

# Trial Design and Statistical Considerations in Rare Disease Clinical Trials

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## Disclosure Statement

- No conflicts of interest
- Nothing to disclose
- This talk reflects the views of the author and should not be construed to represent FDA's views or policies
- In this talk “drug” refers to both drugs and biologics

## Outline

- Design
- Endpoint
- Analysis
- Quality data

## Randomized, double-blinded, and placebo controlled trial design is most commonly used

### Most reliable design to determine effectiveness of a drug

- **Randomization:** unbiased assignment of patients to trial arms
- **Double-blinded:** assigned treatments are blinded to patients and investigators
- Minimize/eliminate potential biases caused by
  - Differences in prognostic patient characteristics (known/unknown)
  - Placebo effect, observer effect, and differences in standard of care
- Placebo control does not imply that the control group is untreated  
→ all patients receive standard of care → limit ethical concern

## Primary Endpoints

- Provide primary assessment of treatment effect
- Consist of multiple components in many rare disease trials
- **Composite endpoint:** components correspond to distinct events  
→ *e.g. cardiac events, renal events, or death for Fabry disease*
- **Multi-component endpoint:** a within-patient combination of multiple components  
→ *e.g. total Chorea score for 7 different parts of the body in patients with Huntington disease*
- **Multiple primary endpoints:** *selected in many rare disease trials due to genetic and clinical heterogeneity, and uncertainty of drug effect*

## Multiple Primary Endpoints: Examples

- *Two primary endpoints are used in trials for late-onset Pompe disease, Hunter syndrome (MPS II), and MPS I*
  - *Distance walked during 6 minute walking test (6MWT)*
  - *Percent predicted forced vital capacity (FVC%)*

### Hypothetical Trial

Change from baseline at 52 weeks	6MWT		FVC%	
	Placebo (N=24)	Drug (N=24)	Placebo (N=24)	Drug (N=24)
Mean (SD)	13 (60)	40 (76)	-0.1 (10)	3.5 (10)
Difference (95% CI) in Mean	<b>27</b> (-13, 67)		<b>3.6</b> (-2.3, 9.4)	
P-value	<b>0.185</b>		<b>0.221</b>	
<b>Two sample t-test</b>	<b>0.185</b>		<b>0.221</b>	

**Challenge:** *Many rare disease trials have low power to demonstrate statistically significant results due to small sample size or small treatment effect*

Analyses adjusted for prognostic variables can improve the power of significance tests and the precision of estimates of treatment effect

### Hypothetical Trial

Change from baseline at 52 weeks	6MWT		FVC%	
	Placebo (N=24)	Drug (N=24)	Placebo (N=24)	Drug (N=24)
Mean (SD)	13 (60)	40 (76)	-0.1 (10)	3.5 (10)
<b>Treatment Comparison</b>				
Difference (95% CI*) in Mean	27 <b>(-11, 65)</b>		3.6 <b>(-2.1, 9.1)</b>	
P-value				
<b>Two sample t-test</b>	<b>0.185</b>		<b>0.221</b>	
<b>ANCOVA*</b>	<b>0.071</b>		<b>0.115</b>	

\*Adjusted for baseline value.



P-values based on ANCOVA decreased by more than 40%

# Global Tests for Multiple Endpoints

## Hypothetical Trial

Change from baseline at 52 weeks	6MWT		FVC%	
	Placebo (N=24)	Drug (N=24)	Placebo (N=24)	Drug (N=24)
Mean (SD)	13 (60)	40 (76)	-0.1 (10)	3.5 (10)
<b>Treatment Comparison</b>				
Difference (95% CI*) in Mean	27 (-11, 65)		3.6 (-2.1, 9.1)	
P-value				
Two sample t-test	0.185		0.221	
ANCOVA*	0.071		0.115	
<b>Global Test</b>				
Rank-Sum-Test			0.026	
Combined-Test-Statistics			0.010	

\*Adjusted for baseline value.



Indicating that **the drug has an effect on at least one endpoint**



## Global Tests for Multiple Endpoints (2)

- **Rank-Sum-Test:** based on the sum of the ranks of data from two endpoints for each patient
  - Combines data at patient-level
- **Combined-test-statistics:** based on the two test statistics for treatment comparison for each endpoint
  - Combines test statistics at endpoint-level

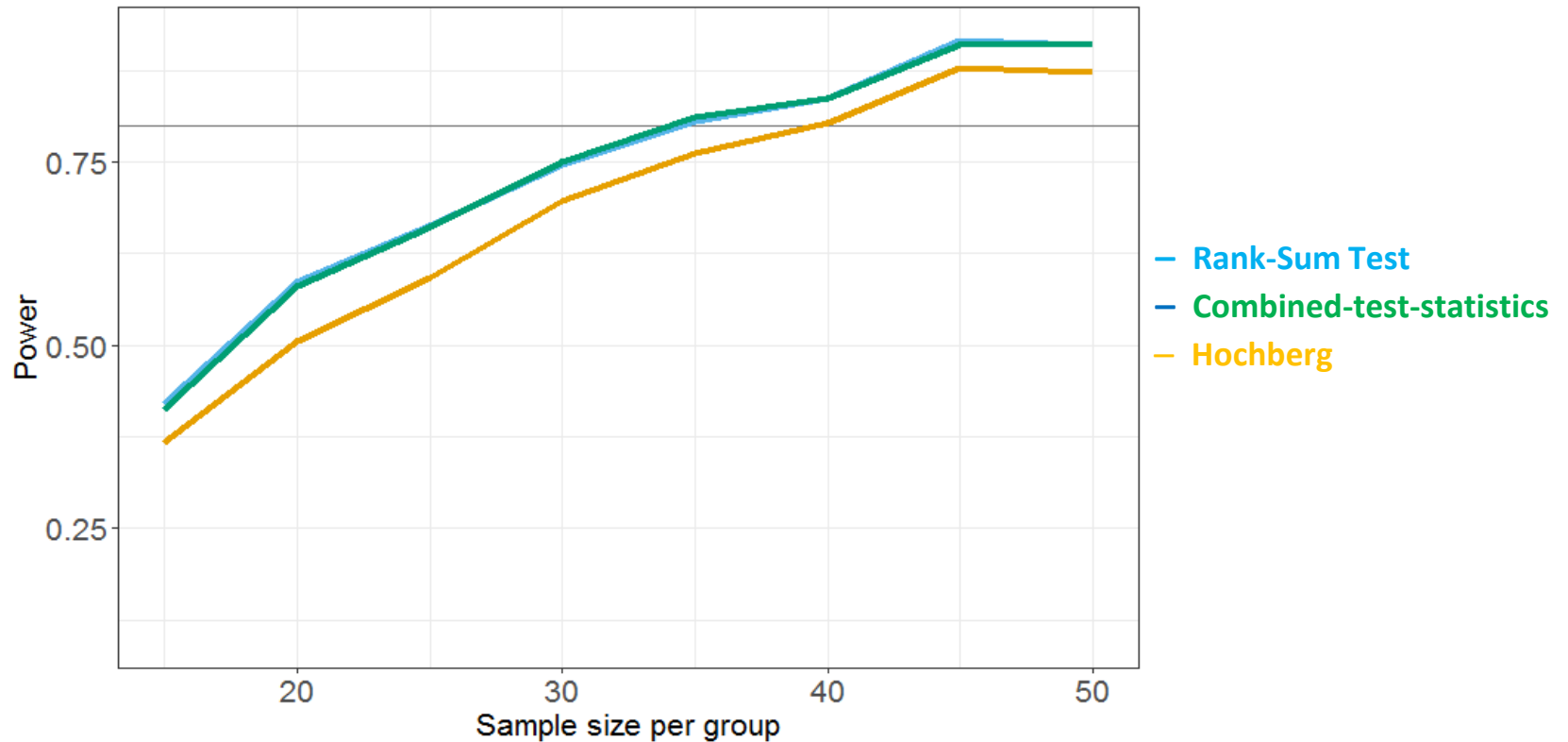
## Global Tests: Interpretations

- Testing a global null hypothesis
  - **The drug has no effect on either endpoint**
- The p-value should be presented and interpreted with descriptive summary statistics for each endpoint
- When  $p\text{-value} < 0.05$ , reject the global null hypothesis and conclude that the drug has an effect on at least one endpoint
  - Justify whether the observed effect(s) are clinically meaningful
  - “ $p\text{-value} < 0.05$ ” may not necessarily indicate an overall benefit if discordant effects are observed

*Similar issue for composite endpoints and multi-component endpoints*

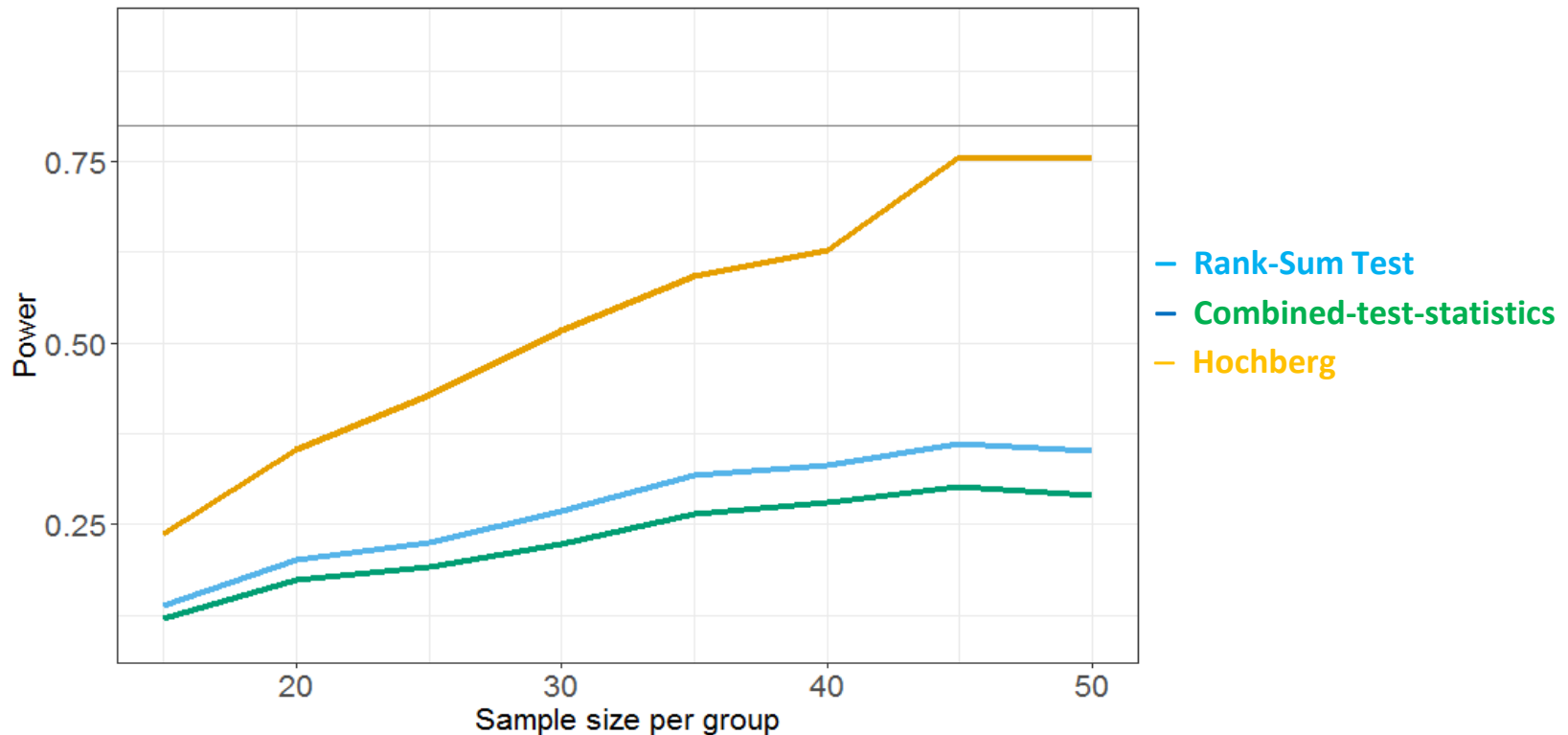
# Simulation Study #1

Global Tests: can be more powerful when a drug has an effect on both endpoints



## Simulation Study #2

**Global Tests: are less powerful when a drug has an effect only on one endpoint**



## Quality Data: Essential to Success of Small Sized Trials

- Reduce noise → reduce variability of outcome measurements  
→ increase statistical power

**Example** Mean difference in FVC% = 5% and N = 40 per arm ( $\alpha=0.05$ )

**10%** Variability ↓ from 10 to 9, **16%** power ↑ from 60% to 70%

- Detailed plans should be developed to
  - Standardize methods and procedures for outcome assessments
  - Minimize dropouts and missing data
  - Train and remind study sites to encourage patients to complete the study even after they stop study treatment early

## Conclusions

To overcome significant challenges in designing and conducting adequate and well-controlled rare disease trials, we support *innovative trial designs and analyses* provided they are well thought through, justified, and able to

*“distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.”<sup>1</sup>*

<sup>1</sup>21 CFR 314.126

## References

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