Bayesian Shared Parameter Analysis of Mortality and Function within an Adaptive Platform Trial for ALS

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Platform Trial Design

- Multiple Treatments
- One Disease
- Statistical/Inferential synergy
- Perpetual/Standing Trial
- Efficiently Evaluate emerging treatments

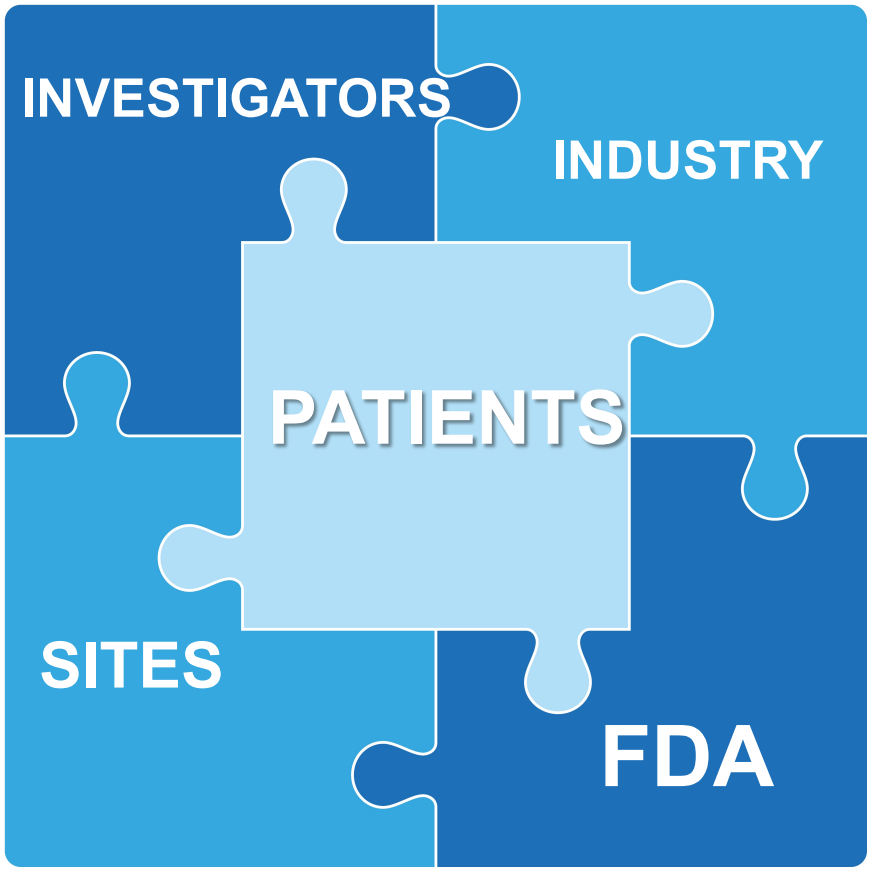
	Tx 1	**Tx 2**	**…**	**Tx N**	**…**
Type A	?	?	?	?	?

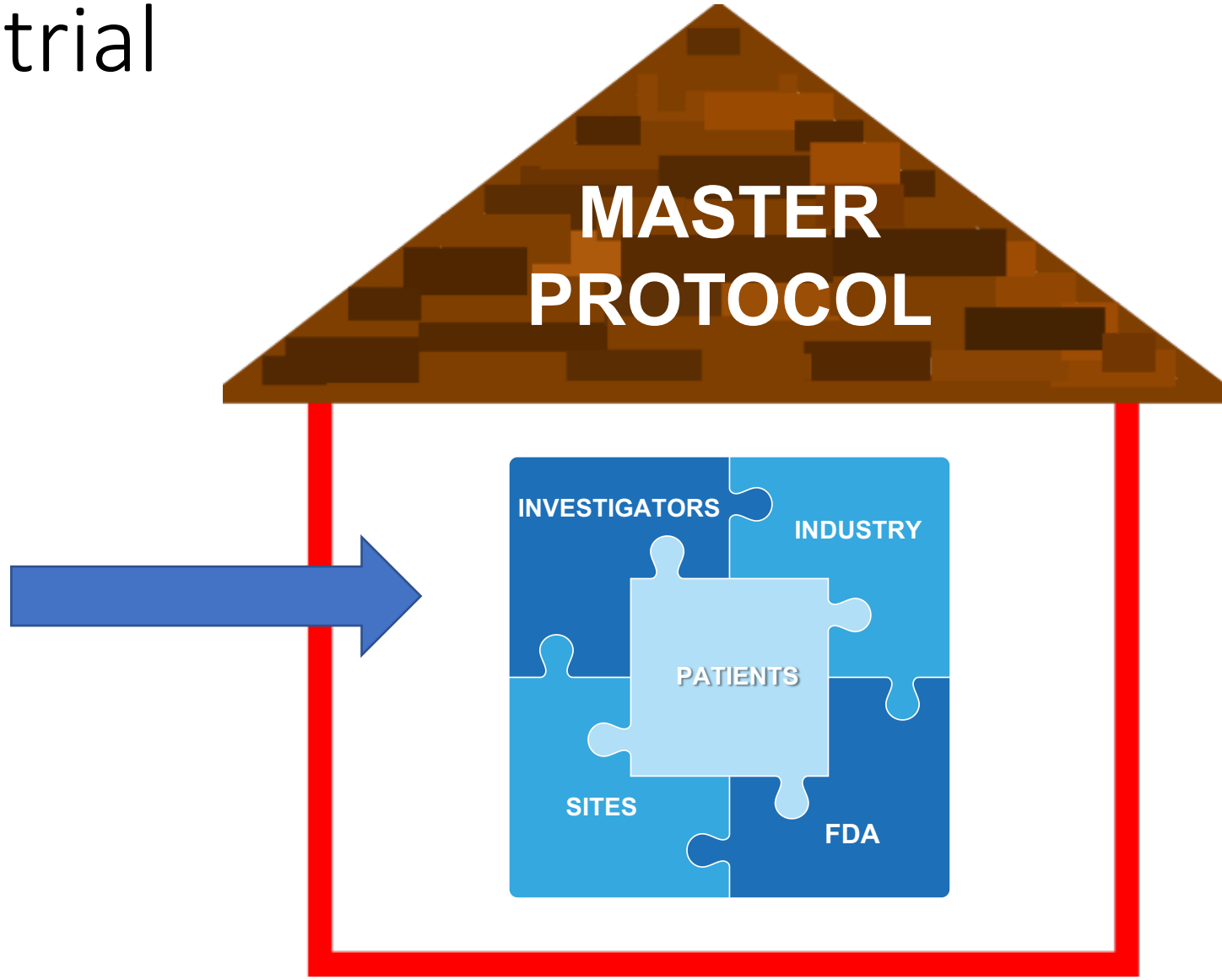
Why Platform trial in ALS?

- Over 130 companies in ALS space
- Thousands of investigators worldwide – many targets
- Need to speed up drug development

“I lost the privilege of working on the human time clock on January 6, 2018 – the ALS clock is a lot faster”
Sandy – Person with ALS

Bringing together a community to reach consensus on platform trial



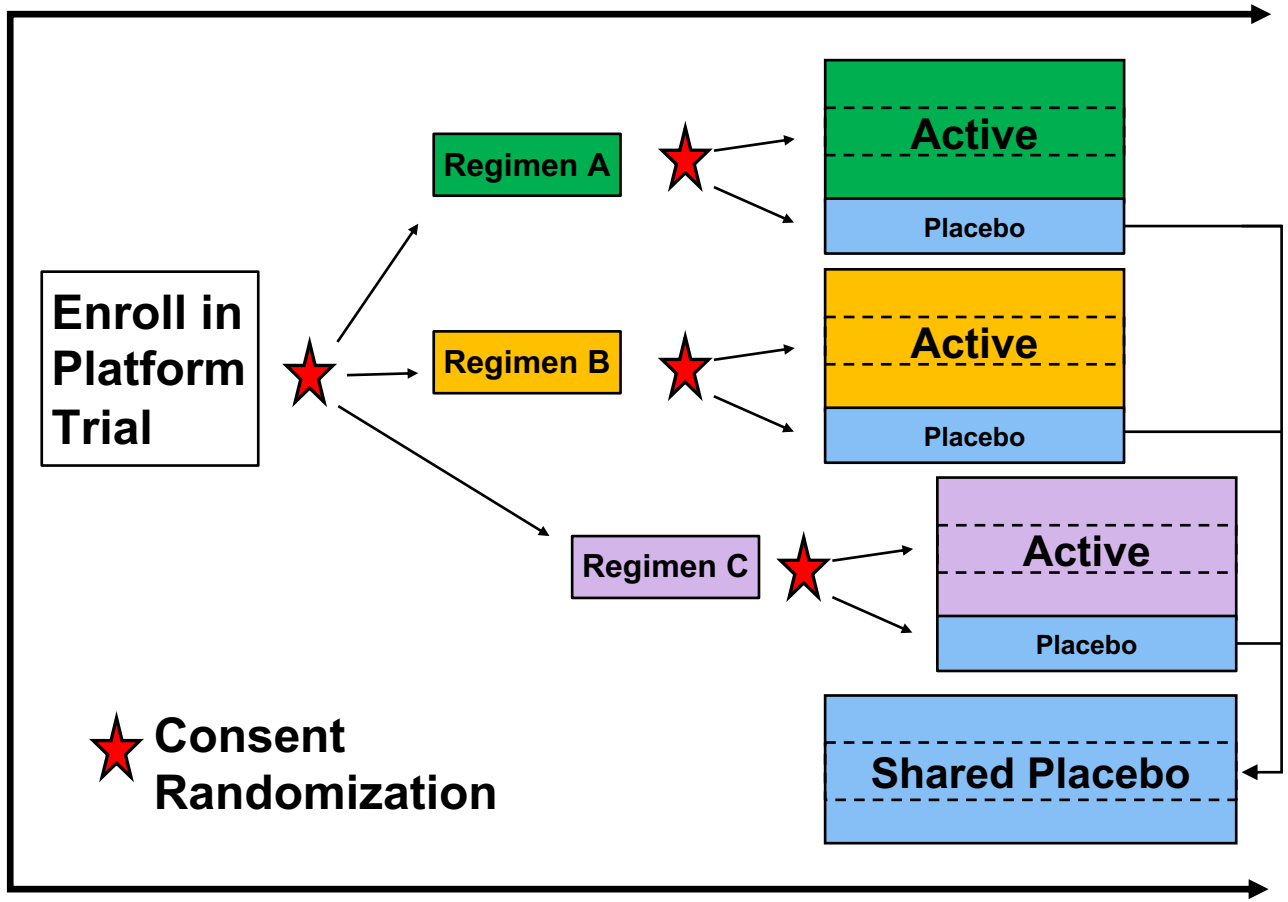


Platform Efficiencies

- Shared infrastructure means quicker time to start a new therapy
- Single consensus reached on optimal design across multiple partners
- Statistical efficiency in terms of sample size from a shared/common control arm
- Fewer participants on control
- Ability to screen more agents faster and quickly reject ineffective therapies

ALS Master Protocol Overview

- **Adaptive Platform Trial**
  - Perpetual trial that continuously tests interventions until cures are found for all people with ALS
  - **Potential to provide confirmatory evidence with overall type I error of 5%**
  - Frequent platform-wide interims to stop regimens for early success/futility
- **N = 160 w/ 3:1 randomization** for each regimen, Active Treatment vs. Placebo
  - Shared placebo among all regimens
  - Uses concurrent and non-concurrent placebos



Master Protocol Statistical Complexities

Primary analysis population shares ALL controls across all regimens including:

- Different modes of administration
- Minor differences in inclusion /exclusion
- Concurrent and non-currently randomized

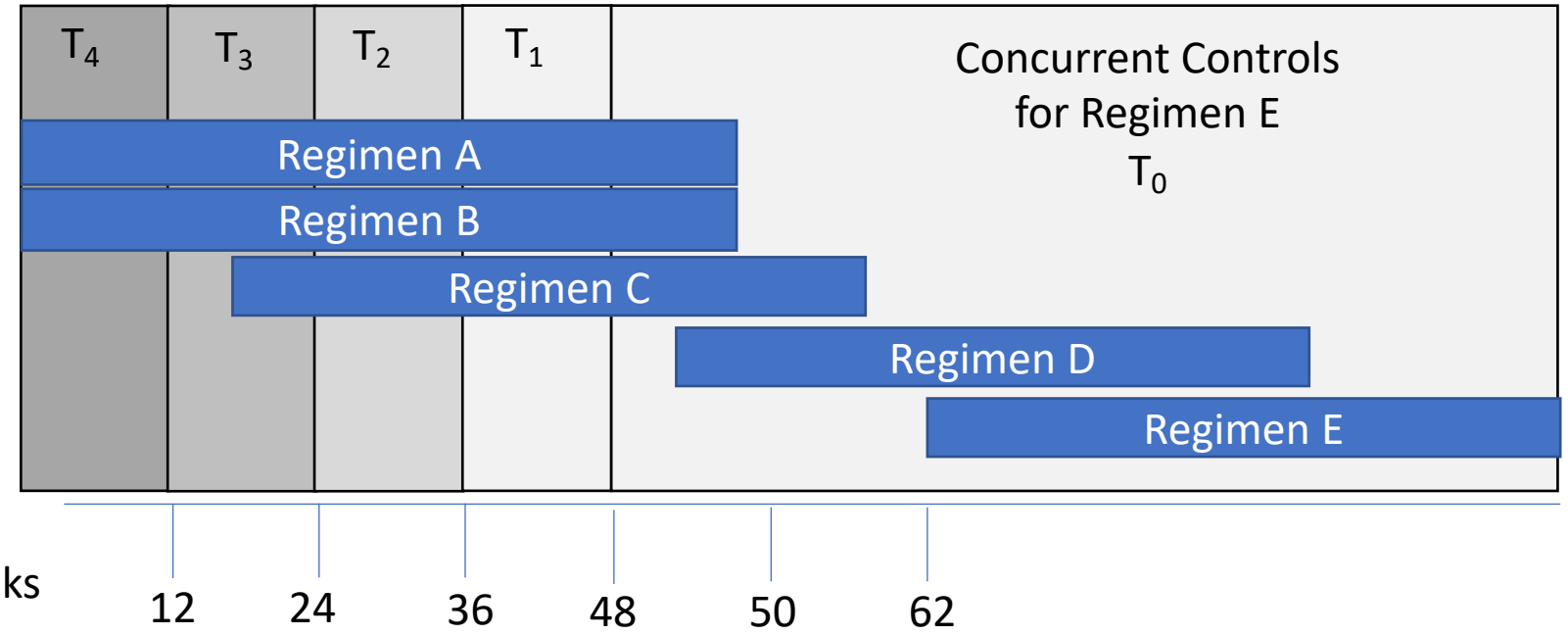
Sharing of controls increases power and decreases the number of participants needed to go on placebo – backbone of the platform trial!

Need to account for potential differences in our shared control (over time and across regimens) within the primary analysis method – Bayesian hierarchical models!

Bayesian modeling of potential differences in shared controls

Differences in controls over time in analysis (time-trend effect)

- Concurrent vs. non-concurrently randomized controls
- All controls randomized within 24 weeks of regimen are considered concurrent.
- Model differences in the concurrent controls and each 12-week time bucket before



Example Simple NDLM

$$T_0 \sim N(0, 10^2);$$

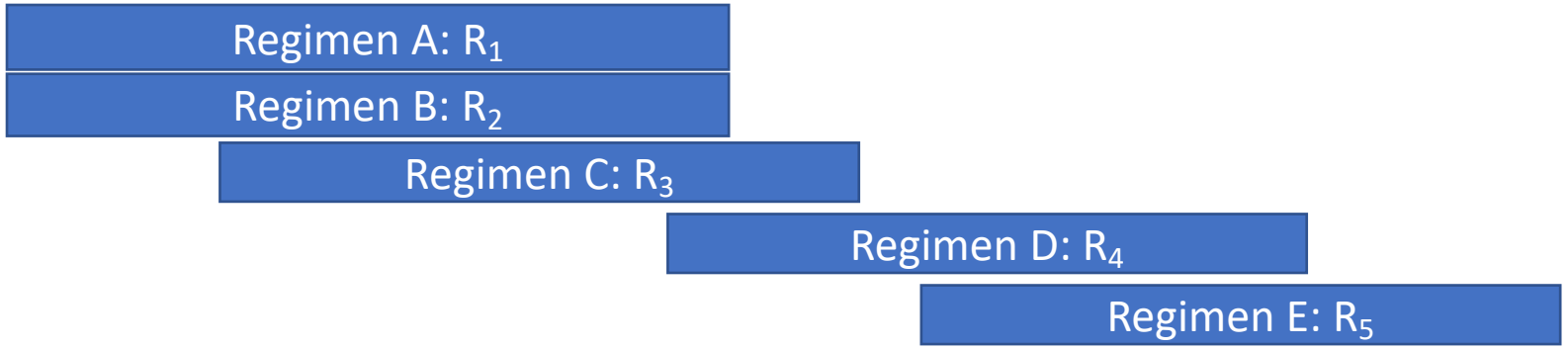
$$T_{n+1} \sim N(T_n, \sigma_t^2); \text{n} = 2{:}4$$

$$1/\sigma_t^2 \sim Gamma(a, b)$$

Bayesian modeling of potential differences in shared controls

Potential differences in controls across regimens (regimen-specific random effects)

- Hierarchical modeling of regimen-specific random effects
- More similar they are = more sharing of information



Example Hierarchical Model

$$R_i \sim N(\mu_R, \sigma_R^2); \mathrm{R} = 1{:}5$$

$$\mu_R \sim N(0, 10^2);$$

$$1/\sigma_R^2 \sim Gamma(a, b)$$

Additional Statistical Complexities *in ALS*

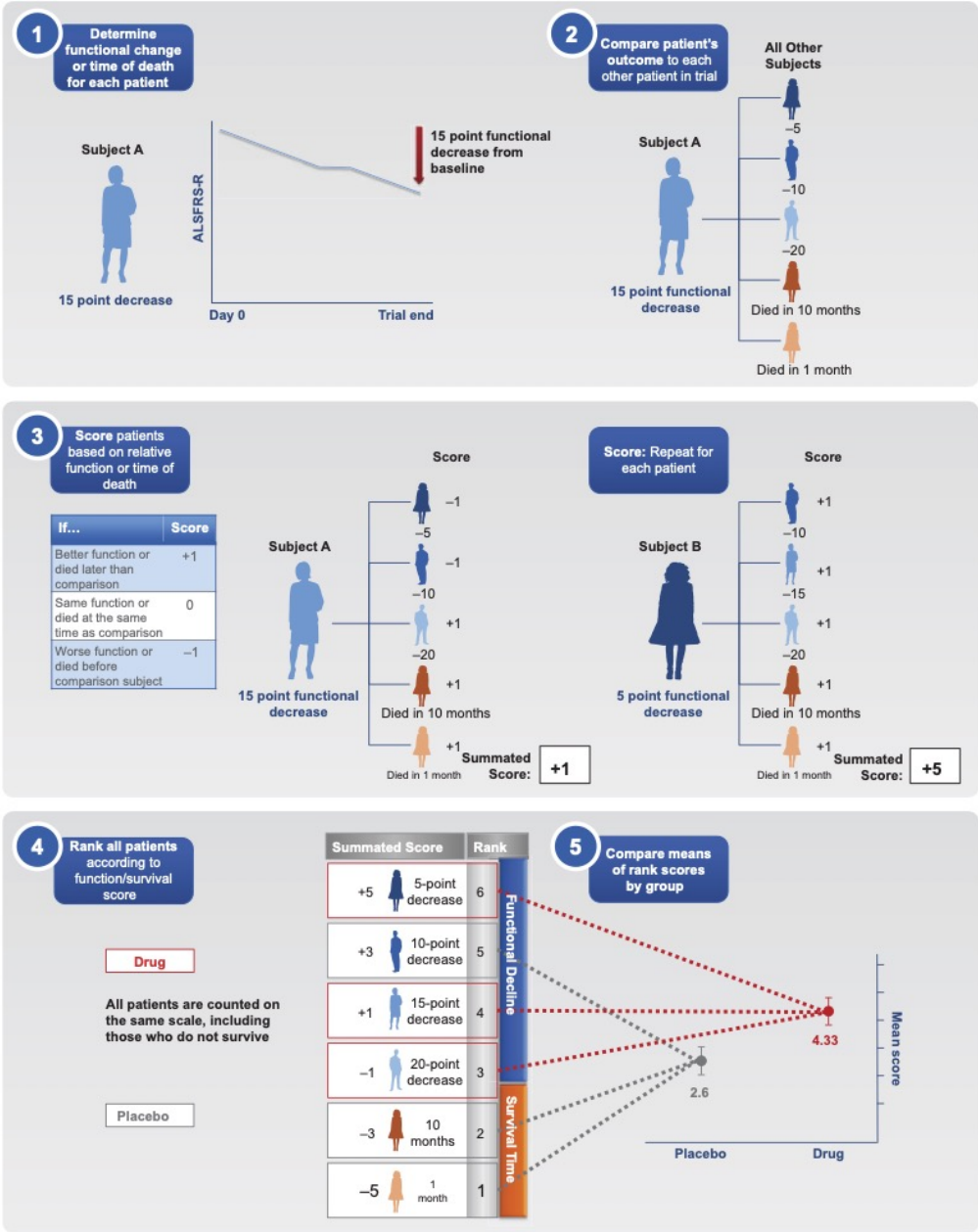
FDA Guidance ALS:

“If patient function is intended to be assessed by the primary outcome, mortality should be integrated into the primary outcome by an analysis method that combines survival and function into a single overall measure, such as the joint rank test**”**

- **Primary Outcome of ALS platform trial**
  - Change in disease severity through 24 weeks
  - ALS Functional Rating Scale-Revised (ALSFRS-R) + Mortality

Traditional Joint Rank analysis of Mort. + Function

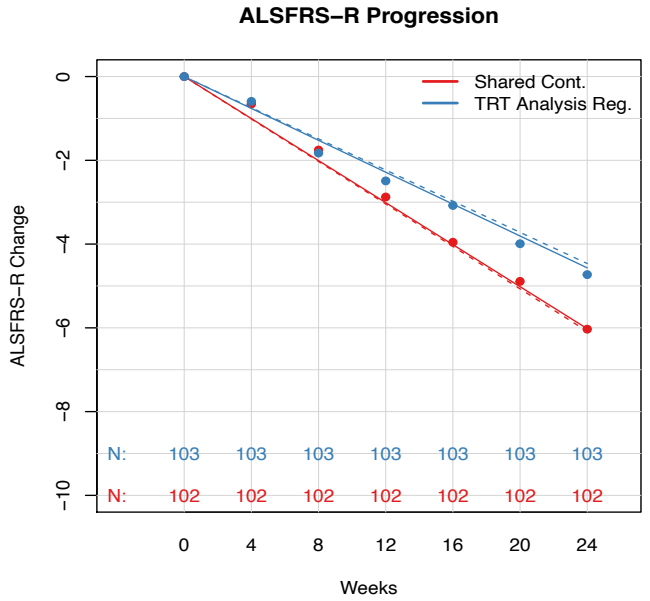
- Traditional approach to integrating mortality and function is a non-parametric joint rank test. (Berry et al. 2013)
- Benefits of joint rank: limited assumptions
- Limitations of Joint rank
  - Does not provide clinically meaningful treatment effect estimate
  - Not clear how to accommodate statistical complexities of the platform trial

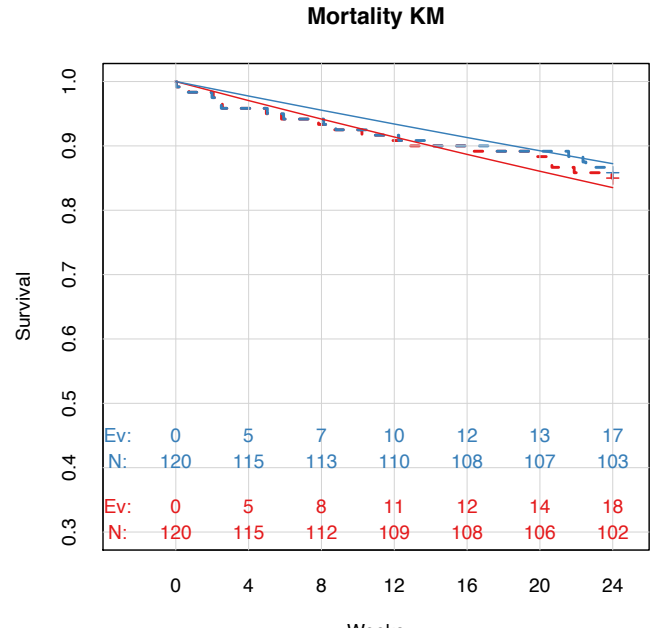


Bayesian Shared Parameter Model of Mort. + Function

Bayesian shared parameter analysis of ALSFRS-R and mortality

- ALSFRS-R: Repeated measures model with linear rate of progression
- Mortality: Exponential time to event
- **Treatment Effect:**
  - *Common slowing in disease*
  - Disease rate ratio (DRR): 1-% slowing in the rate of progression of disease for treatment relative to control between ALSFRS-R and Mortality
  - Weight each component contributes to treatment effect depends on mortality rates
- Adjust for differences in shared controls over time and across regimens





Characterization of Analysis Assumptions + Sensitivity Analyses

Important to characterize key assumptions of the novel analysis method and assess the sensitivity of the results to these assumptions

Sensitivity analyses address key assumptions made in primary analysis model

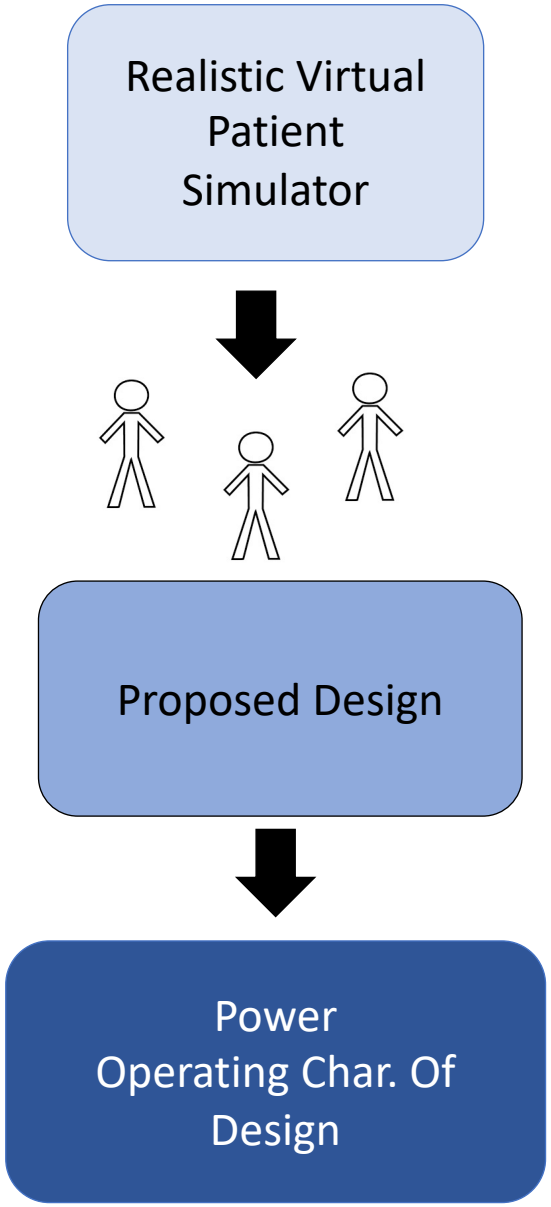
- Linearity of ALSFRS-R over 24 weeks
- Common proportional treatment effect over time
- Common treatment effect between mortality and function
- Similarity in shared controls

Traditional CAFS (joint rank analysis) will be performed as key secondary analysis.

How can we better understand and characterize the performance of this new model?

Clinical Trial Simulation

- Understand operating characteristics of proposed design / analysis method
- Optimize design/analysis under key trial parameters
- Understand robustness of results to modeling assumptions



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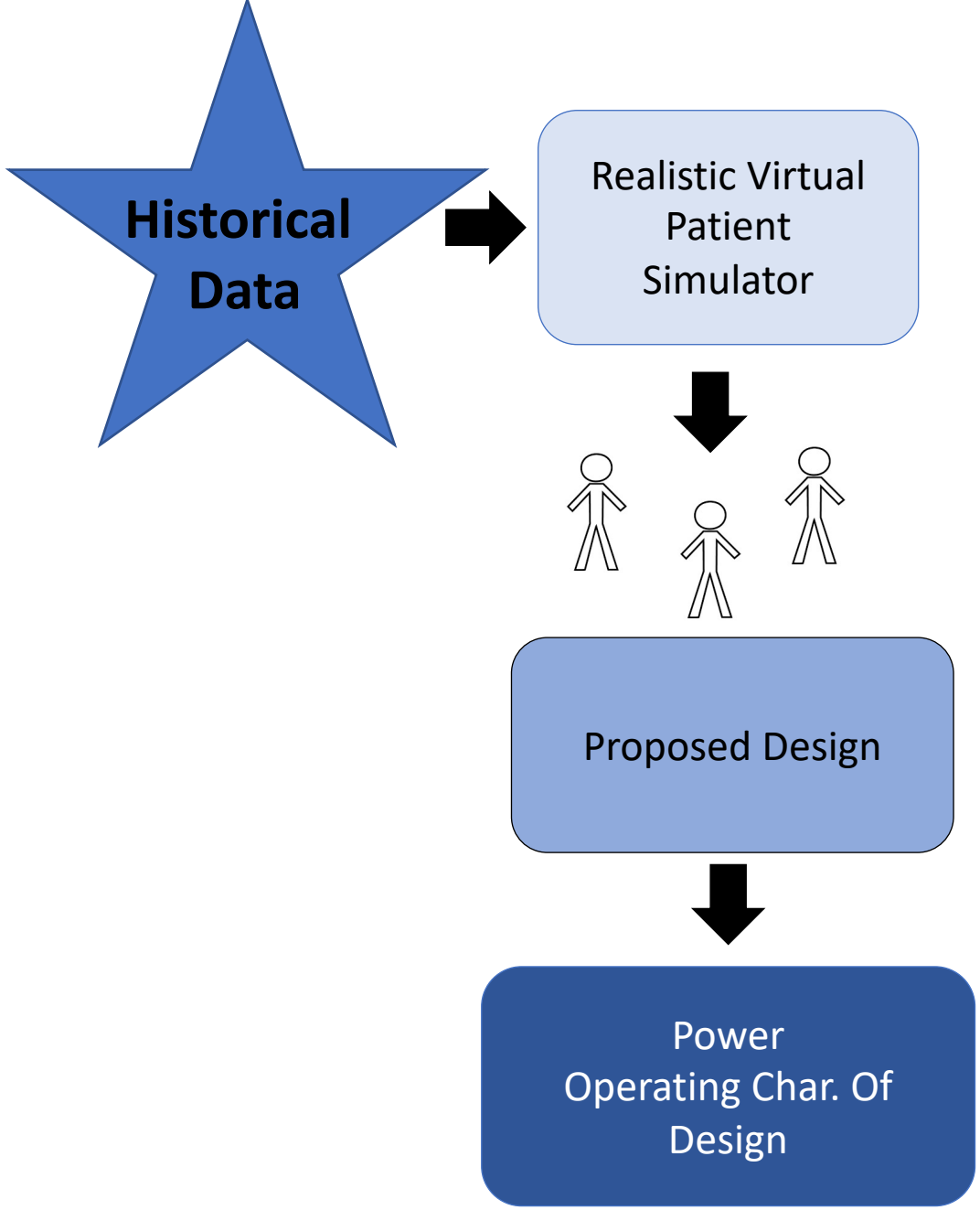
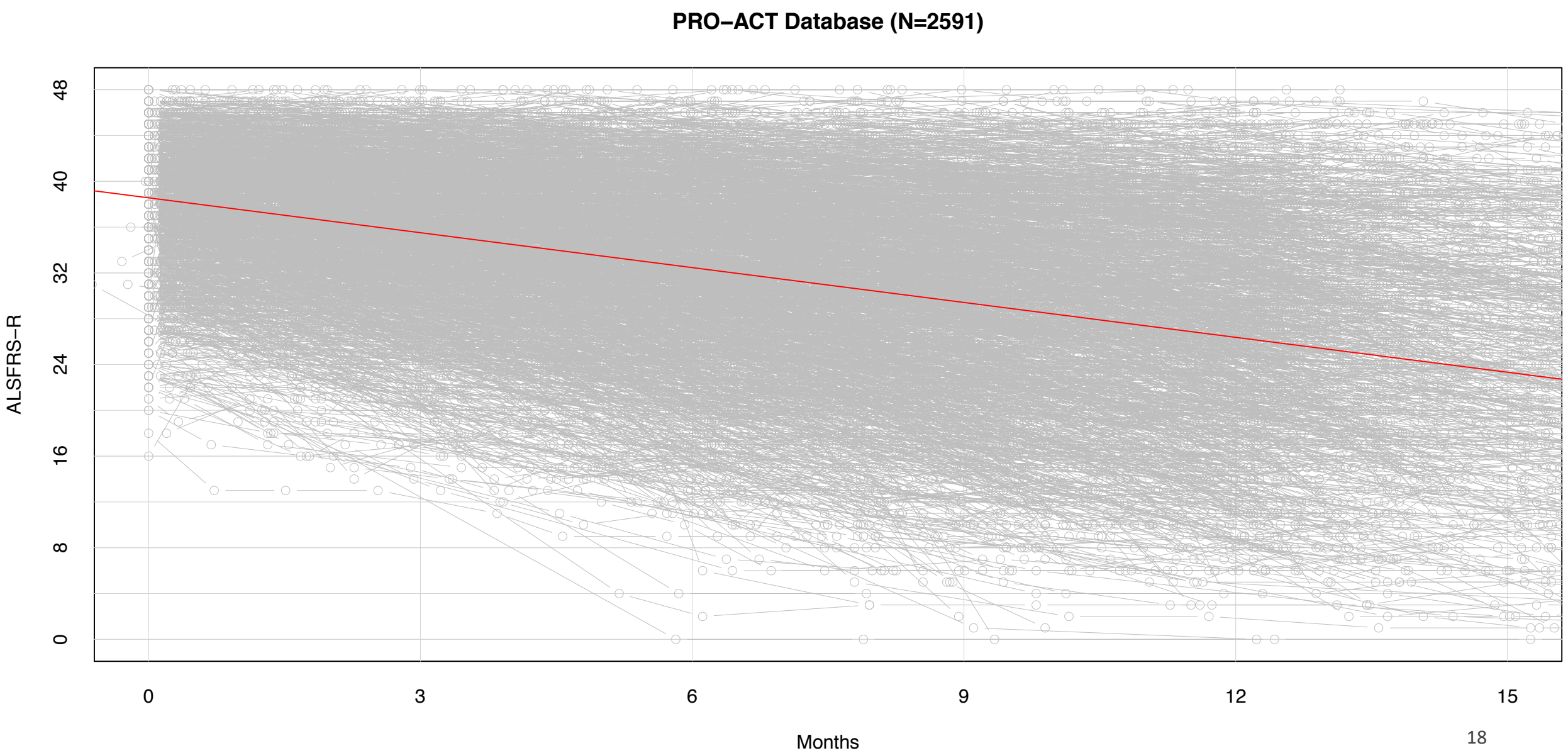


ALS PRO-ACT Database

- Pooled Resource Open-Access ALS Clinical Trials Database
- Over 10,700 de-identified clinical patient records from 23 Phase II/III Clinical Trials
- Over 10 million longitudinal collected data points

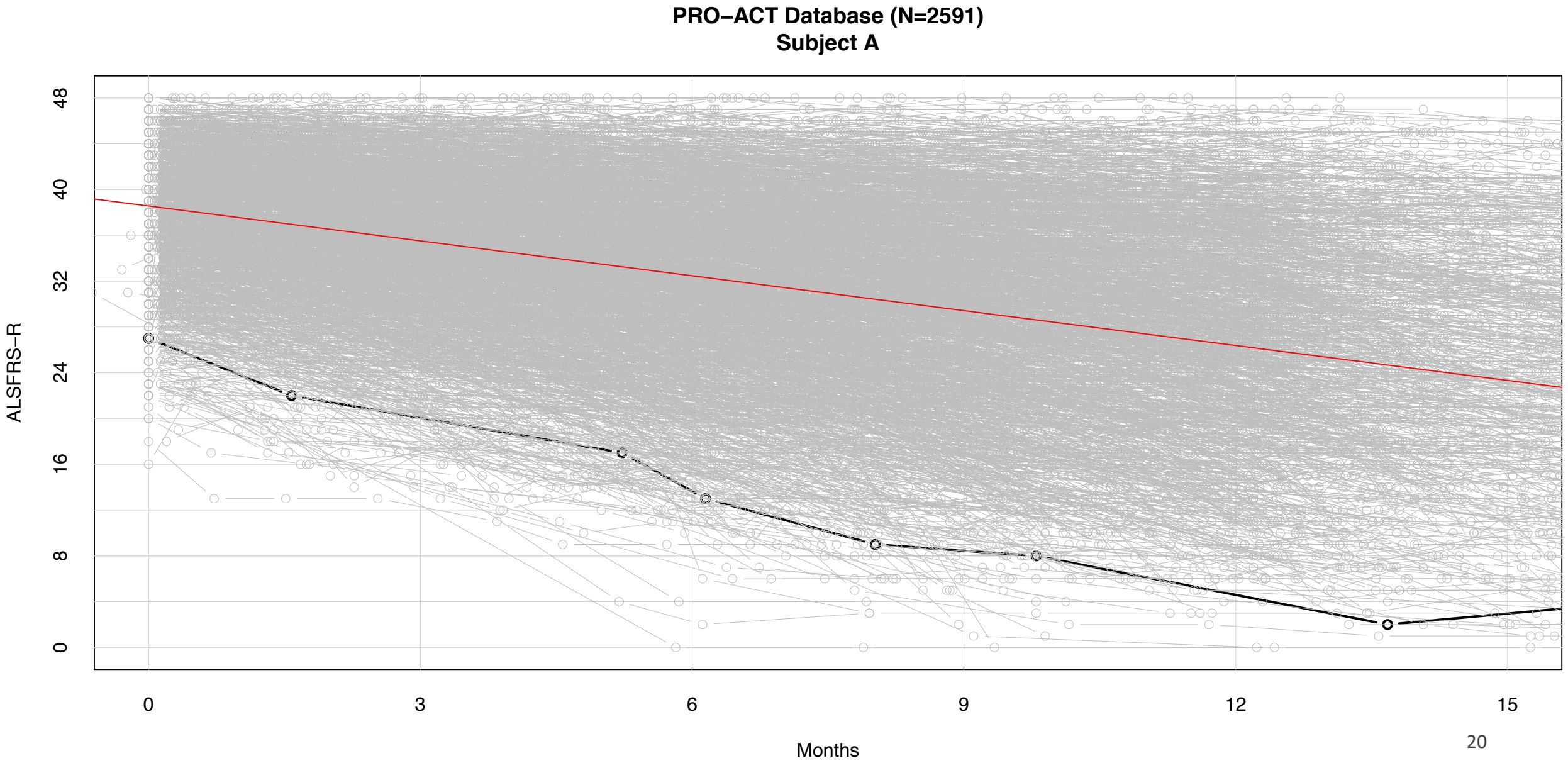
Virtual Patient Simulation w/ ALS PRO-ACT Database



Virtual Patient Simulation w/ ALS PRO-ACT Database

- Option 1: Summarize PRO-ACT Data (mean and SD of decline, residual error) and use these summaries to simulate trial data
- ***Option 2: Bootstrap simulations using observed data***
  - ***Draw a random participant from database***
  - ***Record observed participant characteristics (survival time, baseline covariates, etc…)***
  - ***Simulate outcome data similar to what is observed***

Virtual Patient Simulation w/ ALS PRO-ACT Database



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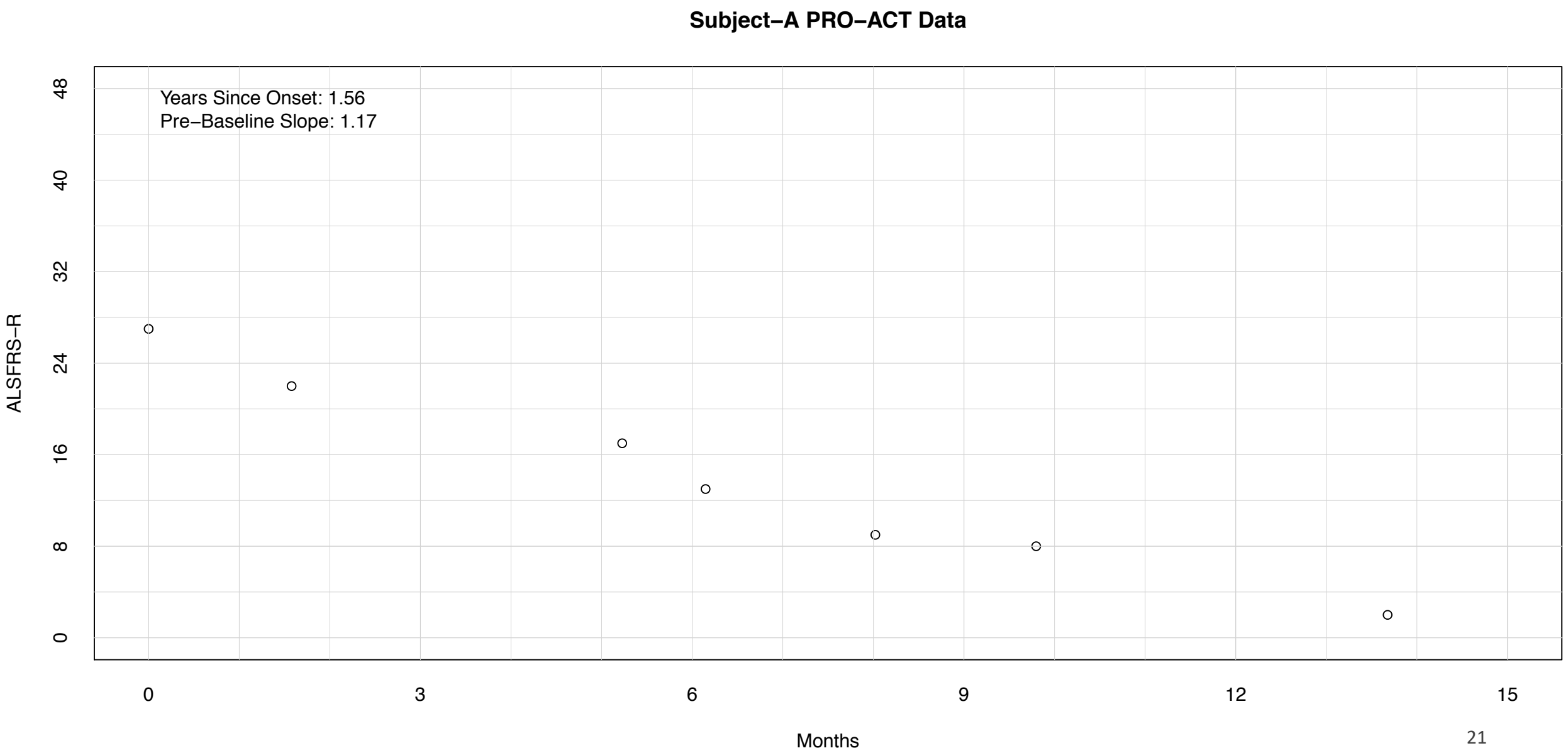

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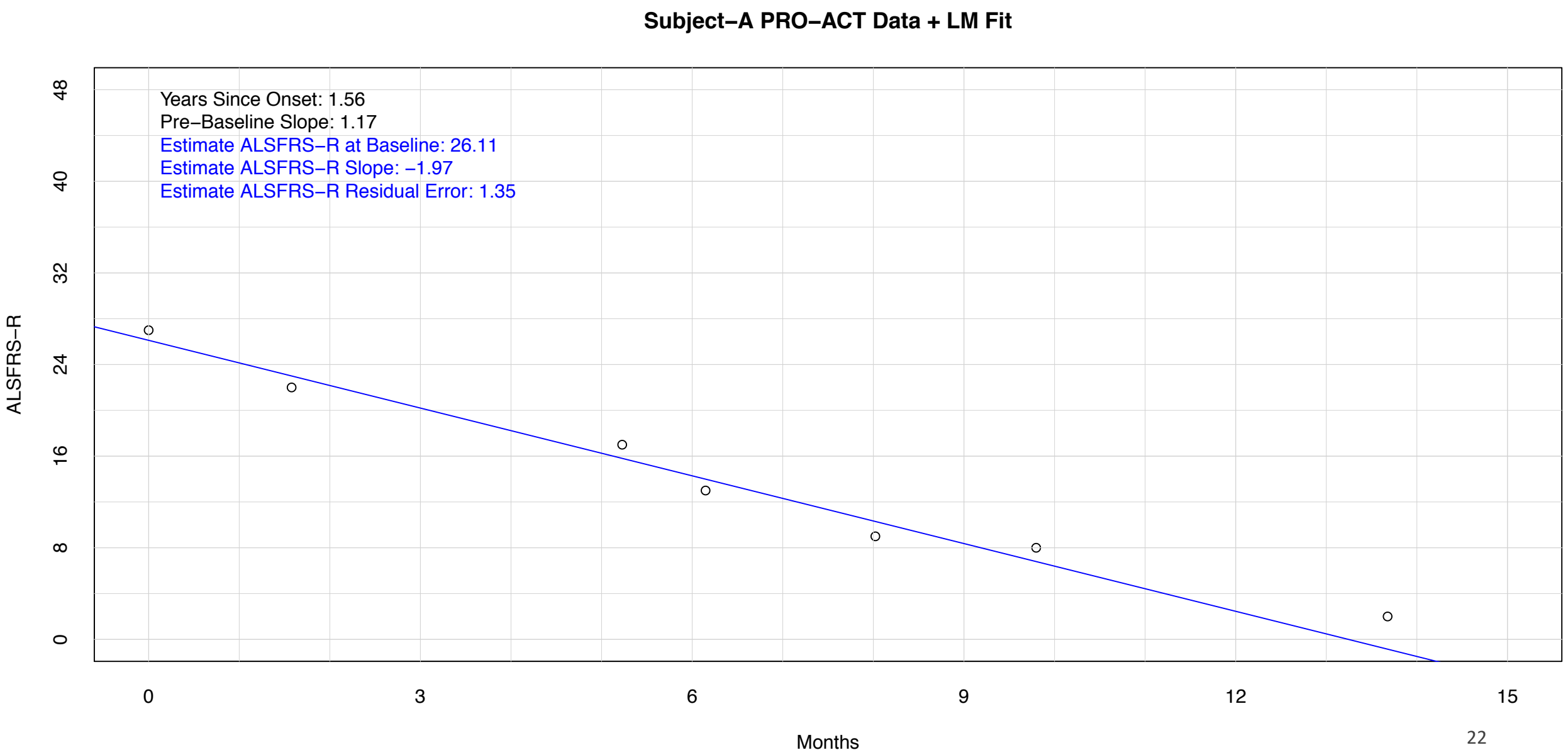
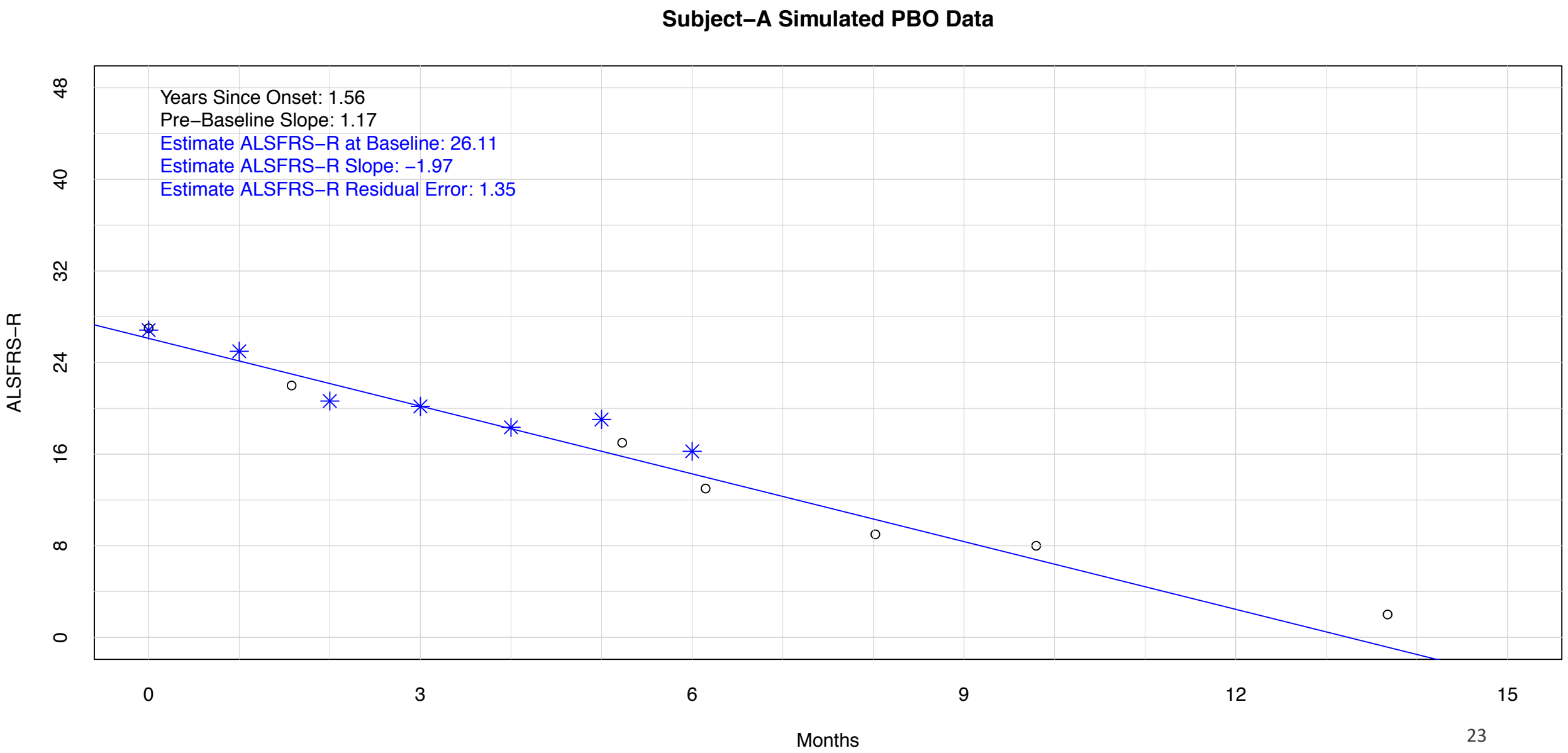


Virtual Patient Simulation w/ ALS PRO-ACT Database



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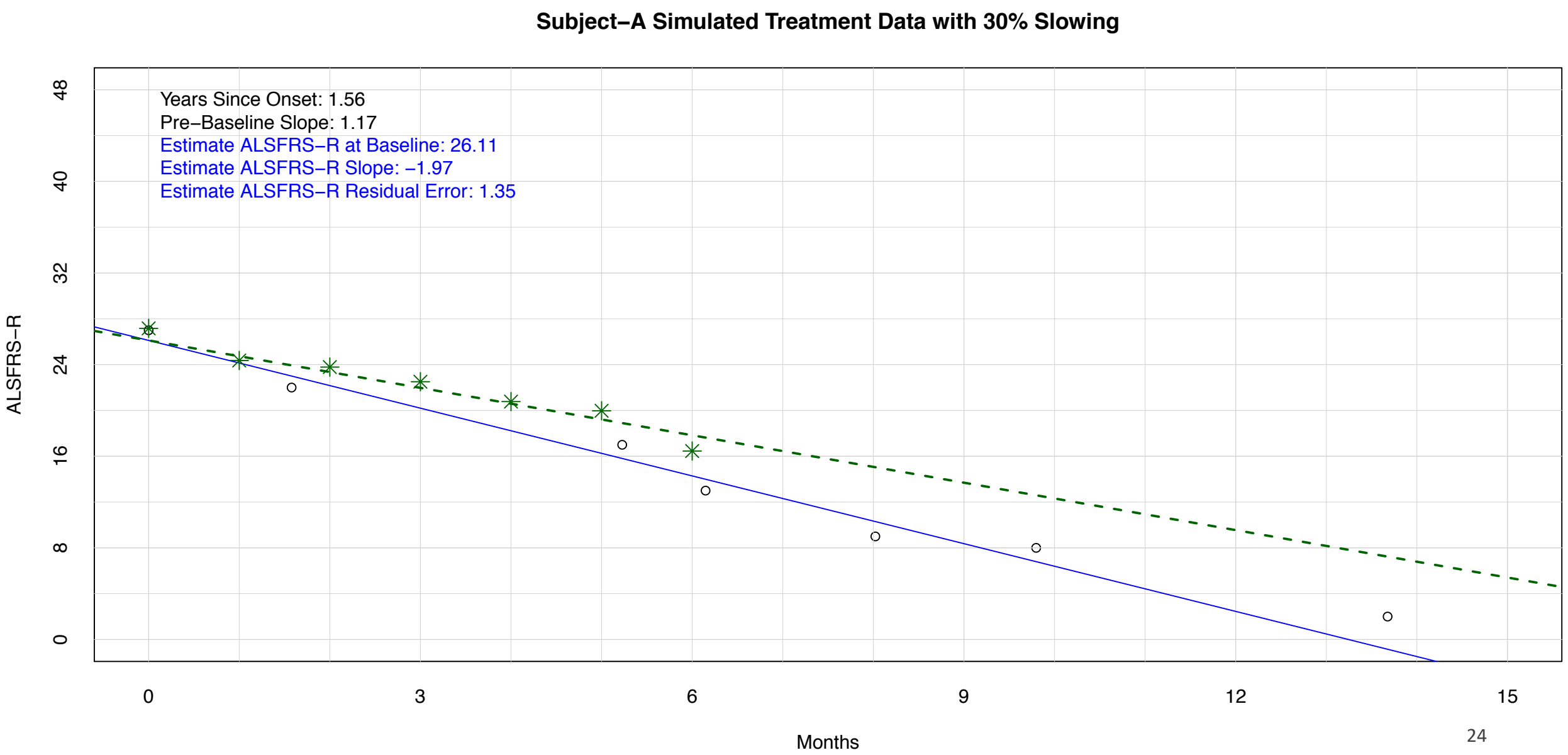


What can we learn from clinical trial simulations/ PRO-ACT database?

- Optimal inclusion / exclusion criteria – 2, 3 or 4 years since onset?
- Sample size and length of follow-up – How many participants do we need in each regimen if following for 24 weeks?
- Important covariates to adjust for in primary analysis – How does our power increase or decrease based on the covariates that we include
- Justification of modeling assumptions – is ALSFRS-R really expected to be linear over 24 weeks, what are the expected mortality rates?
- ***Characterization of novel primary analysis method***

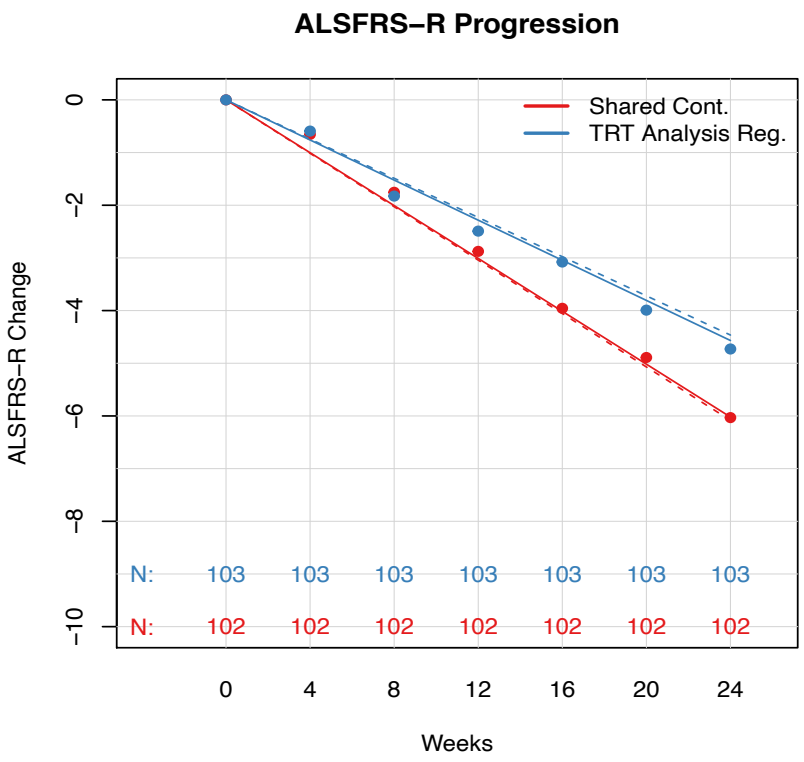
Primary Analysis Characterization with Simulation

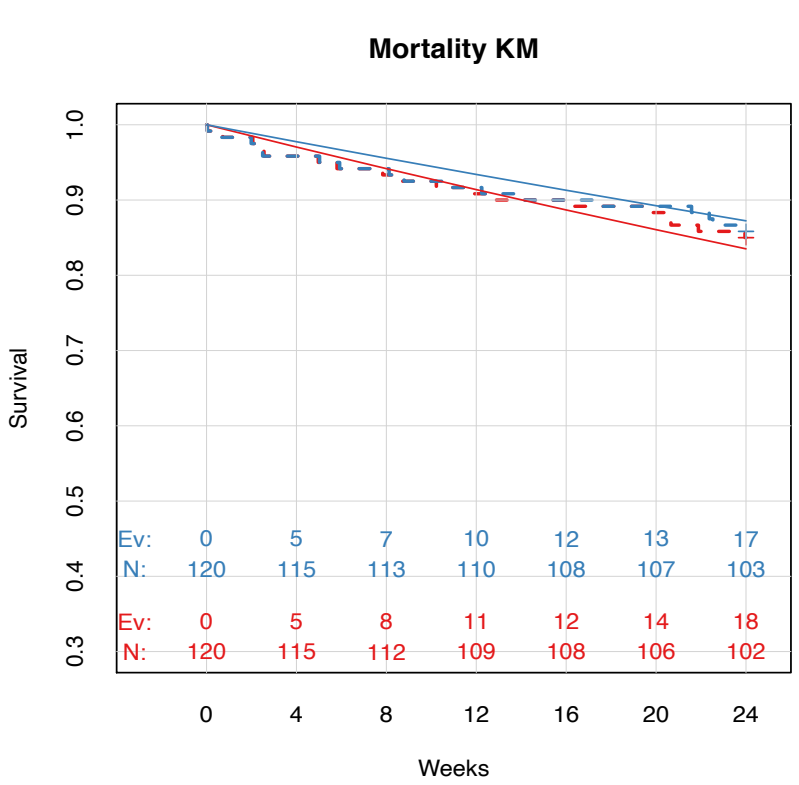
- How does our analysis method integrate mortality and function?
- How sensitive are the results to differences in the shared controls?

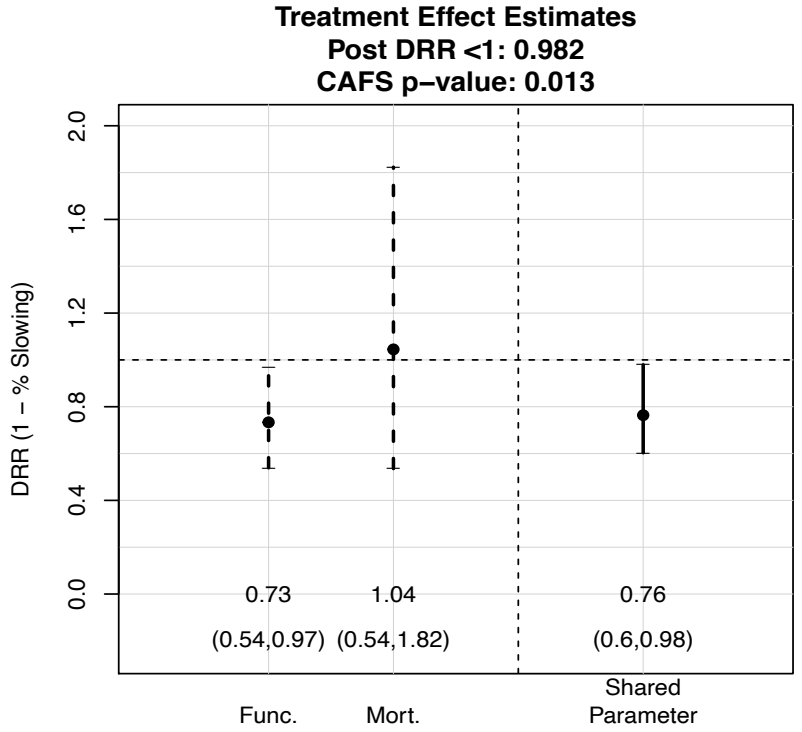
Integration of Mort. + Function

Primary Analysis Method: Integration of Mortality & Function

- ***Common treatment effect estimated across mortality and function***
- ***Weight each component plays depends on the percentage of patients within each component. Higher mortality rate = more weight is given to effect on mortality***







Primary Analysis Method: Integration of Mortality & Function

- ***How sensitive is the analysis to differences between treatment effect in mortality & function?***

Deaths PBO	Deaths TRT	Posterior Mean Estimate		CAFS P-Value	Posterior Probability of DRR <1
		Mortality DRR (HR)	Common DRR		
11	6	0.66	0.71	0.001*	0.998*
11	7	0.77	0.73	0.003*	0.993*
11	8	0.87	0.74	0.004*	0.992*
11	9	0.96	0.75	0.006*	0.988*
11	10	1.06	0.75	0.009*	0.982*
11	11	1.13	0.78	0.013*	0.979*
11	12	1.21	0.78	0.014*	0.976
11	13	1.27	0.78	0.017*	0.975
11	14	1.33	0.80	0.028	0.961
11	16	1.45	0.80	0.036	0.959
11	17	1.49	0.82	0.058	0.939
11	19	1.57	0.85	0.085	0.917

Primary Analysis Method: Integration of Mortality & Function

- ***How sensitive is the analysis to differences between treatment effect in mortality & function?***

Deaths PBO	Deaths TRT	Posterior Mean Estimate		CAFS P-Value	Posterior Probability of DRR <1
		Mortality DRR (HR)	Common DRR		
18	11	0.68	0.73	0.002*	0.994*
18	13	0.81	0.73	0.003*	0.991*
18	14	0.87	0.74	0.005*	0.988*
18	17	1.04	0.76	0.013*	0.982*
18	18	1.10	0.77	0.015*	0.975
18	19	1.15	0.78	0.022*	0.973
18	21	1.27	0.79	0.028	0.972
18	23	1.36	0.80	0.035	0.956
18	24	1.41	0.81	0.056	0.950
18	26	1.48	0.82	0.091	0.948
18	27	1.52	0.84	0.135	0.908
18	29	1.58	0.88	0.233	0.853

Primary Analysis Method: Integration of Mortality & Function

Base and Sensitivity Scenarios on Combining Mortality and Function						
Scenario	**DRR ALSFRS-R= 1.0 DRR Mort. = 1.0**		**DRR ALSFRS-R = .70**			
			DRR Mort. = .70		**DRR Mort. = 1.0**	
	Type I Error	**Mean Est. DRR**	**Power Bayes**	**Mean Est. DRR**	**Power**	**Mean Est. DRR**
Base (5% Mort. Rate)	0.024	1.0	***0.77***	0.69	***0.72***	0.71
10% Mort. Rate	0.023	1.0	***0.77***	0.69	***0.67***	0.72
20% Mort. Rate	0.024	1.0	***0.77***	0.69	***0.56***	0.75

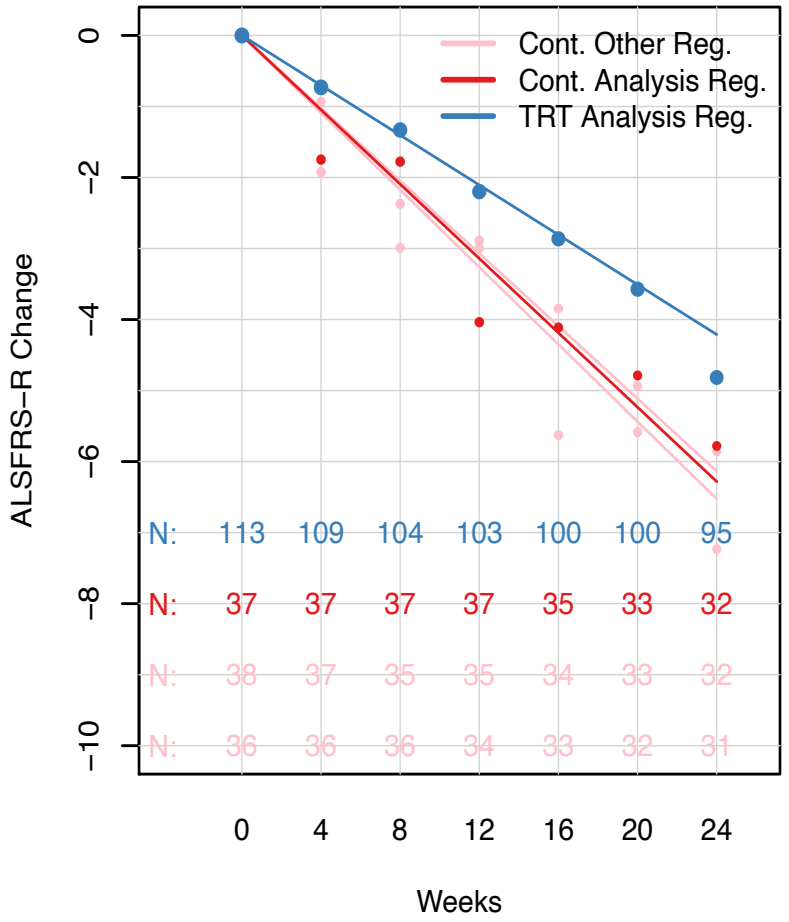
Account for potential differences in shared controls

Primary Analysis Method: Differences in Shared Controls

- *Primary analysis introduces regimen-specific random effects to account for potential differences in the shared control*
- *Dynamic borrowing across regimens*

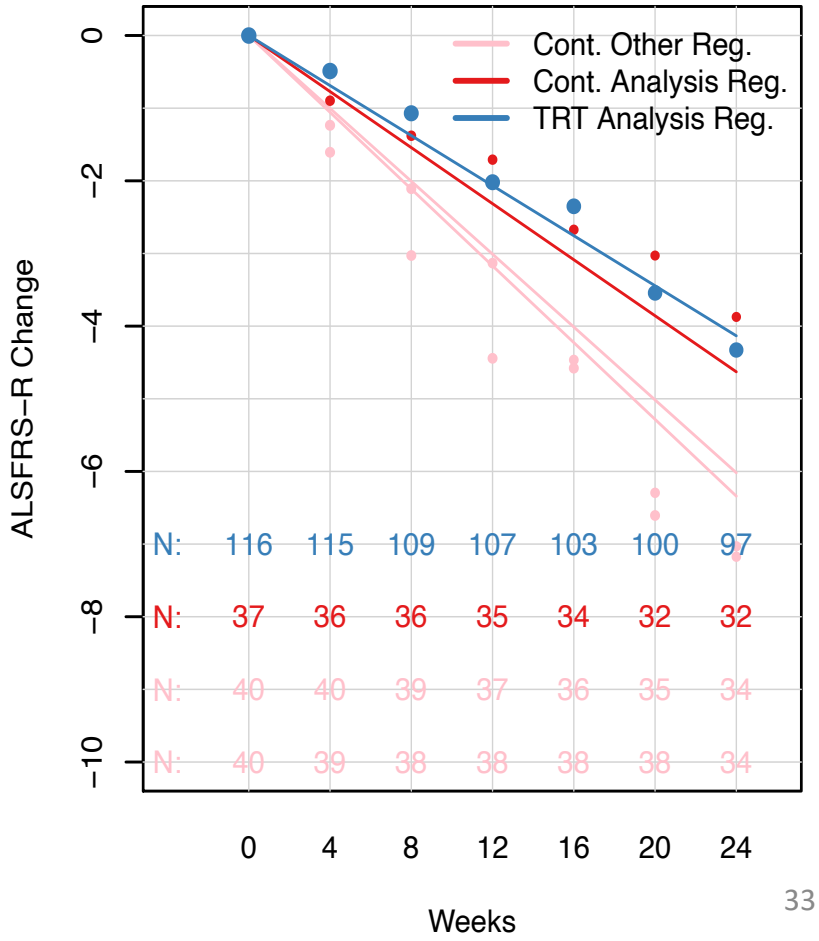
Similar results across regimens = more borrowing

ALSFRS–R Progression



Differences across results = less borrowing

ALSFRS–R Progression

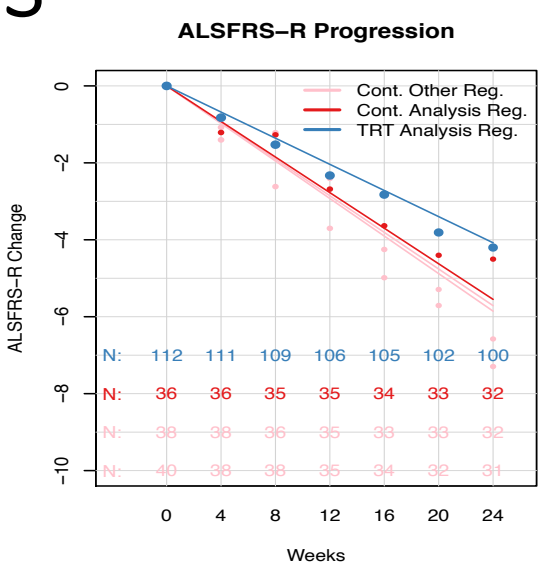


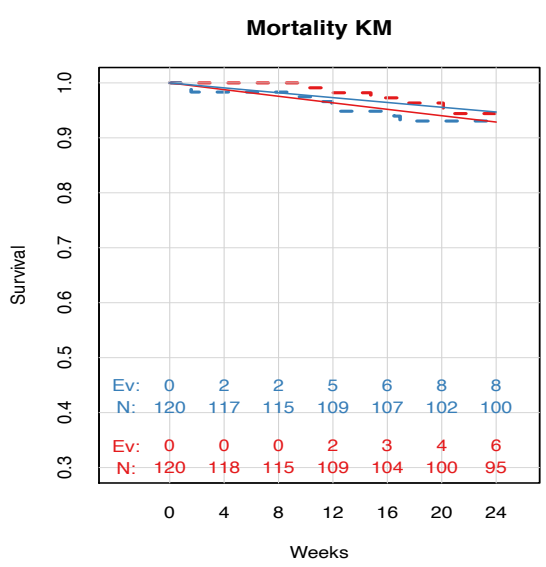
Primary Analysis Method: Differences in Shared Controls

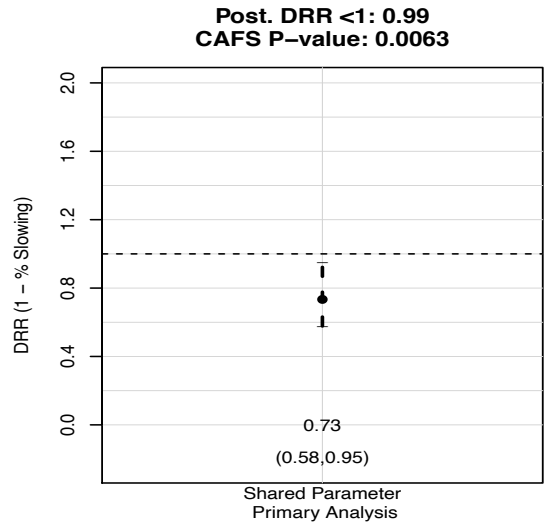
Base and Sensitivity Scenarios on Differences Across Regimens; No Early Futility Stopping; Common Mortality and Function Effect				
Scenario	Null DRR 1.0		Alternative DRR 0.70	
	Type I Error	Mean Est. DRR	Power	Mean Est. DRR
Base	***0.024***	1.01	0.77	0.69
ALSFRS-R 10% Slower Progress Analysis Reg.	***0.060***	0.96	0.85	0.66
ALSFRS-R 10% Faster Progress Analysis Reg.	***0.010***	1.05	0.67	0.72

Primary Analysis Method: Differences in Shared Controls

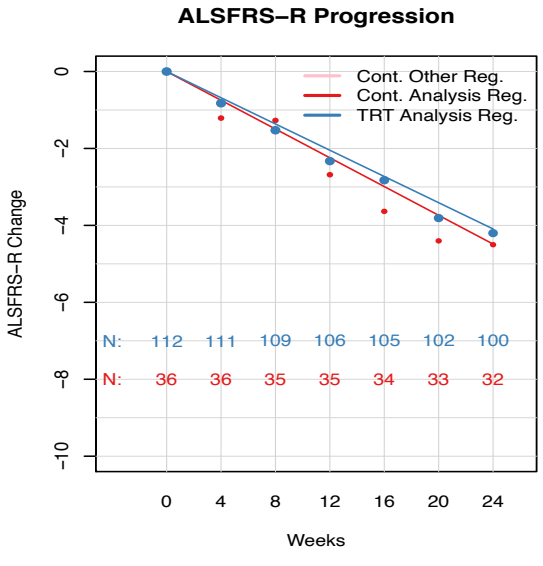
How would we know if we are making a type I error due to sharing very different controls?

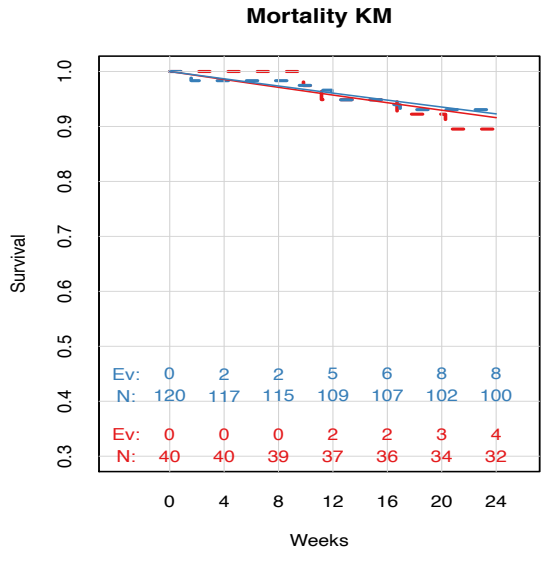


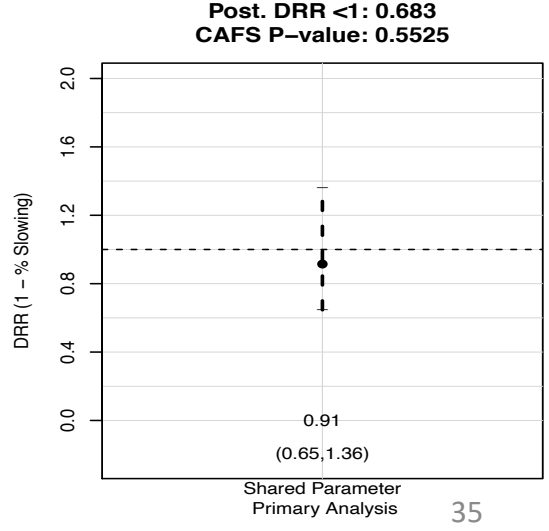




Are the results with the regimen only controls similar?

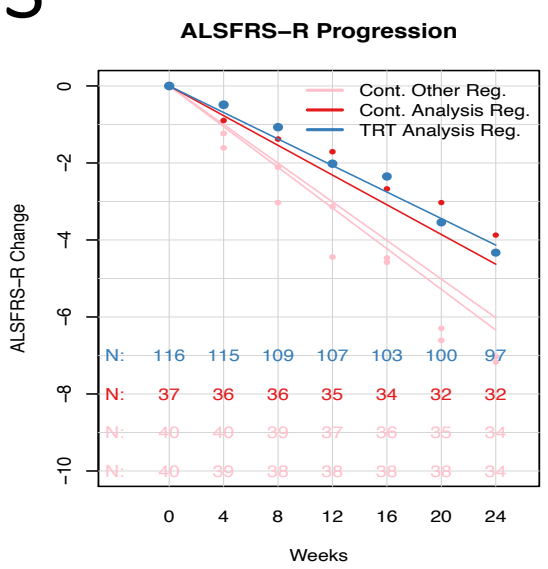


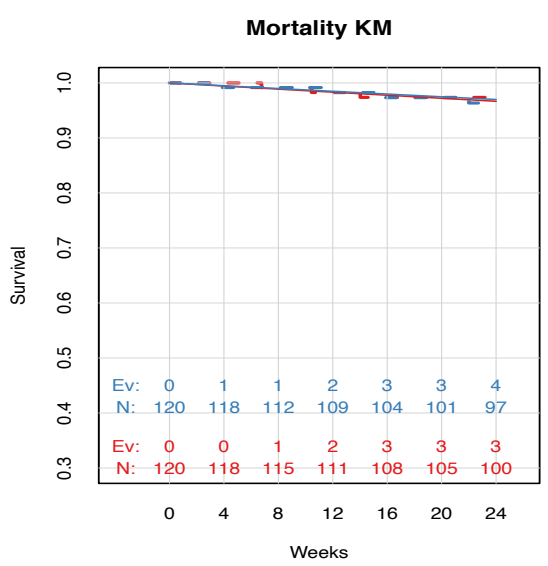


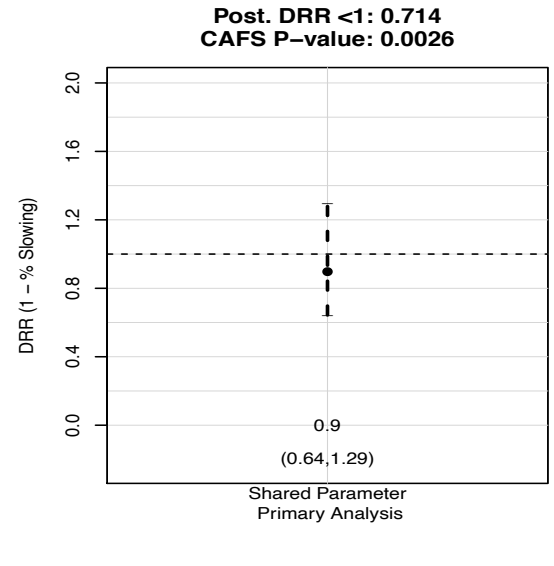


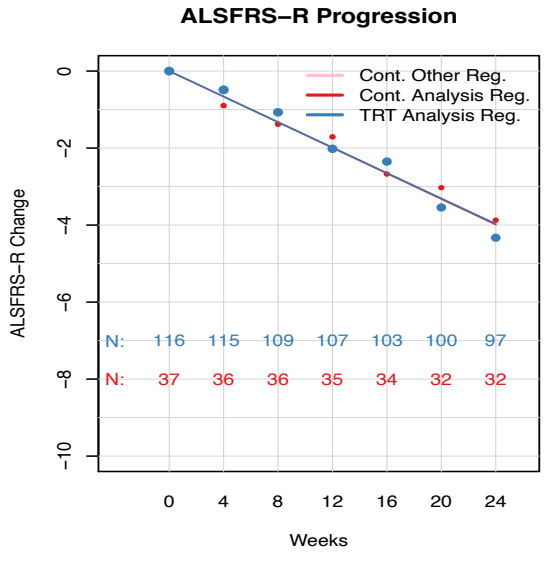
Primary Analysis Method: Differences in Shared Controls

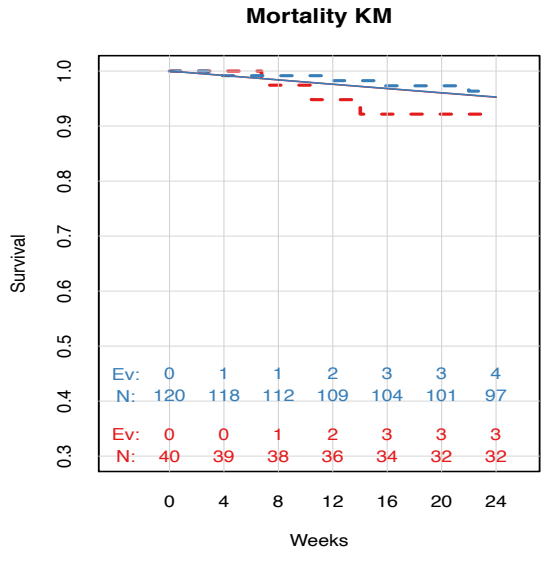
Importance of Bayesian model to allow for dynamic borrowing

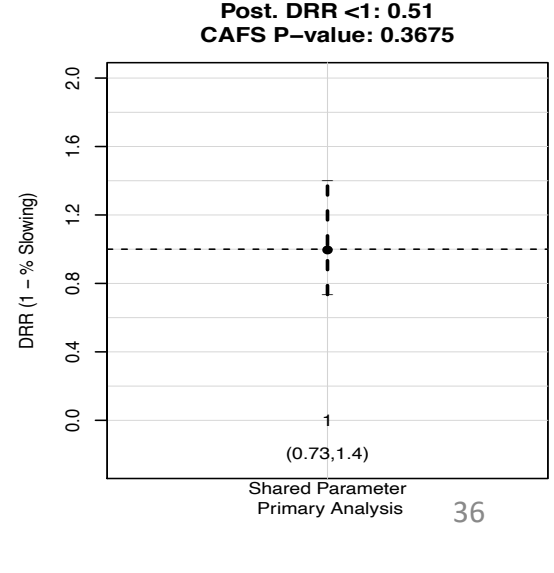






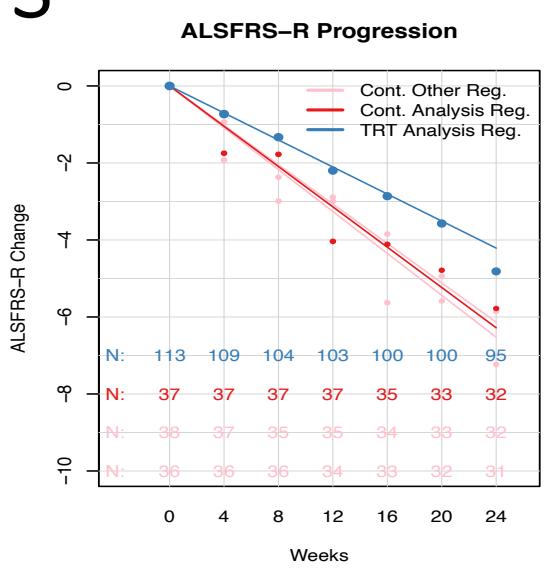


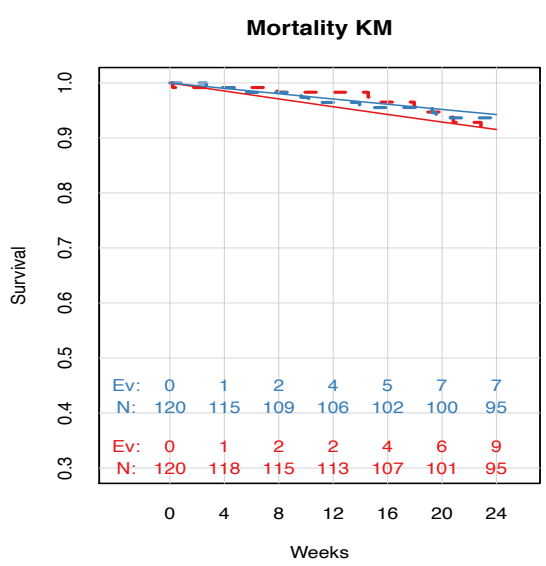


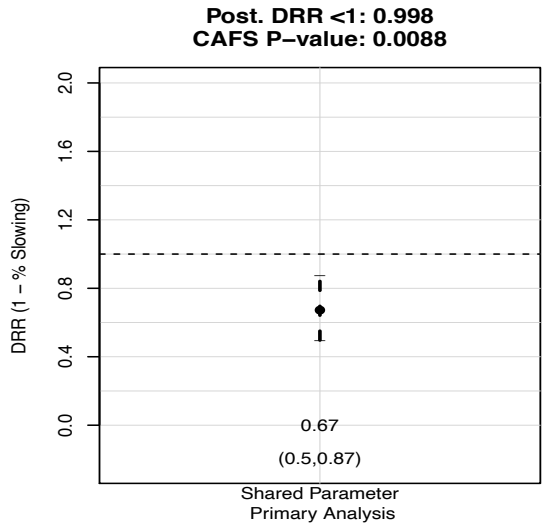


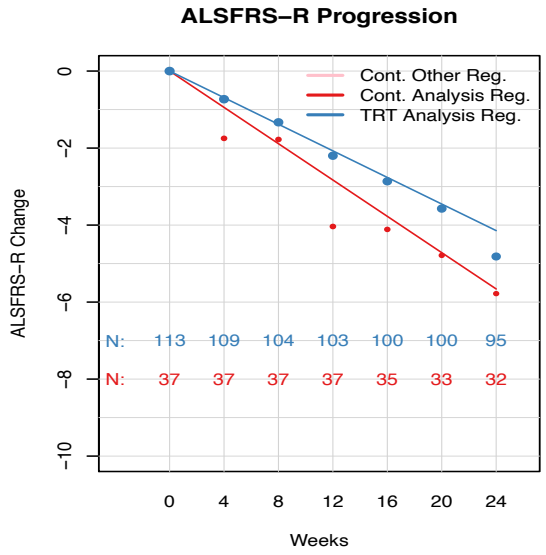
Primary Analysis Method: Differences in Shared Controls

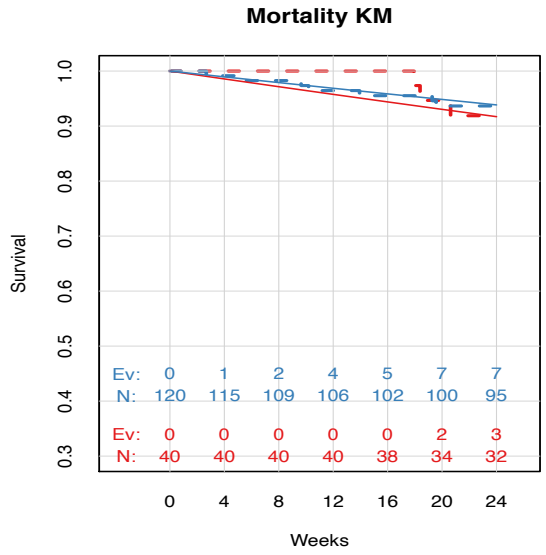
Consistent results across primary and sensitivity analysis – Confidence in the primary result!

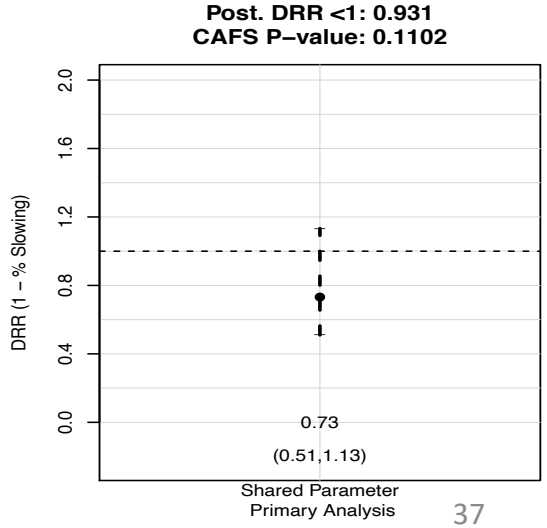












Summary

- Speak with partners early and often – important that all parties are comfortable with the novel approach
- Clearly define key modeling assumptions and specify sensitivity analyses that will be performed to address those
- Clinical trial simulation is the key to understanding + getting approval of novel / complex approaches