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PAGE 27, May 30th 2018

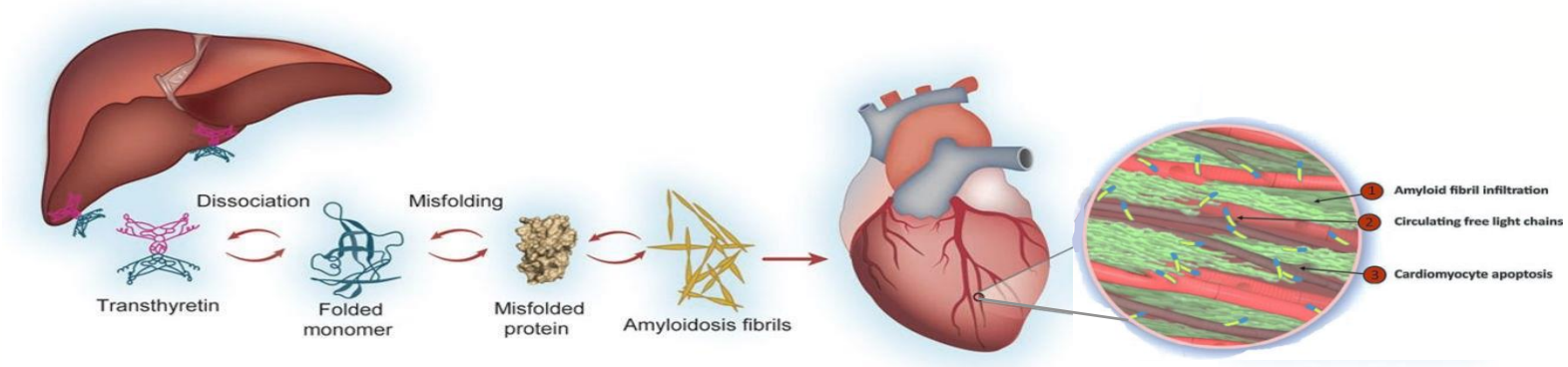
Power Assessment for Hierarchical Combination Endpoints Using Joint Modelling of RTTE and TTE Models versus Finkelstein-Schoenfeld Method

Transthyretin Amyloidosis (ATTR)

- **Transthyretin (TTR) is a circulating plasma protein that normally exists as a stable homotetramer. In diseased patients an unstable tetramer structure leads to formation of amyloid fibrils and subsequent tissue deposition in organs/tissues.**

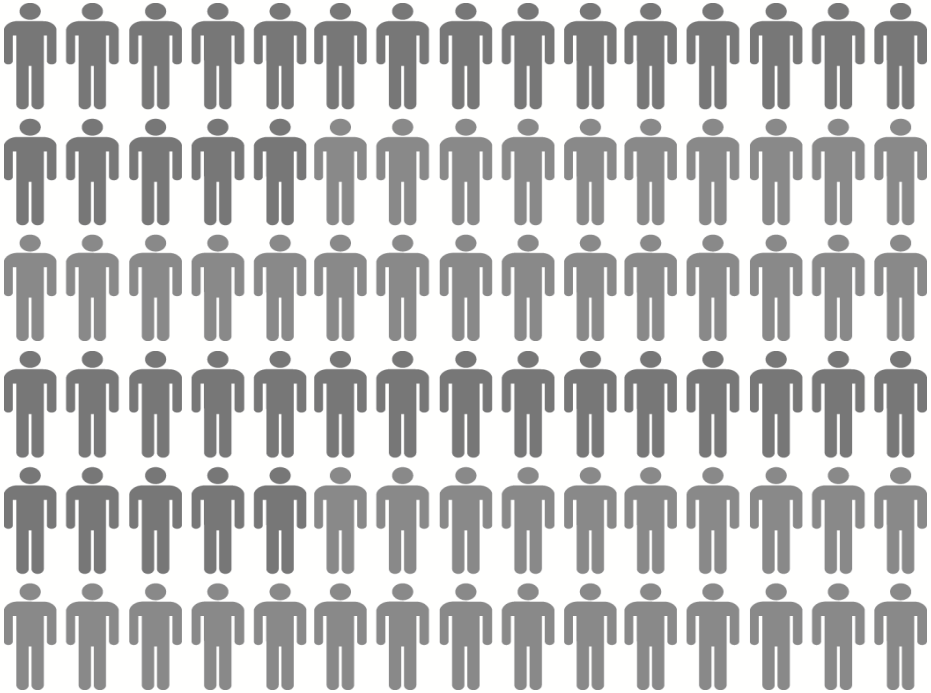
- **Two distinct clinical presentations of the amyloidosis: transthyretin familial amyloid polyneuropathy (ATTR-FAP) when the peripheral nerves are primarily affected and transthyretin amyloid cardiomyopathy (ATTR-CM) when the heart is primarily affected**

- **ATTR-CM is a late onset disease and is rarely diagnosed. Death in most patients with cardiomyopathy is from cardiac causes, including sudden death, heart failure, and myocardial infarction.**



It’s a RARE Disease

- **Cardio-vascular trial sample size ~10 000 - 20 000 patients**



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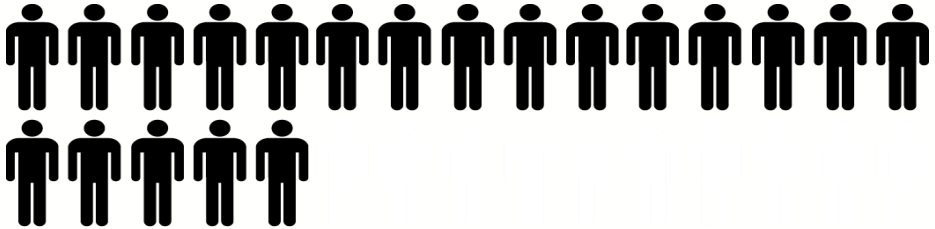


“Approximately 800-1000 diagnosed patients with ATTR-CM worldwide.”[1]

n = ~ 400 available

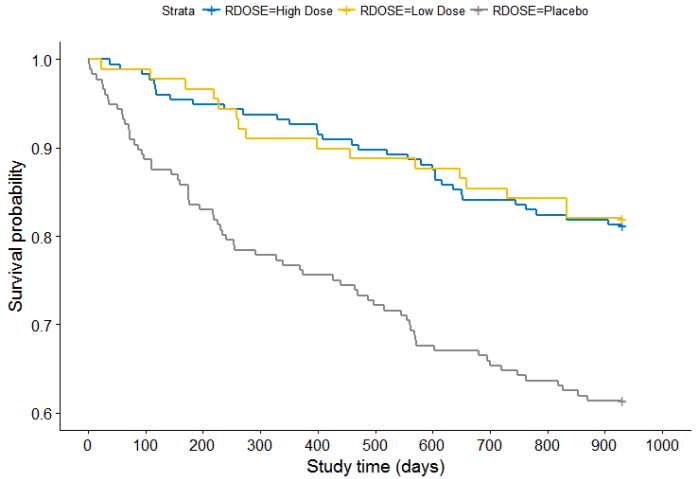
[1] Ando Y et al. Guideline of transthyretin-related hereditary amyloidosis from clinicians. Orphanet Journal of Rare Diseases. 2013;8:31

It's a RARE CARDIO-VASCULAR Disease

- **Cardio-vascular trial sample size ~10 000 - 20 000 patients**

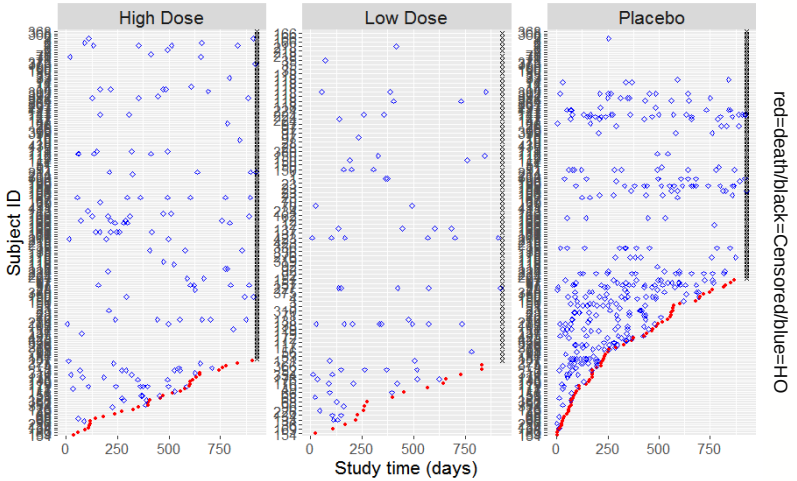
Survival is the golden standard CV-related endpoint:

Low power to detect drug effect with the available sample size, too long to show benefit alone



Hence, use of an ancillary longitudinal endpoint:

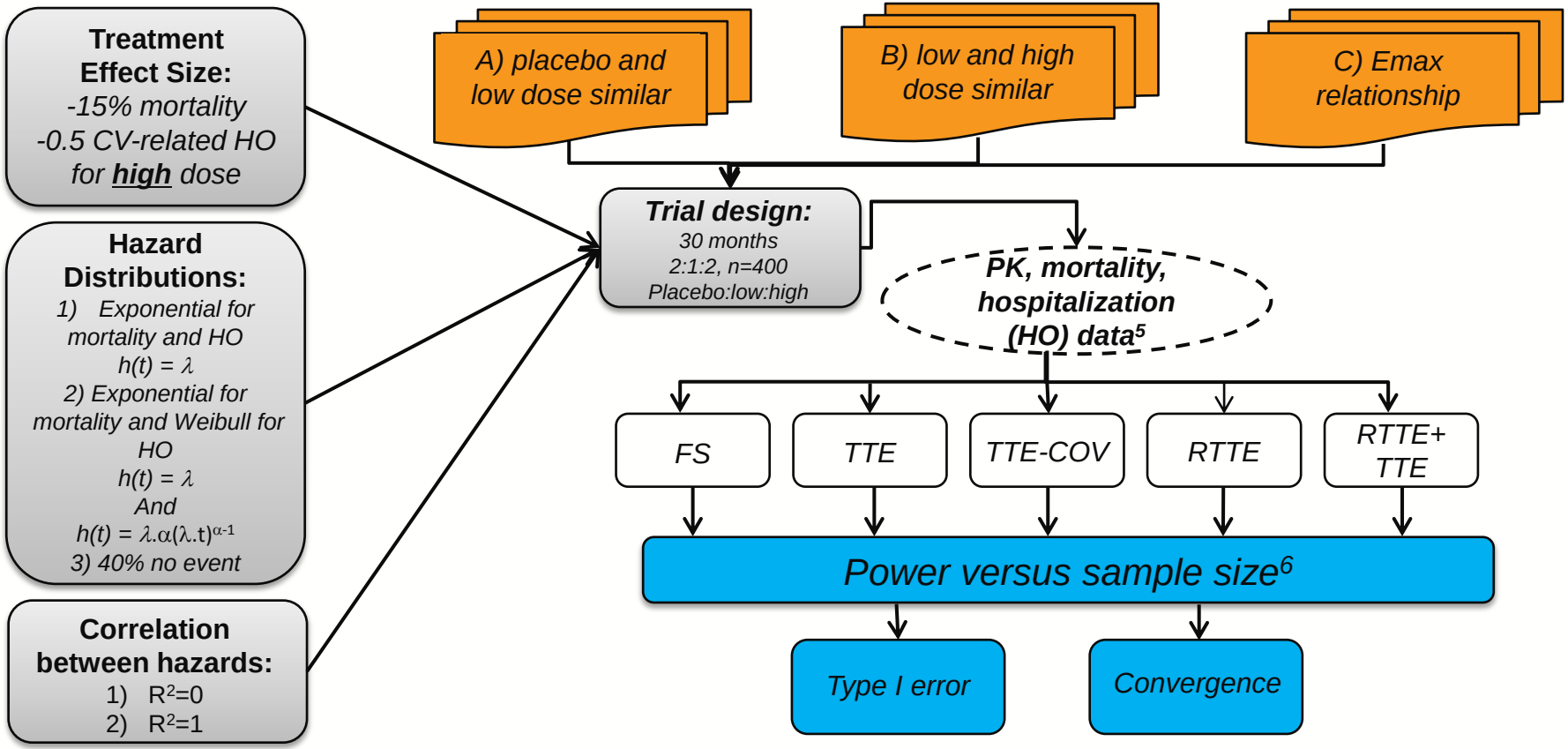
Frequency of cardiovascular-related hospitalization visits



Objectives

- **Compare power performances to detect a (small) drug effect for the purpose of informing a dose recommendation for a rare disease**
  - Apply the non-parametric Finkelstein-Schoenfeld (FS) test
  - Enhance trial analytical metric with a model-based approach
    - Exposure - Time-to-Event (TTE) for survival data
    - Exposure - TTE with hospitalization frequency as time-varying covariate (TTE-COV)
    - Exposure - Repeated Time-to-Event (RTTE) for hospitalization frequency
    - Joint Exposure Repeated Time-to-Event and Time-to-Event (Joint RTTE+TTE)

Methodology Framework – Assumptions

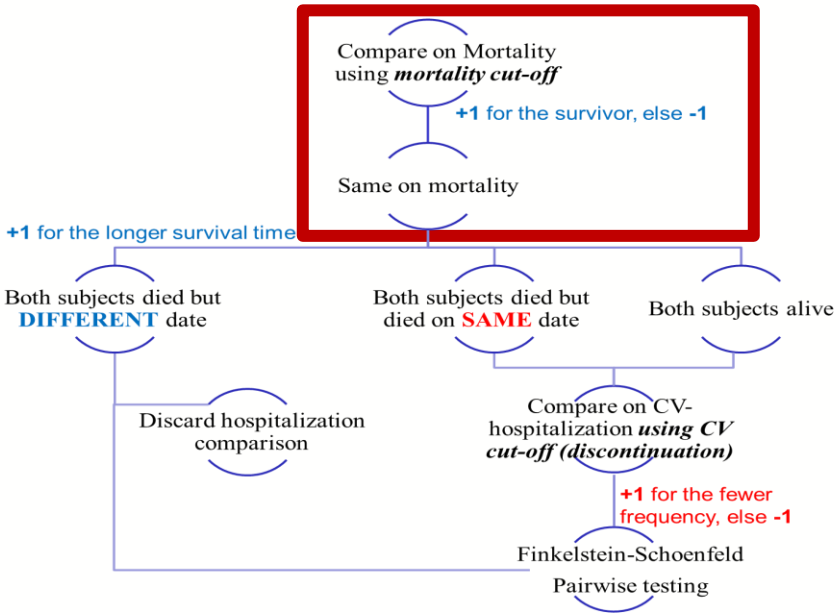


[5] Nyberg J. Simulating large time-to-event trials in NONMEM. https://www.page-meeting.org/default.asp?abstract=3166

[6] Ueckert S. Accelerating Monte-Carlo Power Studies through Parametric Power Estimation. J Pharmacokinet Pharmacodyn. 2016 Apr;43(2):223-34

Finkelstein-Schoenfeld (FS)

- **Prior regulatory history in cardiac medical device trials [3,4]**
- **Non-parametric hierarchical & pairwise test derived from patient-to-patient comparison**



	0	-1	-1		-1	
	+1	0		+1		
	+1		0	+1		
		-1	-1	0	-1	
	1+			+1	0	

1) Black and grey died

[3] Leon MB et al. N Engl J Med 2010; 363:1597-1607, [4] https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100041b.pdf

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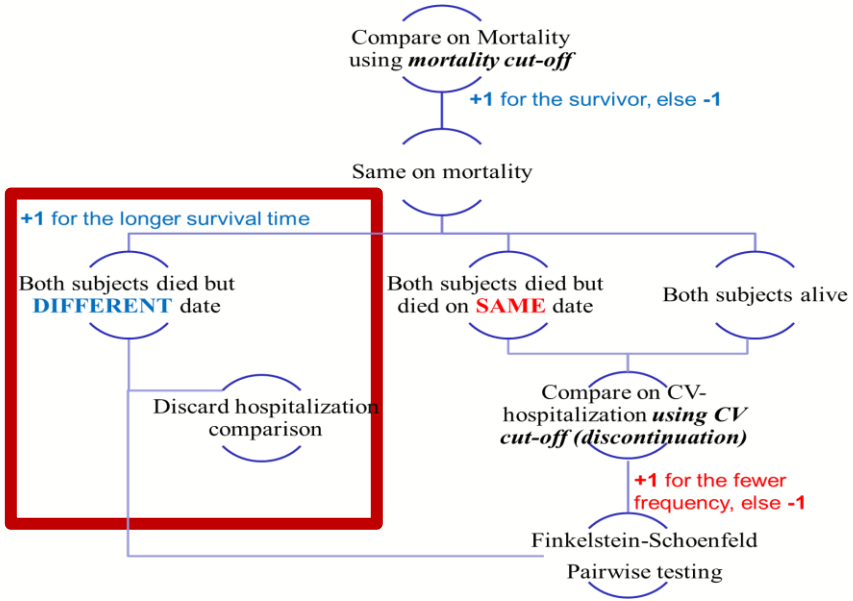

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	+1	0		+1		
	+1		0	+1		
	+1	-1	-1	0	-1	
	1+			+1	0	

1) Black and grey died but…
2) Black died before grey

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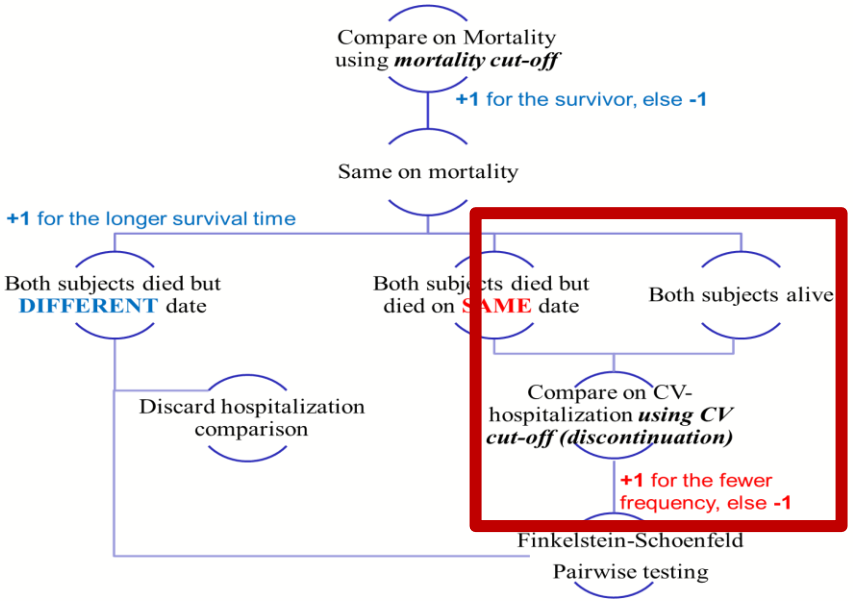

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	+1	0		+1		
	+1		0	+1		
	+1	-1	-1	0	-1	
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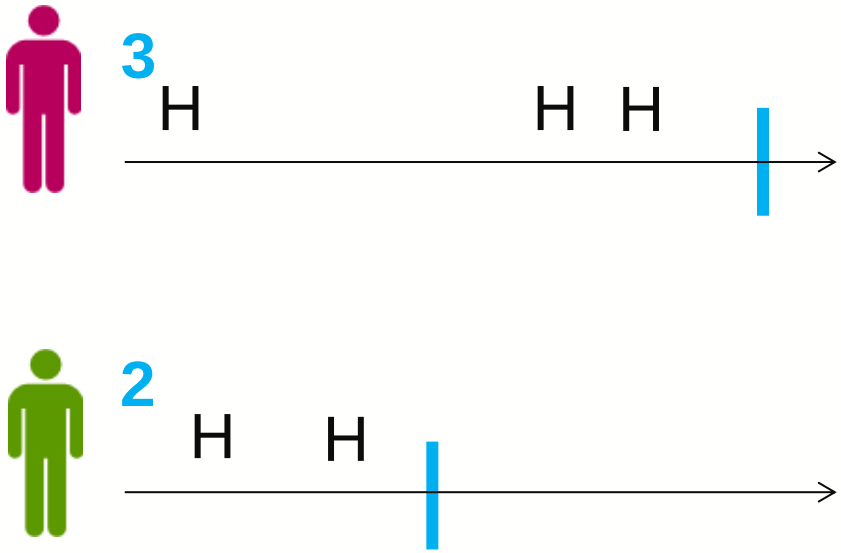

	0	-1	-1	-1	-1	
	+1	0		+1		
	+1		0	+1		
	+1	-1	-1	0	-1	
	1+			+1	0	

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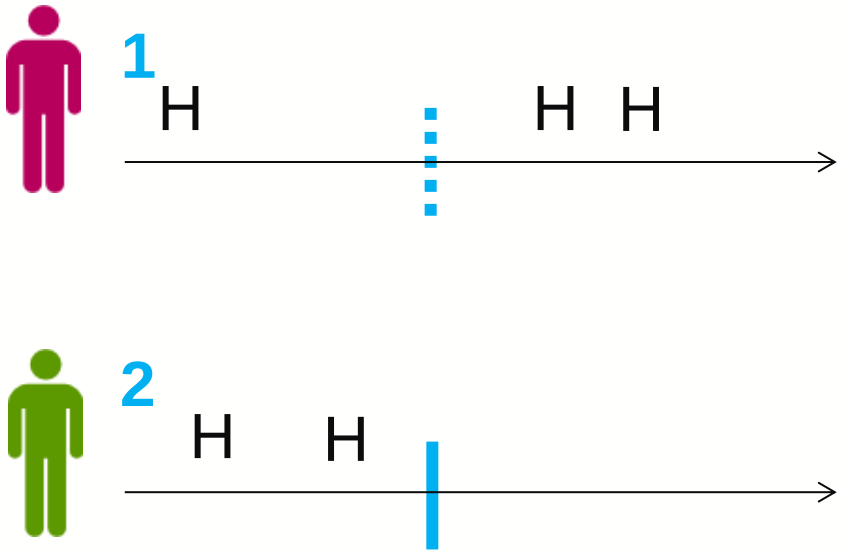

	0	-1	-1	-1	-1	
	+1	0		+1		
	+1		0	+1		
	+1	-1	-1	0	-1	
	1+			+1	0	

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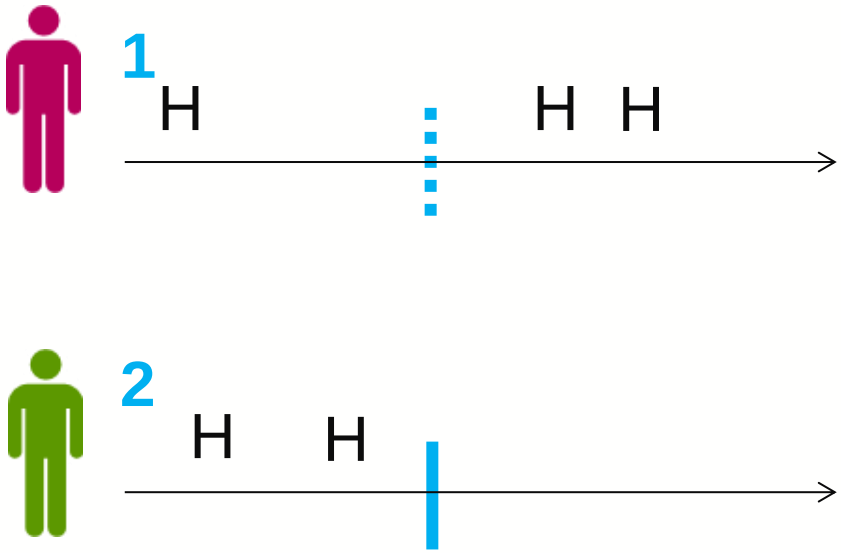

	0	-1	-1	-1	-1	
	+1	0	+1	+1		
	+1	-1	0	+1		
	+1	-1	-1	0	-1	
	1+			+1	0	

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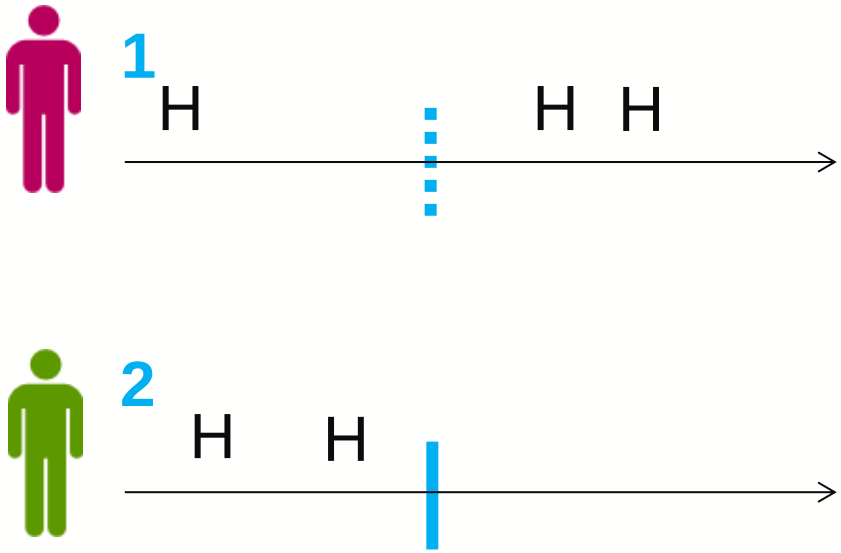

	0	-1	-1	-1	-1	
	+1	0	+1	+1	+1	
	+1	-1	0	+1	-1	
	+1	-1	-1	0	-1	
	1+	-1	+1	+1	0	

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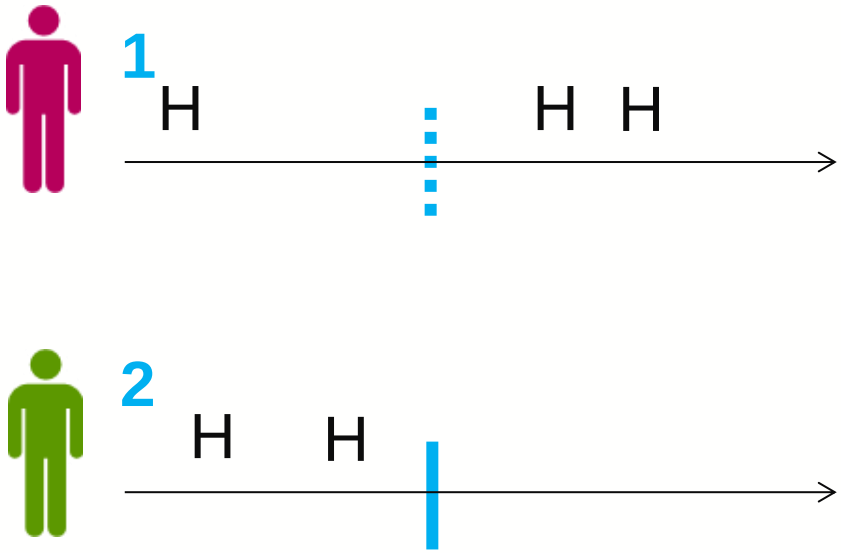


						U_i
	0	-1	-1	-1	-1	**-4**
	+1	0	+1	+1	+1	**+4**
	+1	-1	0	+1	-1	**0**
	+1	-1	-1	0	-1	**-2**
	1+	-1	+1	+1	0	**+2**

In each stratrum

Finkelstein-Schoenfeld (FS)

- **Prior regulatory history in cardiac medical device trials**
- **Non-parametric hierarchical & pairwise test derived from patient-to-patient comparison**

Active

$\sum U_i$

Placebo

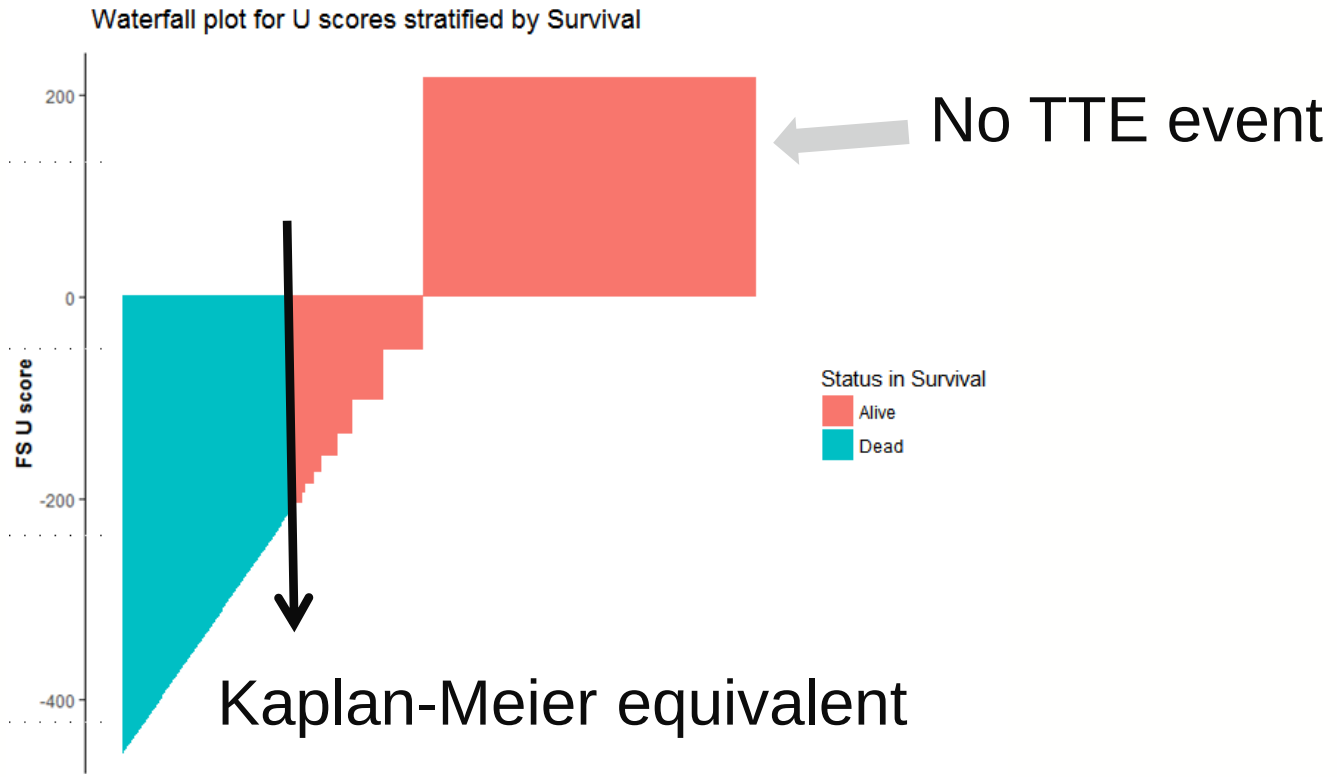
$\sum U_i$

Generalized Gehan Wilcoxon test

p-value

	+			+		U_i
+	0	-1	-1	-1	-1	**-4**
	+1	0	+1	+1	+1	**+4**
	+1	-1	0	+1	-1	**0**
+	+1	-1	-1	0	-1	**-2**
	1+	-1	+1	+1	0	**+2**

Results: FS U-score distributions



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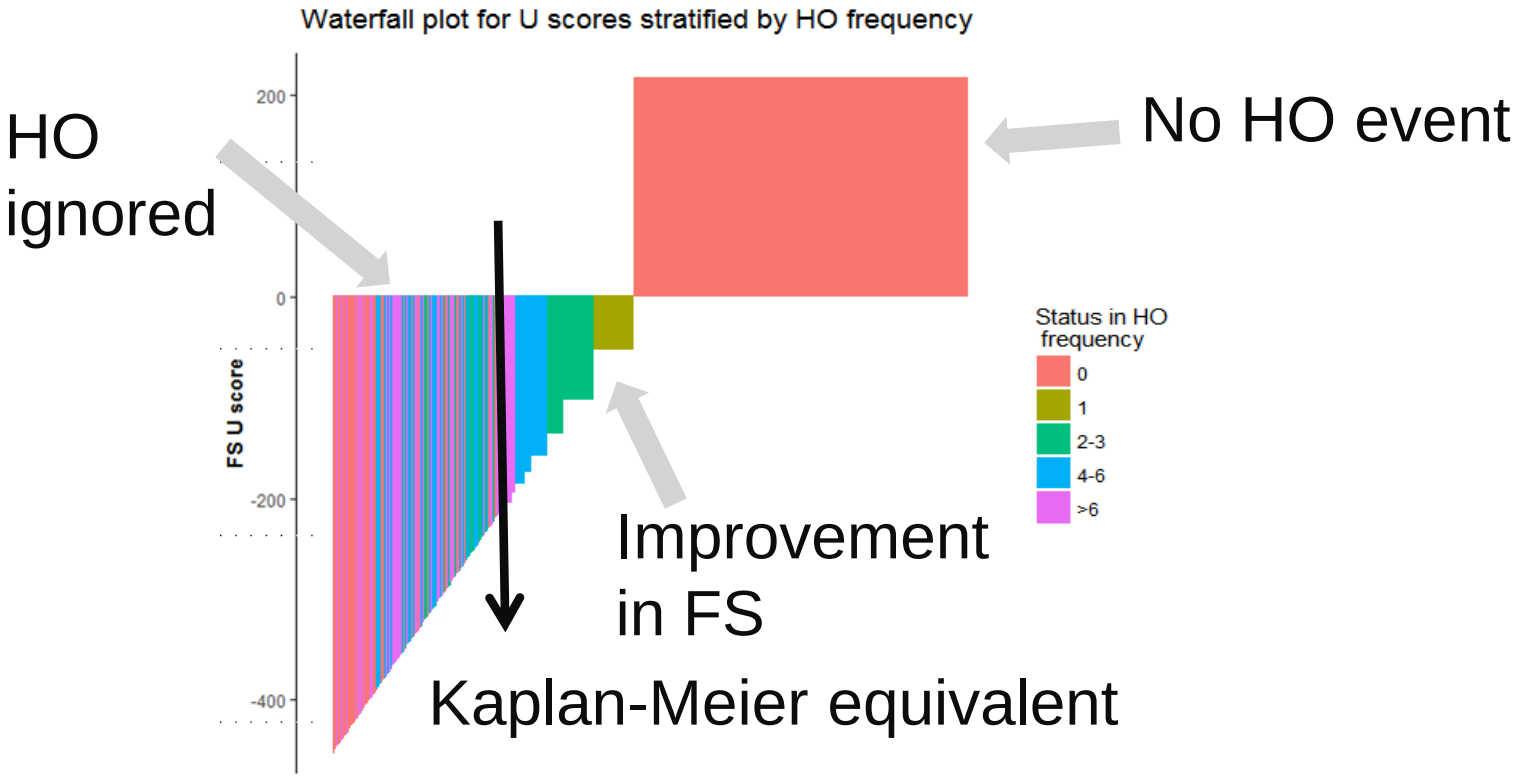
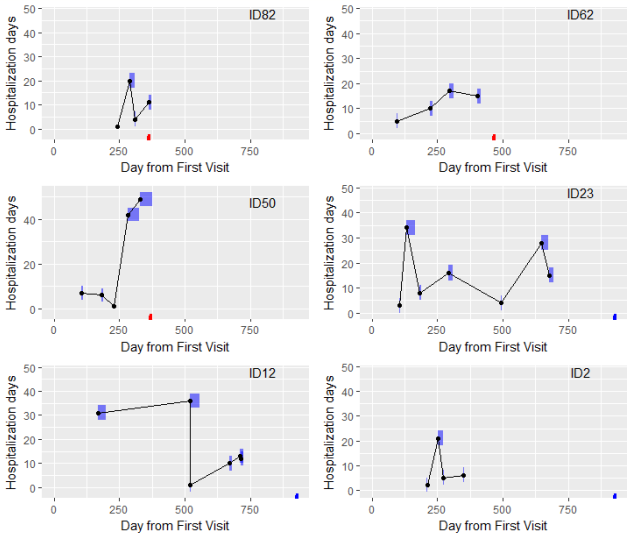


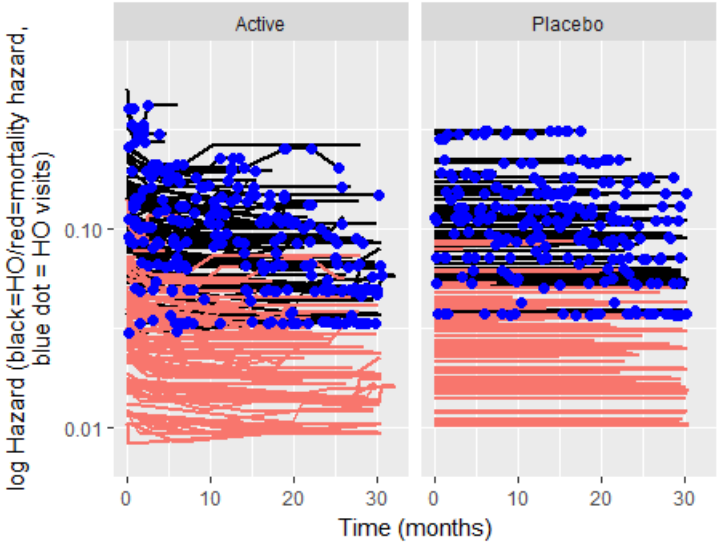
Drawbacks with Finkelstein-Schoenfeld

- **FS maintains the hierarchy (Mortality > HO), but**
  - Ignores the assessment of the HO endpoint in patients who die in the trial
- **FS ignores the longitudinal aspect of the events**
  - Drop-out if it's a competitive risk to death or dose interruption not accounted for
- **FS cannot test a dose-response if more than 1 active group**
  - Differentiation of doses requires multiple subgroup comparisons
- **FS is based on fixed set of strata (ie. categorical covariates)**
  - Integration of continuous covariates only if categorized
  - Smaller N in each stratum to perform the test

Joint RTTE + TTE

- Shared random effects (log-normal)
- Link function as an estimated scaling factor (on baseline and/or on shape)
- $MIX to have 40% of the population without an event
- DRUG effect = Emax reduction on the baseline hazard of RTTE/TTE (and/or shape of Weibull)
- One-inflated negative binomial for hospitalization duration





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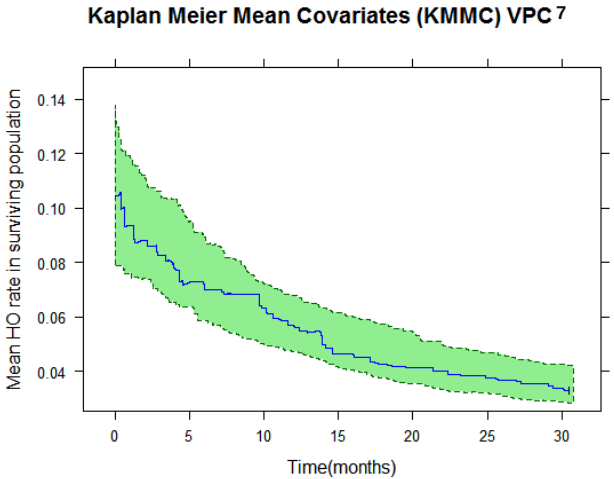
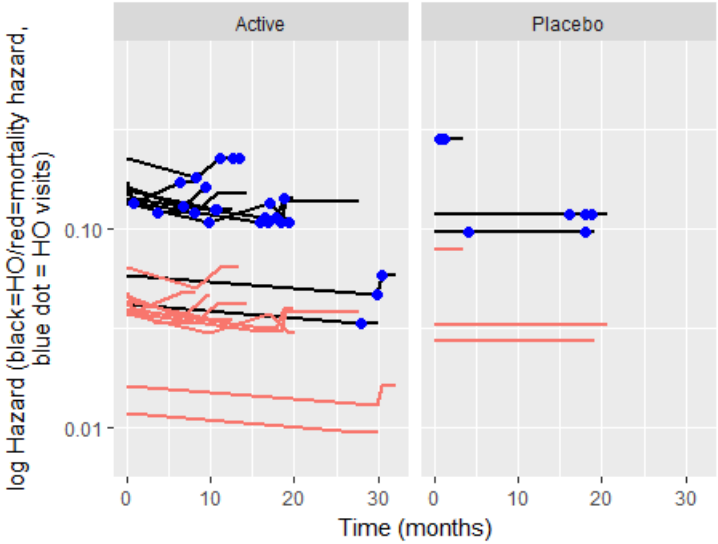
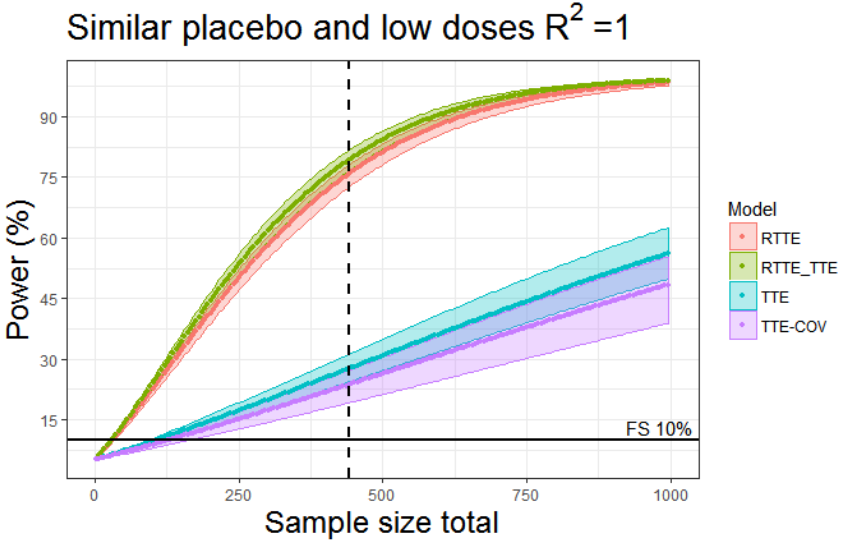
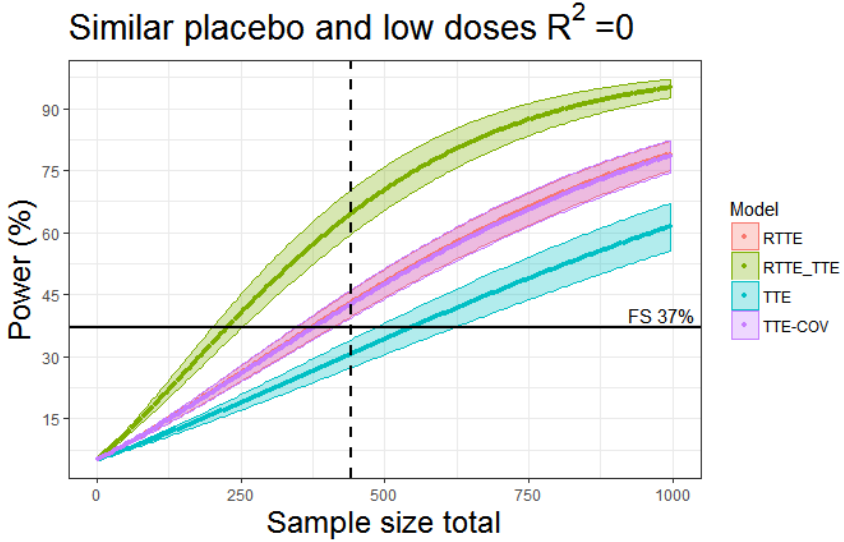




[7] PAGE 21 (2012) Abstr 2564 [www.page-meeting.org/?abstract=2564]

Results : Scenario A - similar placebo/low dose



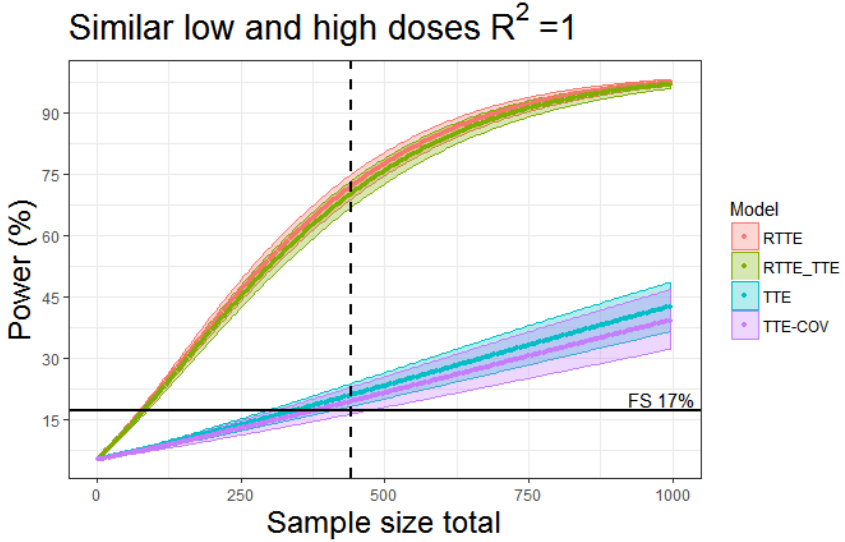


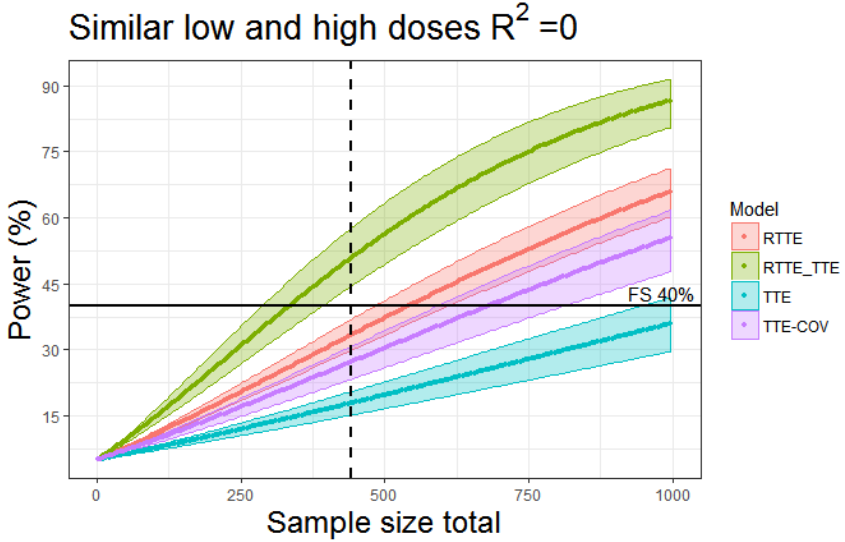
Method	FS	TTE	TTE-COV	RTTE	Joint RTTE+TTE
Power *(%)	**10**	**27** (77%)	**23** (69%)	**75** (90%)	**79** (93%)

Method	FS	TTE	TTE-COV	RTTE	Joint RTTE+TTE
Power *(%)	**37**	**29** (77%)	**42** (76%)	**42** (60%)	**65** (95%)

* Convergence in brackets

Results : Scenario B - similar low/high dose



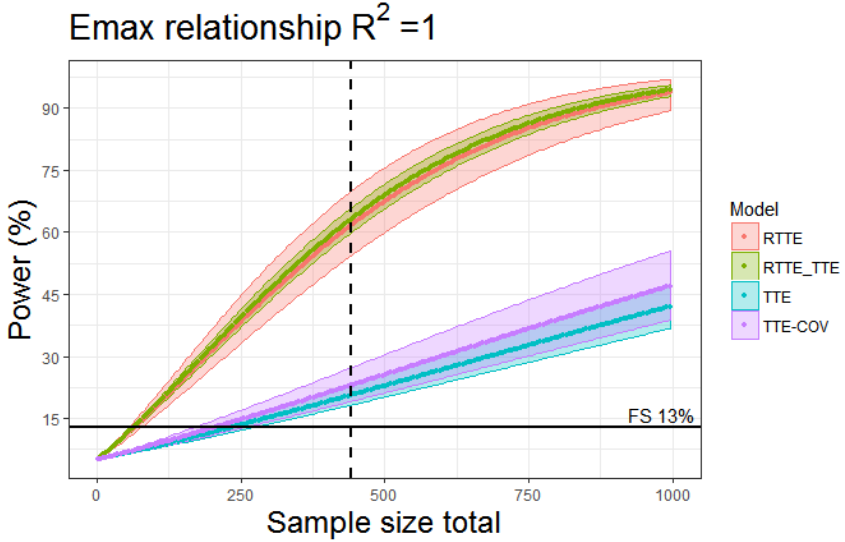


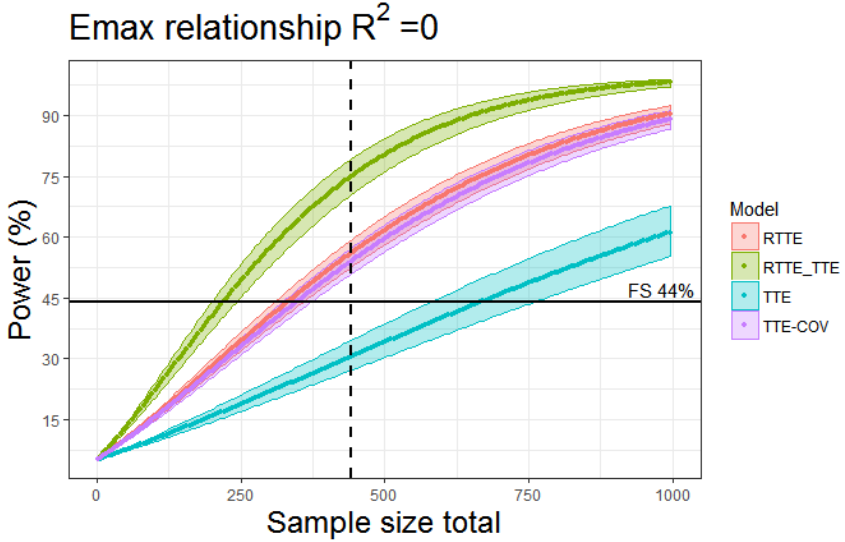
Method	FS	TTE	TTE-COV	RTTE	Joint RTTE+TTE
Power *(%)	**17**	**20** (67%)	**19** (62%)	**71** (83%)	**70** (83%)

Method	FS	TTE	TTE-COV	RTTE	Joint RTTE+TTE
Power *(%)	**40**	**18** (50%)	**28** (53%)	**33** (77%)	**49** (72%)

* Convergence in brackets

Results : Scenario C – Emax relationship





Method	FS	TTE	TTE-COV	RTTE	Joint RTTE+TTE
Power *(%)	13	20 (77%)	23 (63%)	61 (86%)	62 (94%)

Method	FS	TTE	TTE-COV	RTTE	Joint RTTE+TTE
Power *(%)	44	30 (85%)	54 (79%)	56 (92%)	75 (96%)

* Convergence in brackets

Results : All scenarios type I error rates

Correlation	Endpoint	Method	Type I* (%)
$R^2 = 1$	Mortality HO data	FS	NA
	Mortality data only	TTE	**4** (43%)
	Mortality HO data	TTE-COV	**7** (45%)
	HO data only	RTTE	**7** (58%)
	Mortality HO data	Joint RTTE+TTE	**2** (57%)
$R^2 = 0$	Mortality HO data	FS	NA
	Mortality data only	TTE	**2** (30%)
	Mortality HO data	TTE-COV	**3** (32%)
	HO data only	RTTE	**4** (37%)
	Mortality HO data	Joint RTTE+TTE	**2** (17%)

* Convergence in brackets

Summary

- **Implementation of a model-based approach to link the probability of survival and the probability of hospitalization events.**
- **In general, the joint RTTE+TTE and the RTTE methods provided the highest power to detect a drug effect.**
  - While correlated, the gain of power from the joint RTTE+TTE model is very moderate.
  - While uncorrelated, the joint RTTE+TTE model added extra power by acknowledging the additional information from the TTE data.
  - FS results were superior to TTE alone in general, but vary across the scenarios.
  - Type I error rates were controlled in general and convergence rates with an Emax model show adequate robustness of the models in power assessment.
- **Challenges in introducing drug effects and characterizing the underlying relationship if multiple confounders exist. In case of informative dropout, a dropout model can be implemented but may be competitive to mortality.**
- **Hierarchical metrics in power assessment could mimic FS decision rules.**
- **Smaller sample sizes to detect a treatment effect in future trials could be achieved using this methodology.**

Acknowledgment

- Jeffrey H Schwartz
- Balarama Gundapaneni
- Daniel Meyer

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- Ken Salatka
- Crima Shah

- Vijayakumar Sundararajan

- Tim Nicholas

- Yea Min Huh
- Sridhar Duvvuri
- Jae Eun Ahn
- Chay Lim

And:

Rare disease patients in the study

THANK YOU !

PATIENTS FIRST