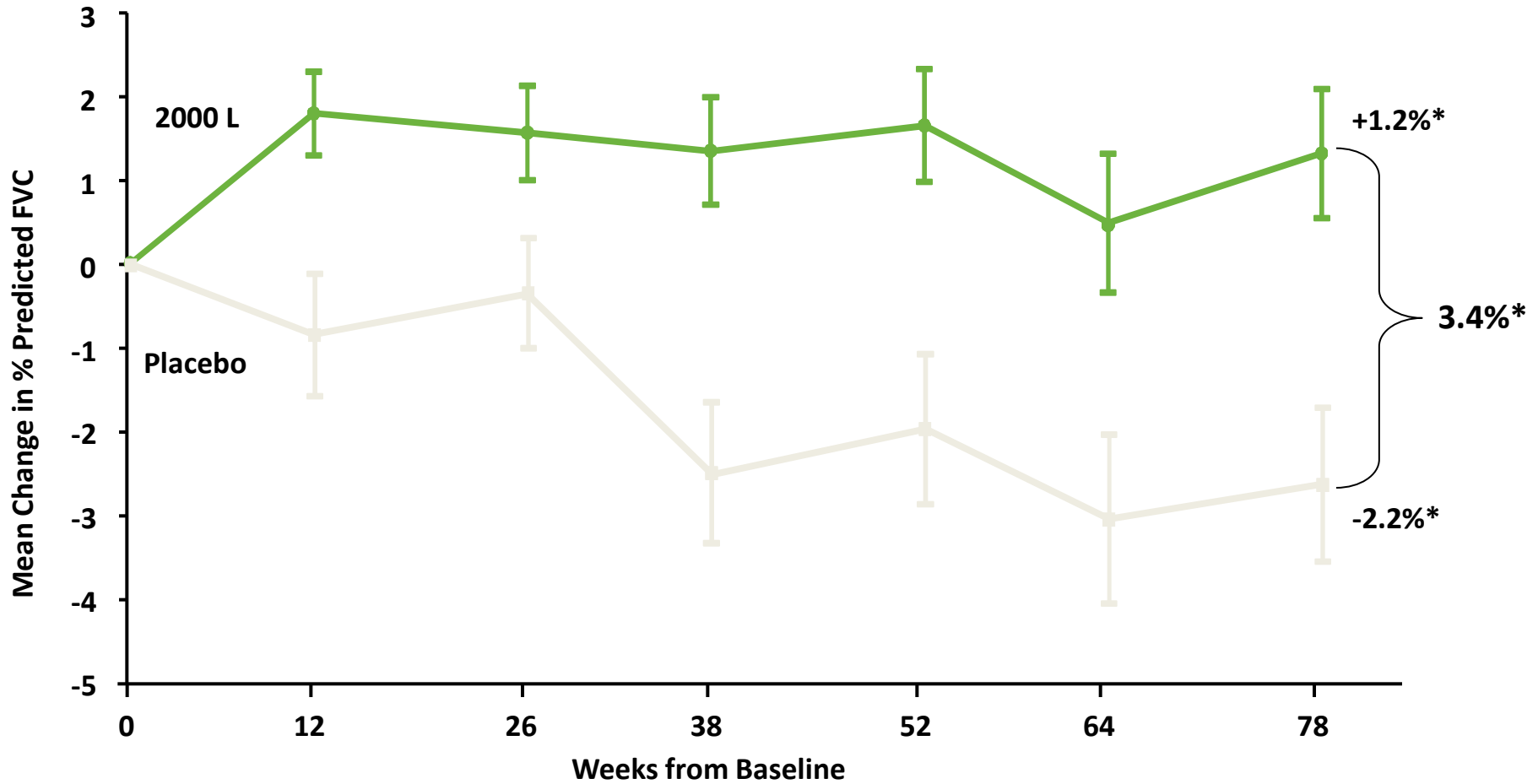


LME p-value = 0.0464

ANCOVA p-value = 0.0347

*ANCOVA estimate of mean

2000 L alglucosidase alfa Stabilizes Pulmonary Function (% Predicted FVC)



LME p-value = 0.0041

ANCOVA p-value = 0.0055

*ANCOVA estimate of mean

Mixed Effects Model

- Strong model assumptions:
- Linear trend over time
- Parametric assumption on the random effects and error term

Mixed Effects Model

- Allow missing at random?
- But only when the model is correctly specified
- When we are interested in the change from the baseline to week 78, we gain little efficiency via repeated measure analysis unless there are quite a few missing observations at Week 78 or the repeated measures are highly correlated.

Sensitivity Analysis when there are missing observations at week 78

- Baseline imputation
- Last observation forward

Missing Completely at Random

- Robust or nonparametric method:
- Wei-Lachin (JASA, 1984); Wei and Johnson (Biometrika, 1985): At each time point, perform a test, then combine the tests over time
- One can invert test to obtain confidence interval for the treatment difference

Responder Analysis

- Define “responder” at Week 78
- Censoring depending on the response as failure
- Non-informative censoring
- Using Kaplan- Meier to estimate the failure rate at Week 78
- Sensitivity analysis by changing definition of responder and also informative censoring

Responder Analysis

- Durability of response over time (say, between week 50 to 78)?
- The placebo patients may lack of such persistent response.

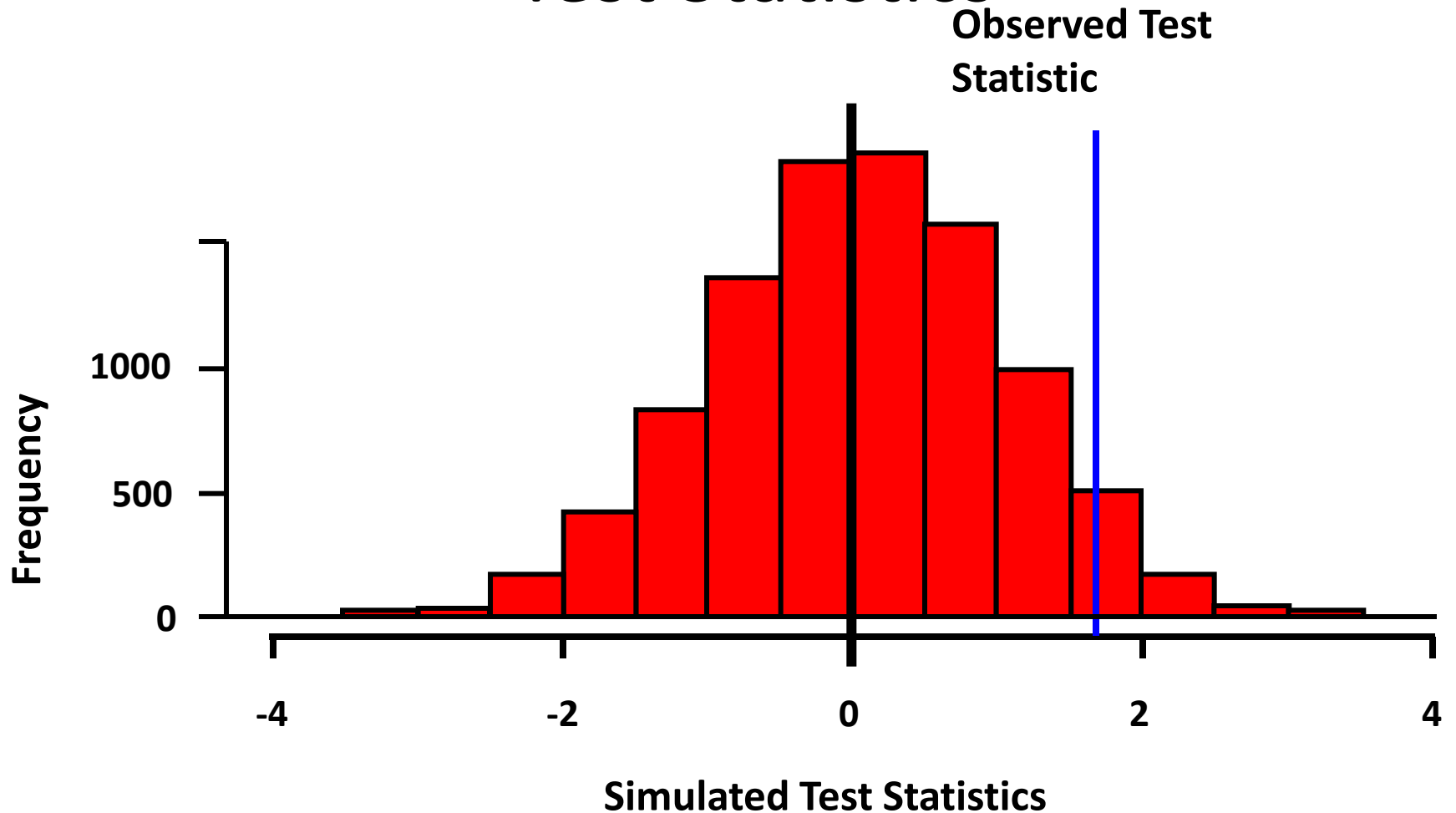
Design issue

- Treatment allocation (dynamic rule)
- Tried to balance with respect to important prognostic factors (disease severity and 8 centers)
- Treatment rule is rather deterministic
- Re-randomization test?

How to Construct a Re-Randomization Test?

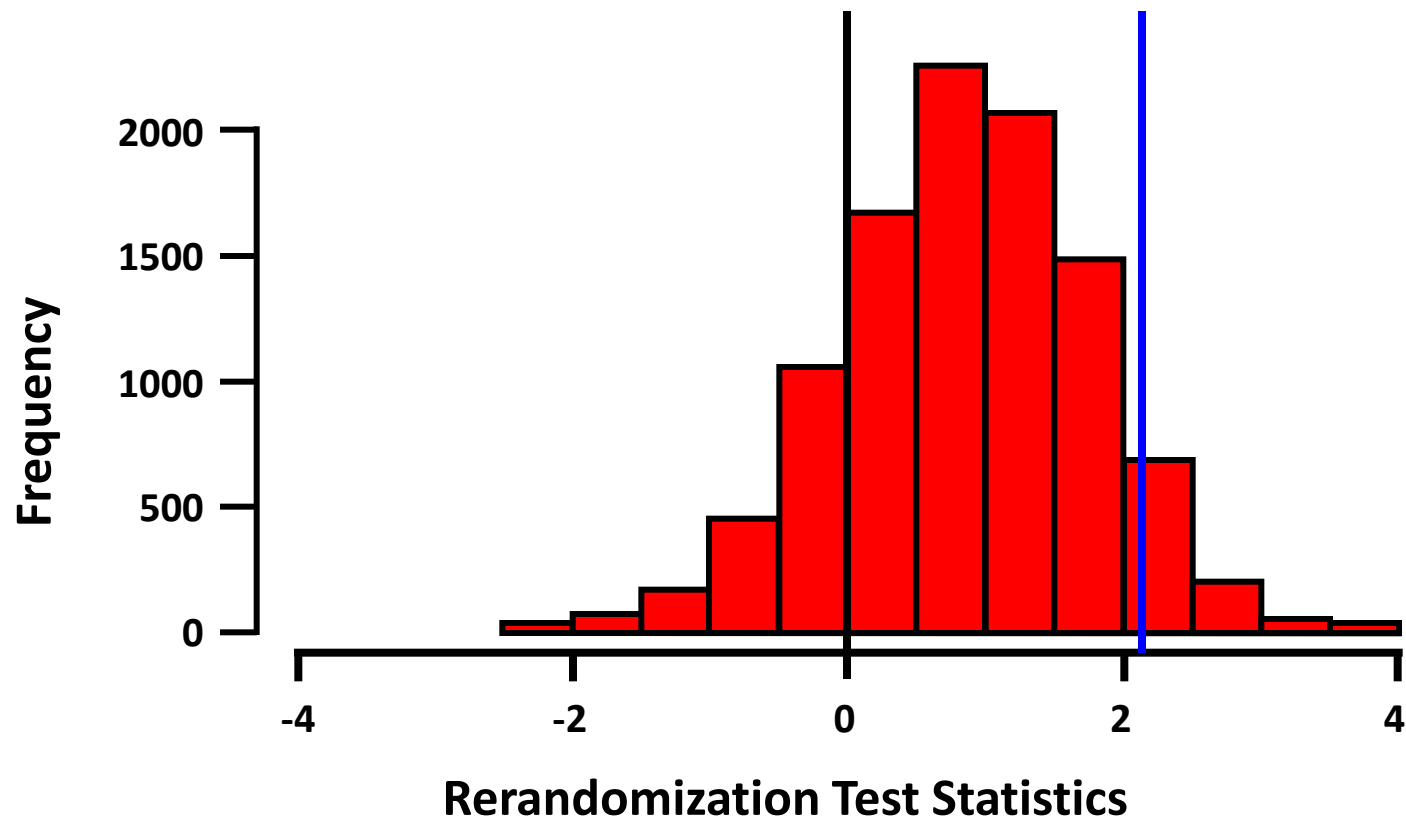
Patient	1	2	3	4	...	
Observed Change in 6MWT	35	20	21	40	...	Test Statistic
Obs. Rx Assignment	m	p	m	m	...	2.15
Rerand 1	M	P	P	M	...	0.63
Rerand 2	M	M	P	P	...	2.4
...						...

Expected Histogram of Rerandomization Test Statistics



Problem with Application of Rerandomization Test

- Distribution of 6MWT ANCOVA test statistics



- Re-randomization test may be considered as a sensitivity analysis, not as the primary analysis
- The re-randomization test is lack of power.
- Maybe we should not use almost deterministic dynamic treatment allocation rules?

LOTS

- Could we use historical controls to add information for analysis of the treatment difference?
- How to utilize a registration study to “validate” the treatment effectiveness with hard clinical endpoints?

Could we do one arm trial?

- Do we have enough natural history information?
- How to select controls?

Using Response Adaptive Design?

- In general, there is a large potential patient population waiting for the treatment.
- The number of study patients is relatively small.
- Therefore, balanced treatment allocation rules are utilized.
- For rare diseases, this is not the case.
- Play the winner rule between patients or within patients?

Repeated Cross-over Design

- Steve Lagakos (2003, NEJM), fungal infection with chronic granulomatous
- A study took 10 years with only 39 patients enrolled