HOCKEY STICKS AND BROKEN STICKS – A DESIGN FOR A SINGLE-TREATMENT, PLACEBO-CONTROLLED, DOUBLE-BLIND, RANDOMIZED CLINICAL TRIAL SUITABLE FOR CHRONIC DISEASES

Hans Hockey & Kristian Brock
Biometrics Matters Ltd, Hamilton, NZ
& Cancer Research UK Clinical Trials Unit, Birmingham, UK

hans@biometricsmatters.com

BBS-EFSPI meeting, Basel, 27 June 2018

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Abstract

This work is motivated and exemplified by a genetic disorder causing early onset diabetes, blindness and deafness, which is extremely rare, inevitably fatal and has no current direct treatment. While the standard placebo-controlled RCT is the gold standard required by the regulatory agency for a new proposed drug study, it is conjectured that potential study participants will prefer a design which guarantees that they are always assigned to the drug under study. A design is proposed which meets this patient need and hence probably increases recruitment and compliance. At the same time, it meets the requirement for full randomization. Analyses which follow naturally from this design are also described and were used in trial simulations for sample sizing and for examination of the effect of underlying assumptions.

Talk outline

- **Motivating example clinical trial**
- **Hockey sticks and broken sticks**
- **A proposed design**
- **Summary**

Talk outline

- **Motivating example clinical trial**

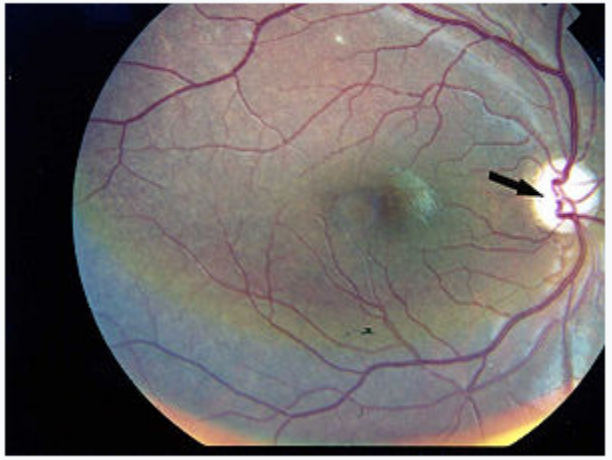
Wolfram Syndrome

Wolfram syndrome affects around 70 people in the UK

It causes loss of vision, diabetes, choking and swallowing difficulties, and brain atrophy

Wolfram syndrome

Synonyms Diabetes insipidus-diabetes mellitus-optic atrophy-deafness syndrome



Photographic image of the patient right eye showing optic atrophy without diabetic retinopathy; from Manaviat et al., 2009[1]

Treatment [edit]

There is no known direct treatment. Current treatment efforts focus on managing the complications of Wolfram syndrome.

Wolfram syndrome case study

A 31-year-old woman was diagnosed with type 1 diabetes mellitus (DM) at age 5 years and subsequently with hypothyroidism at age 16 years. She developed progressive visual loss at age 19 years and progressive hearing loss at age 28 years. She was clinically and radiologically diagnosed with Wolfram syndrome (**figures 1 and 2**). Wolfram syndrome, first described in 1938, is a rare autosomal recessive disorder.[1] It features diabetes insipidus (DI), DM, optic atrophy (OA), and deafness (D) (DIDMOAD).[1,2] It is caused by a mutation in the *WFS1* gene that encodes wolframin, a transmembrane protein of pancreatic β cells.[1] The life expectancy of patients diagnosed with this syndrome is about 30 years.

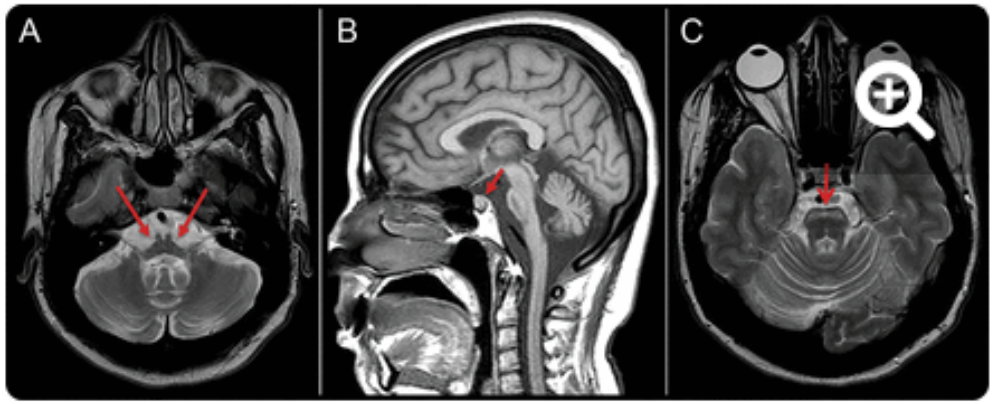


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Figure 1

Brain MRI findings of a 31-year-old woman with Wolfram syndrome

Axial T2-weighted image (A) and sagittal T1-weighted image (B) demonstrate atrophy of brainstem. Note absence of neurohypophyseal "bright signal" on sagittal T1 image (B). T2-weighted image (C) shows atrophy of cerebellum and hyperintense signal at ventral part of the pons.

The TreatWolfram study

Phase II efficacy study

MRC Medical Research Council

- A Phase II, Multicentre, International, Randomised, Double-blind, Efficacy and Safety trial of Sodium Valproate, in paediatric and adult patients with Wolfram syndrome
- **Primary objective (A)**
  - To determine efficacy of sodium valproate on clinical parameters:
    - Visual acuity
    - MRI Pons Volume
- **Primary objective (B)**
  - To assess the safety and tolerability of sodium valproate administered orally at a maximum dose of 40mg/kd/day in divided doses in patients with Wolfram syndrome.
- To show efficacy of valproate with 80% power to detect at least a 60% reduction in rate of progression of visual acuity and brainstem volume

The TreatWolfram study

- Treatment with sodium valproate, an epilepsy drug
- Double-blind, randomised, placebo-controlled trial
- International (4 countries)
- Children and adults
- Endpoint: Visual acuity (VA) – logMAR
- N=70 (2:1) gives 80% power to detect 50% lower rate of progression in VA with mixed model analysis
- VA will be assessed at baseline and every 6 months

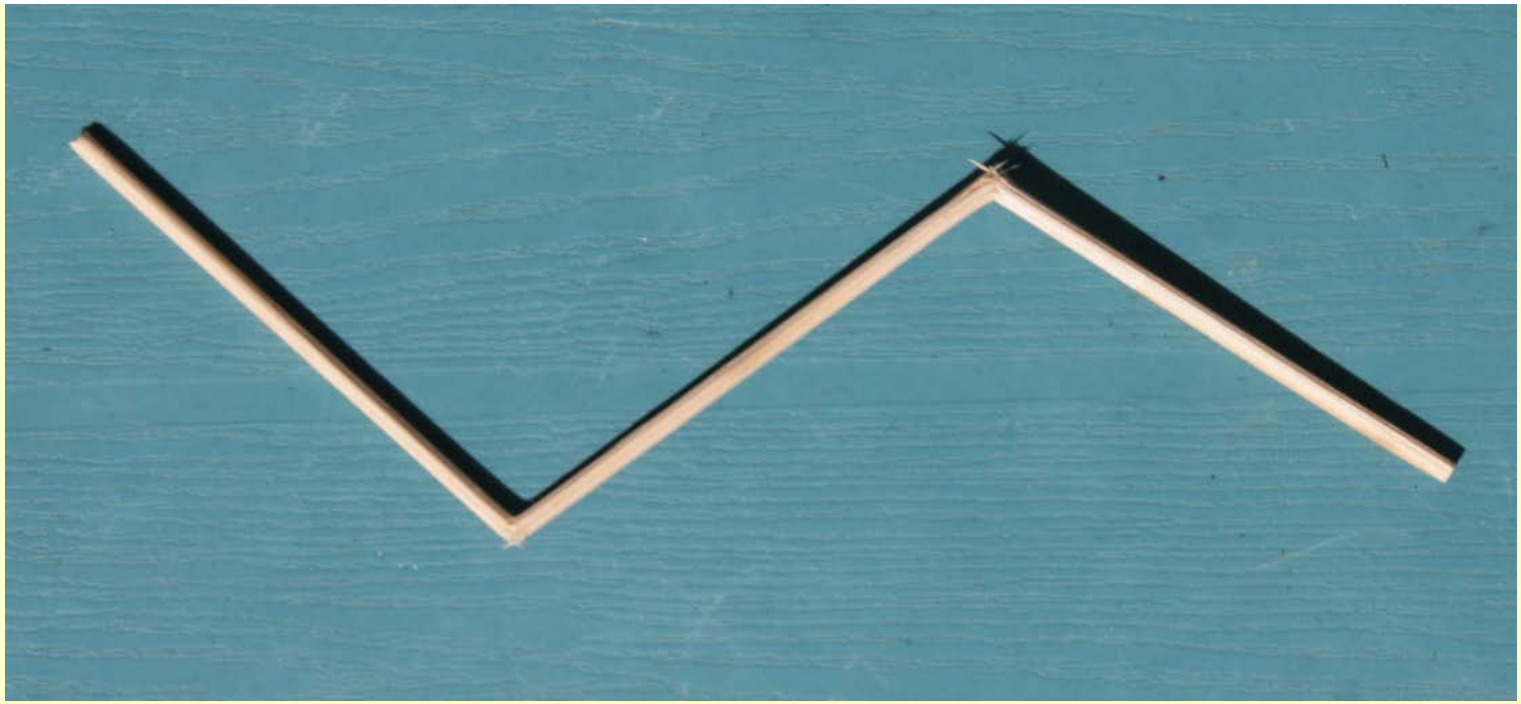
t = (0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0) years

Talk outline

- Motivating example clinical trial
- **Hockey sticks and broken sticks**

What are hockey sticks and broken sticks?

What are hockey sticks and broken sticks?



This is not a hockey stick

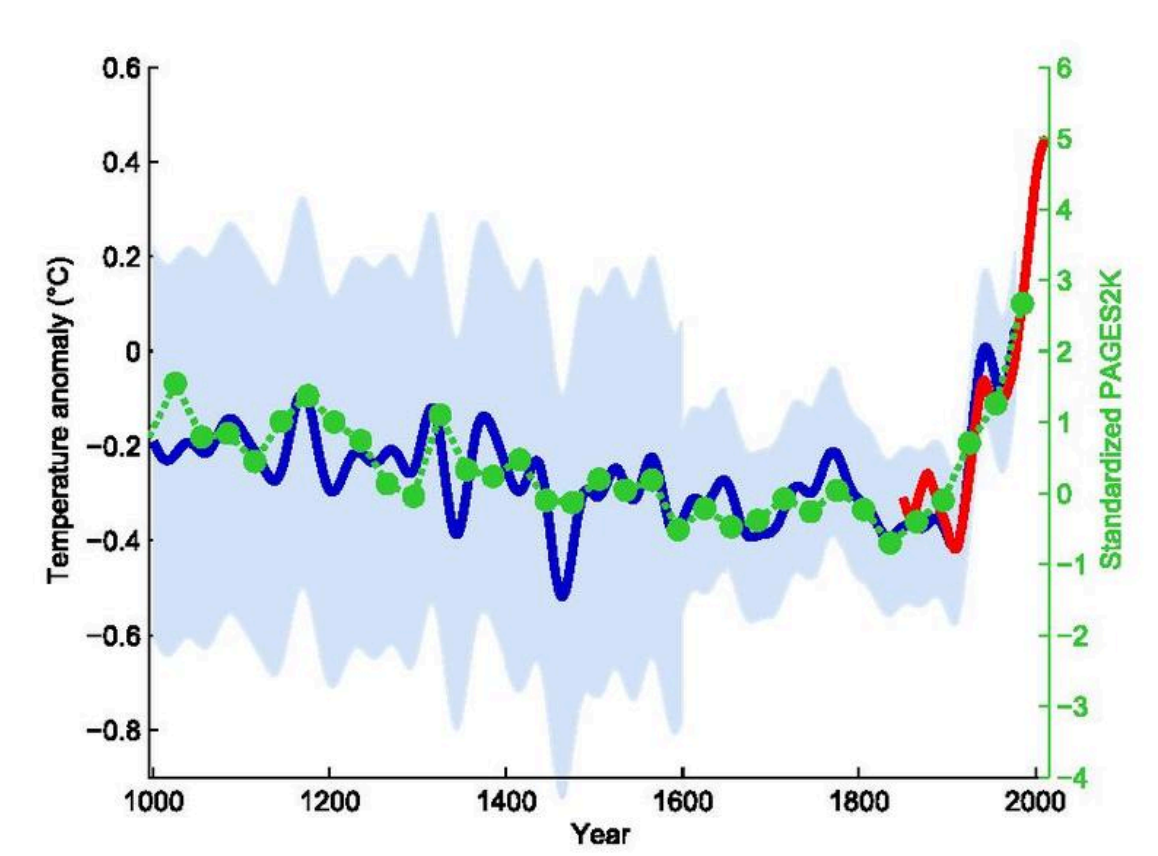
with apologies to René Magritte

This is the most famous hockey stick

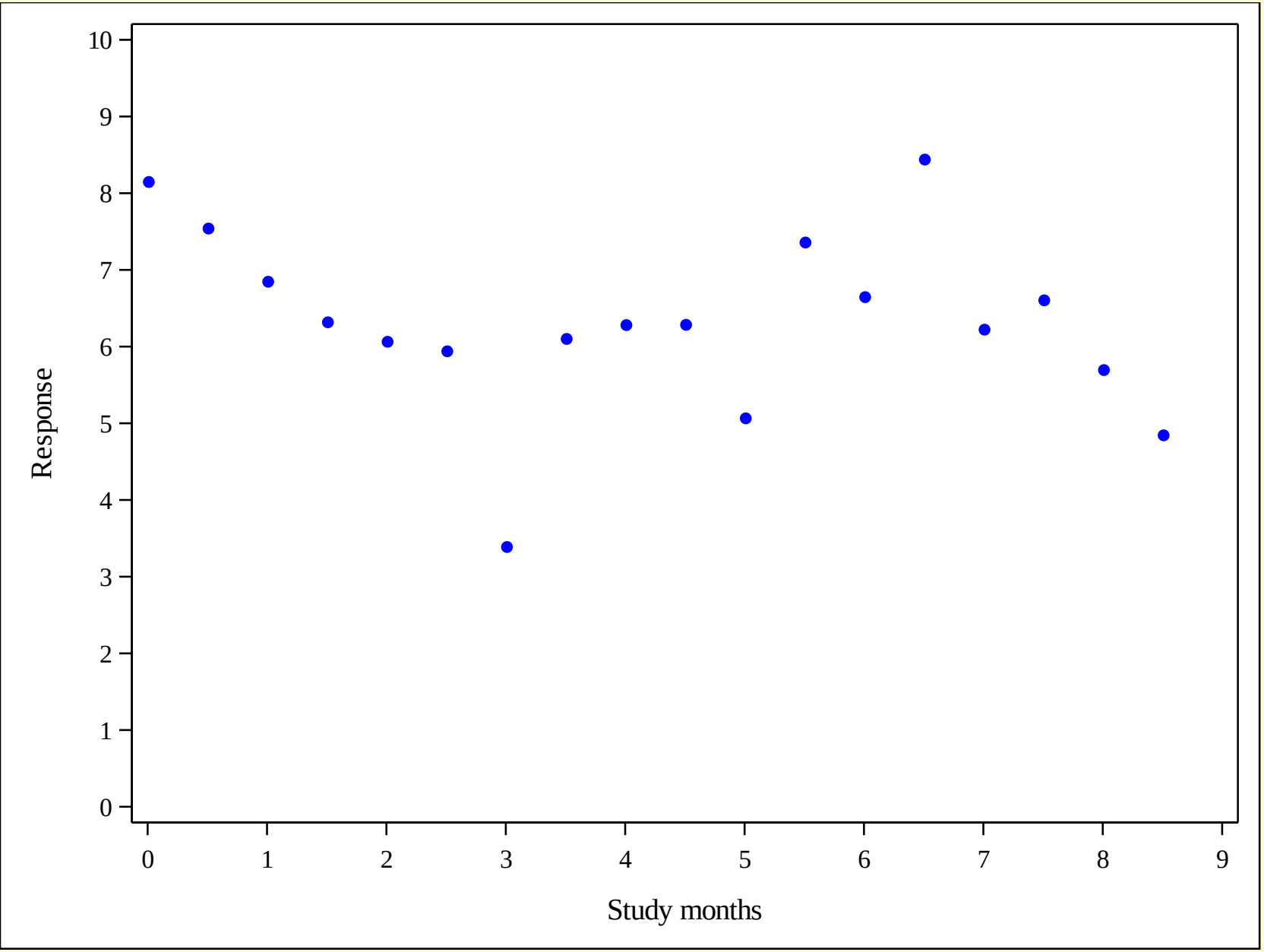
This is the most famous hockey stick

The Hockey Stick: The Most Controversial Chart in Science, Explained

Climate deniers threw all their might at disproving the famous climate change graph. Here's why they failed.



Some data



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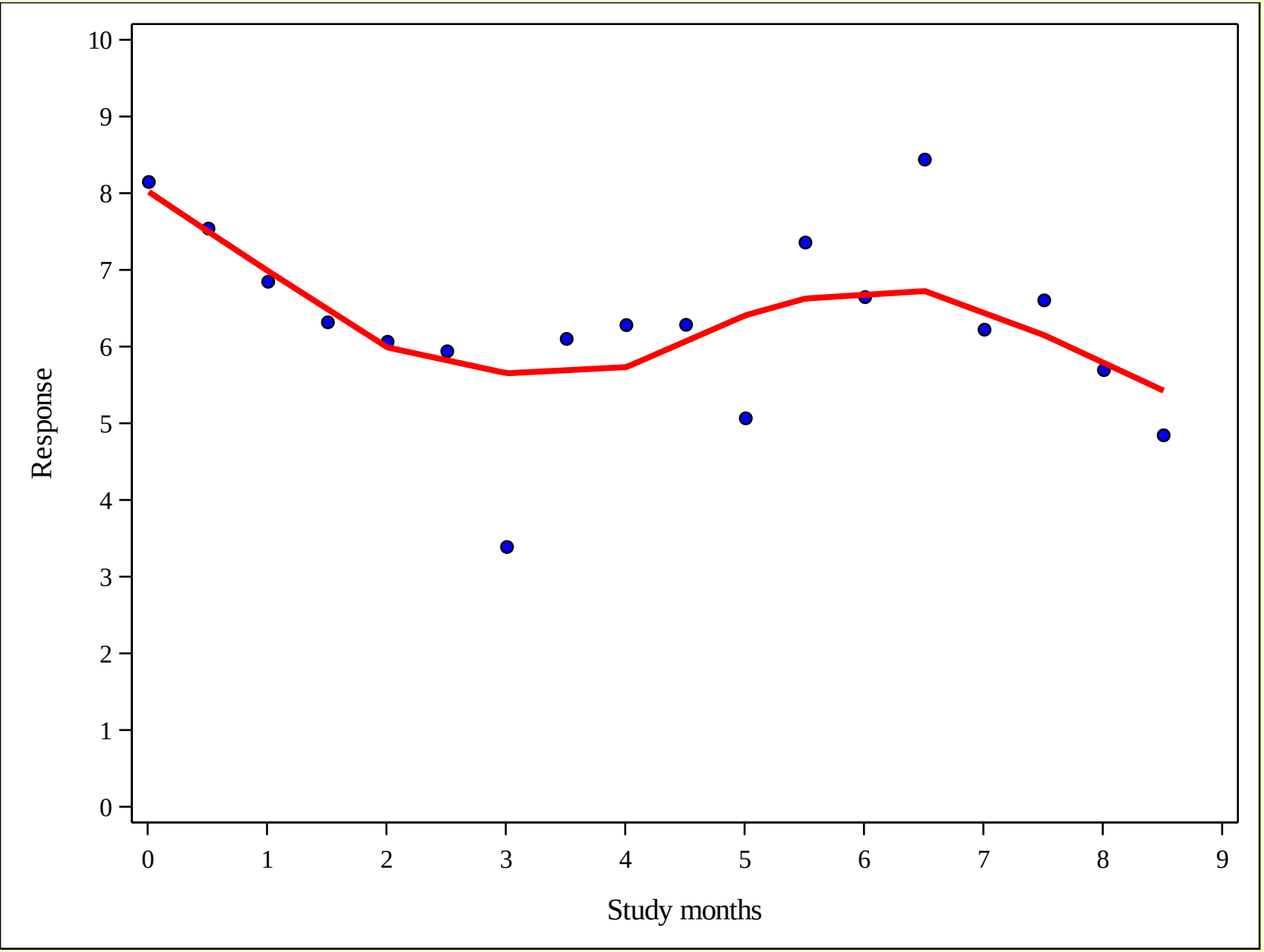
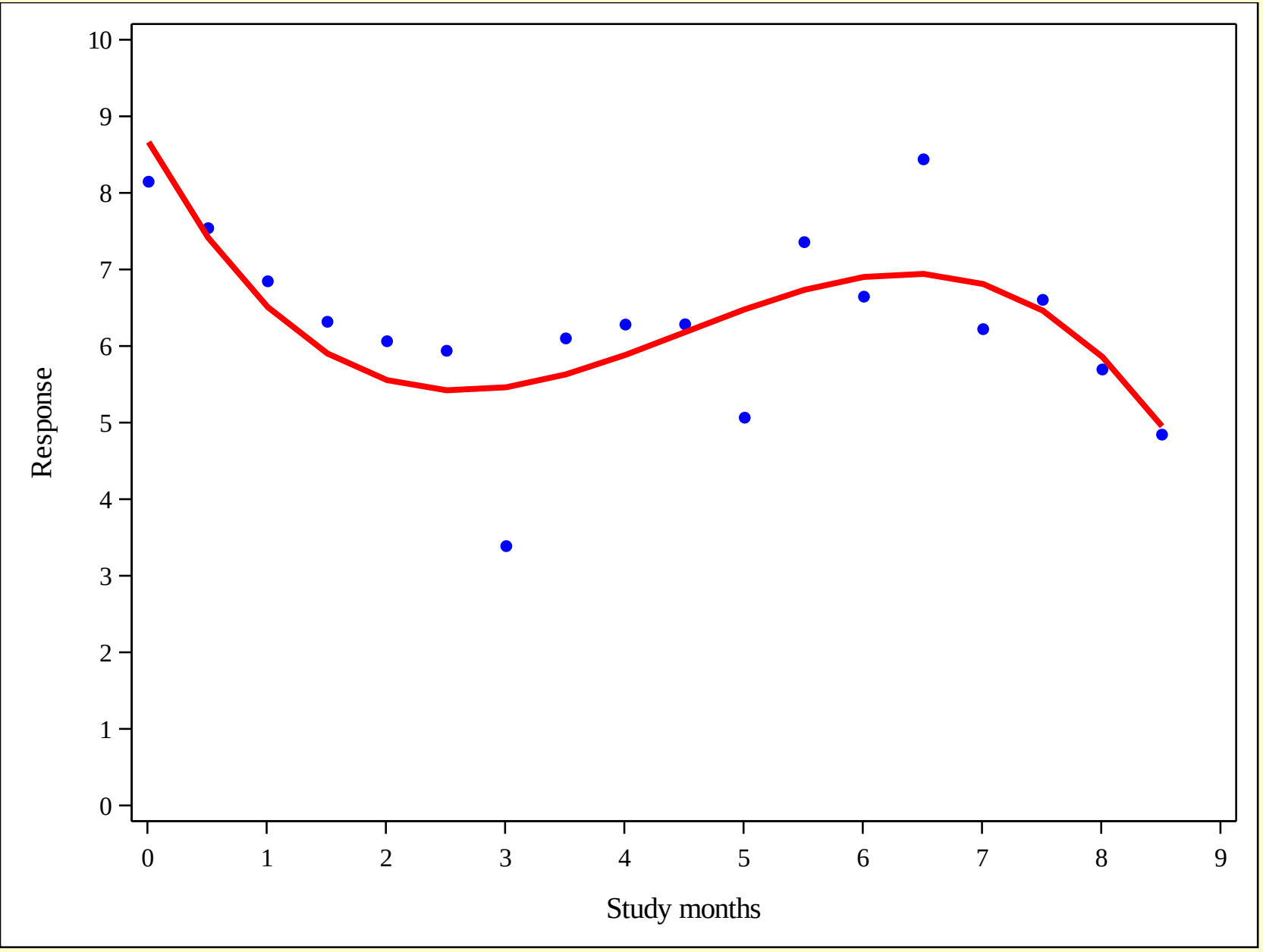
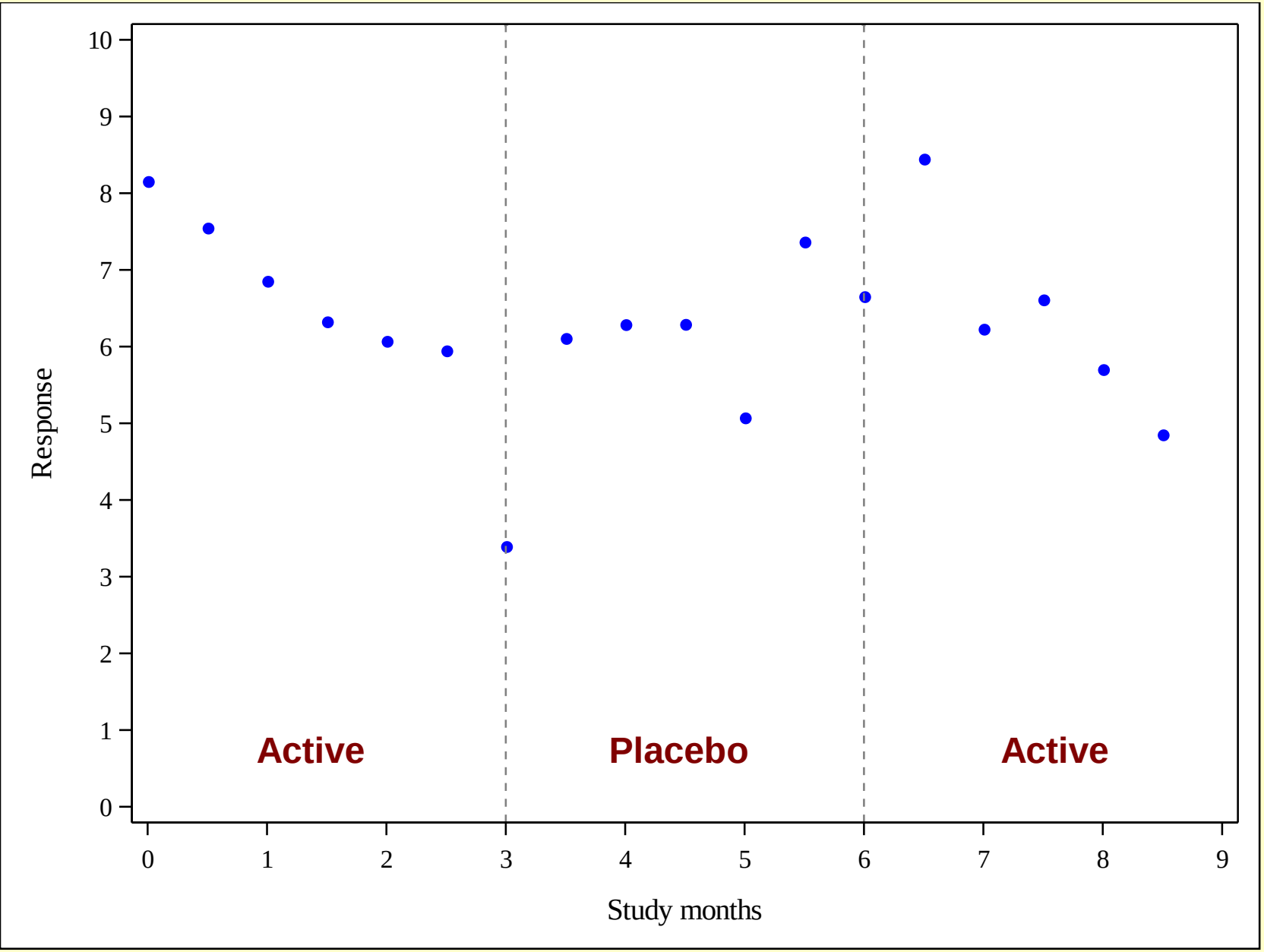


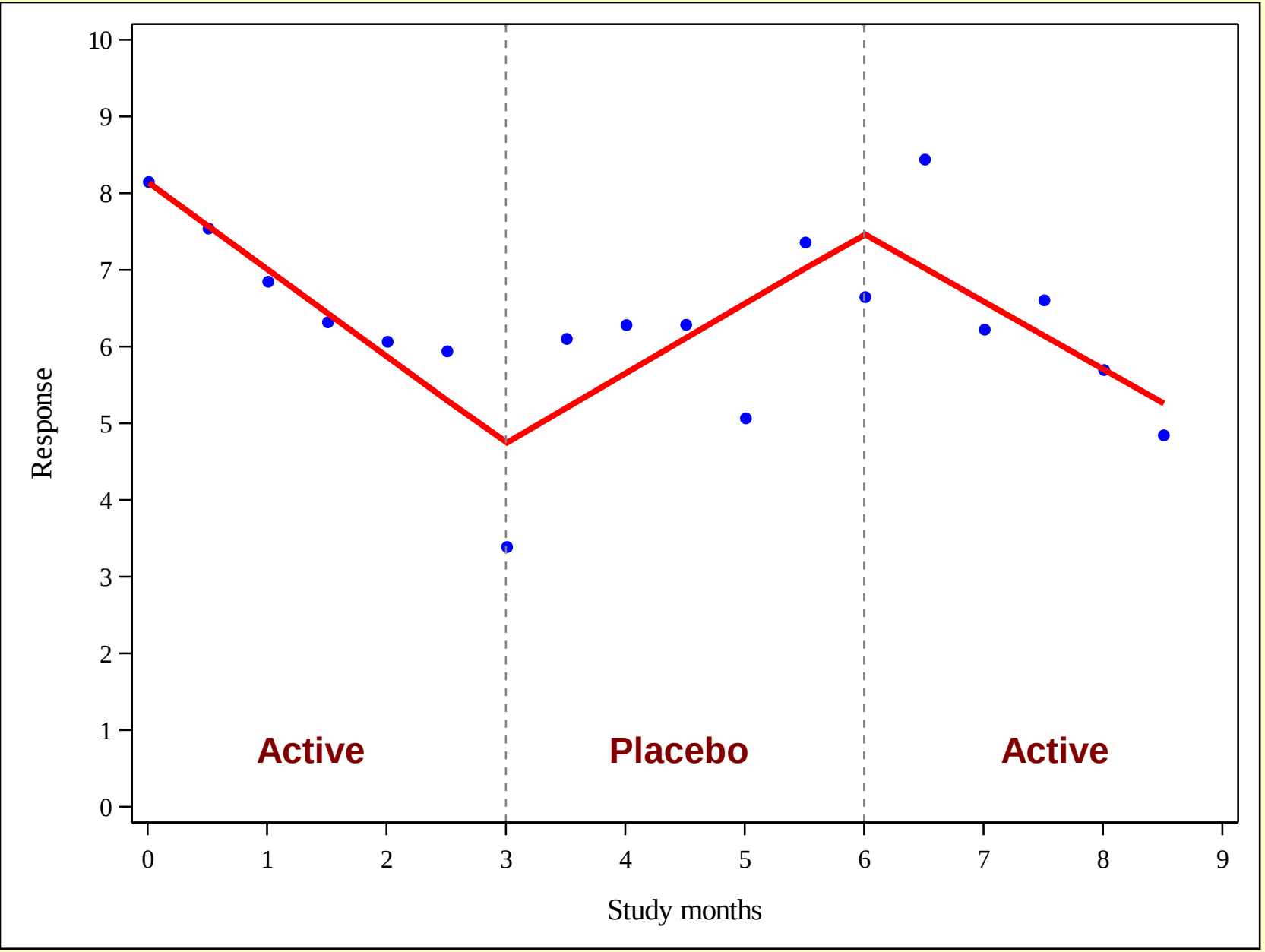
Some data



Data for broken stick model?



Data for broken stick model?



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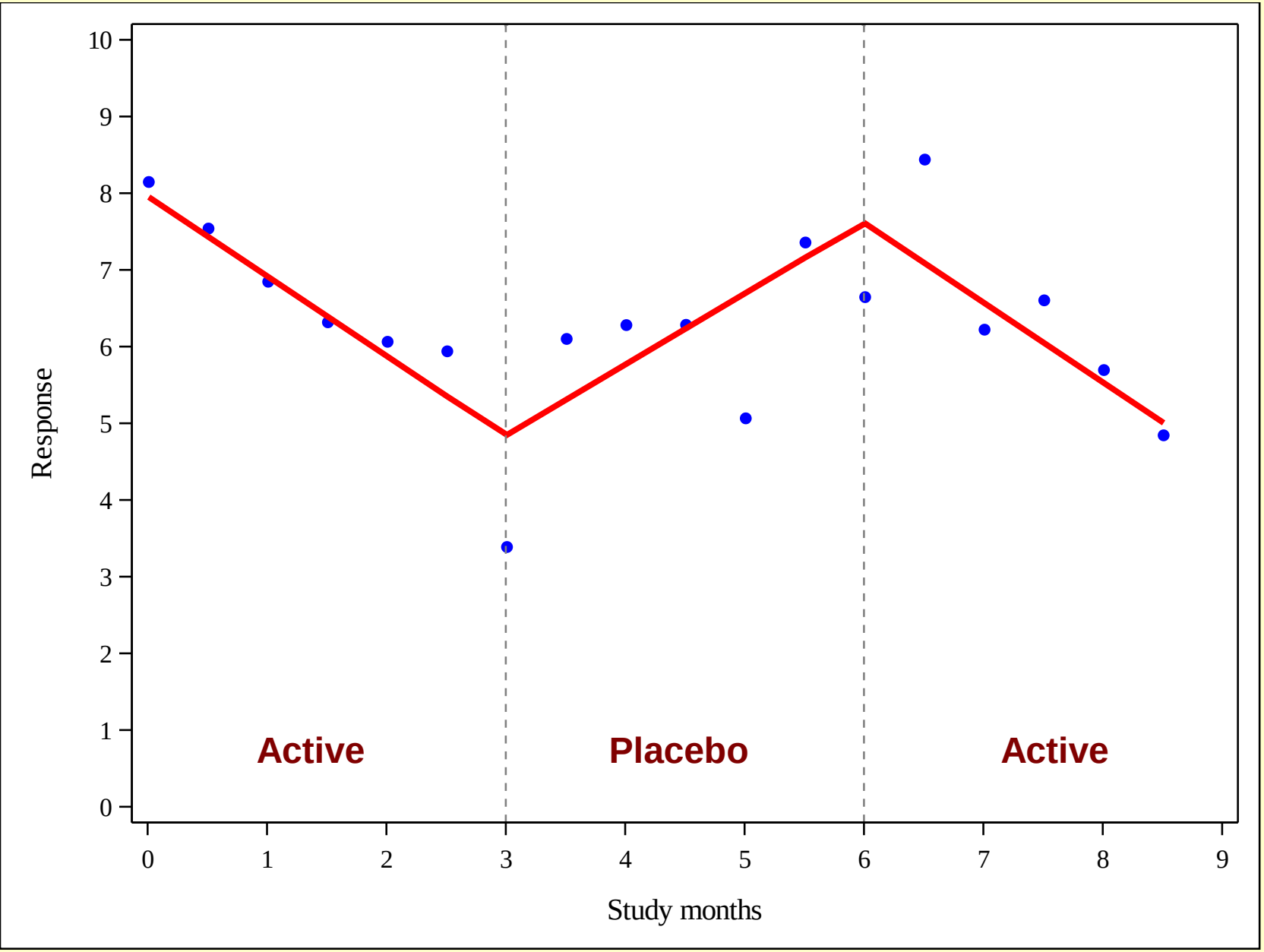
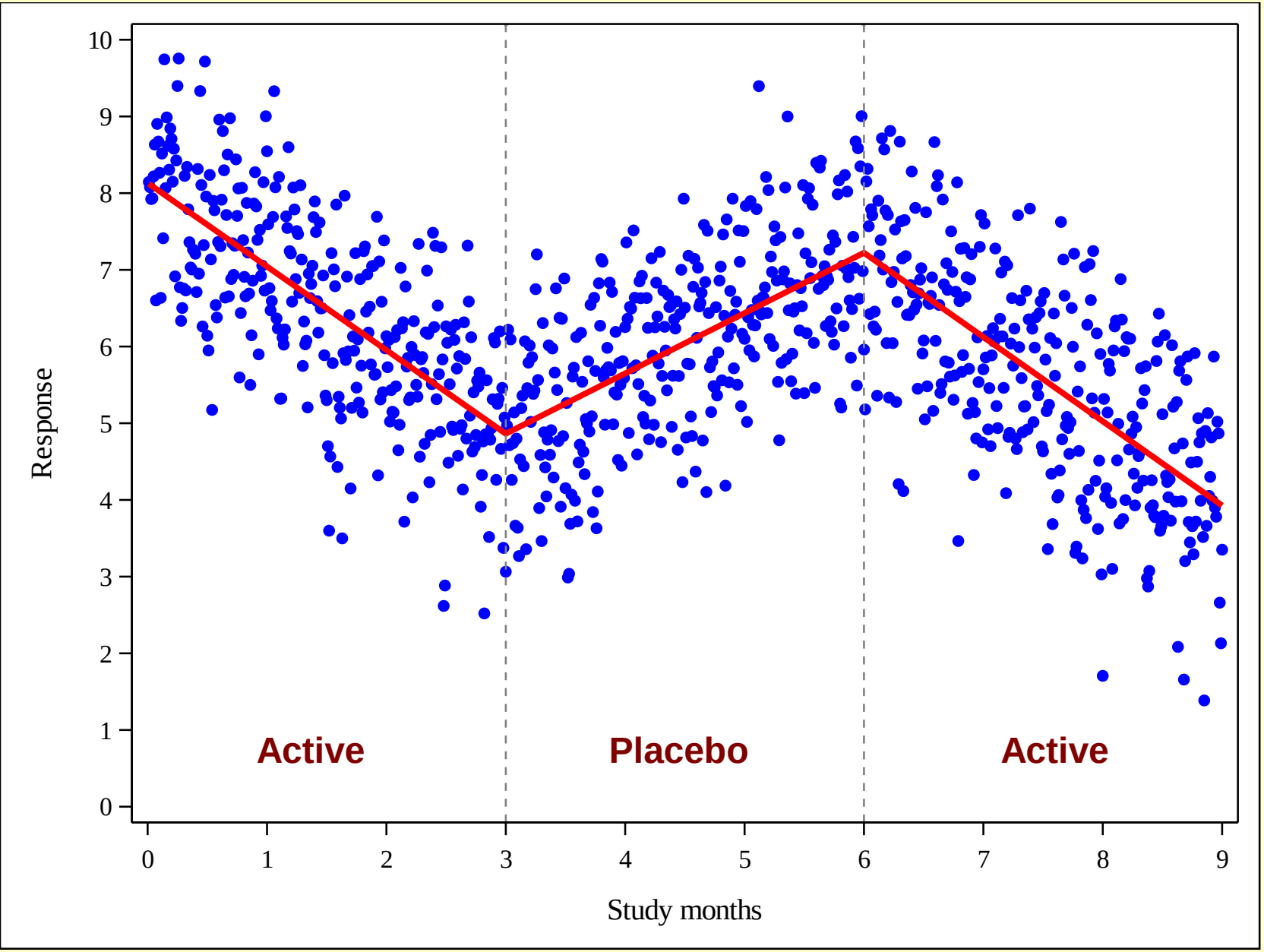


Data for broken stick model?



How to fit hockey stick models?

```
model y = x;     *simple linear model;

model y = x x2; *hockey stick model, one break;
```

x	x2	y	yhat
300	0	4.75	4.71
340	0	4.40	4.58
400	0	4.52	4.38
425	0	4.42	4.30
460	0	4.10	4.18
480	0	4.27	4.12
500	0	.	4.05
570	70	3.55	3.43
600	100	2.90	3.16
650	150	2.57	2.71
675	175	2.21	2.49
720	220	2.49	2.09
800	300	1.39	1.38

How to fit hockey stick models with pivot point to be estimated?

```
proc nlin;

  parameters Pivotx Pivoty SlopeBefore SlopeChange;

  Before = (x le Pivotx)*(x - Pivotx);
  After  = (x gt Pivotx)*(x - Pivotx);

  model y =  Pivoty + SlopeBefore*Before + SlopeChange*After;

run;
```

Talk outline

- Motivating example clinical trial
- Hockey sticks and broken sticks
- **A proposed design**

Figure 1: What is the design and what is the model? Based on historical data

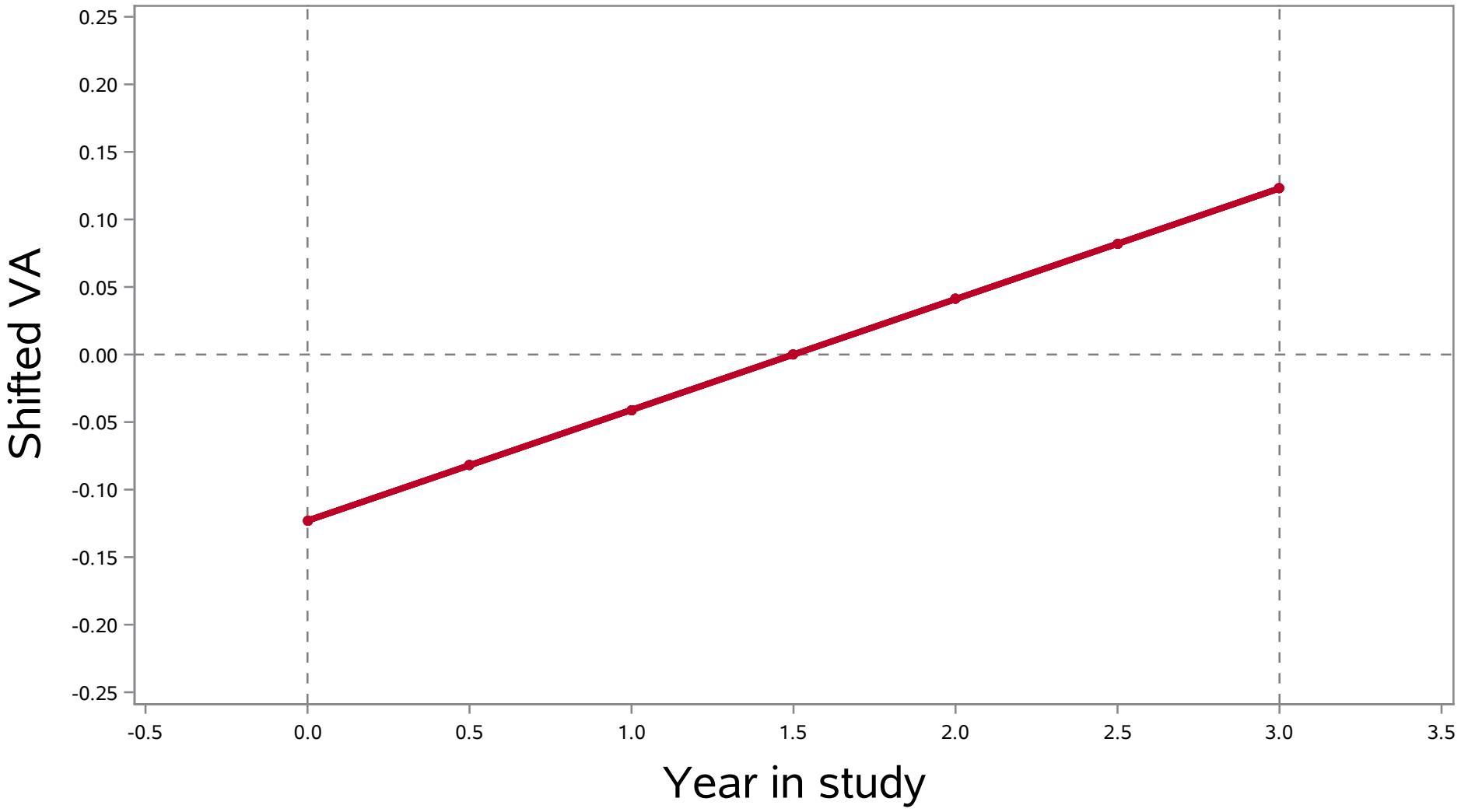


Figure 2: What is the current design and what is the model?

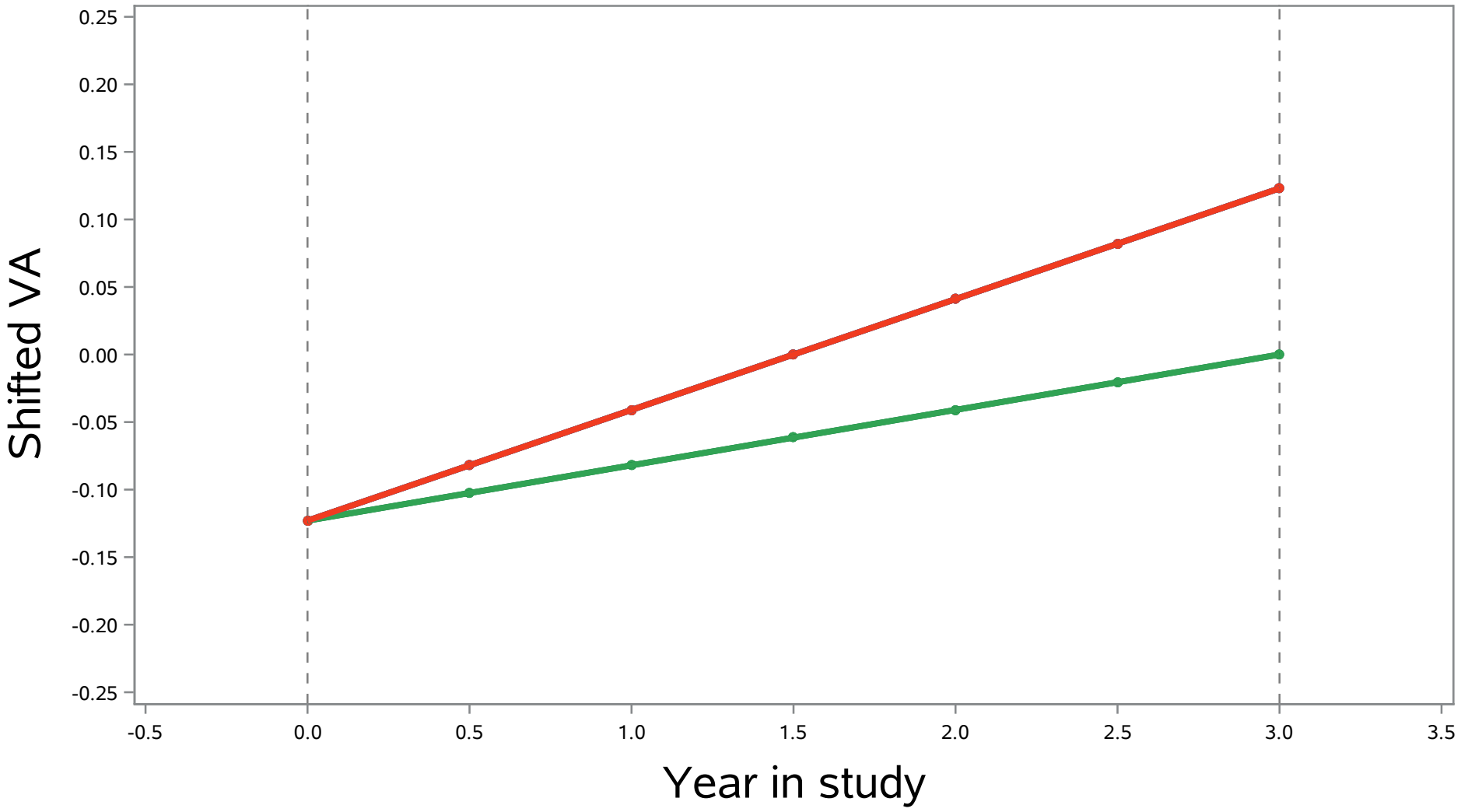


Figure 3: What is the proposed design and what is the model?

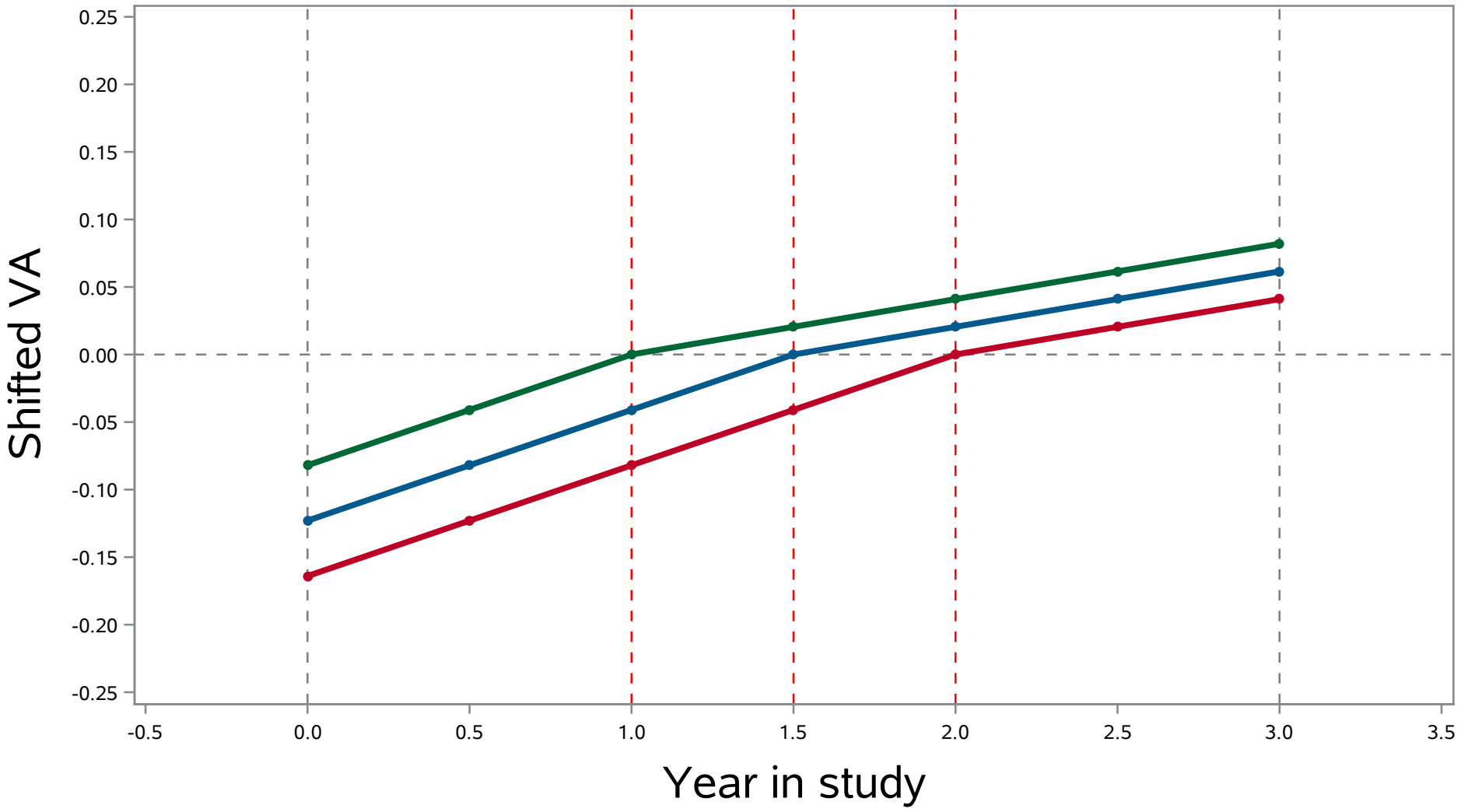


Figure 4: What is the proposed design and what is the model?

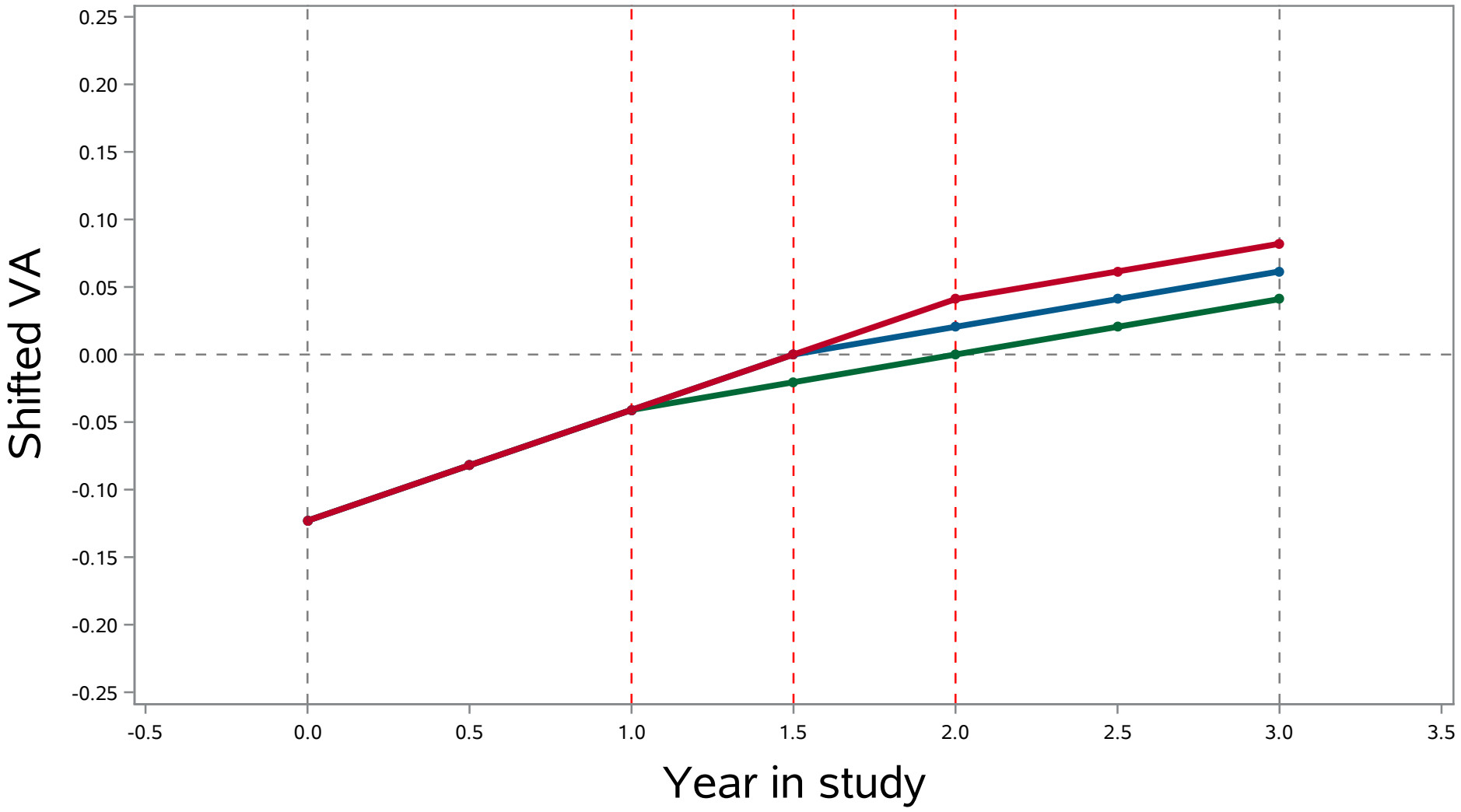


Figure 5: Simulation model based on treatment effect on slope

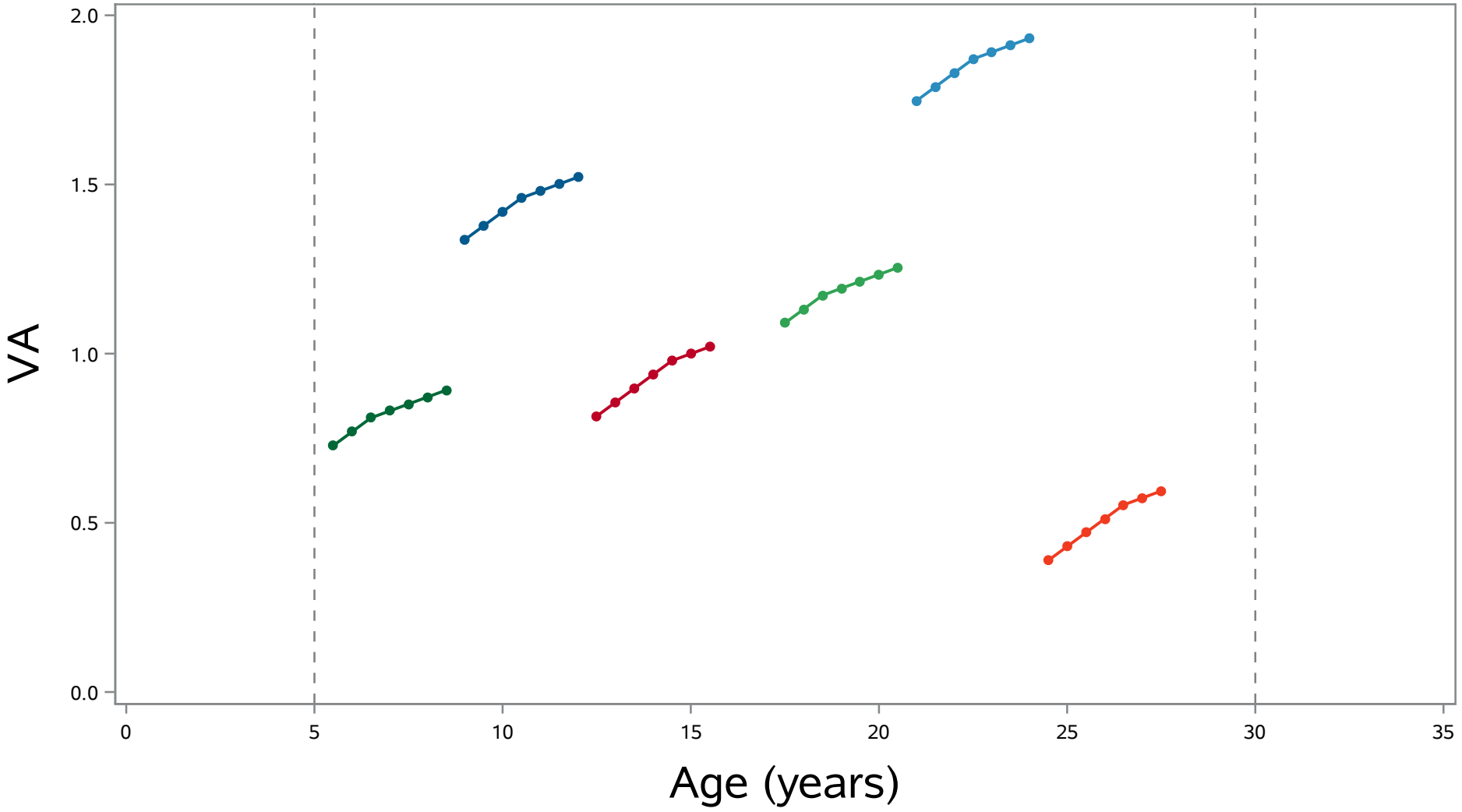


Figure 6: Simulation model has random variation in treatment effect on slope

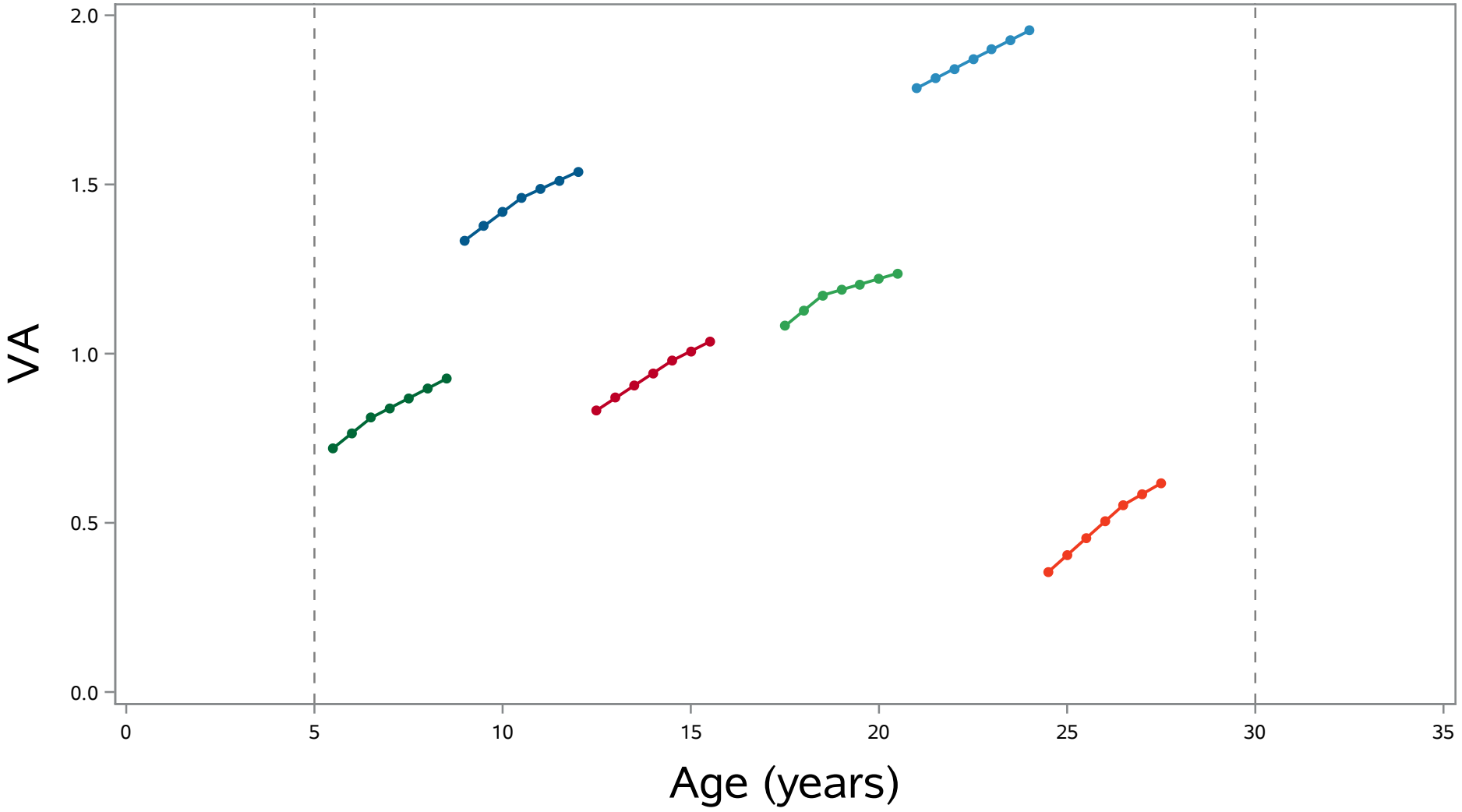


Figure 7: Simulation model adds random error to each time of VA assessment

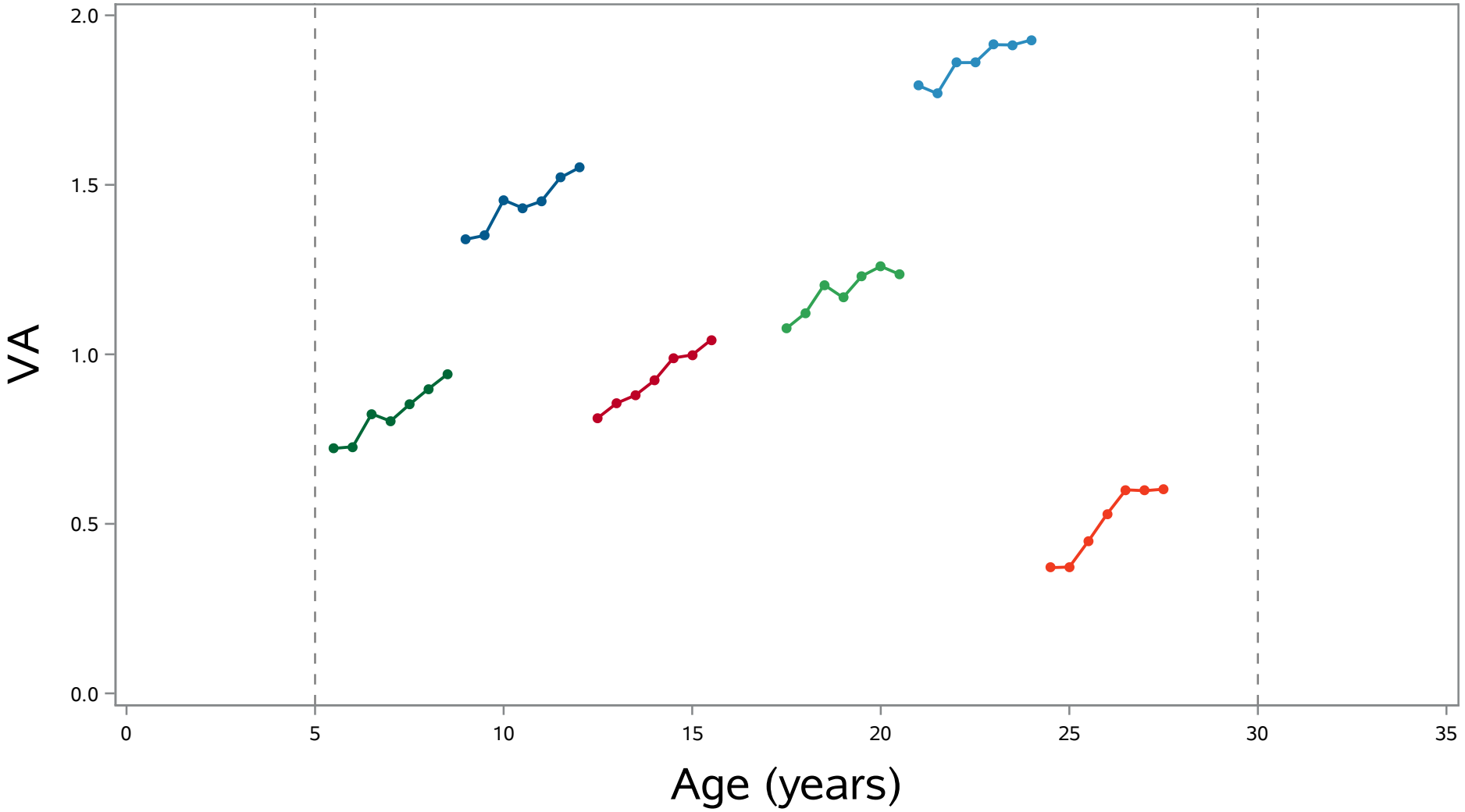


Figure 8: Simulated data shifted to age relative to treatment start

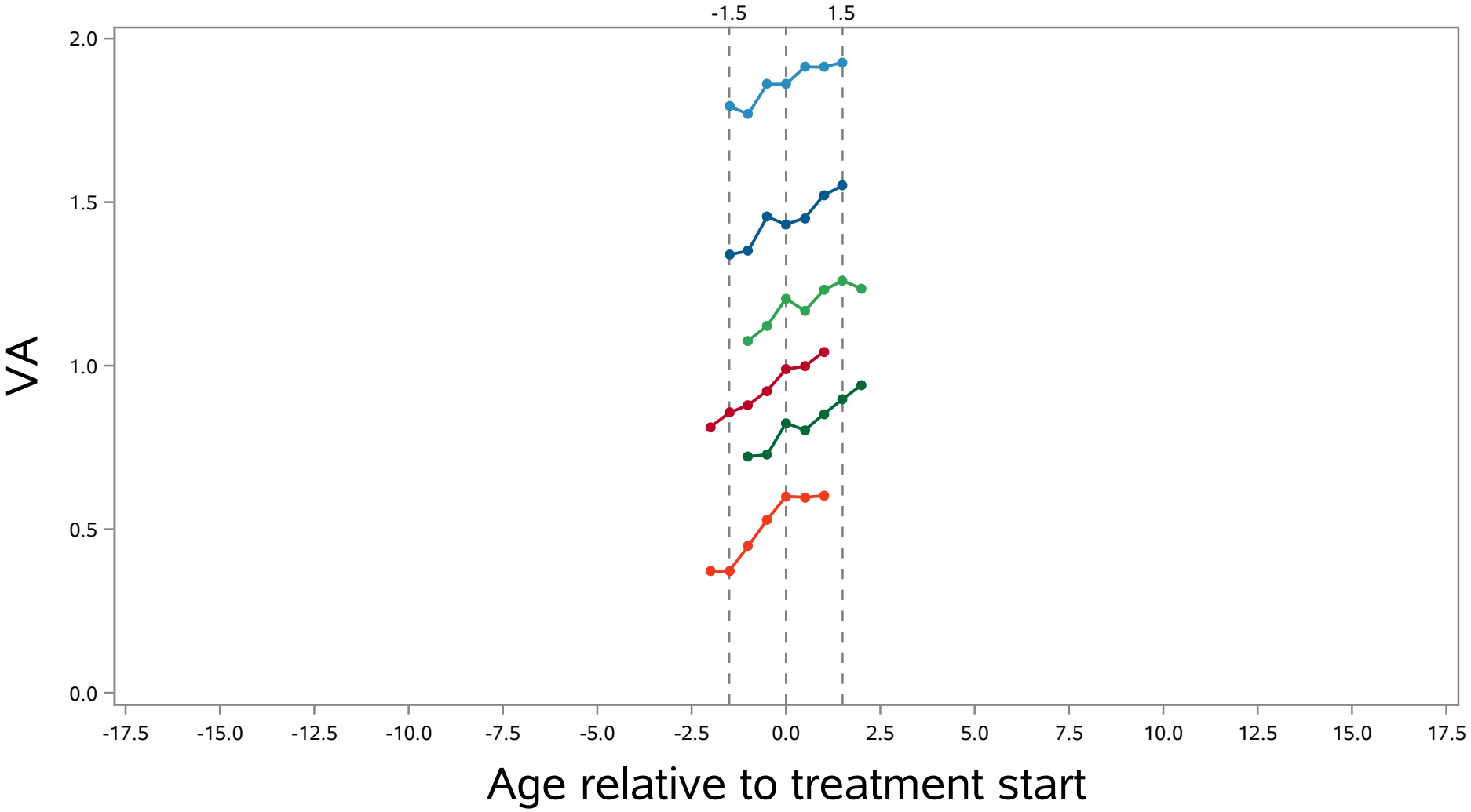


Figure 9: Simulated data shifted to study year over three years

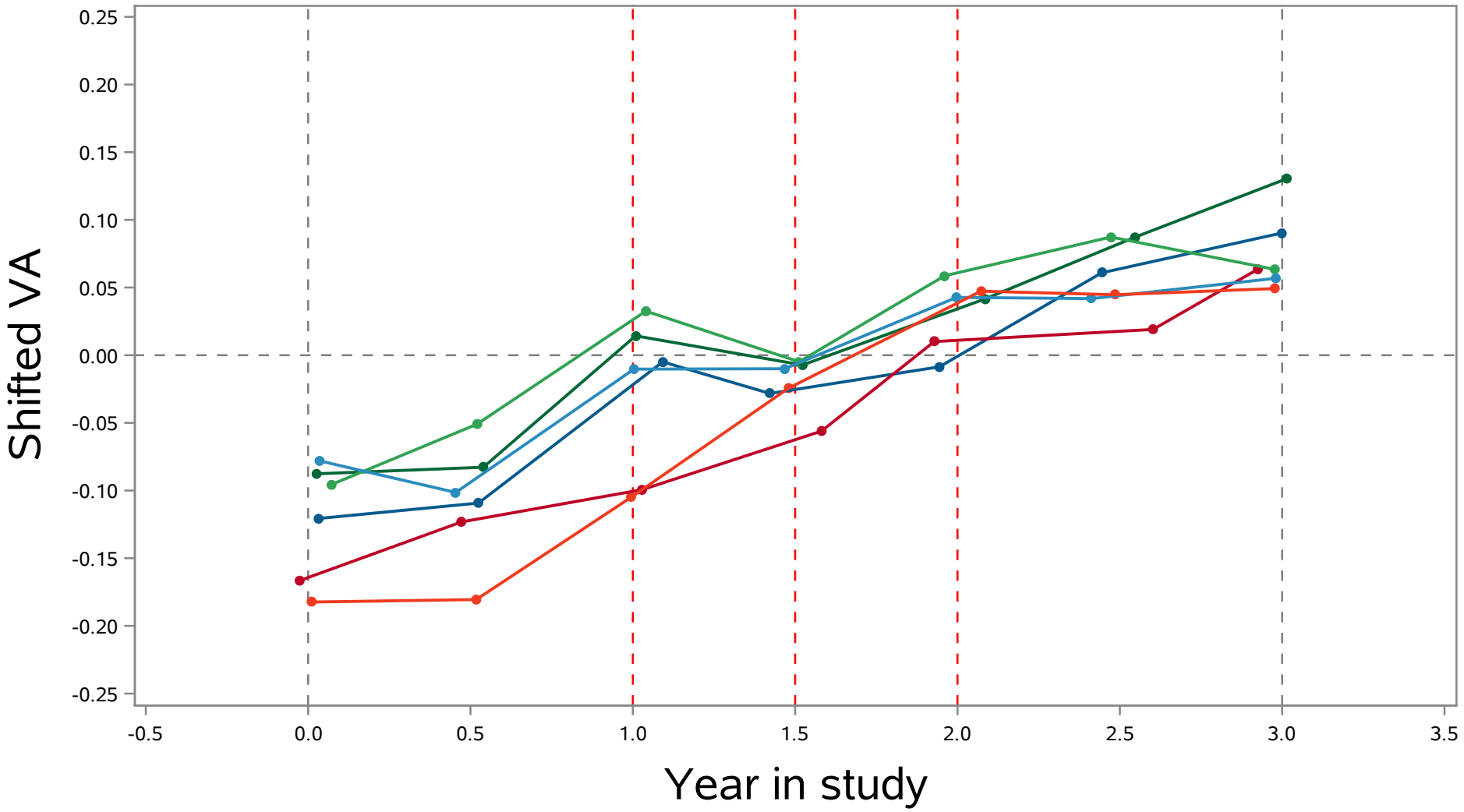


Figure 10: Simulated data shifted to year of treatment with underlying model

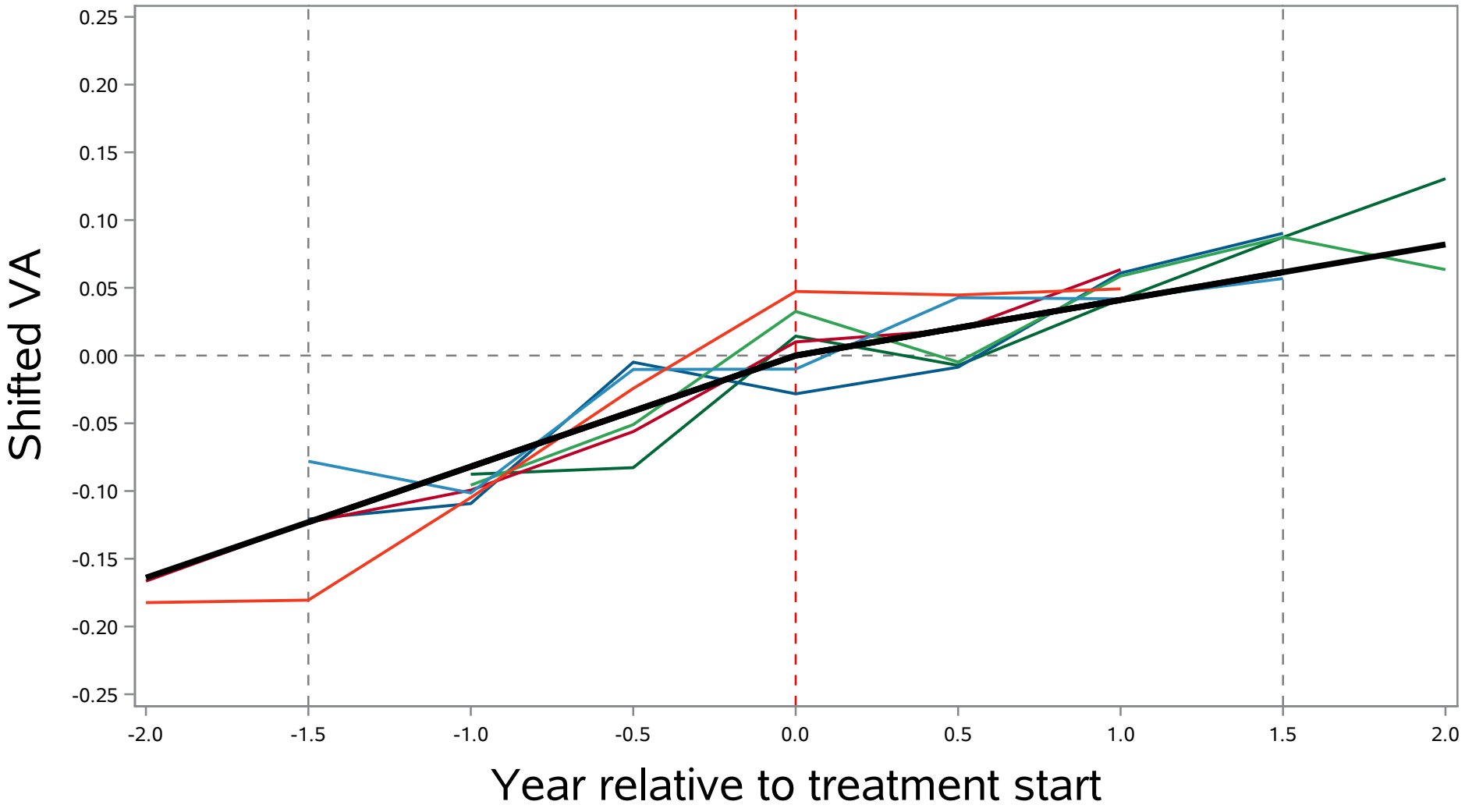


Figure 11: Simulated data shifted to year of treatment with underlying model

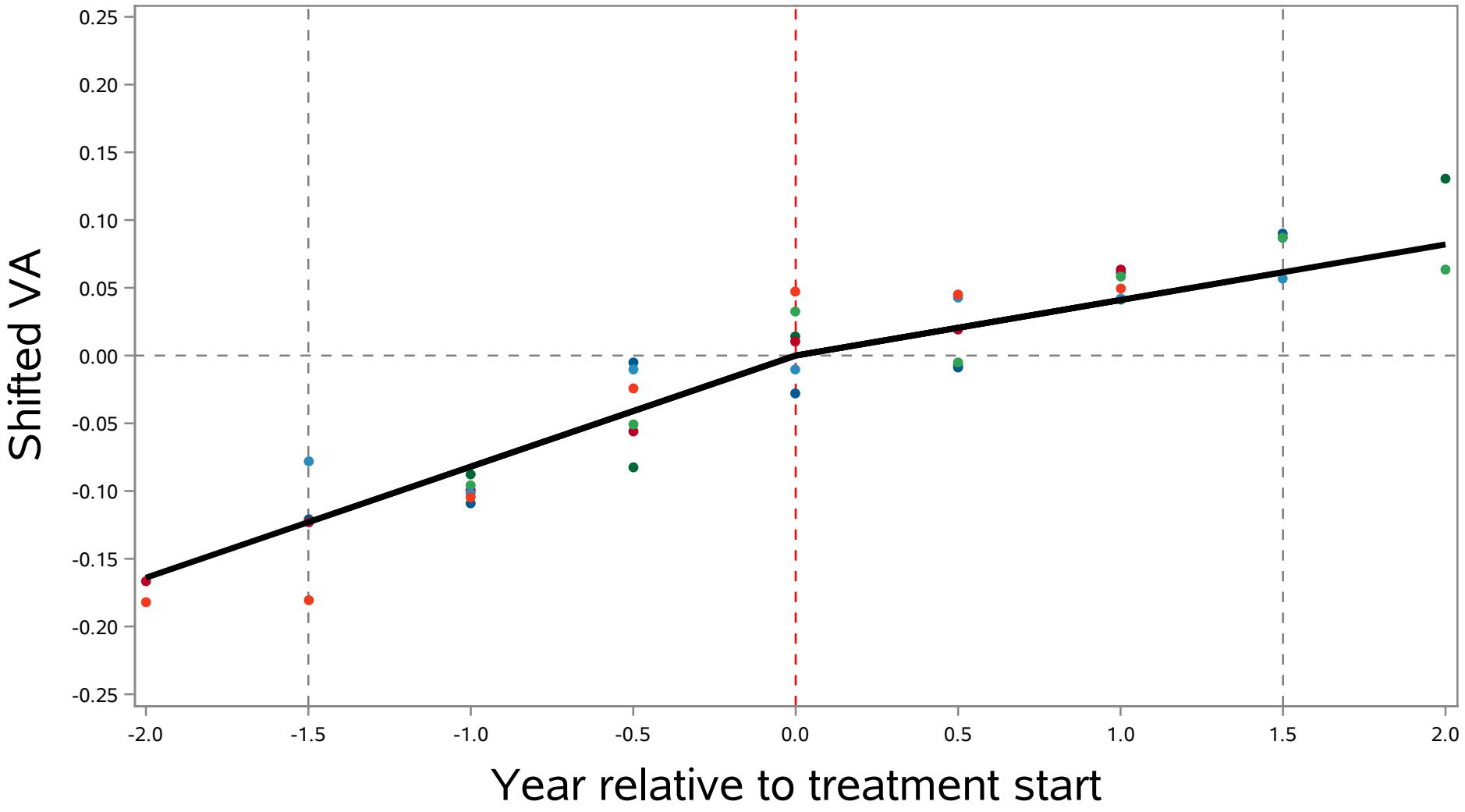
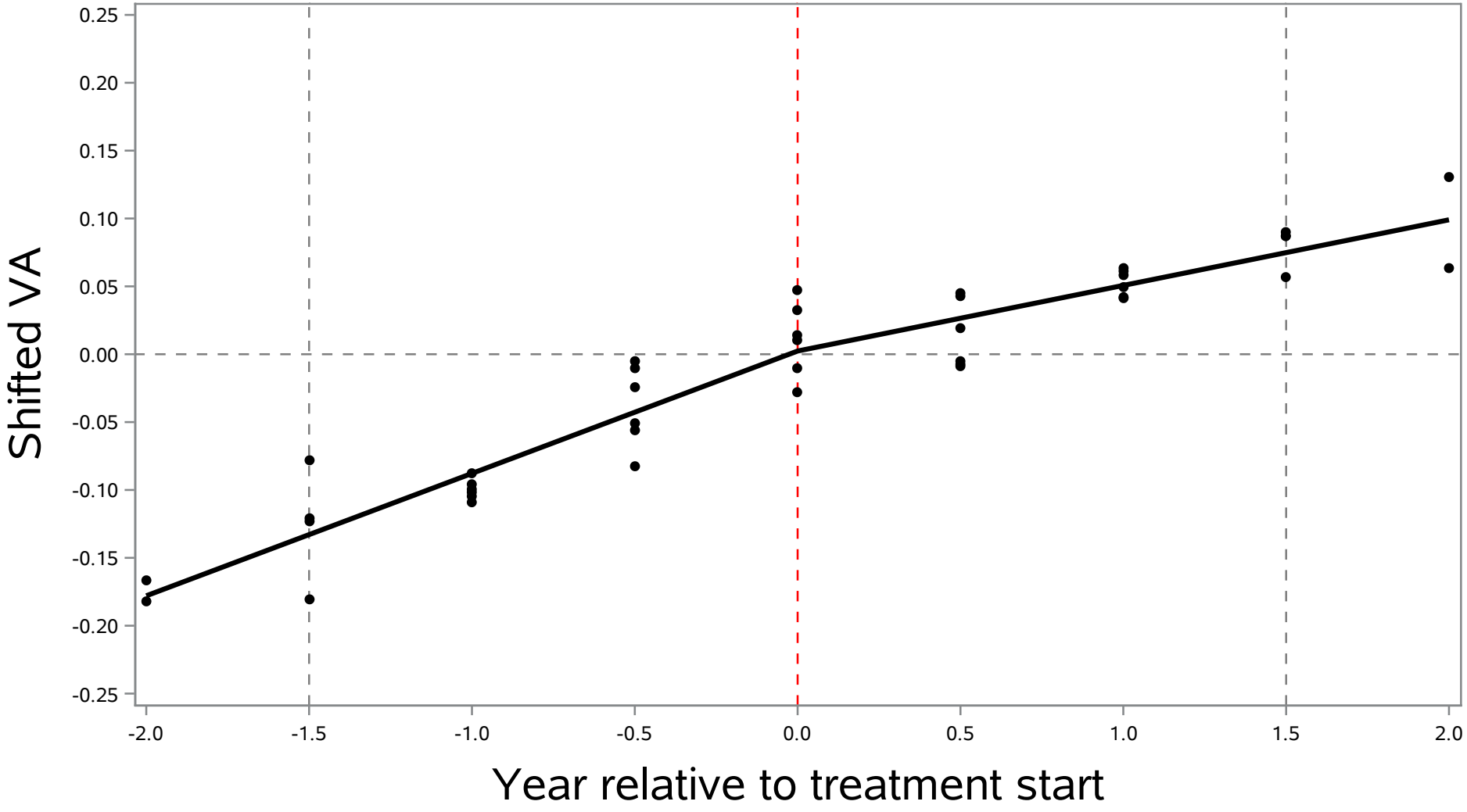


Figure 12: Simple hockey/broken stick model fit

Effect	Estimate	SE	DF	t Value	Pr > |t|
SlopeChangeYear	-0.04183	0.01279	39	-3.27	0.0023



Hockey stick model RC estimates

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	0.001594	0.009252	5	0.17	0.8700
TrtYear	0.08741	0.01045	5	8.36	0.0004
SlopeChangeYear	-0.03953	0.01898	5	-2.08	0.0918

Solution for Random Effects

Effect	Pt No	Estimate	Std Err Pred	DF	t Value	Pr > |t|
Intercept	1	-0.01338	0.01176	24	-1.14	0.2668
TrtYear	1	-0.01475	0.01383	24	-1.07	0.2967
SlopeChangeYear	1	0.02897	0.02589	24	1.12	0.2742
Intercept	2	-0.01072	0.01205	24	-0.89	0.3824
TrtYear	2	-0.01212	0.01394	24	-0.87	0.3931
SlopeChangeYear	2	0.02340	0.02638	24	0.89	0.3838
Intercept	3	-0.00245	0.01149	24	-0.21	0.8330
TrtYear	3	-0.00263	0.01311	24	-0.20	0.8424
SlopeChangeYear	3	0.005263	0.02503	24	0.21	0.8353
Intercept	4	0.009073	0.01176	24	0.77	0.4481
TrtYear	4	0.01044	0.01383	24	0.75	0.4578
SlopeChangeYear	4	-0.01992	0.02589	24	-0.77	0.4491
Intercept	5	-0.00329	0.01205	24	-0.27	0.7871
TrtYear	5	-0.00513	0.01394	24	-0.37	0.7161
SlopeChangeYear	5	0.008071	0.02638	24	0.31	0.7622
Intercept	6	0.02076	0.01149	24	1.81	0.0834
TrtYear	6	0.02420	0.01311	24	1.85	0.0772
SlopeChangeYear	6	-0.04578	0.02503	24	-1.83	0.0799

Figure 13: RC broken stick model with per patient predicted lines (random effect)

Effect	Estimate	SE	DF	t Value	Pr > |t|
SlopeChangeYear	-0.03953	0.01898	5	-2.08	0.0918

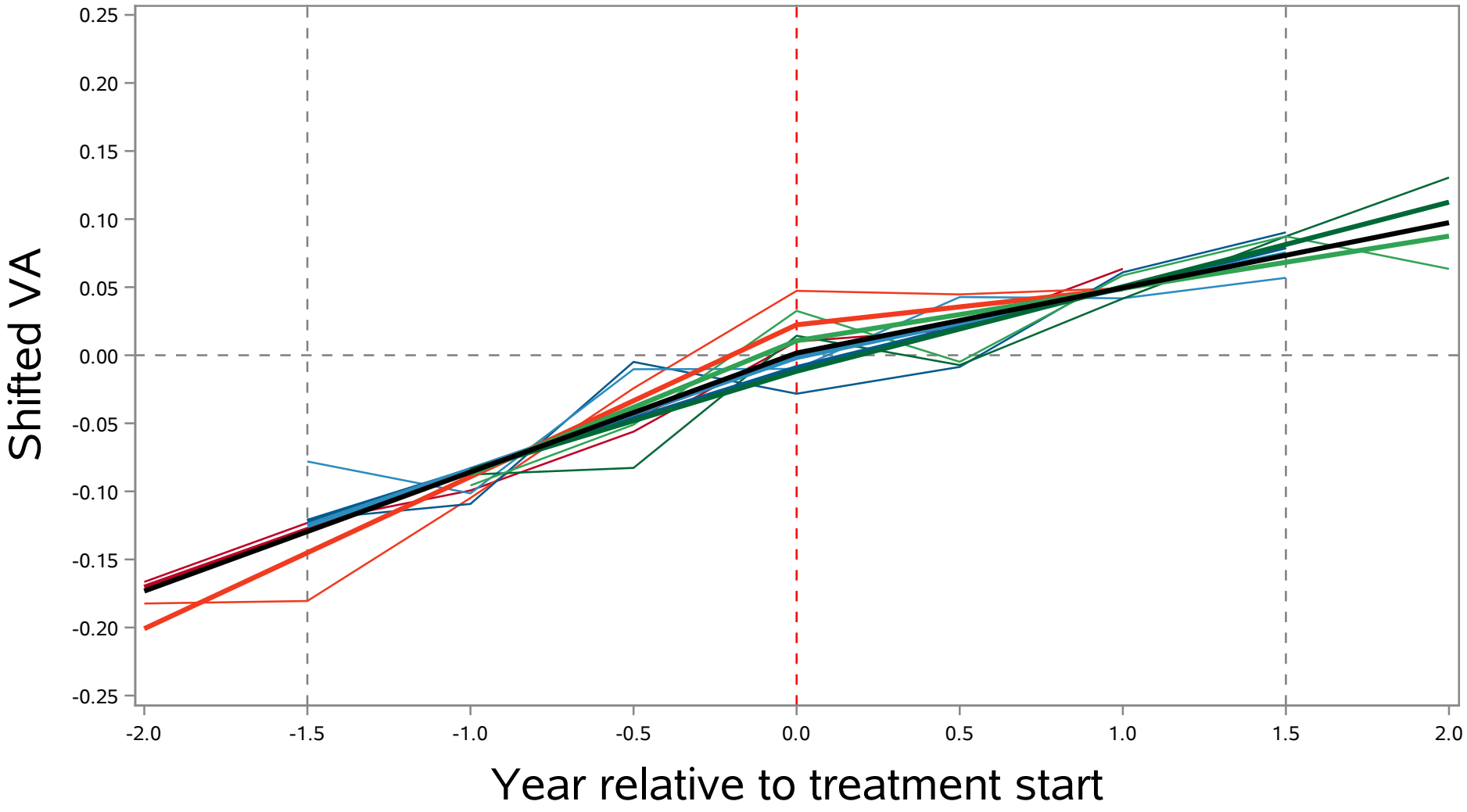


Figure 14: Per patient (fixed effect) broken stick model predicted lines

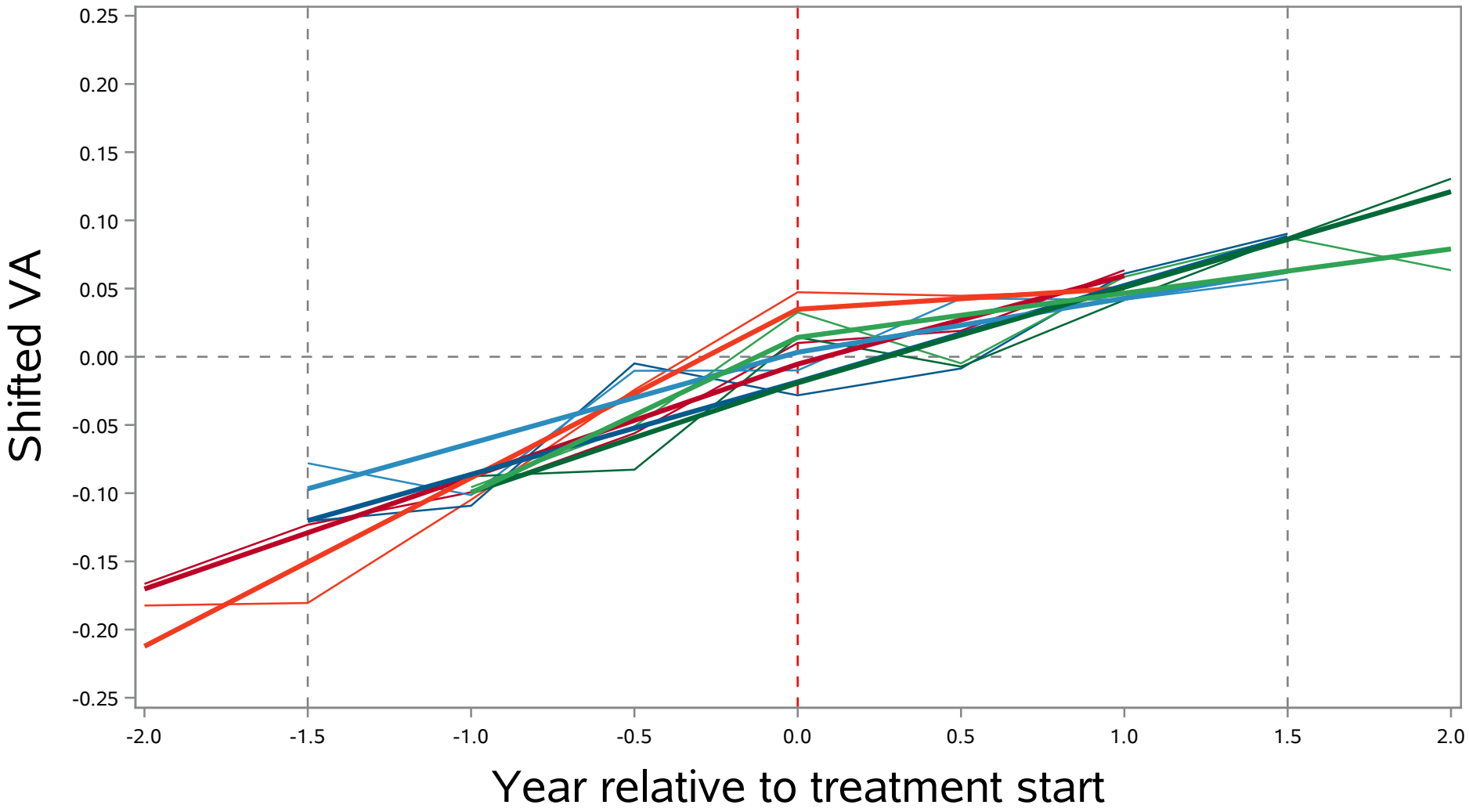


Figure 15: RC broken stick model standardized to same initial slope

Effect	Estimate	SE	DF	t Value	Pr > |t|
SlopeChangeYear	-0.03953	0.01898	5	-2.08	0.0918

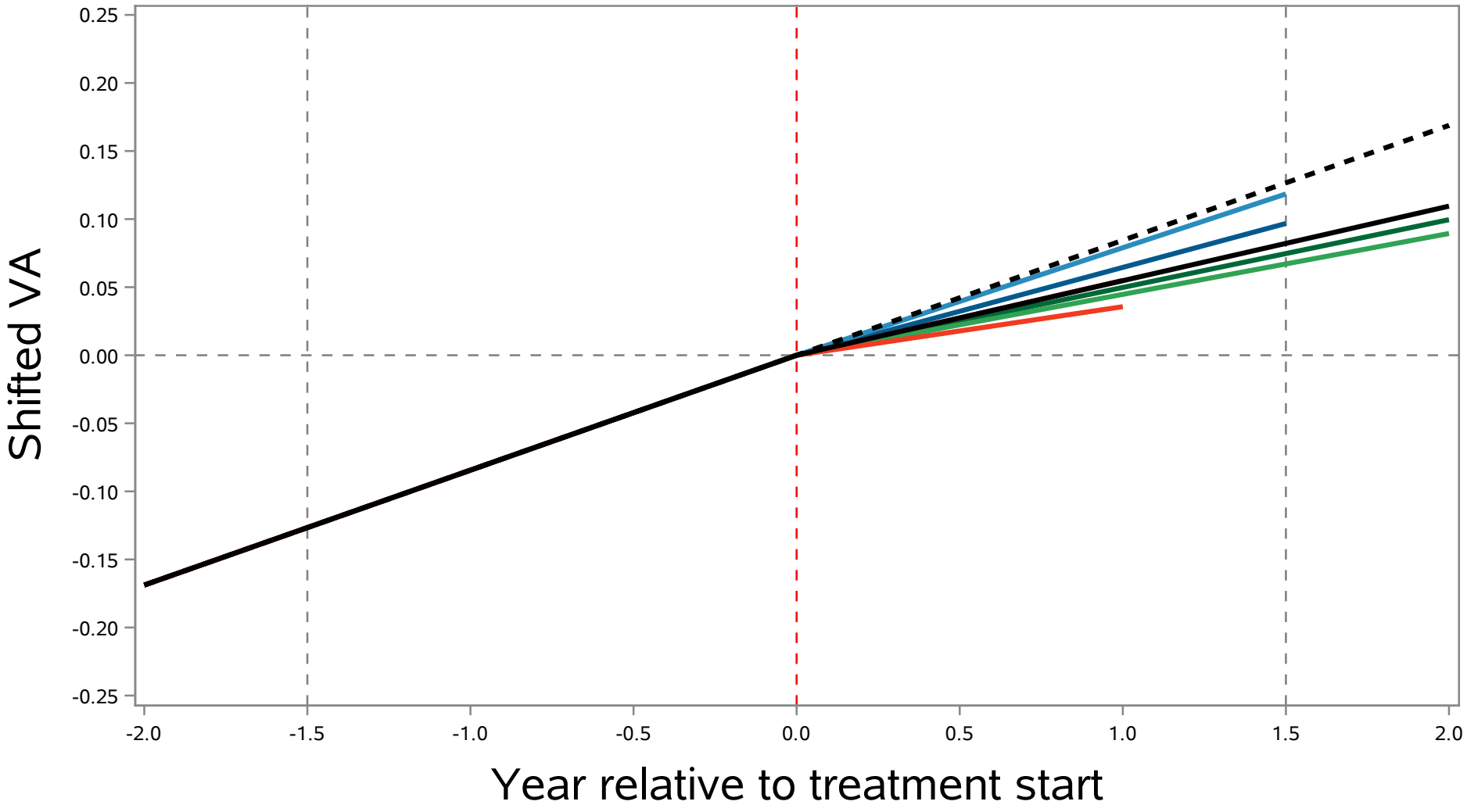


Figure 16: RC broken stick model standardized to same initial slope, with jitter

Effect	Estimate	SE	DF	t Value	Pr > |t|
SlopeChangeYear	-0.03953	0.01898	5	-2.08	0.0918

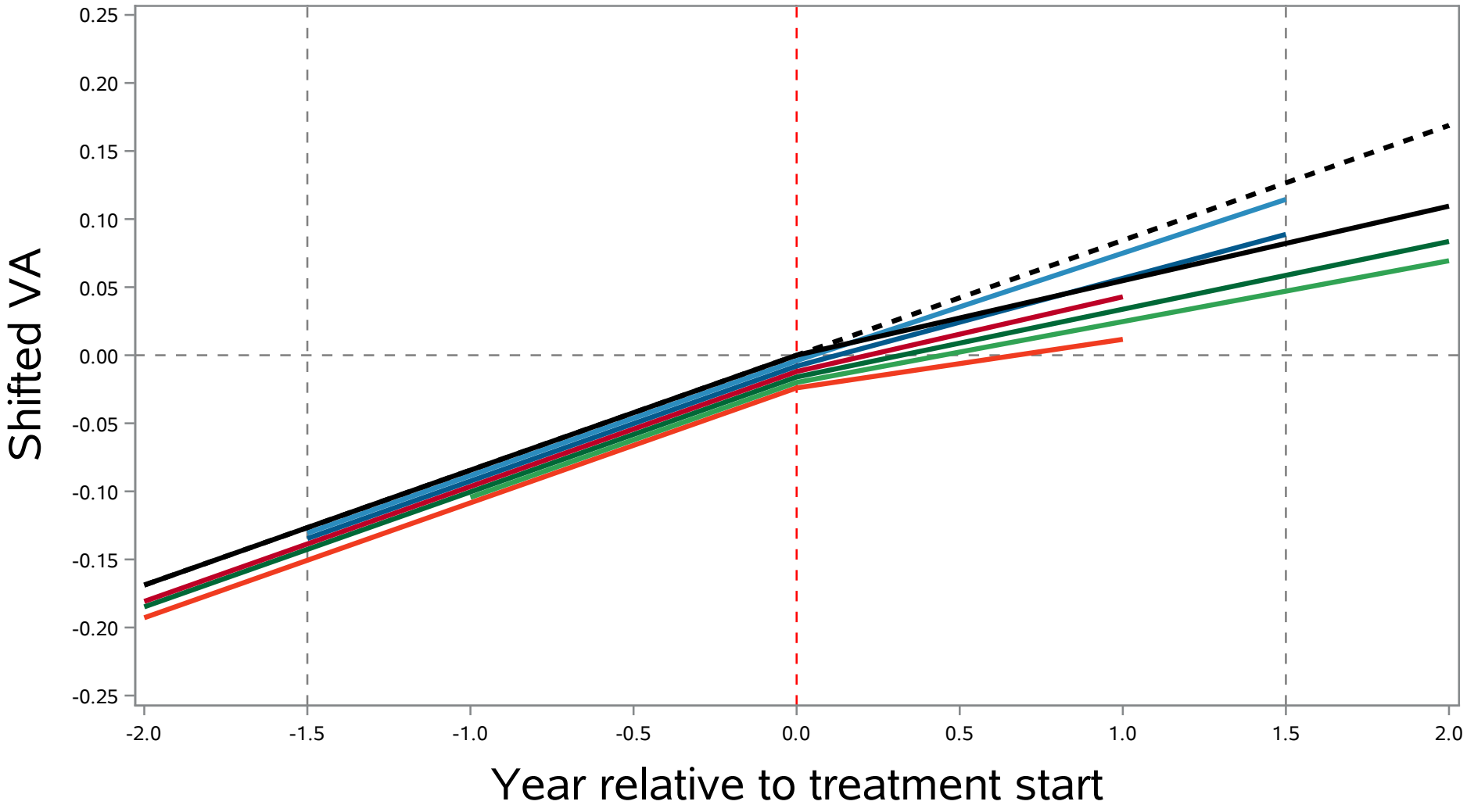


Figure 17: Broken stick model fit with pivot point estimated (non-linear model)

Parameter	Estimate
Pivotx	-212E-17

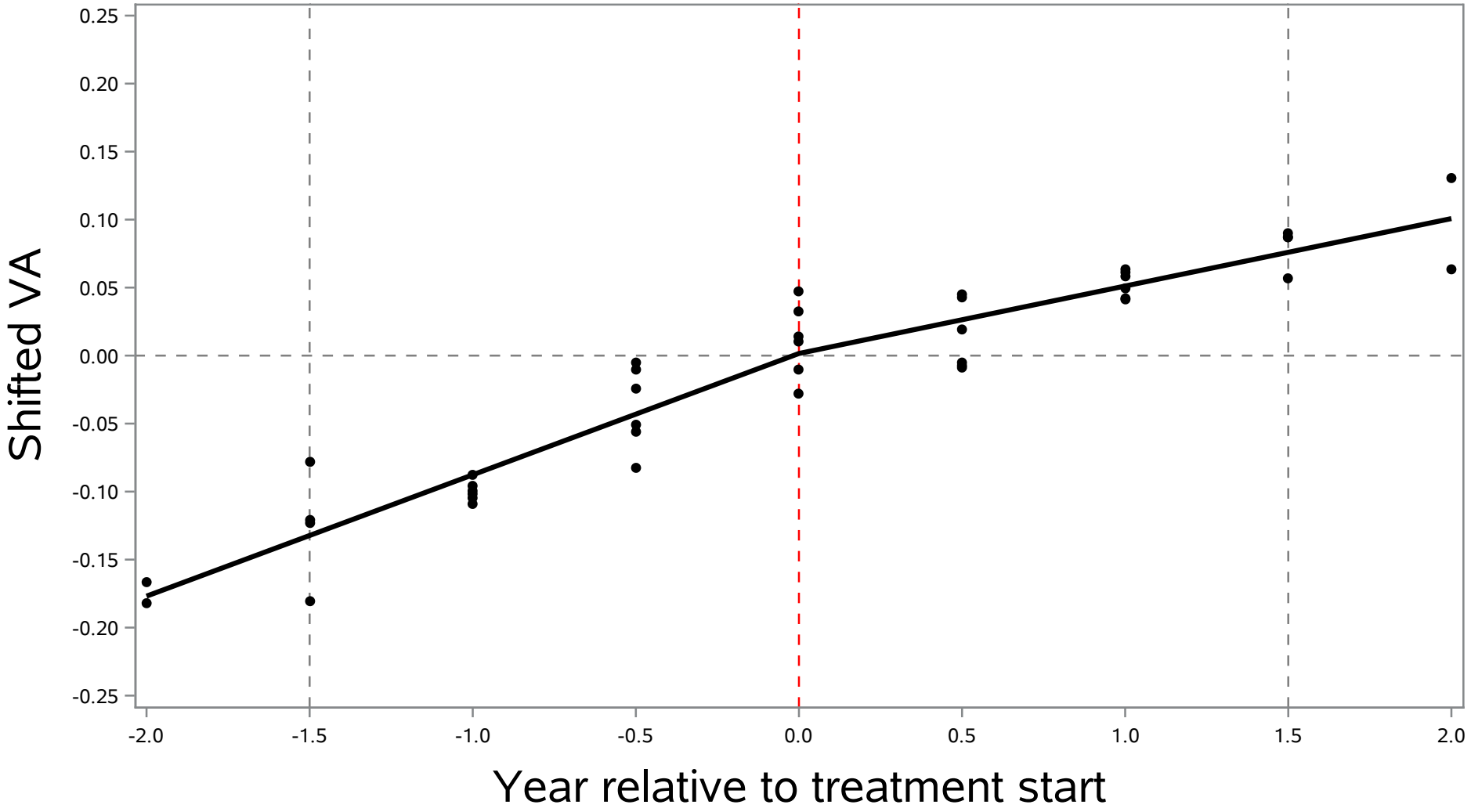
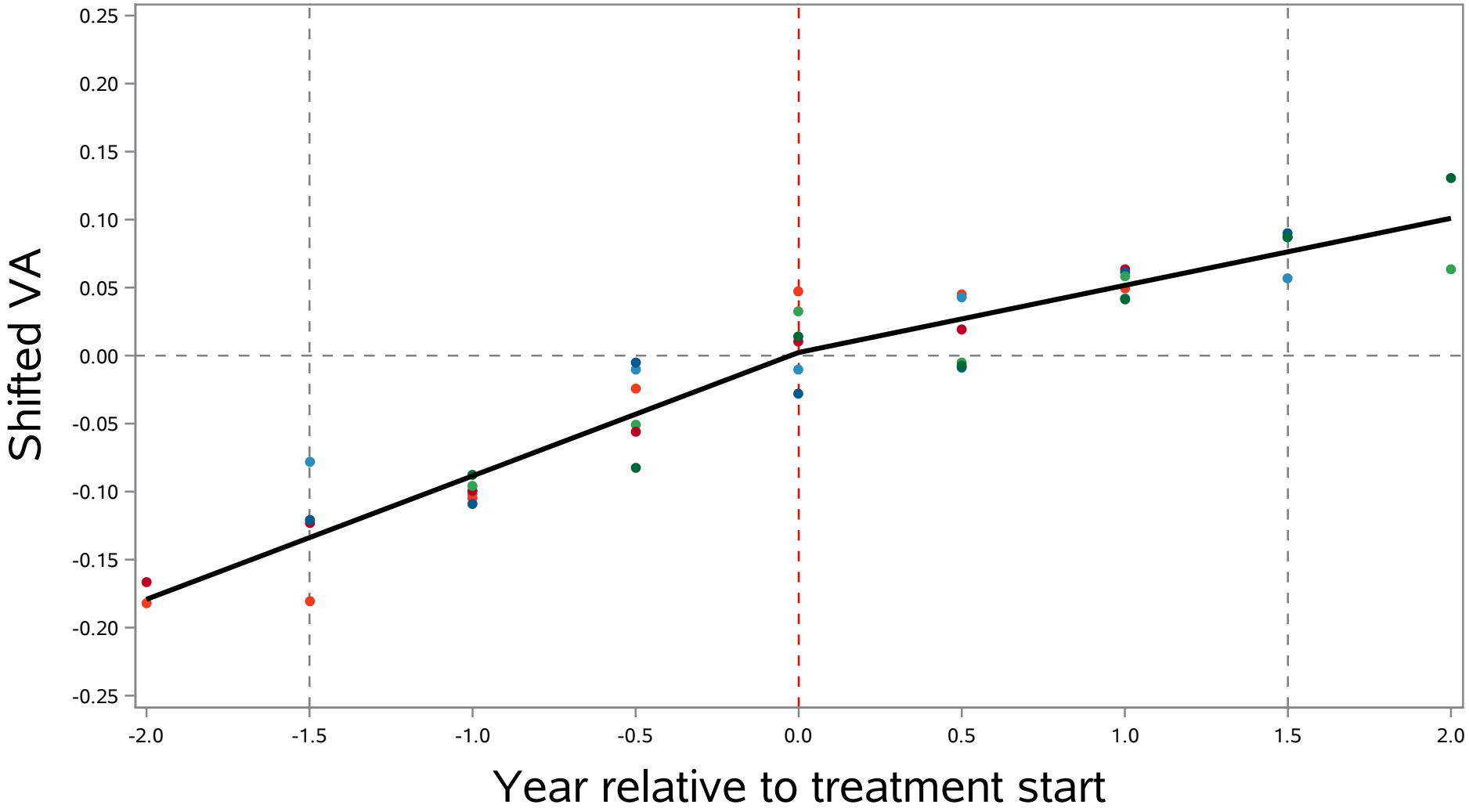


Figure 18: Broken stick model fit with pivot point estimated (non-linear mixed model)

Parameter	Estimate
Pivotx	-0.00047



Talk outline

- Motivating example clinical trial
- Hockey sticks and broken sticks
- A proposed design
- Summary

Figure 2: Current design

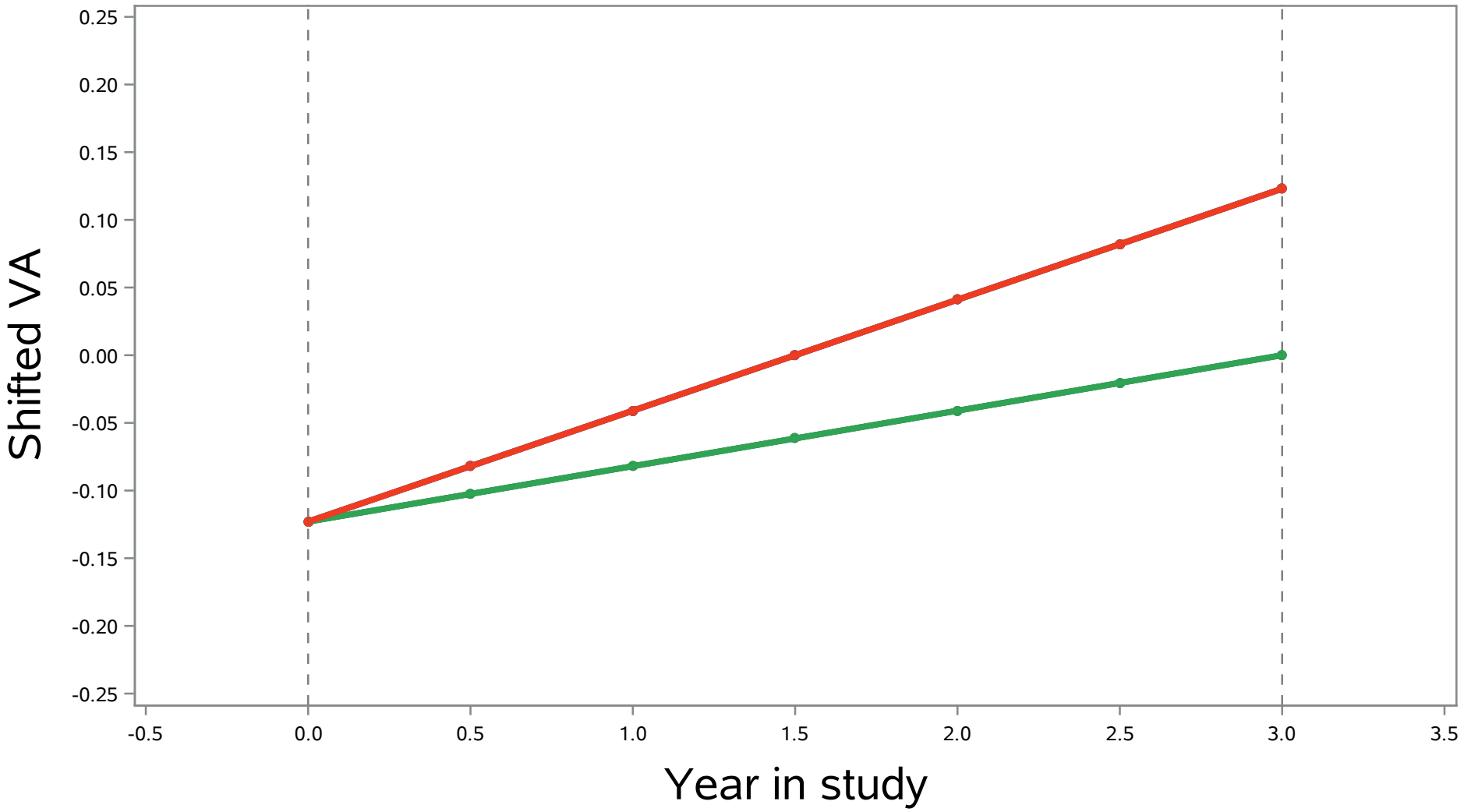
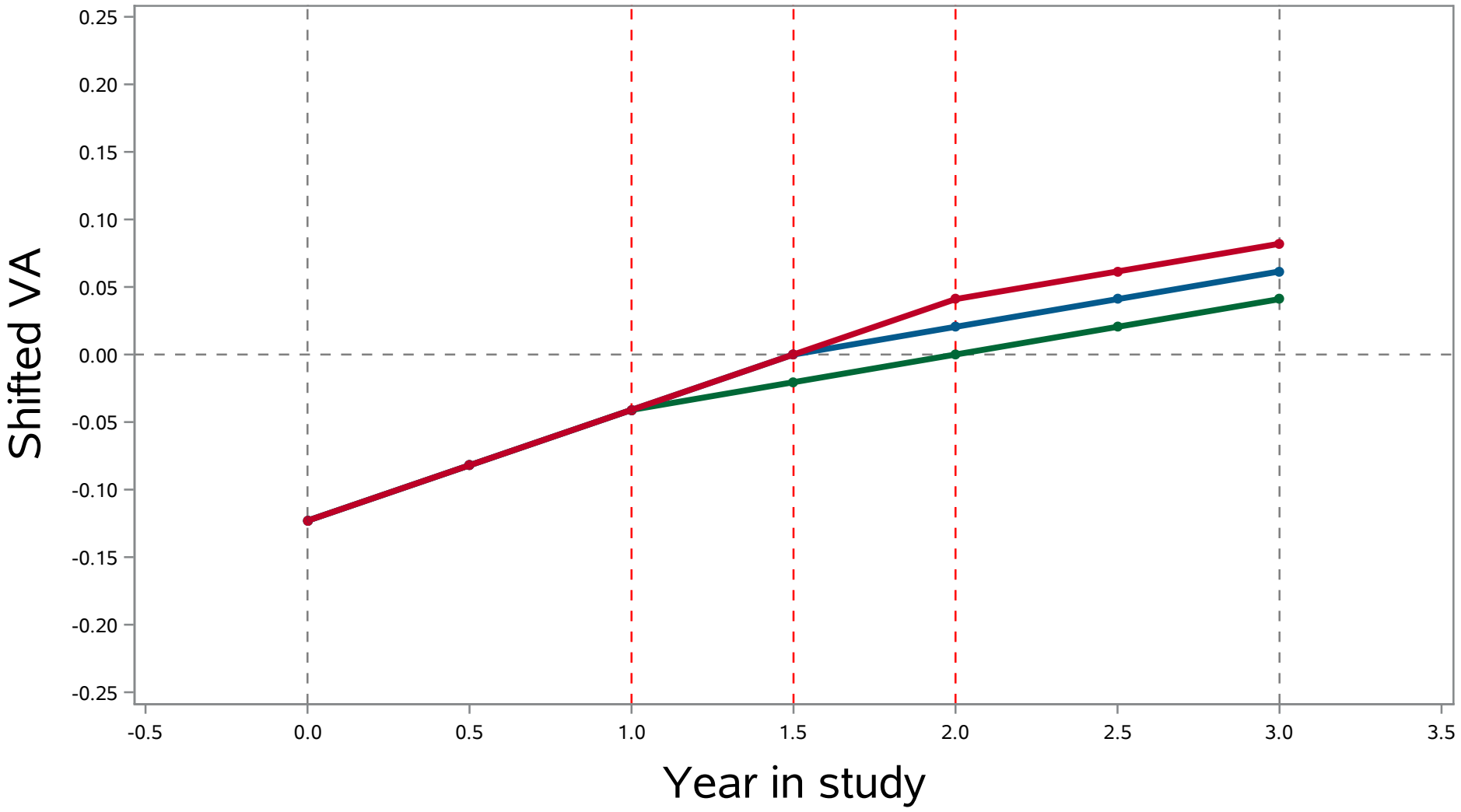


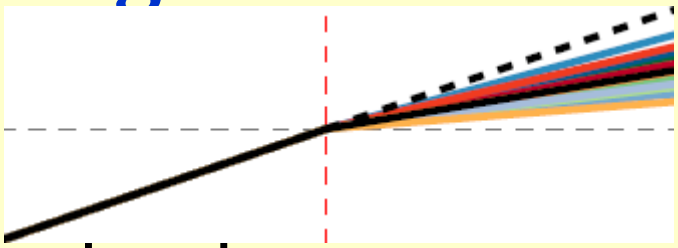
Figure 3: Proposed design



Consider a Hockey stick design when:

Consider a hockey stick design when:

Consider a hockey stick design when:



- No current treatment exists, but
- Placebo is unethical, or having no placebo encourages recruitment
- Randomization is mandatory
- Meets patient preference
- Study is longitudinal, because
- Disease is chronic, long-term
- Response is continuous, not greatly variable
- Drug effect is more rapid than size of gap
- (Endpoint data history available and valid helps)

Simulations?

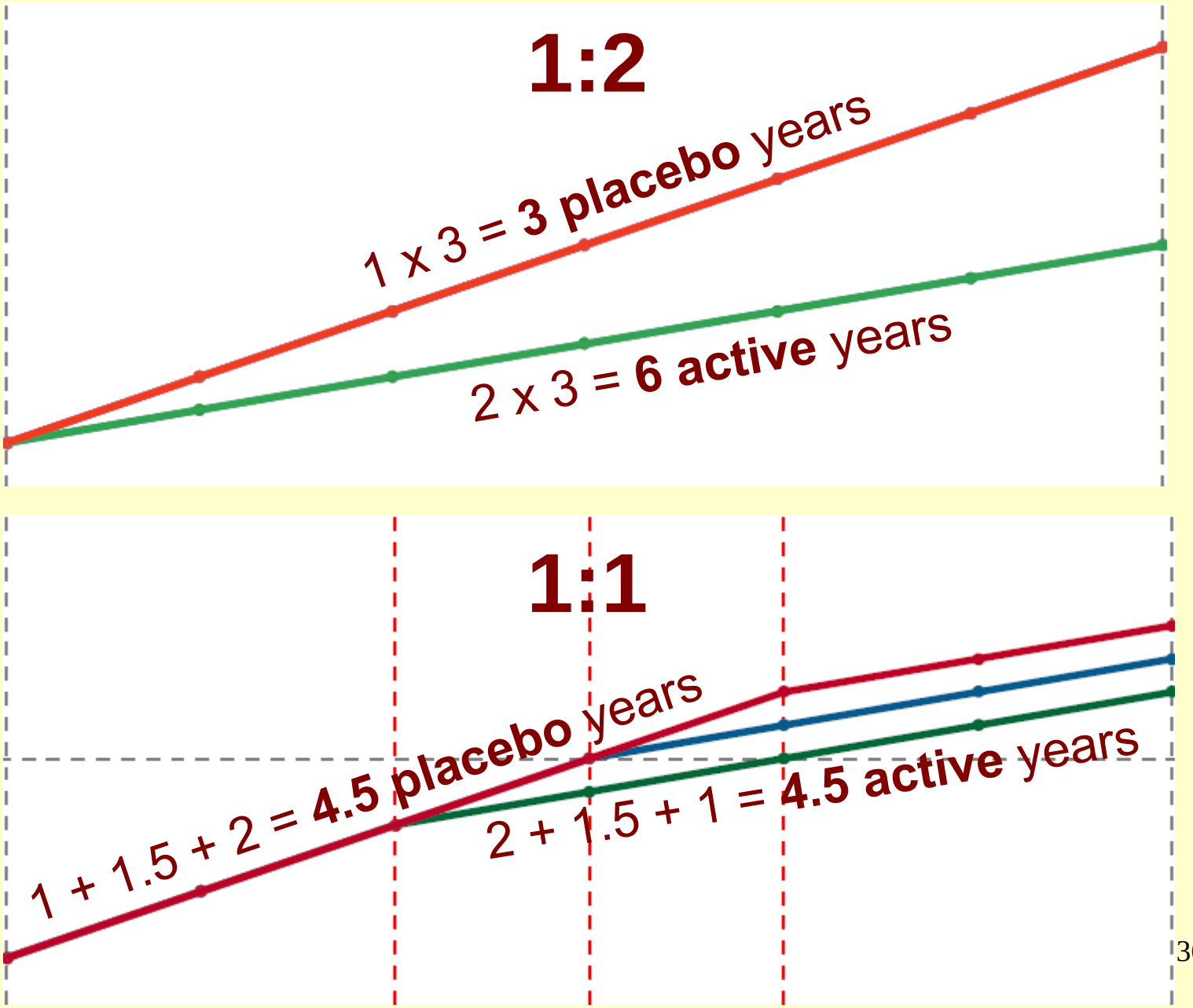
Why?

Simulations?

Why?

- Within-patient studies should be more powerful than between-patient (and more informative of mechanism)
- Realistic differential dropout simulation must favour hockey stick design
- Equal replication of two treatments being compared is more powerful than unequal replication ...

Three patients on either design (9 years total)



References

Google:

Broken stick models

Hockey stick model

Line segment regression

Interrupted time series (ITS)

....

Thank you for your attention!

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