Case Studies in Designing Clinical Trials in Rare Disease

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Regulatory-Industry Statistics Workshop

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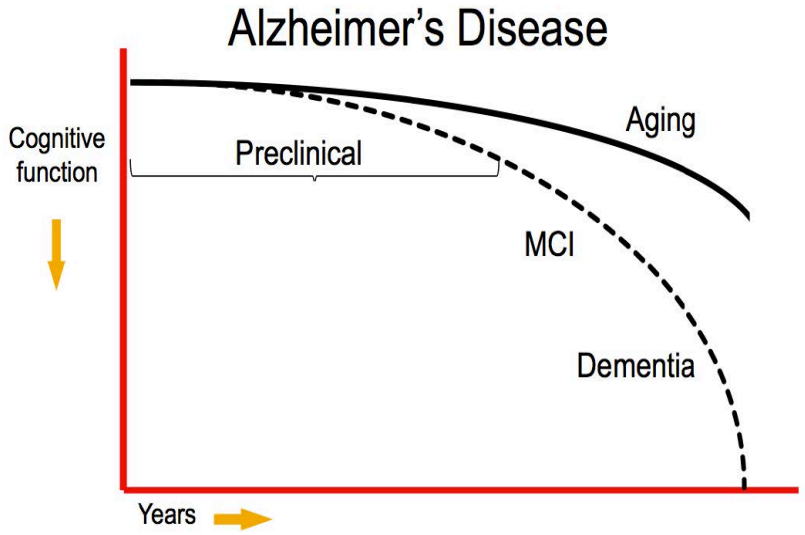
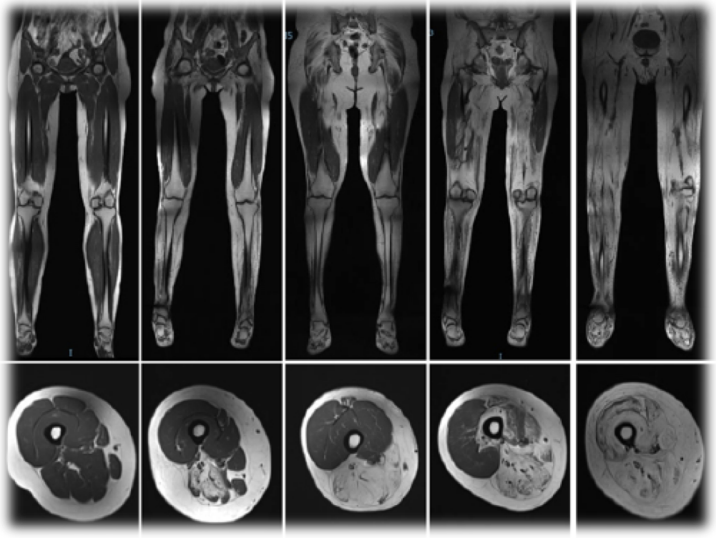
Dominantly Inherited Alzheimer's

- Rare genetic form of Alzheimer's (<1% of total Alzheimer's population)
- Early age of onset: 30-50
- *Goal: Does the treatment slow cognitive progression?*



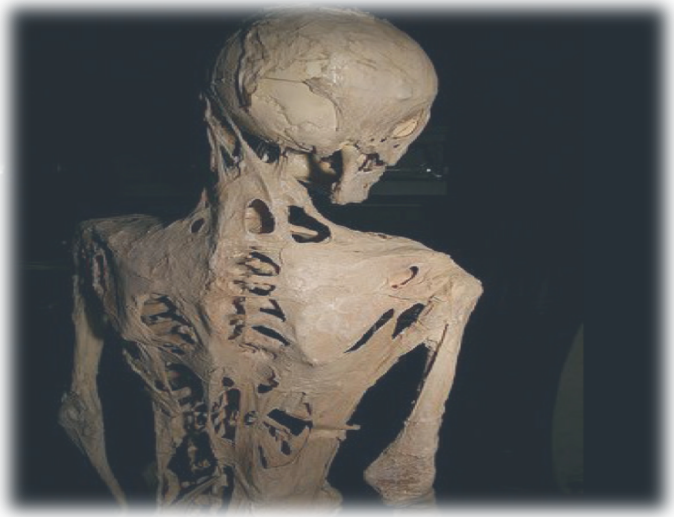
GNE Myopathy

- Rare genetic muscle disease
- Slowly progressive muscle weakness and atrophy effecting different muscle groups at different stages of the disease
- *Goal: Does the treatment slow decline of muscle strength?*



Fibrodysplasia Ossificans Progressiva (FOP)

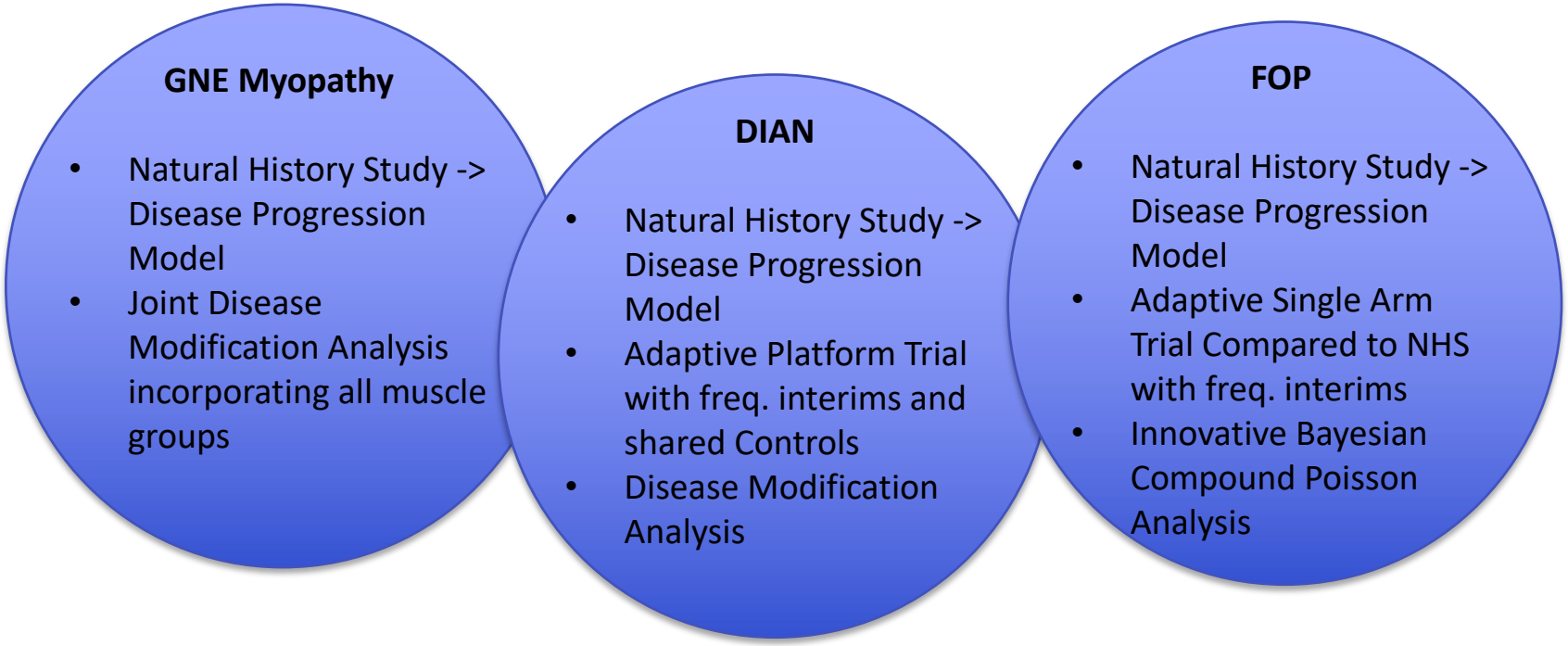
- Rare genetic connective tissue disease causing fibrous tissue to be ossified spontaneously or when damaged.
- Median age at diagnosis is 5 years
- *Goal: Does the treatment reduce the amount of bone growth?*



Complexity in Rare Disease

- Heterogeneity in progression
- Large variability in key clinical endpoints
- Different endpoints are affected at different stages of the disease
- *Common Solutions:*
  - Enroll a more homogenous subset
  - Enroll a large enough sample size to overcome heterogeneity
  - *Both not ideal in a rare disease setting!*

Solutions for Rare Disease



- Natural History Studies -- Know what you are working with!
- Innovative Designs
  - More powerful analysis methods
  - Adaptive designs with frequent interims
  - Use all available data

NATURAL HISTORY STUDIES

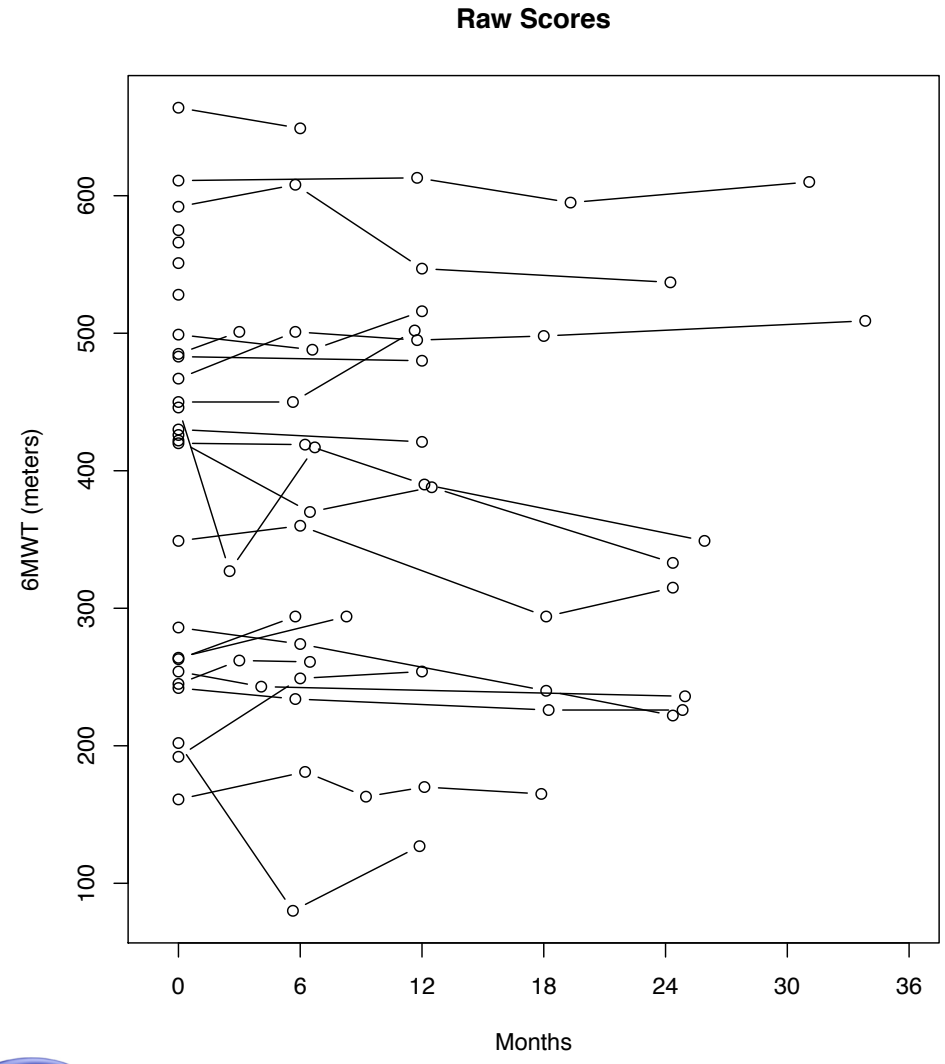
Natural History Studies

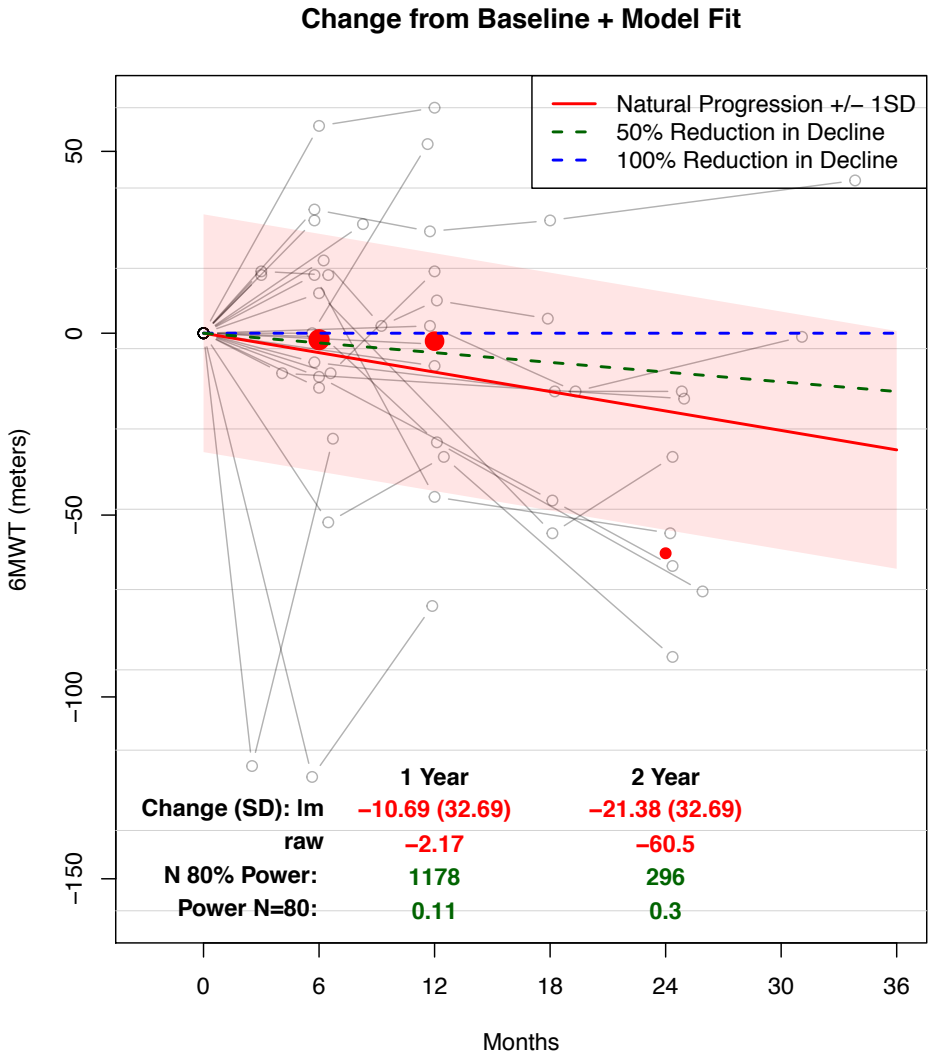
- Understand behavior of candidate primary endpoints
- Create Realistic Evidence-Based Virtual Patient Simulator
- Understand Power / Operating Characteristics of Proposed Design

GNE Natural History Data

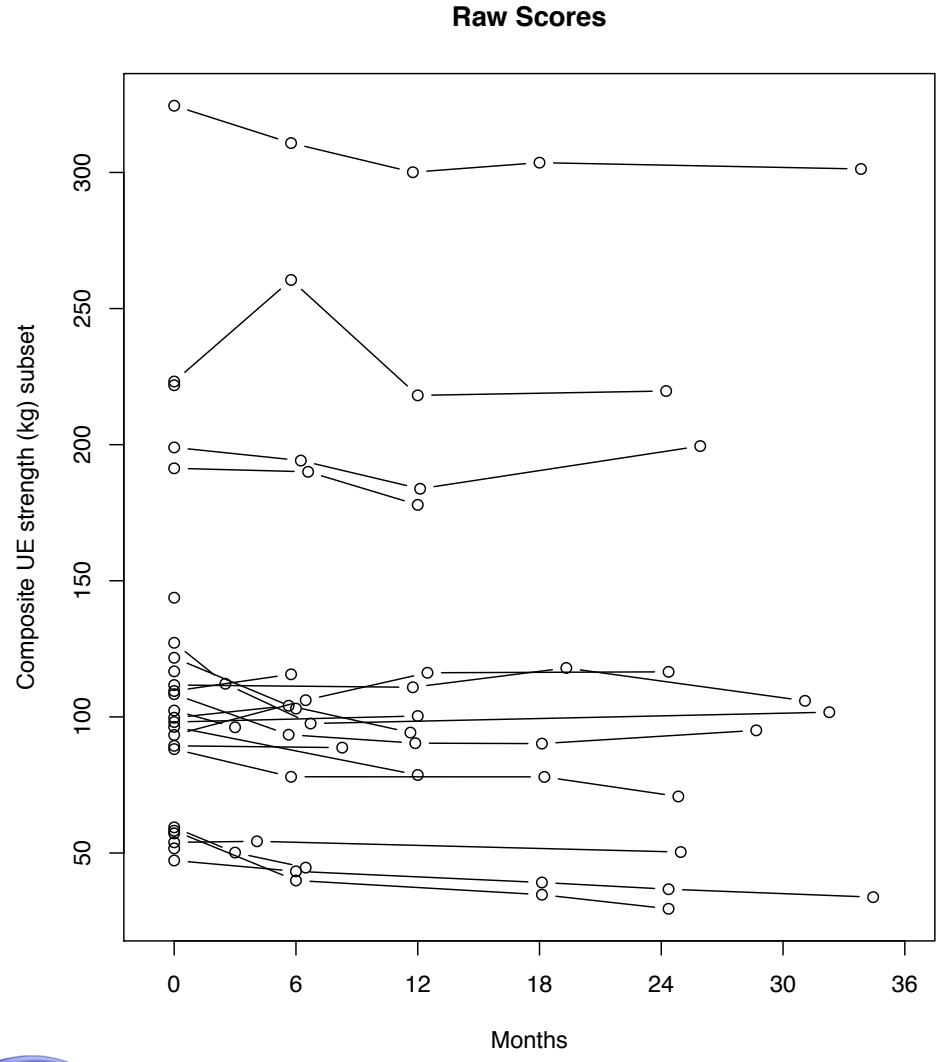
- **Sample Size: 38** Patients
- **Visits:** Every 3-6 months
  - Number of months from baseline per patient ranges from 0-32
- **Measurements taken on possible primary endpoints:**
  - Six minute walk
  - Quantitative Muscle Assessment (QMA) for multiple muscle groups

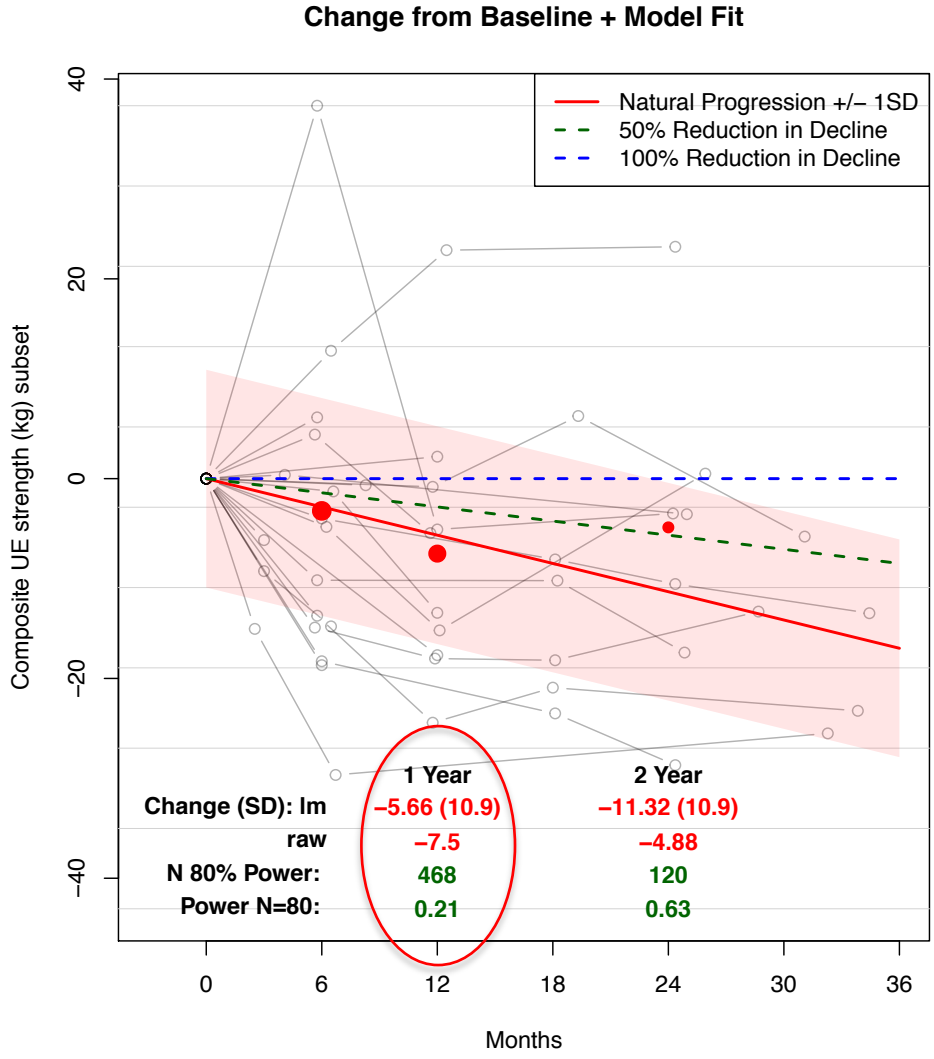
Possible Primary Endpoints: 6 Min. Walk





Possible Primary Endpoints: Upper Extremity Composite Subset*





Aug 22, 2017

Ultragenyx Announces Top-Line Results from Phase 3 Study of Ace-ER in GNE Myopathy

Study did not meet its primary endpoint

NOVATO, Calif., Aug. 22, 2017 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ:RARE), a biopharmaceutical company focused on the development of novel products for rare and ultra-rare diseases, today announced that a Phase 3 study evaluating aceneuramic acid extended release (Ace-ER) in patients with GNE Myopathy (GNEM) did not achieve its primary endpoint of demonstrating a statistically significant difference in the upper extremity muscle strength composite score compared to placebo. The study also did not meet its key secondary endpoints. Adverse events were generally balanced between Ace-ER and placebo and safety was consistent with previously released Ace-ER data. Ultragenyx plans to discontinue further clinical development of Ace-ER.

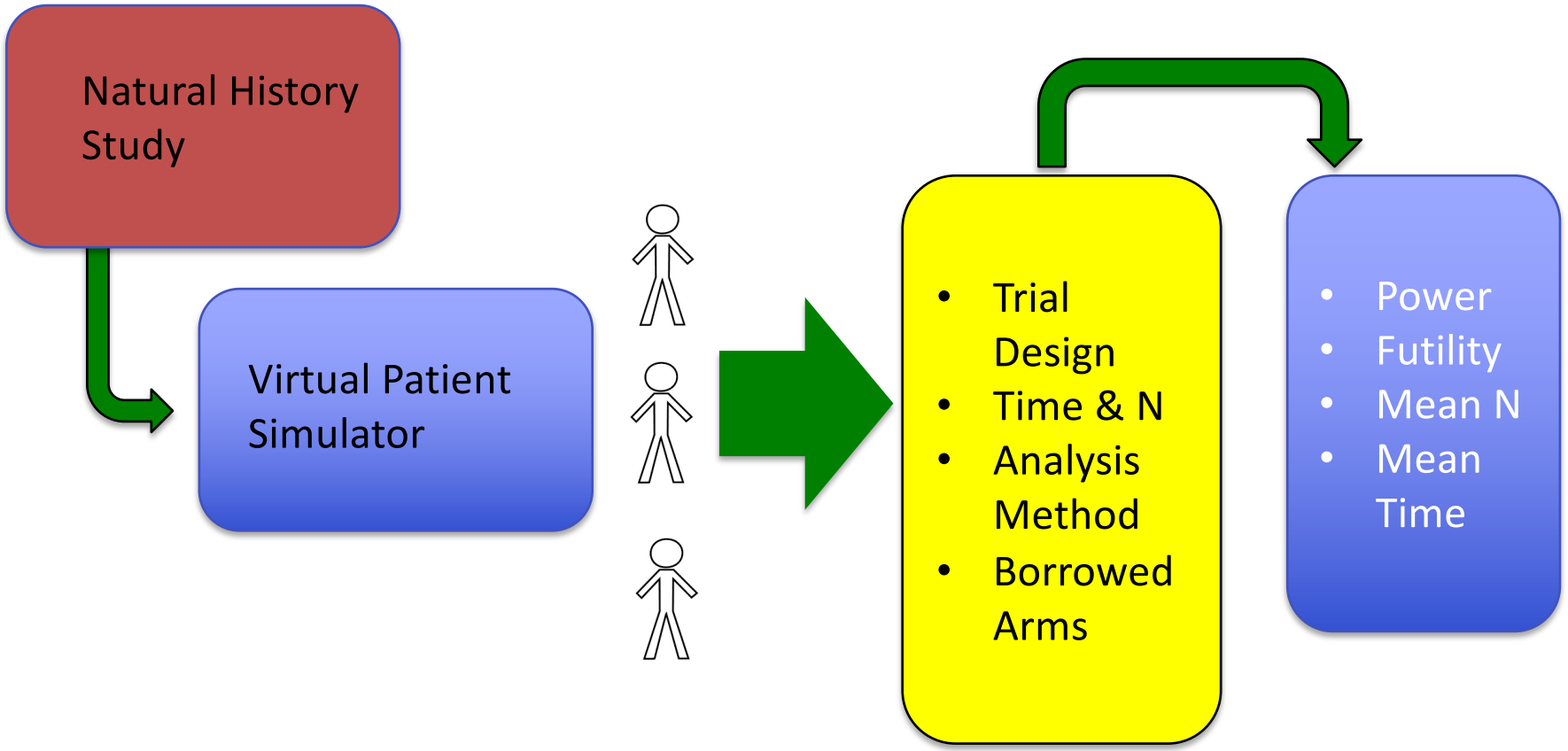
"We are disappointed by these results, as we had hoped that Ace-ER would offer a new option for GNEM patients. We would like to thank the patients, caregivers, and investigators involved in the Ace-ER development program," said Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. "This outcome does not affect our overall strategy, as the company moves forward with multiple preclinical and clinical programs and regulatory filings."

The Phase 3 Ace-ER study enrolled 89 adults with GNEM able to walk $\geq$ 200 meters in the six minute walk test. Patients were randomized 1:1 to Ace-ER at a dose of 6g/day or placebo for 48 weeks. The study did not meet the primary endpoint of demonstrating a statistically significant improvement in UEC score (+0.74 kg, p=0.5387) for Ace-ER treated patients (n=45, -2.25 kg) compared to placebo (n=43, -2.99 kg) patients for the change from baseline to 48 weeks. There were three pre-specified key secondary endpoints, including the lower extremity muscle strength composite score as measured by hand-held dynamometry (HHD), physical functioning using the Mobility domain of the GNE Myopathy-functional activity scale (GNEM-FAS), and a measure of muscle strength in knee extensors. The study did not meet any of these key secondary endpoints.

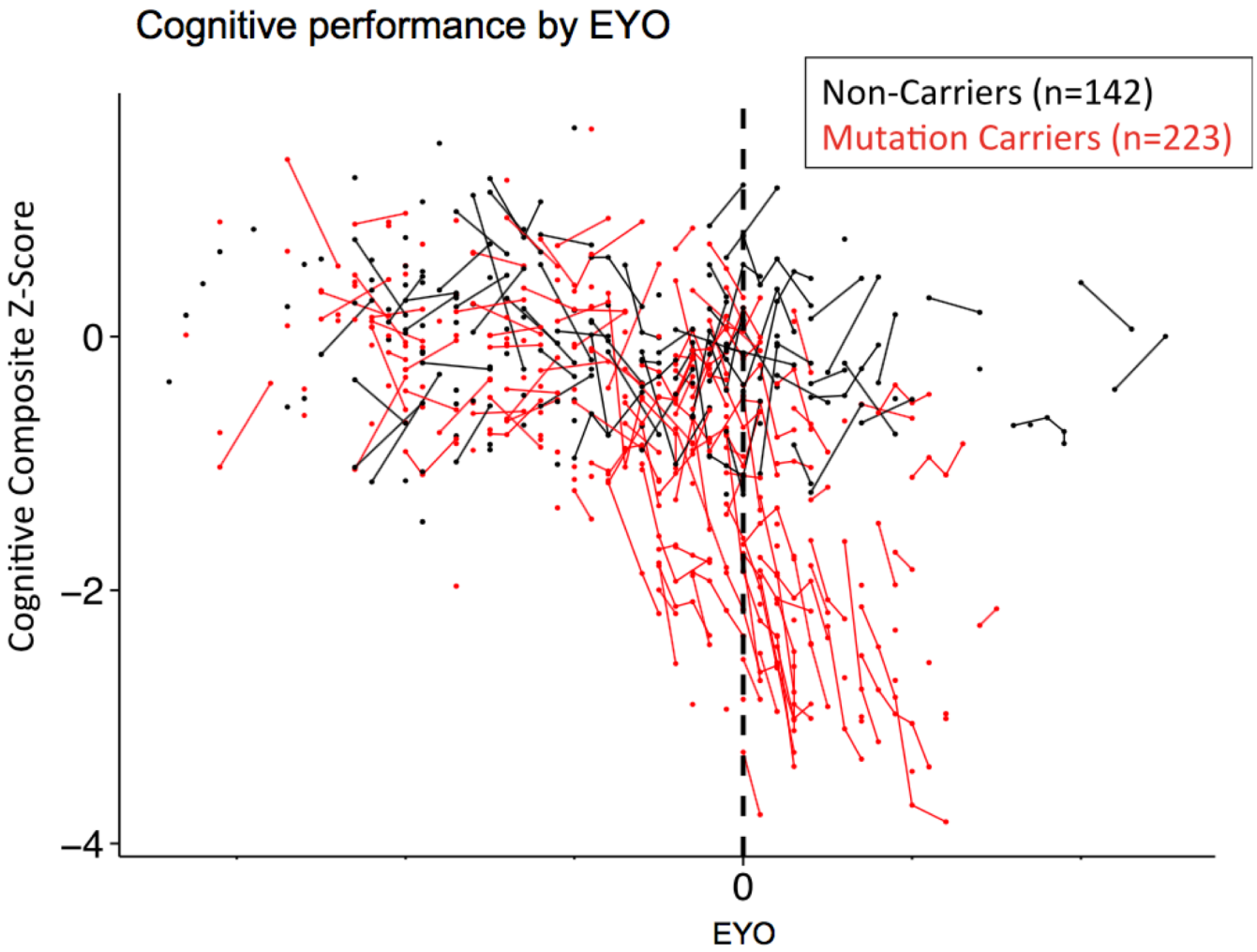
Natural History Studies

- Understand behavior of candidate primary endpoints
- Create Realistic Evidence-Based Virtual Patient Simulator
- Understand Power / Operating Characteristics of Proposed Design

Virtual Patient Simulations



DIAN Observational Data



DIAN Disease Progression

$$Y_{ij} = \gamma_i + f\left(EYO_{ij} + \delta_i|\alpha\right) + \epsilon_{ij}$$

$$f(x) = \begin{cases} 0 & x \leq -15 \\ (1 + \lfloor x \rfloor - x)\alpha_{\lfloor x \rfloor} + (x - \lfloor x \rfloor)\alpha_{\lfloor x \rfloor + 1} & -15 < x \leq 15 \\ \alpha_{15} & x > 15 \end{cases}$$

- Expected progression as a function of EYO
  - Monotonically decreasing spline with knots at each integer value for EYO between -15 and +15
  - Subject-level random effect for the adjustment in the estimated age of onset (EYO_{ij})
  - Subject-level random effect for the cognitive score at the healthy stage EYO < -15

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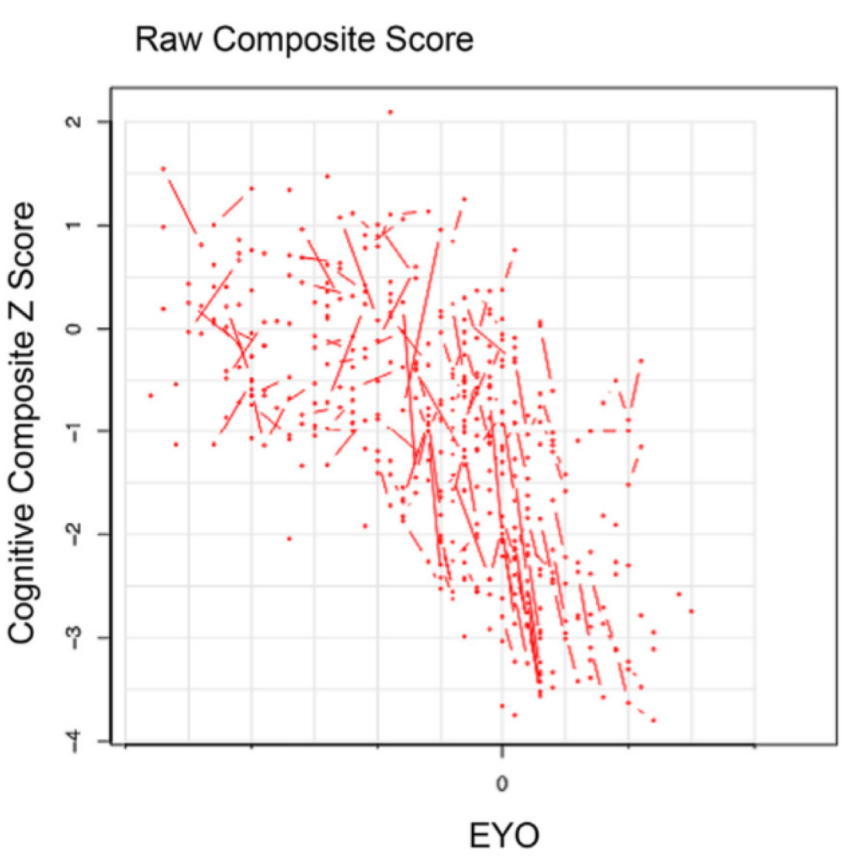
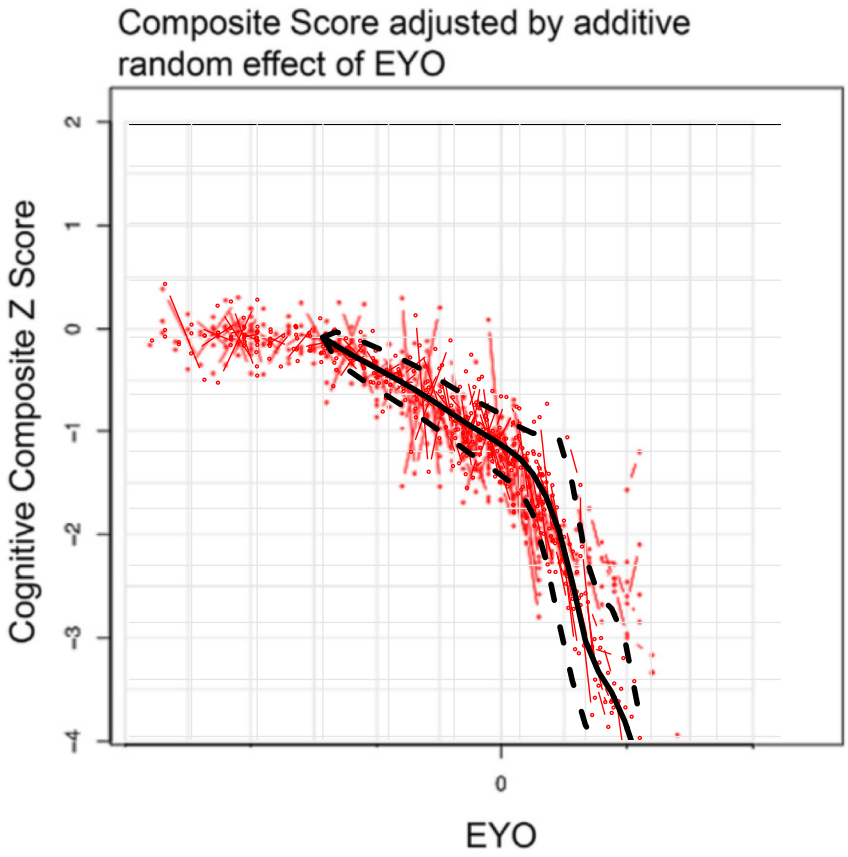
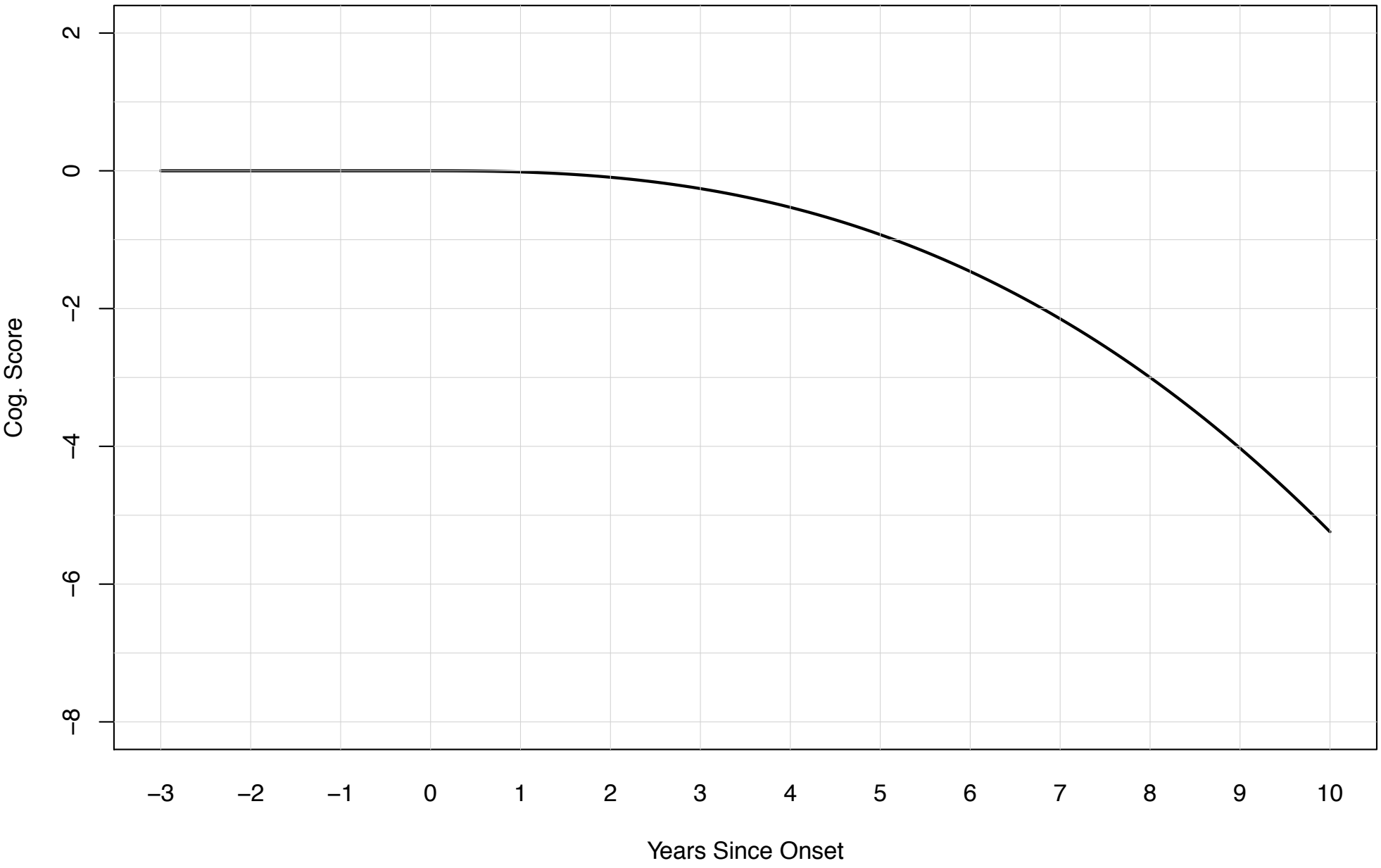
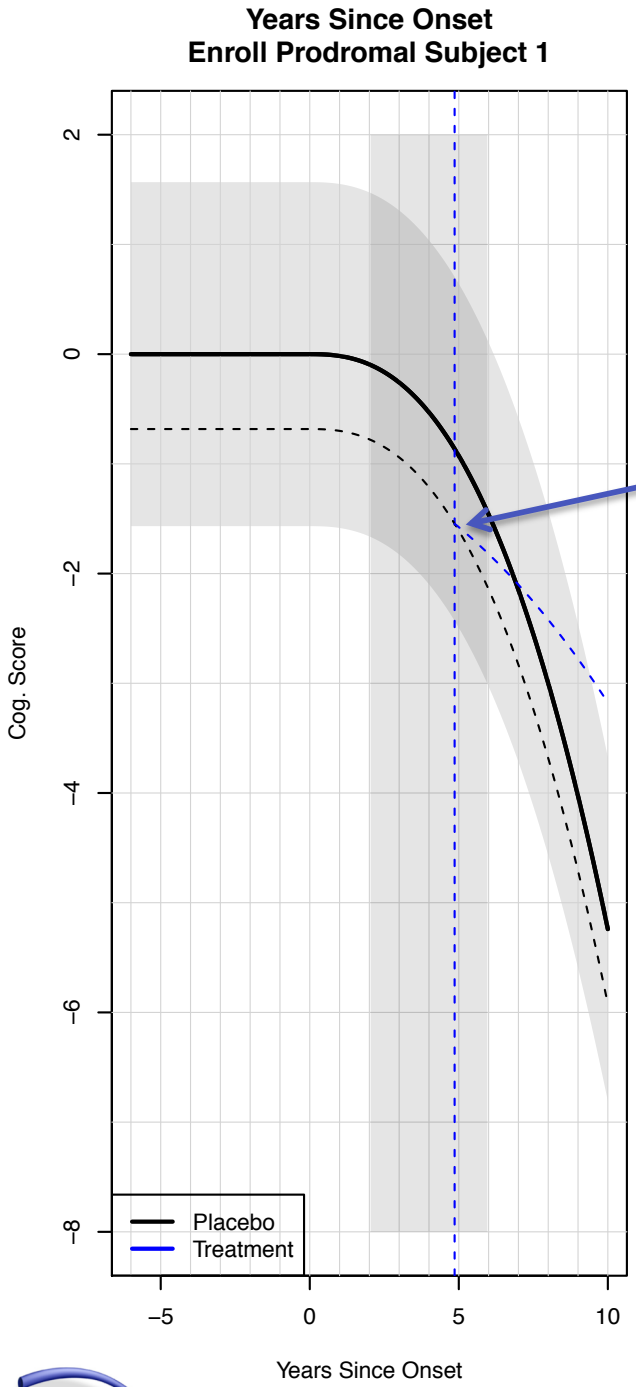
DIAN Disease Progression





Natural Cognitive Decline



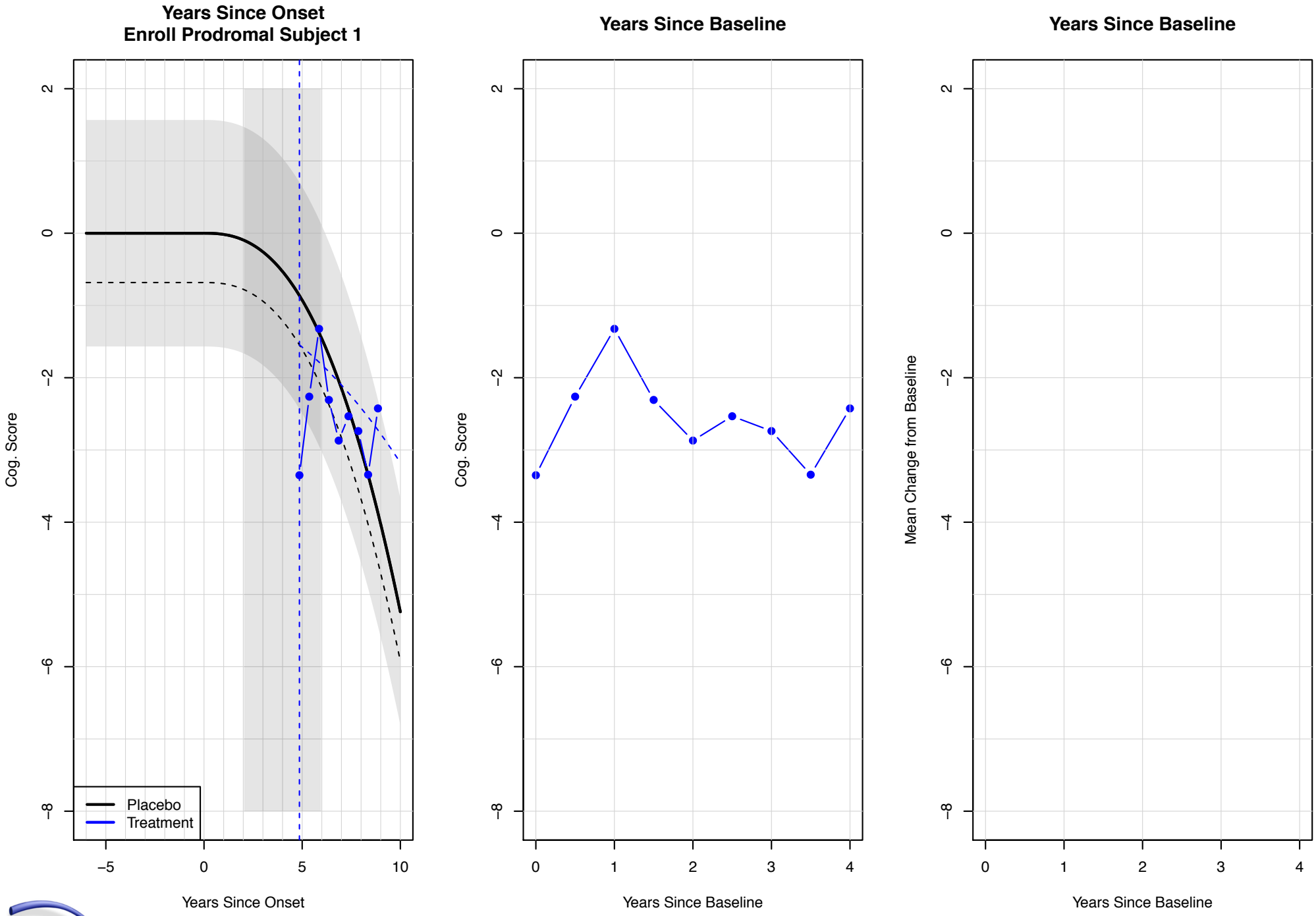


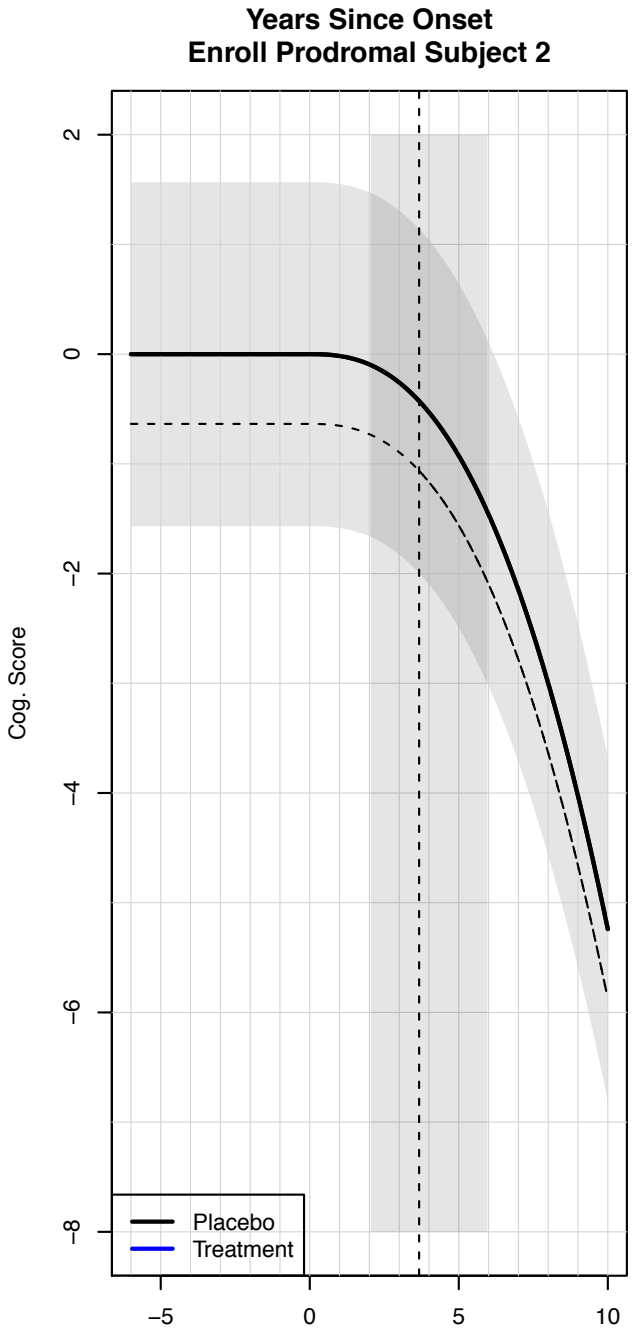
Subject 1:

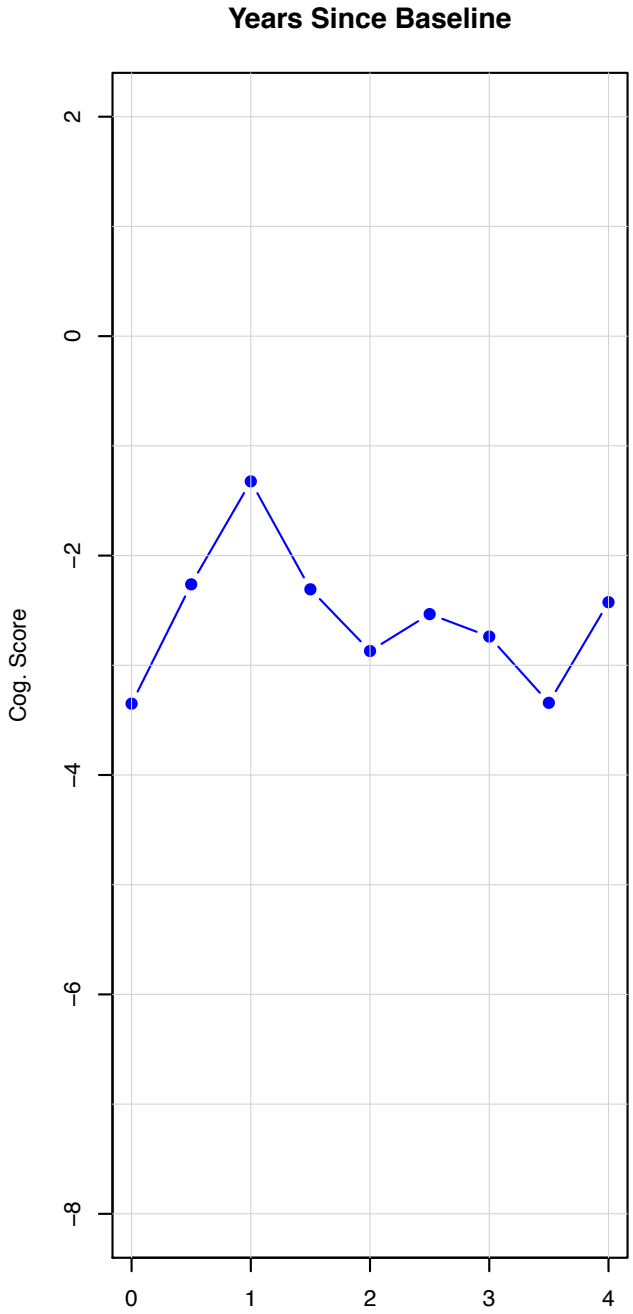
Subject-level random effect: -.8

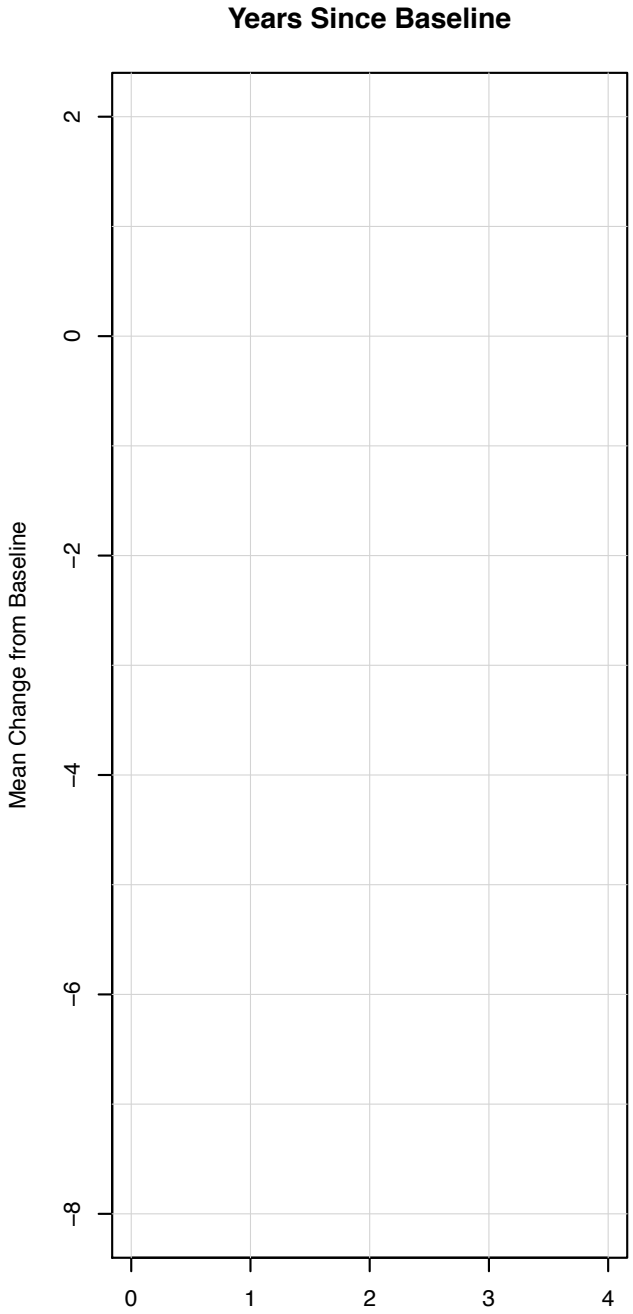
Years since onset at enrollment: 5

Enrolled to treatment group


Years Since Onset
Enroll Prodromal Subject 1
Cog. Score
2
0
−2
−4
−6
−8
−5
0
5
10
Placebo
Treatment
Years Since Onset
Years Since Baseline
Cog. Score
0
1
2
3
4
Years Since Baseline
Years Since Baseline
Mean Change from Baseline
Years Since Baseline


Years Since Onset
Enroll Prodromal Subject 2
Cog. Score
2
0
−2
−4
−6
−8
−5
0
5
10
Placebo
Treatment
Years Since Onset


Years Since Baseline
Cog. Score
2
0
−2
−4
−6
−8
0
1
2
3
4
Years Since Baseline


Years Since Baseline
Mean Change from Baseline
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0
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−4
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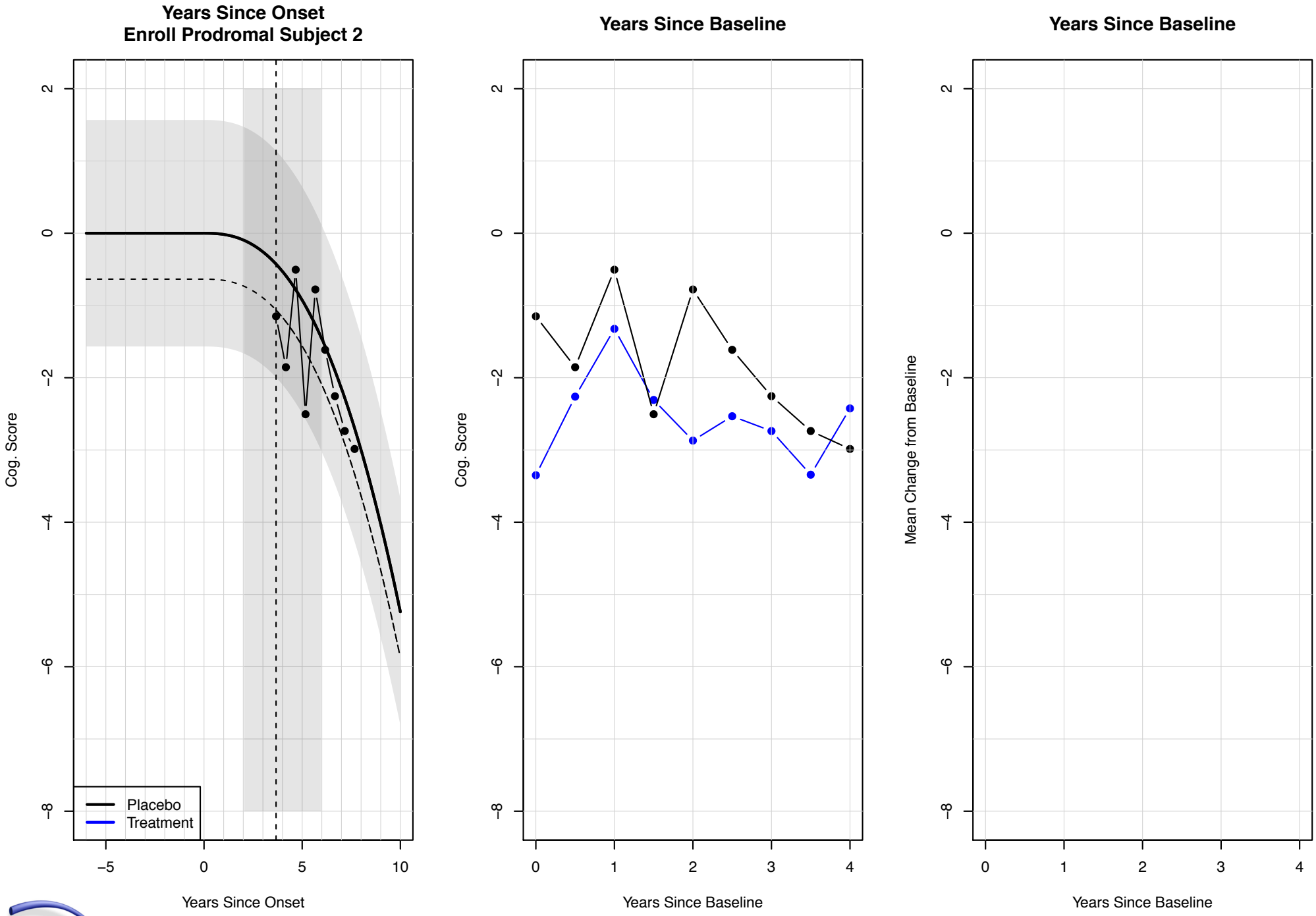
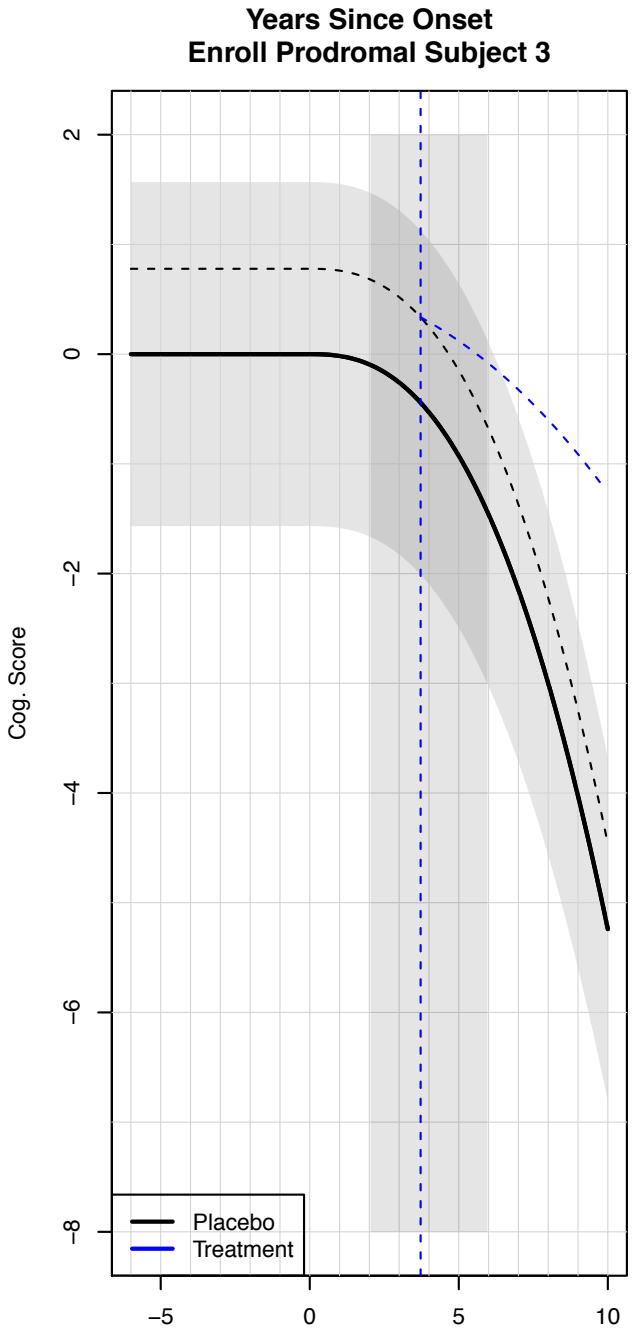
−8
0
1
2
3
4
Years Since Baseline


Years Since Onset
Enroll Prodromal Subject 2
Cog. Score
2
0
−2
−4
−6
−8
−5
0
5
10
Placebo
Treatment
Years Since Onset
Years Since Baseline
Cog. Score
0
1
2
3
4
Years Since Baseline
Years Since Baseline
Mean Change from Baseline
Years Since Baseline


Years Since Onset
Enroll Prodromal Subject 3
Cog. Score
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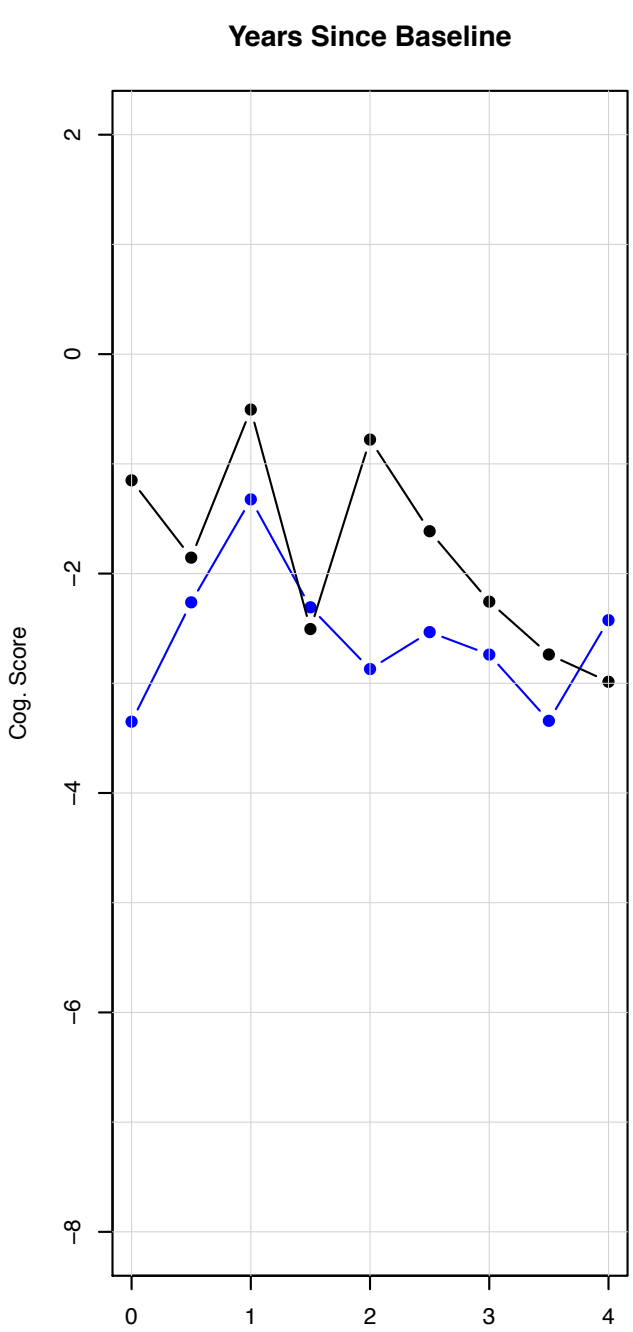
0
−2
−4
−6
−8
−5
0
5
10
Placebo
Treatment
Years Since Onset


Years Since Baseline
Cog. Score
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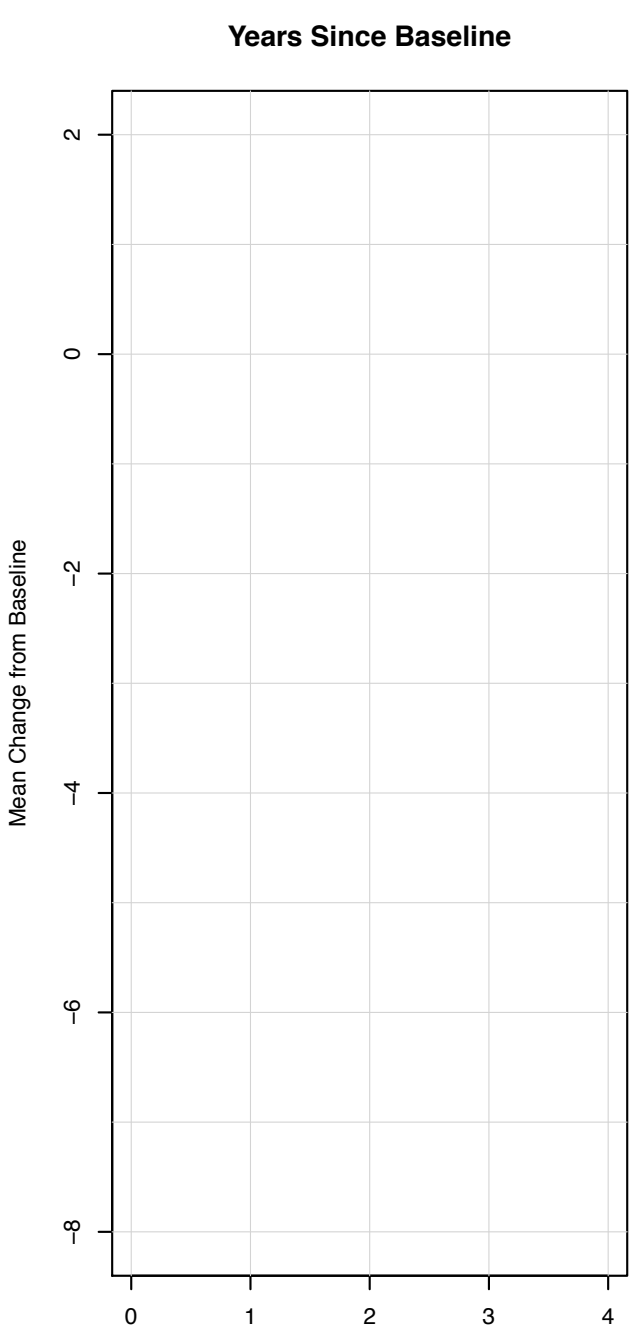
3
4
Years Since Baseline


Years Since Baseline
Mean Change from Baseline
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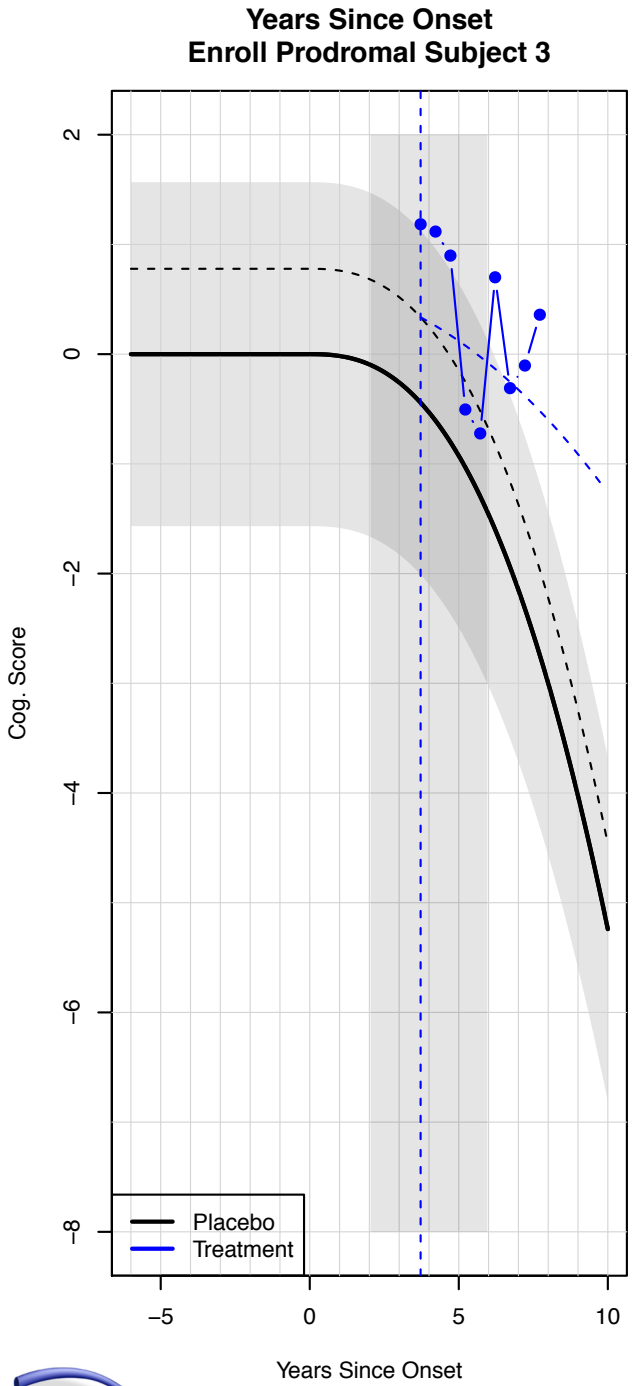
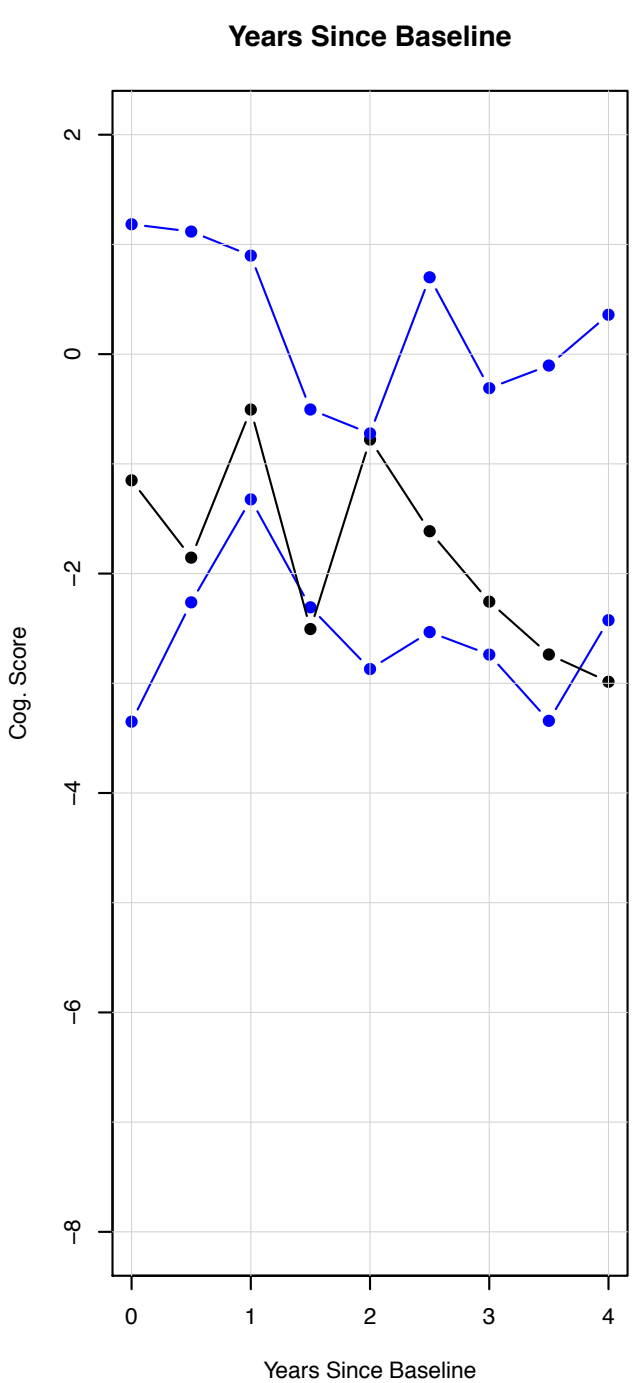
0
1
2
3
4
Years Since Baseline


Years Since Onset
Enroll Prodromal Subject 3
Cog. Score
2
0
−2
−4
−6
−8
−5
0
5
10
Years Since Onset
Placebo
Treatment


Years Since Baseline
Cog. Score
2
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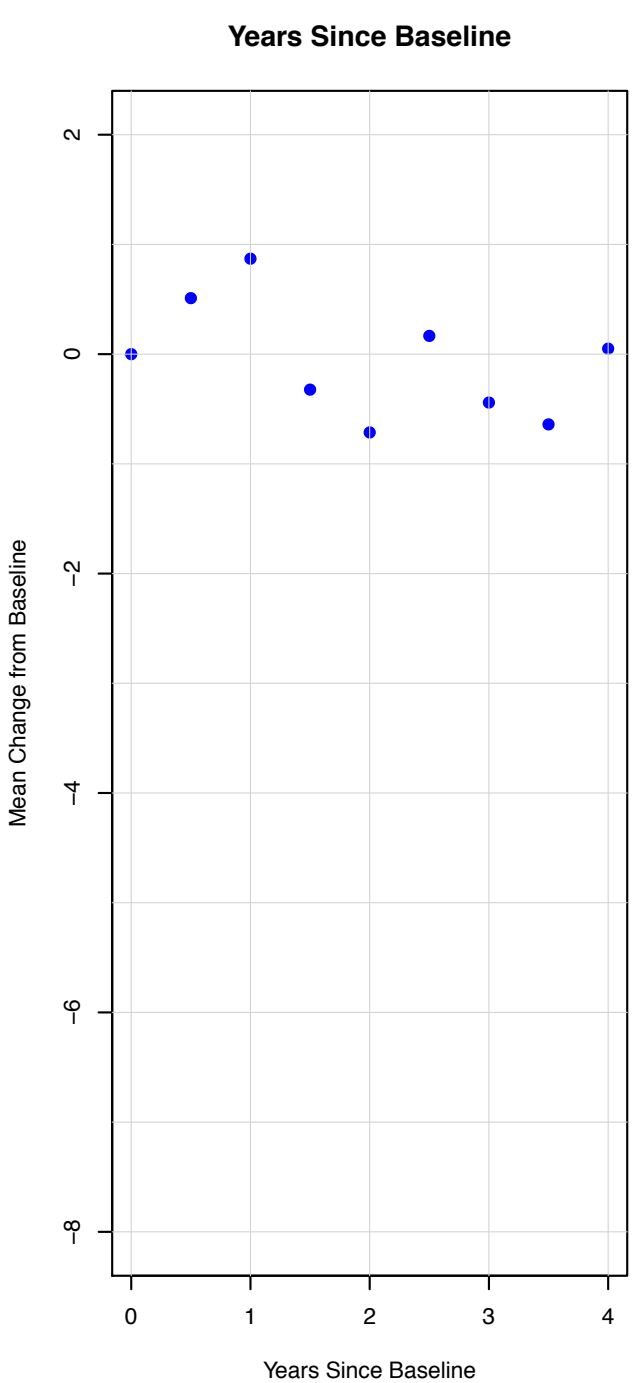
Years Since Baseline


Years Since Baseline
Mean Change from Baseline
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2
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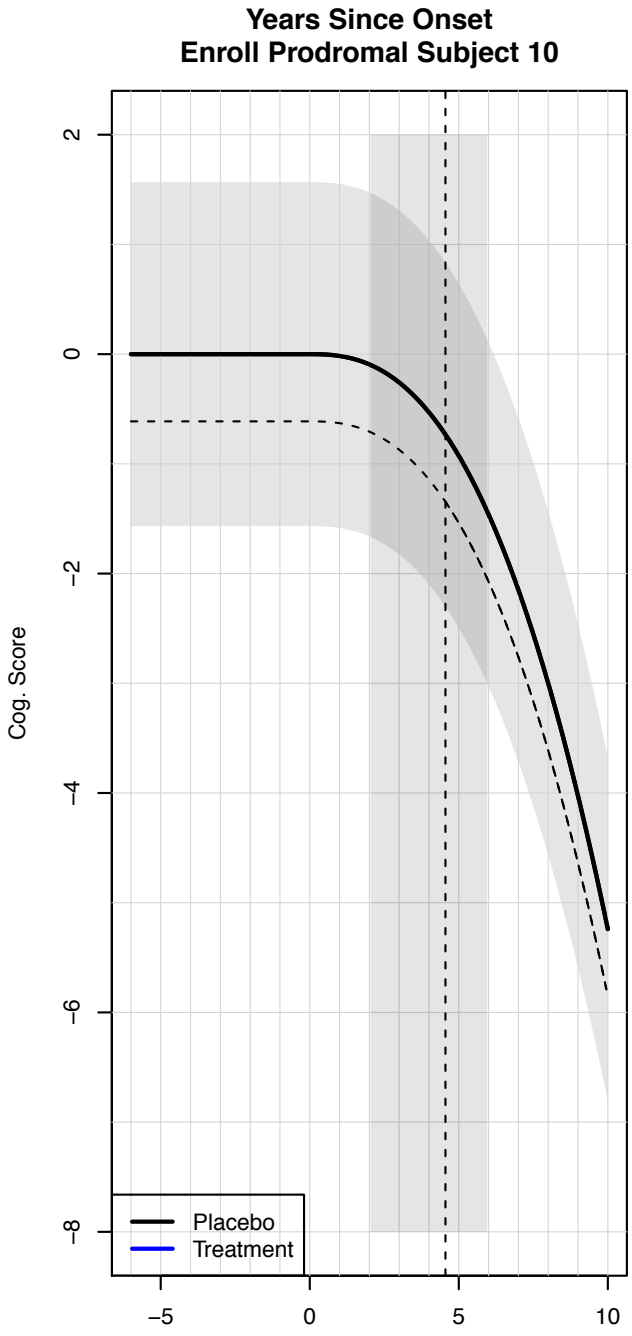
Years Since Baseline


Years Since Onset
Enroll Prodromal Subject 10
Cog. Score
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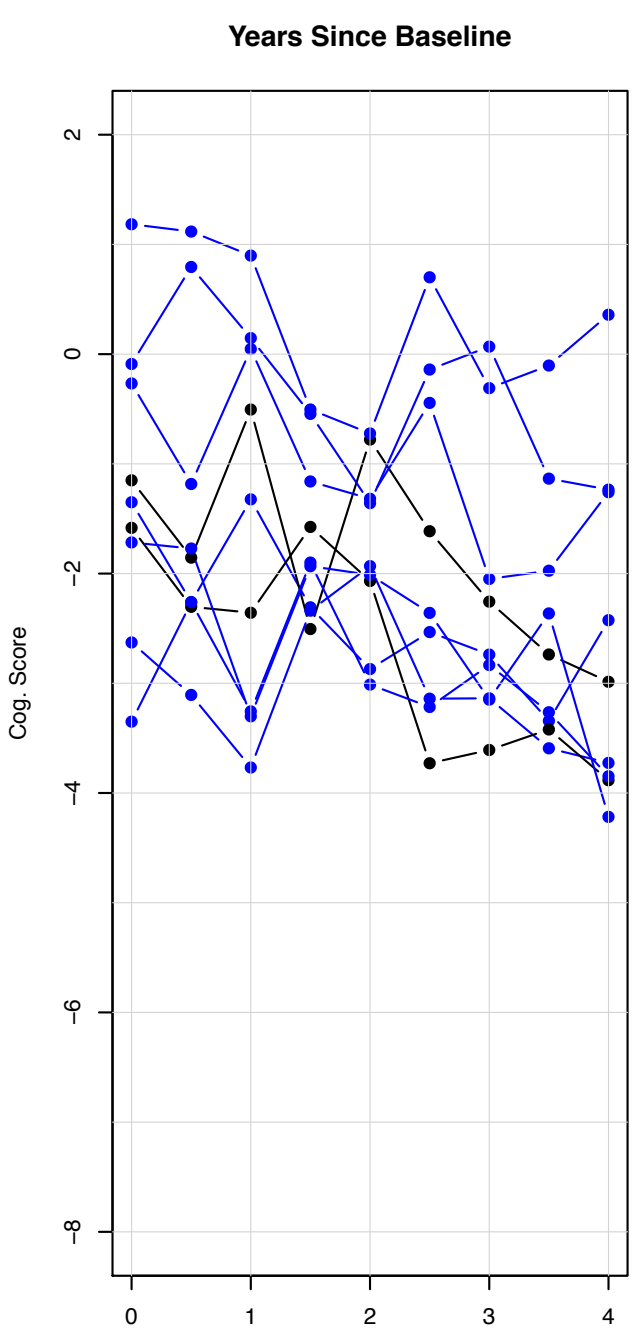
−2
−4
−6
−8
−5
0
5
10
Years Since Onset
Placebo
Treatment


Years Since Baseline
Cog. Score
2
0
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1
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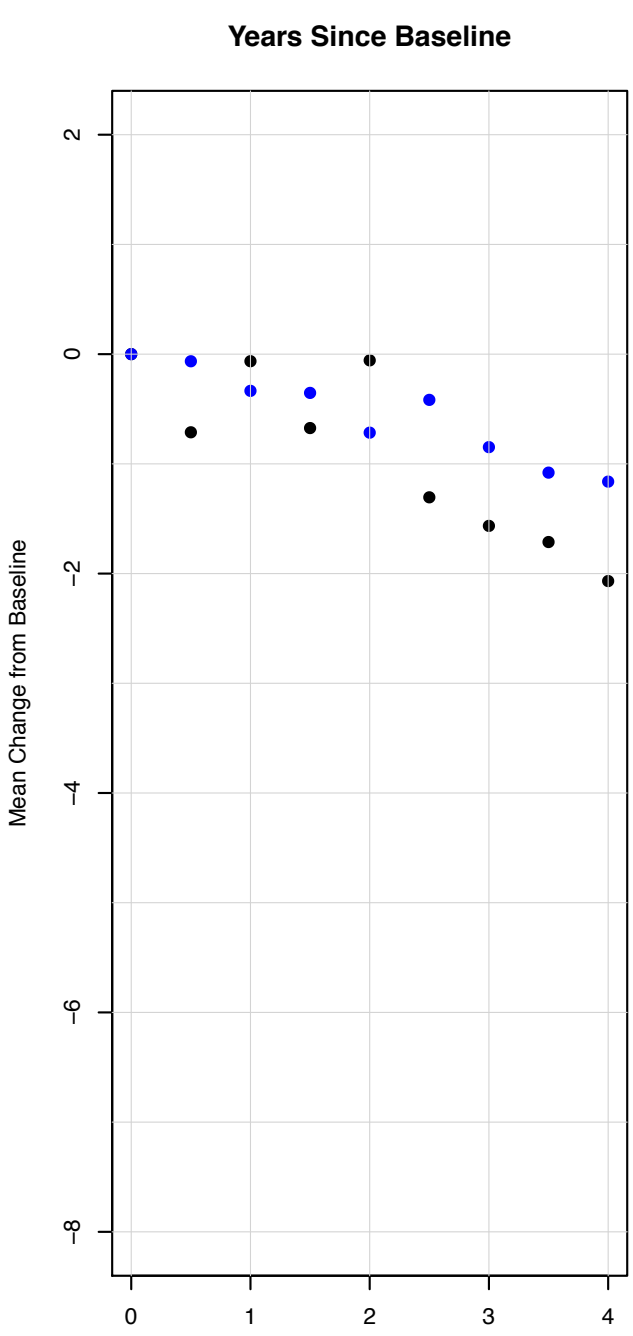
Years Since Baseline


Years Since Baseline
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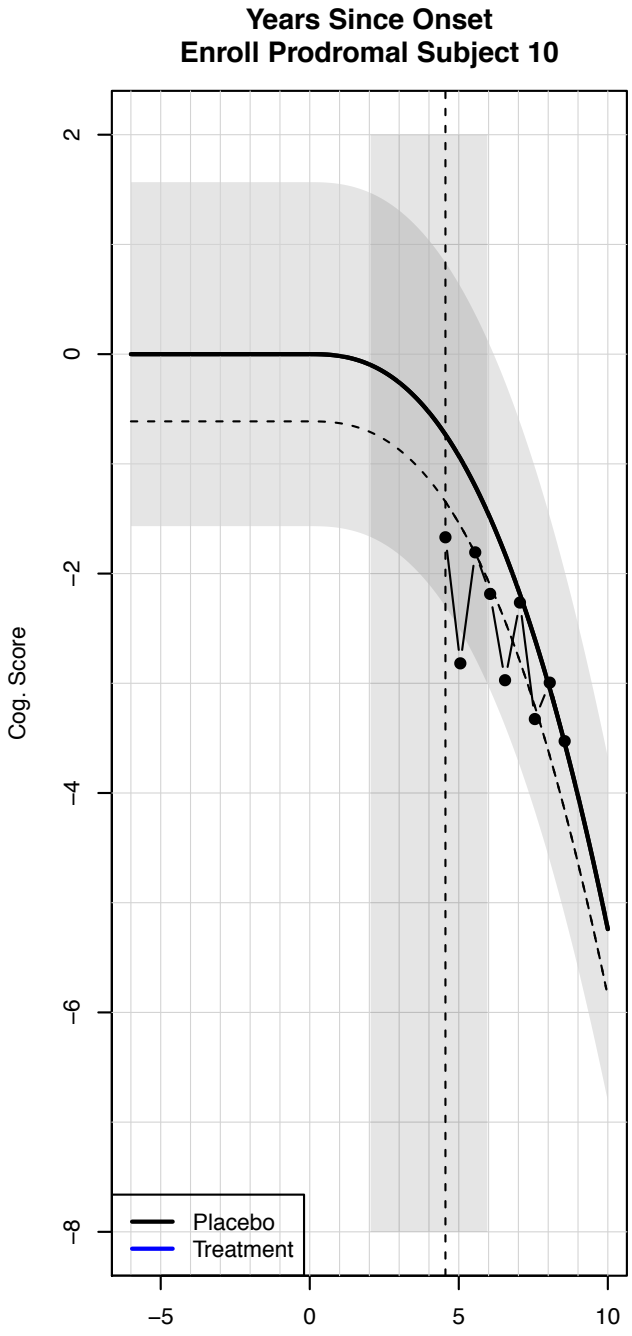
Years Since Baseline


Years Since Onset
Enroll Prodromal Subject 10
Cog. Score
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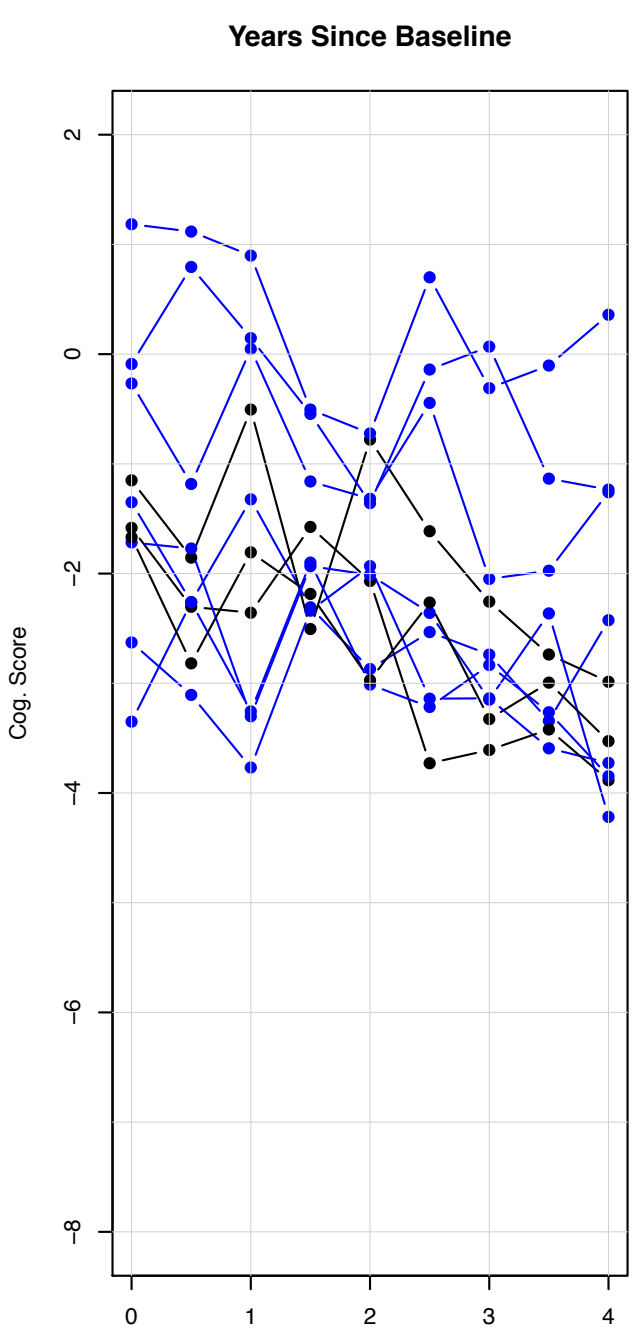
Years Since Onset
Placebo
Treatment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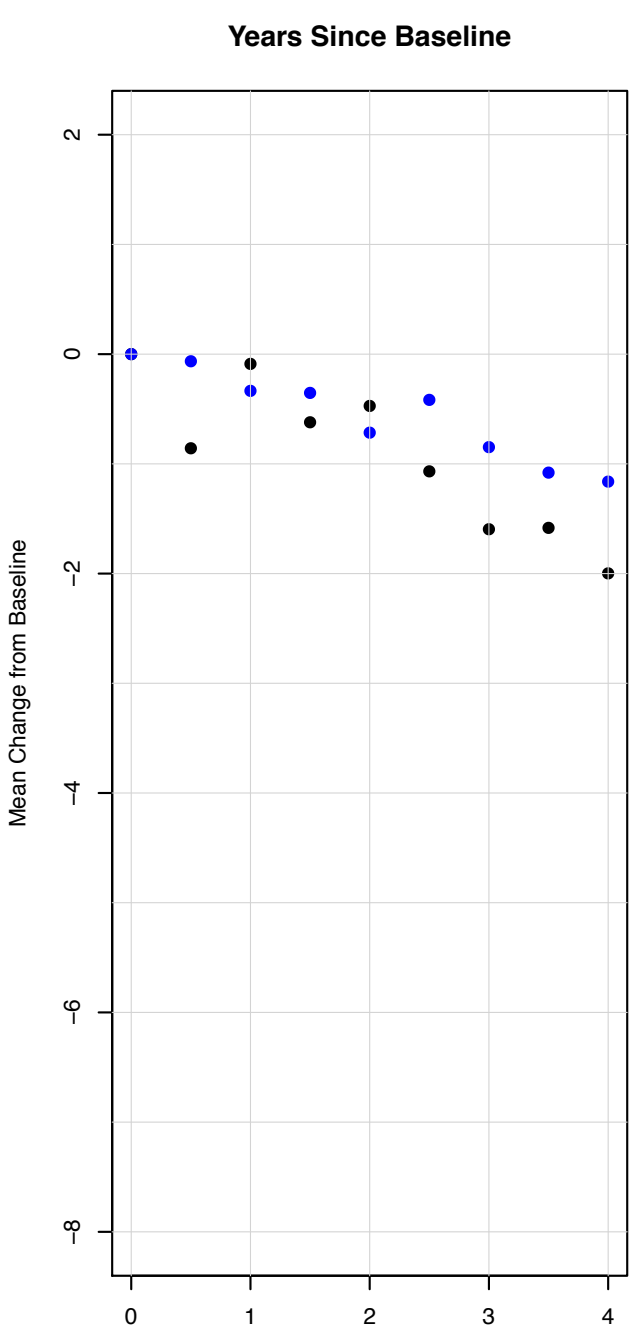
Years Since Baseline
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0
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Years Since Baseline

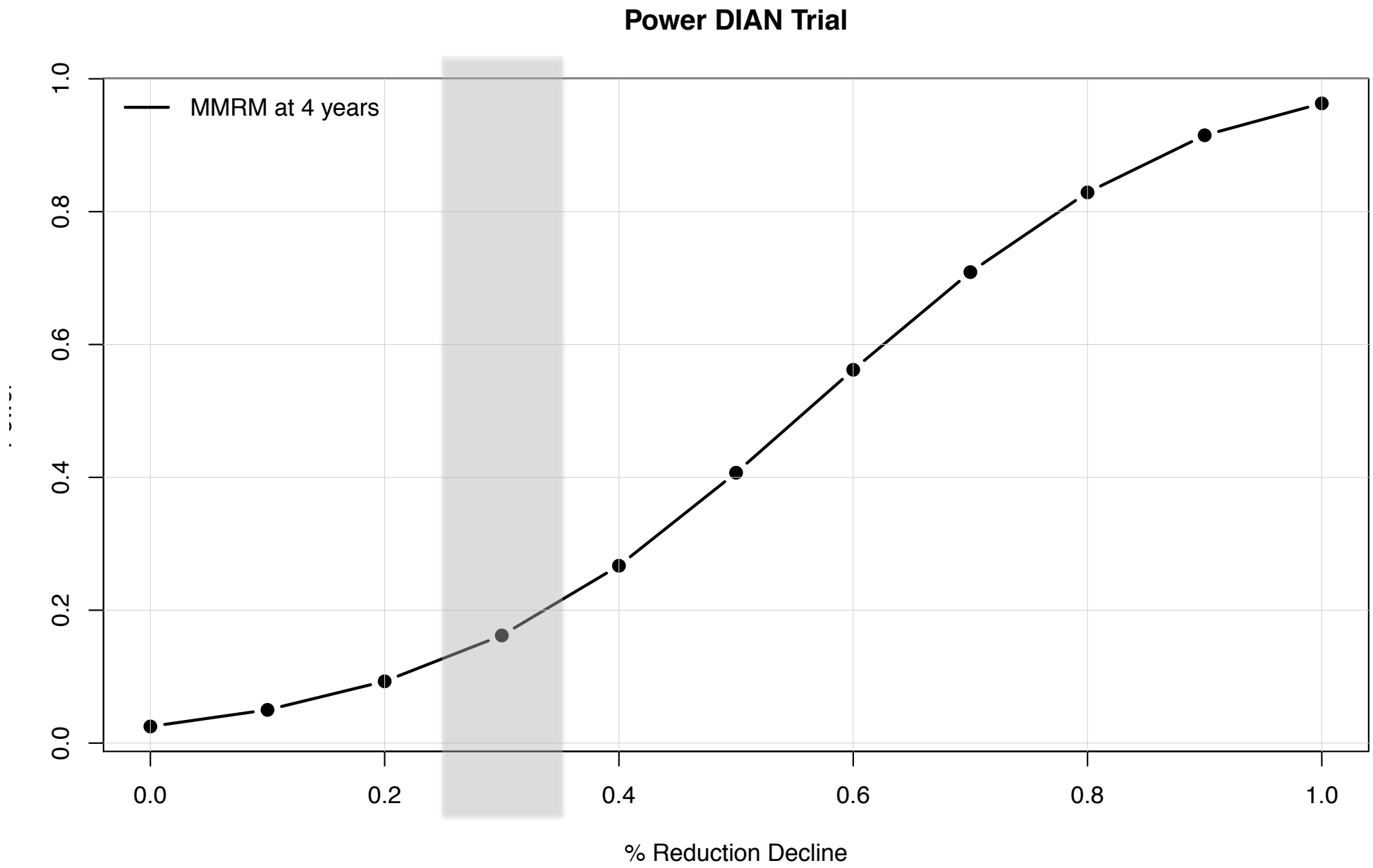
Natural History Studies

- Understand behavior of candidate primary endpoints
- Create Realistic Evidence-Based Virtual Patient Simulator
- Understand Power / Operating Characteristics of Proposed Design

DIAN Initial Proposed Design

Proposed Design:

- 80 subjects per arm randomized 3:1 (Treatment: Control)
- Max length of follow-up: 4 years
- Primary Analysis Method: MMRM


Power DIAN Trial
MMRM at 4 years
0.0
0.2
0.4
0.6
0.8
1.0
% Reduction Decline

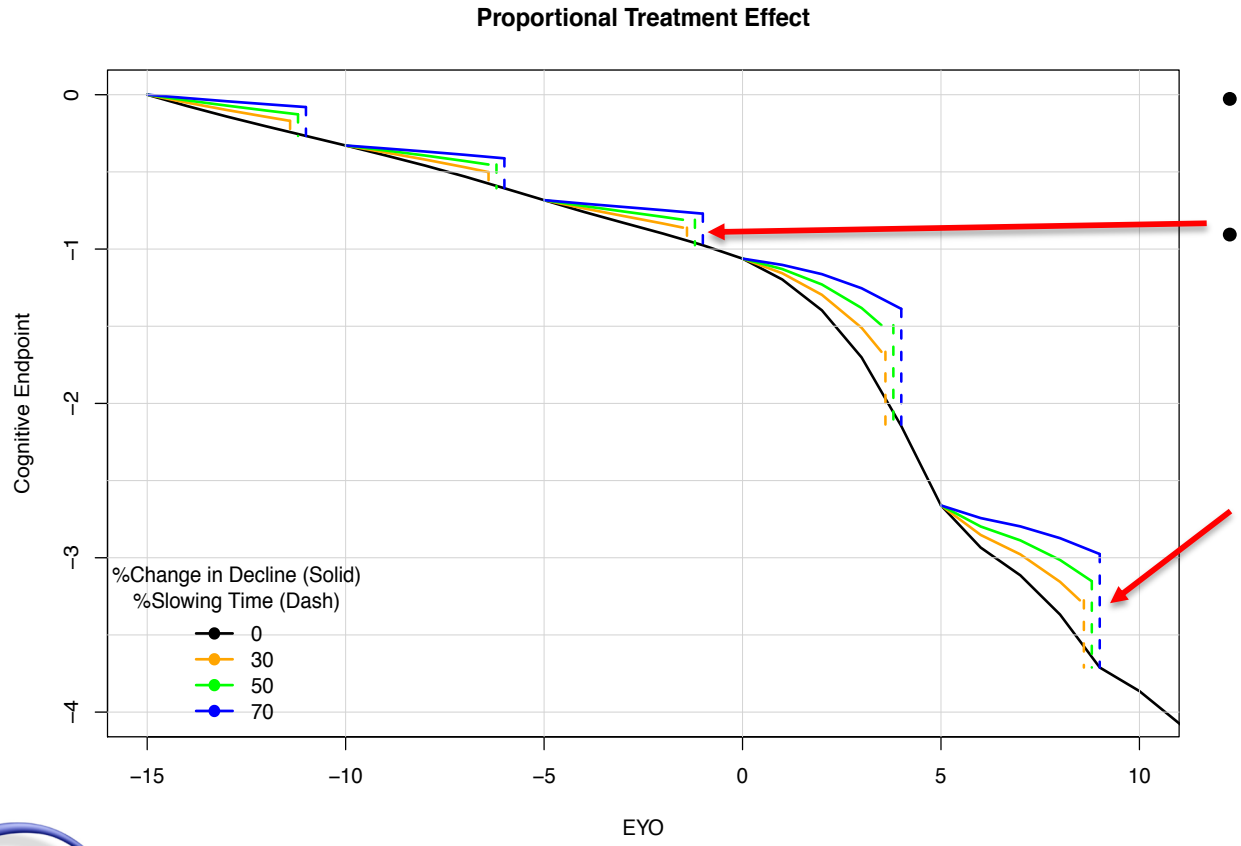
DESIGN INNOVATIONS

Common Primary Analysis: MMRM

- MMRM Issues :
  - Dilution of effect due to subjects not expected to progress (very early or very late disease)
  - Test effect at a single time point

Disease Progression Modification Analysis

- *DPMA: Assume proportional treatment effect at each EYO*

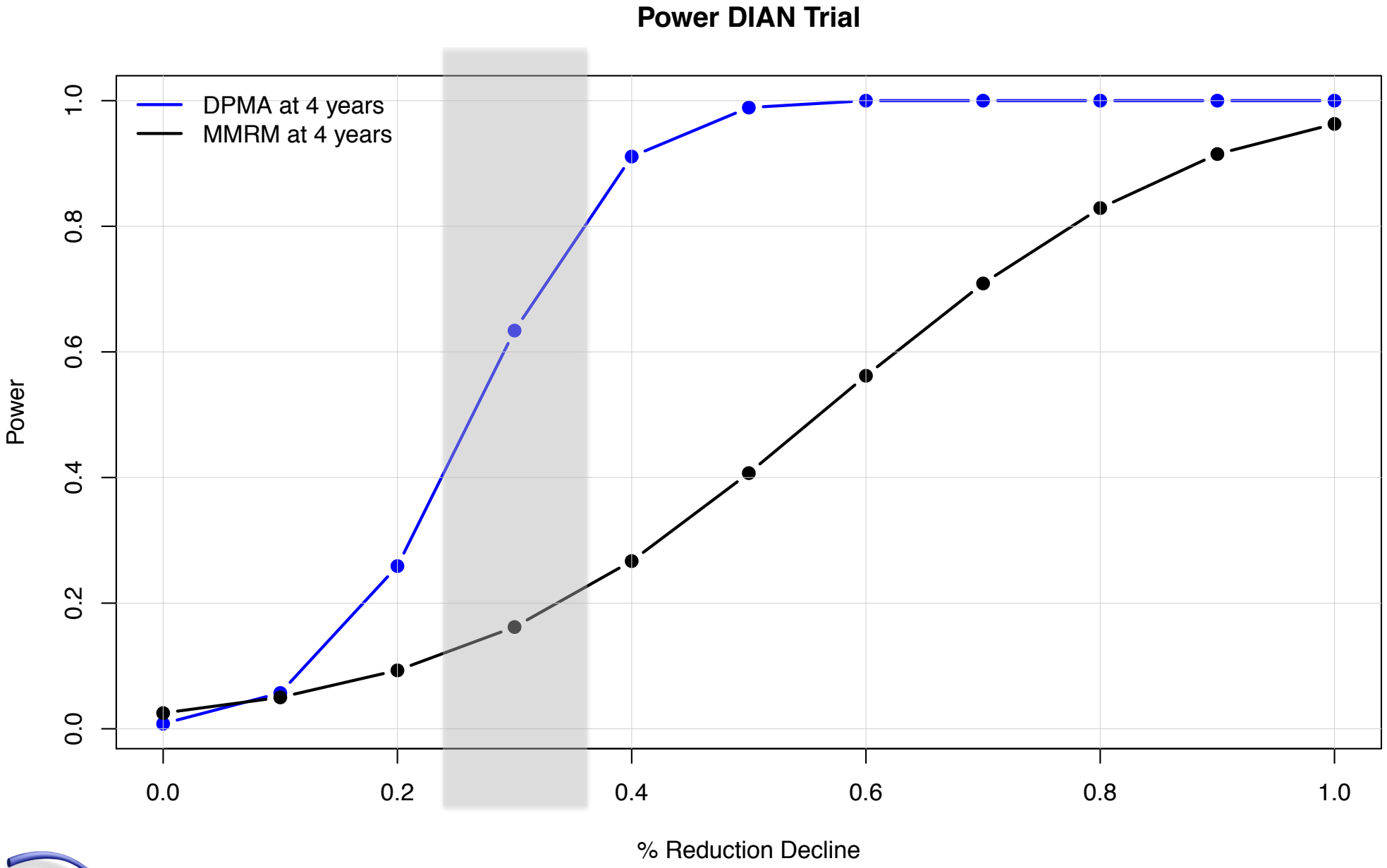


- Proportional to the expected decline on control
- 50% Treatment effect
  - **EYO -5**: Abs. Δ = .125
  - **EYO 5**: Abs. Δ = .4

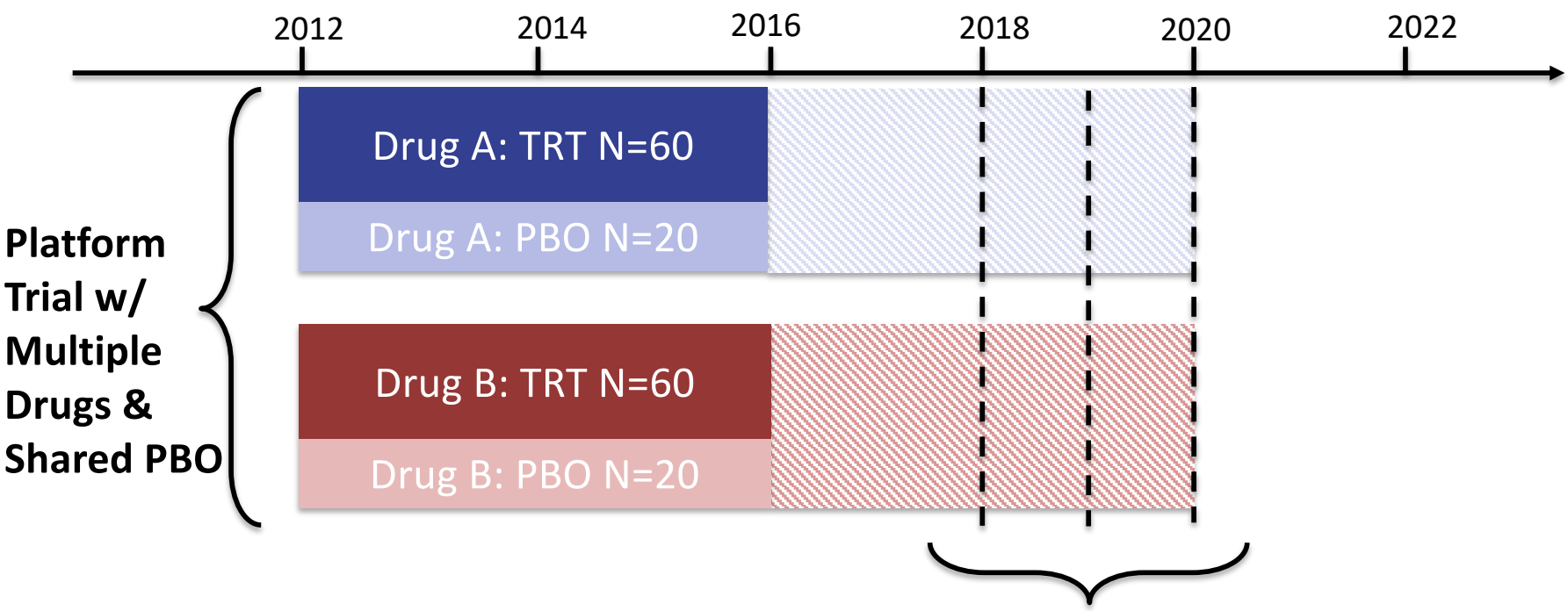
Disease Progression Modification Analysis

- *DPMA: Assume proportional treatment effect at each EYO*
  - Adjusts for expected decline given EYO
  - Uses all timepoints
    - Incorporate differential follow-up: Due to missing data; early interim analyses, extended follow-up
    - Extended follow-up = Greater Power

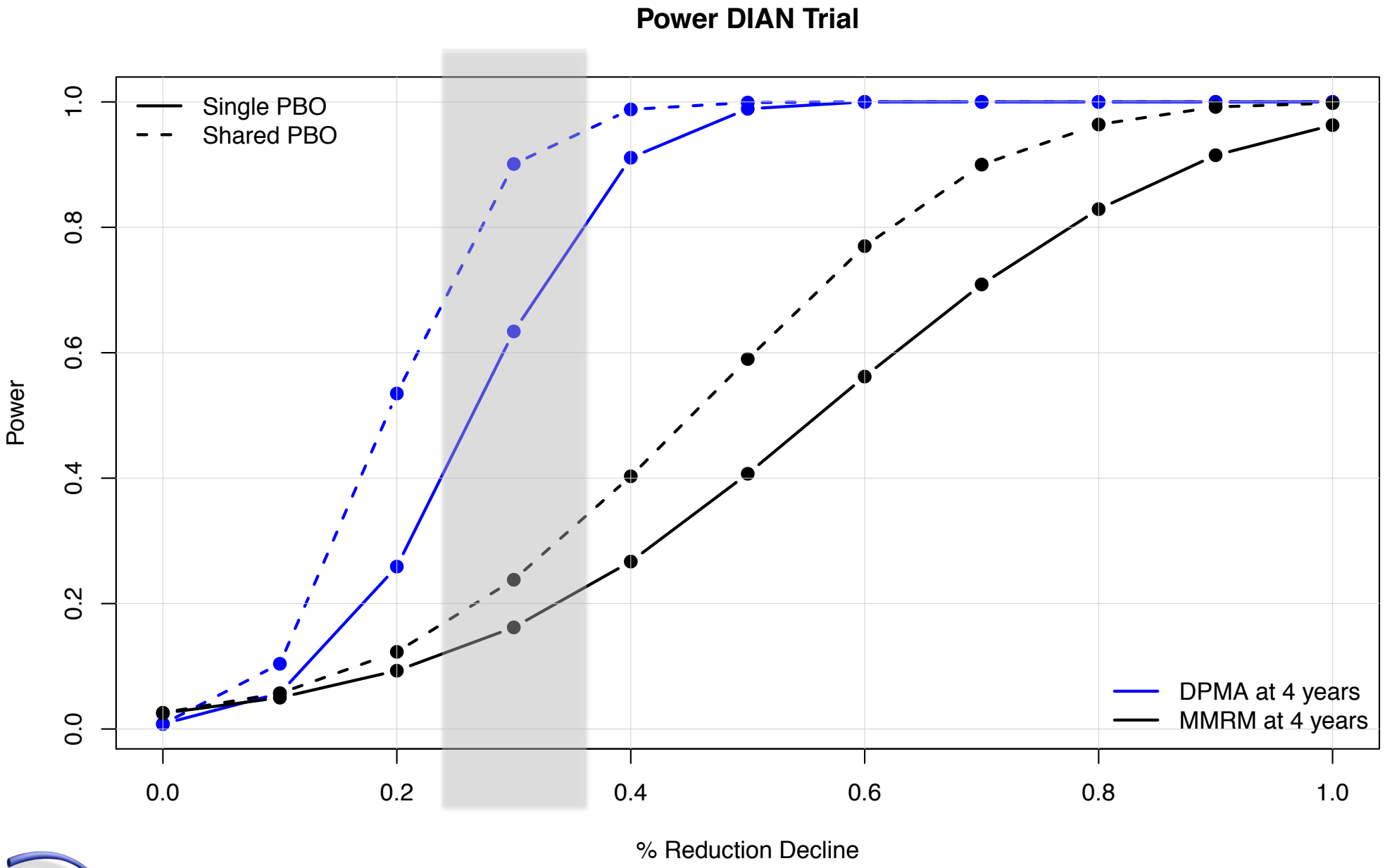
DPMA vs. MMRM


Power DIAN Trial
DPMA at 4 years
MMRM at 4 years
Power
0.0
0.2
0.4
0.6
0.8
1.0
% Reduction Decline

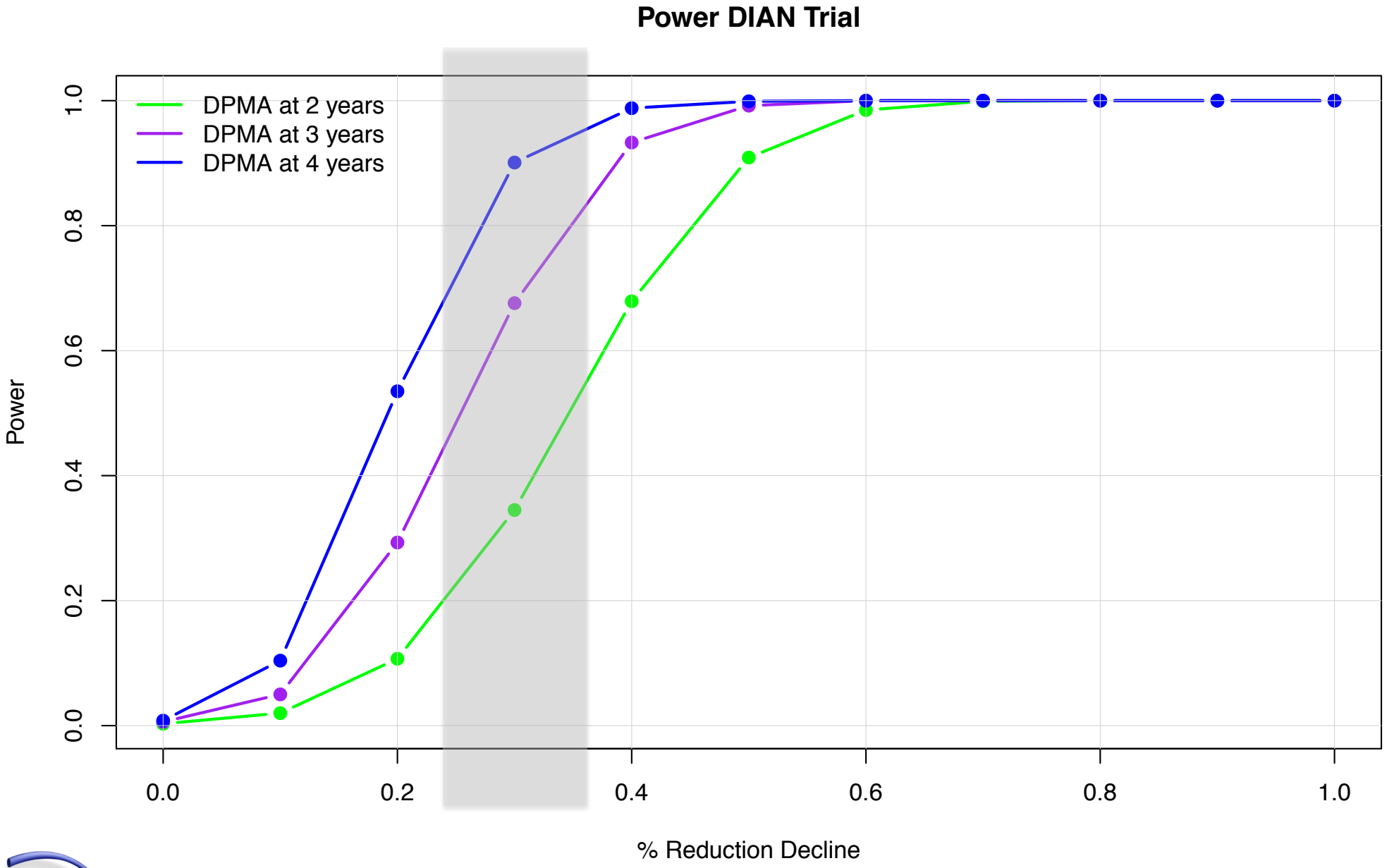
DIAN Adaptive Platform Trial



Borrowed Controls



Frequent Interim Analyses



Summary

- Natural History Studies + Clinical Trial Simulation = More Informed Trial Design!
  - Original DIAN Power = < 20%
- Need for better analysis methods that use all available data and adjust for expected progression
  - Innovative DPMA + Shared PBO leads to increase in DIAN power from <20% to > 80%!

References

- ***The DIAN-TU Next Generation Alzheimer's prevention trial: Adaptive design and disease progression model.*** Bateman, Randall J. et al. Alzheimer's & Dementia: 2017;13;1:8 – 19
- ***A novel cognitive disease progression model for clinical trials in autosomal-dominant Alzheimer's disease.*** Wang G, Berry S, Xiong C, et al. *Statistics in Medicine*. 2018;37:3047–3055.