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

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AASC, Rotorua, NZ, 5 December 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.

If time, comparison with other possible designs will be made, still from the patient perspective. Which would YOU choose?

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.

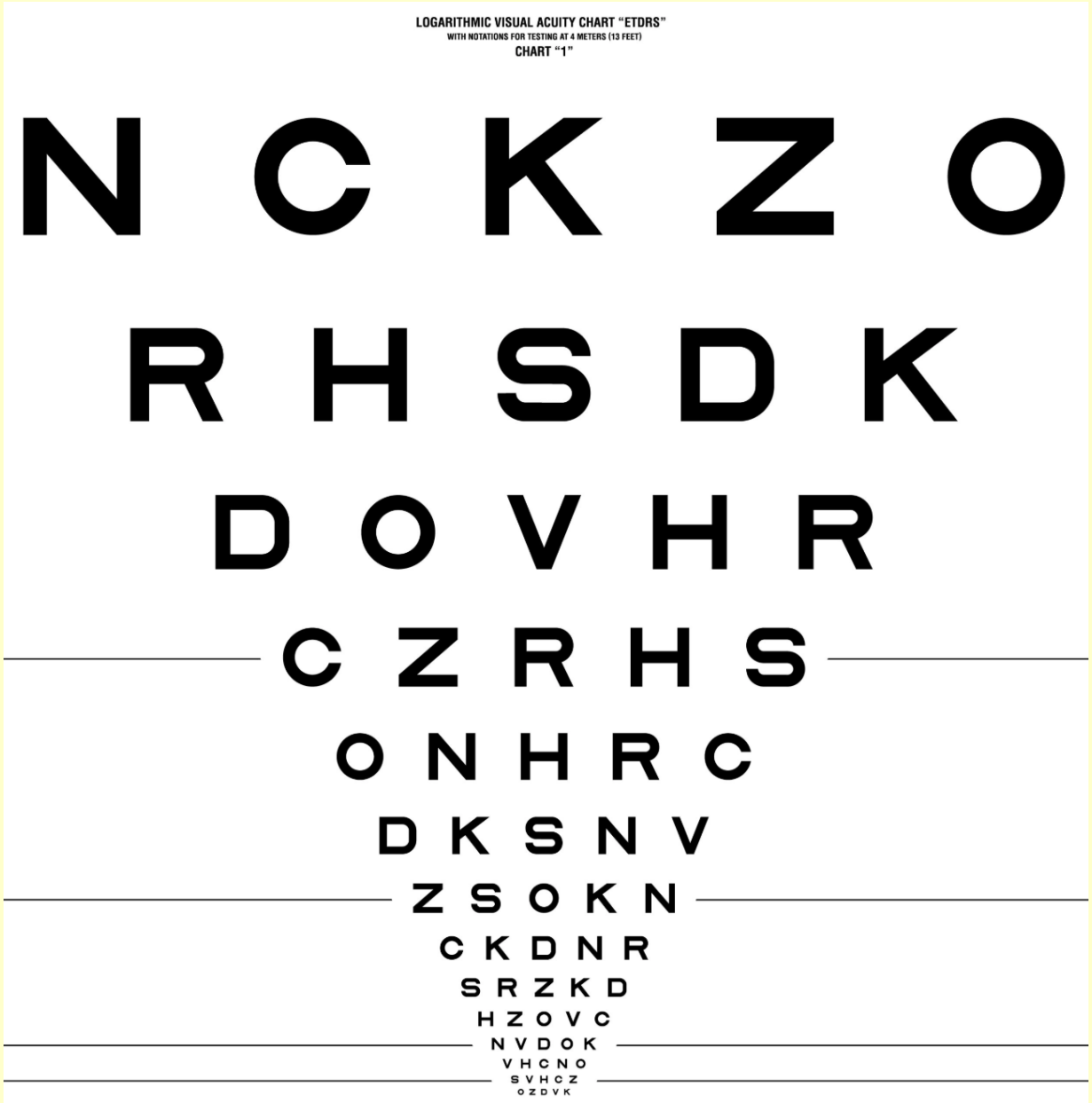
A 31-year-old woman was diagnosed with type 1 diabetes at age 5, with hypothyroidism at age 16. She developed progressive visual loss at age 19 and progressive hearing loss at age 28. Life expectancy with this disease is about 30 years.

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

Visual acuity (VA) – log Minimum Angle of Resolution



Talk outline

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

What are hockey sticks and broken sticks?

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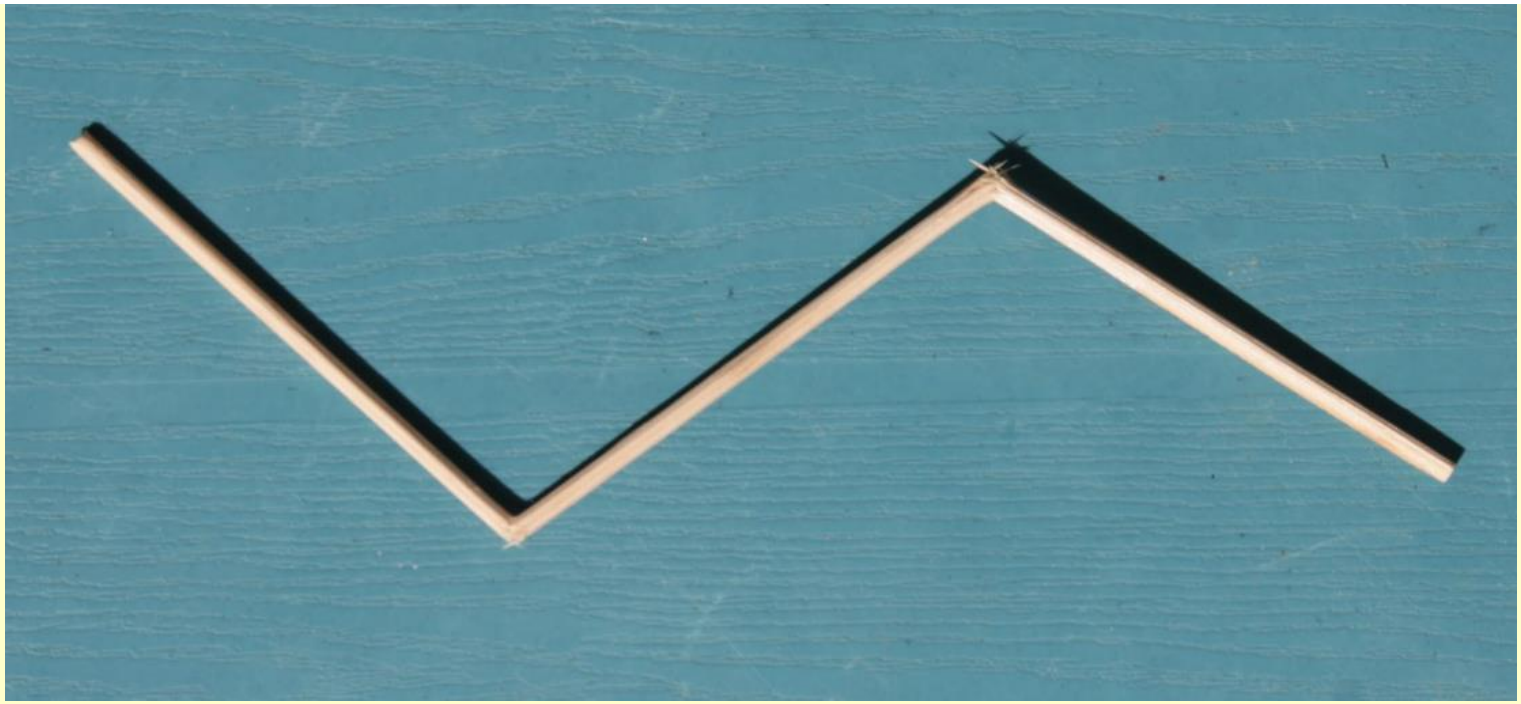


This is not a hockey stick

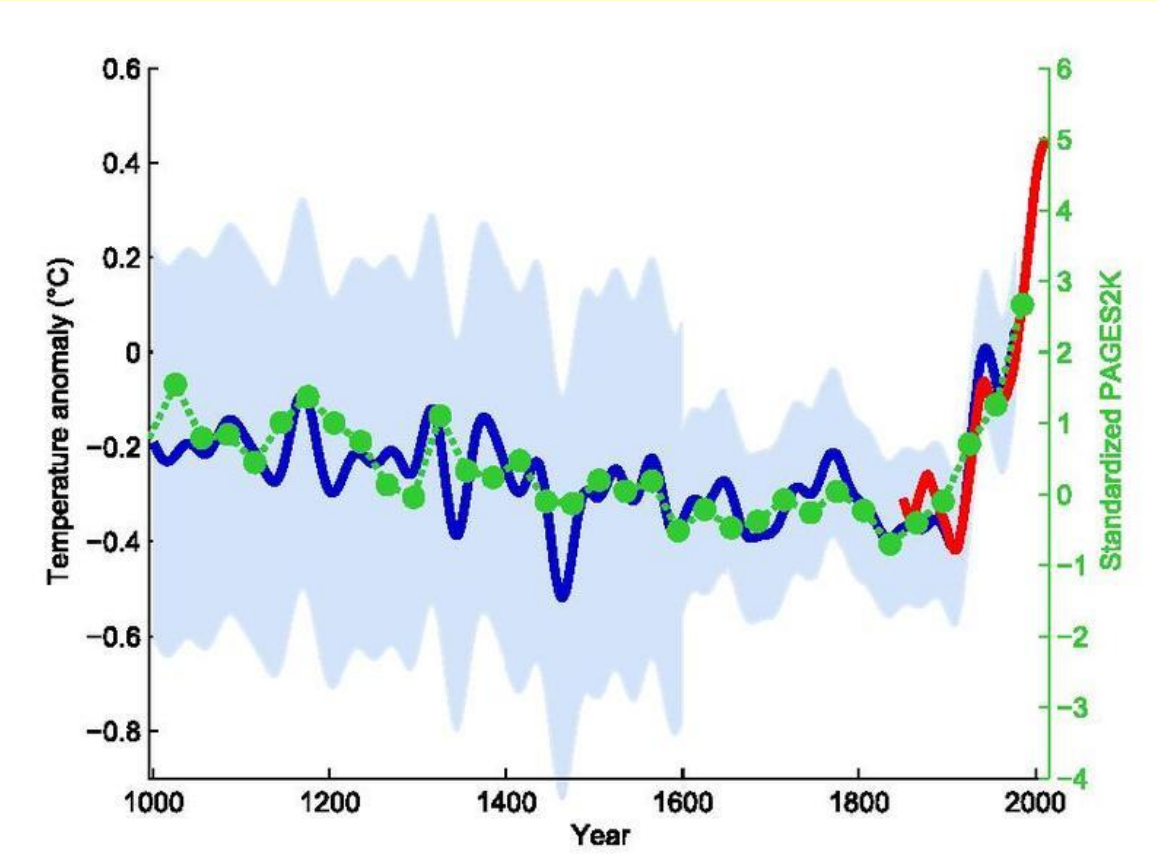
with apologies to René Magritte

This is the most famous hockey stick ?

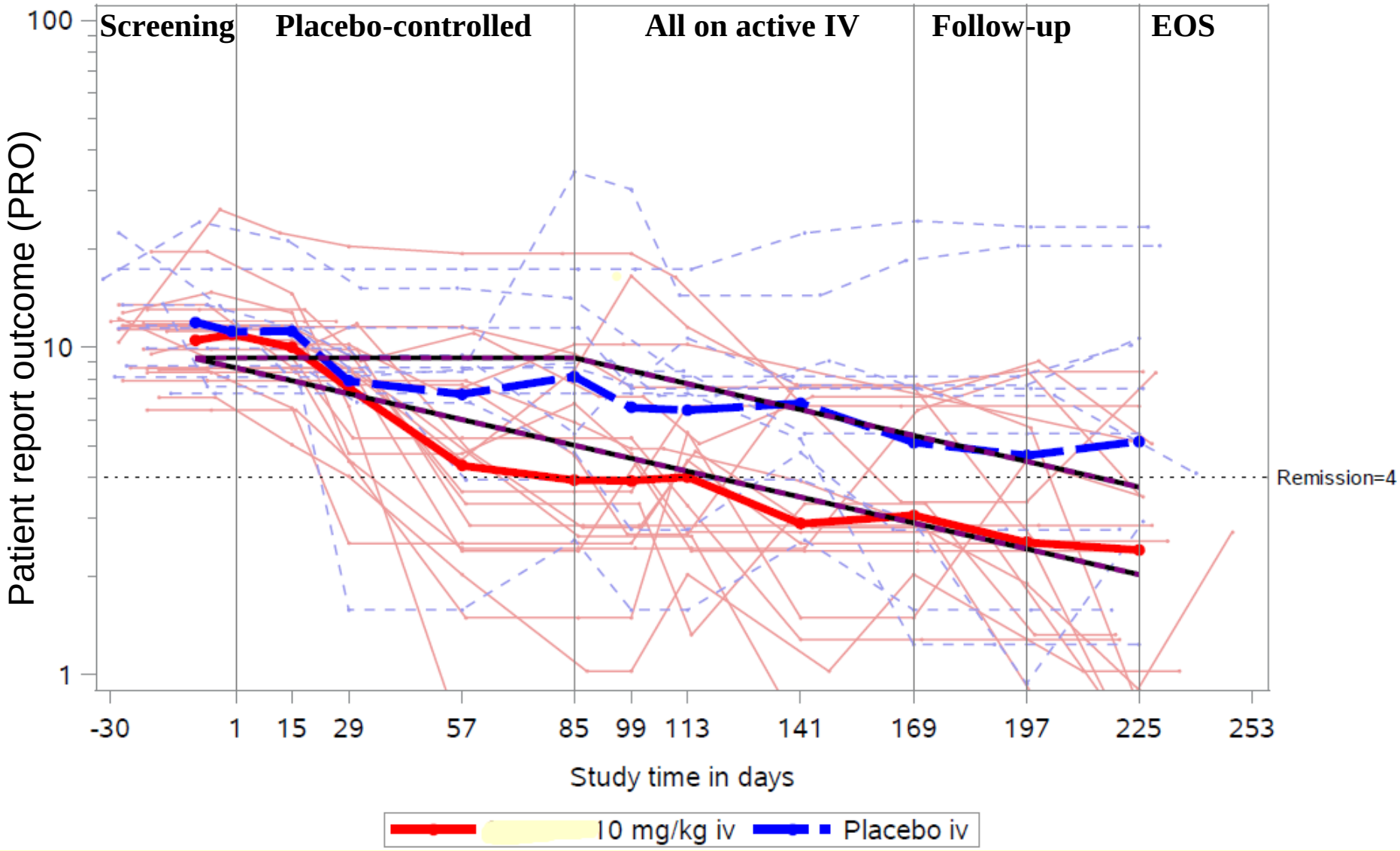
This is the most famous hockey stick

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.

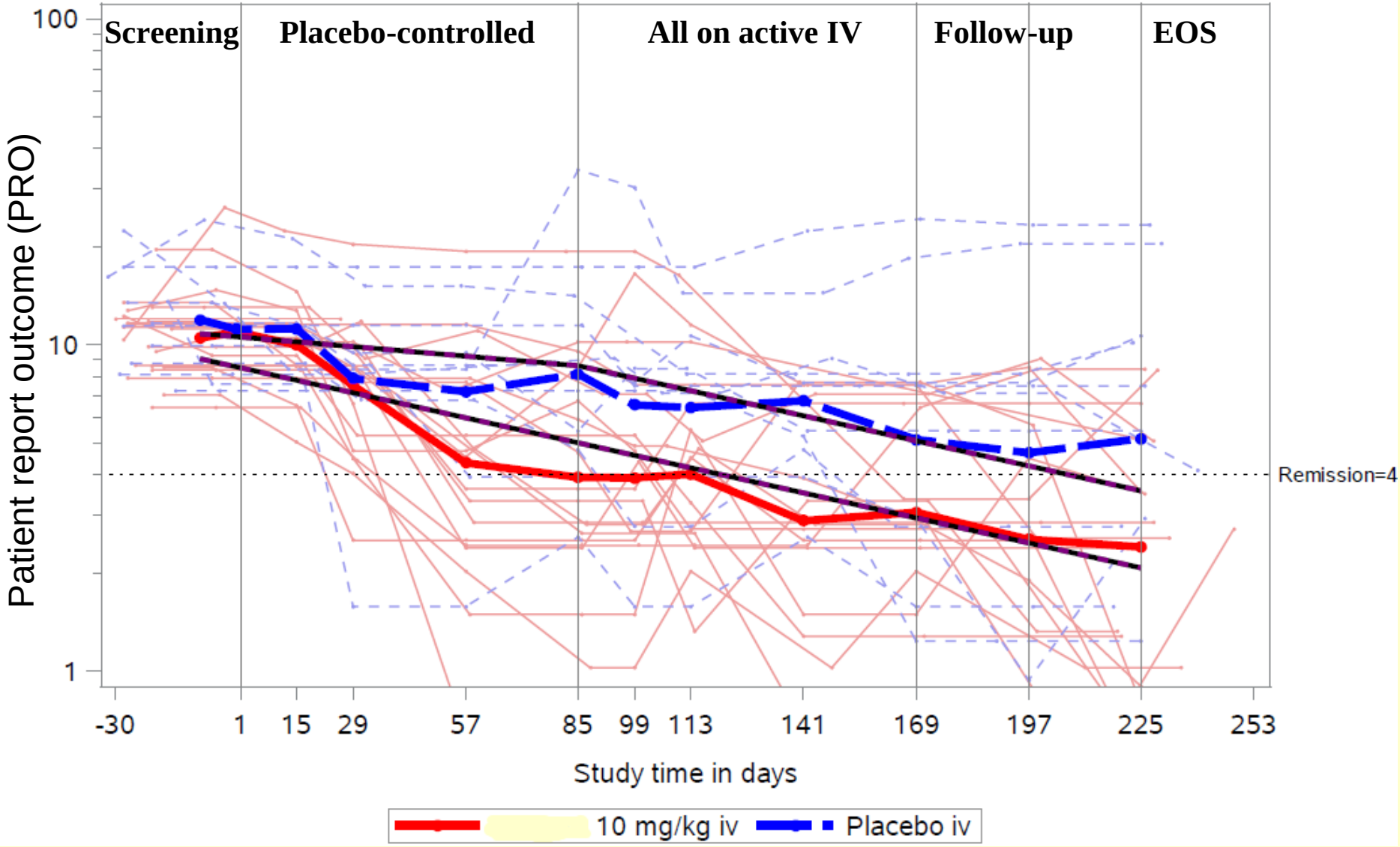


A real hockey stick example



Partially controlled design

A real hockey stick example

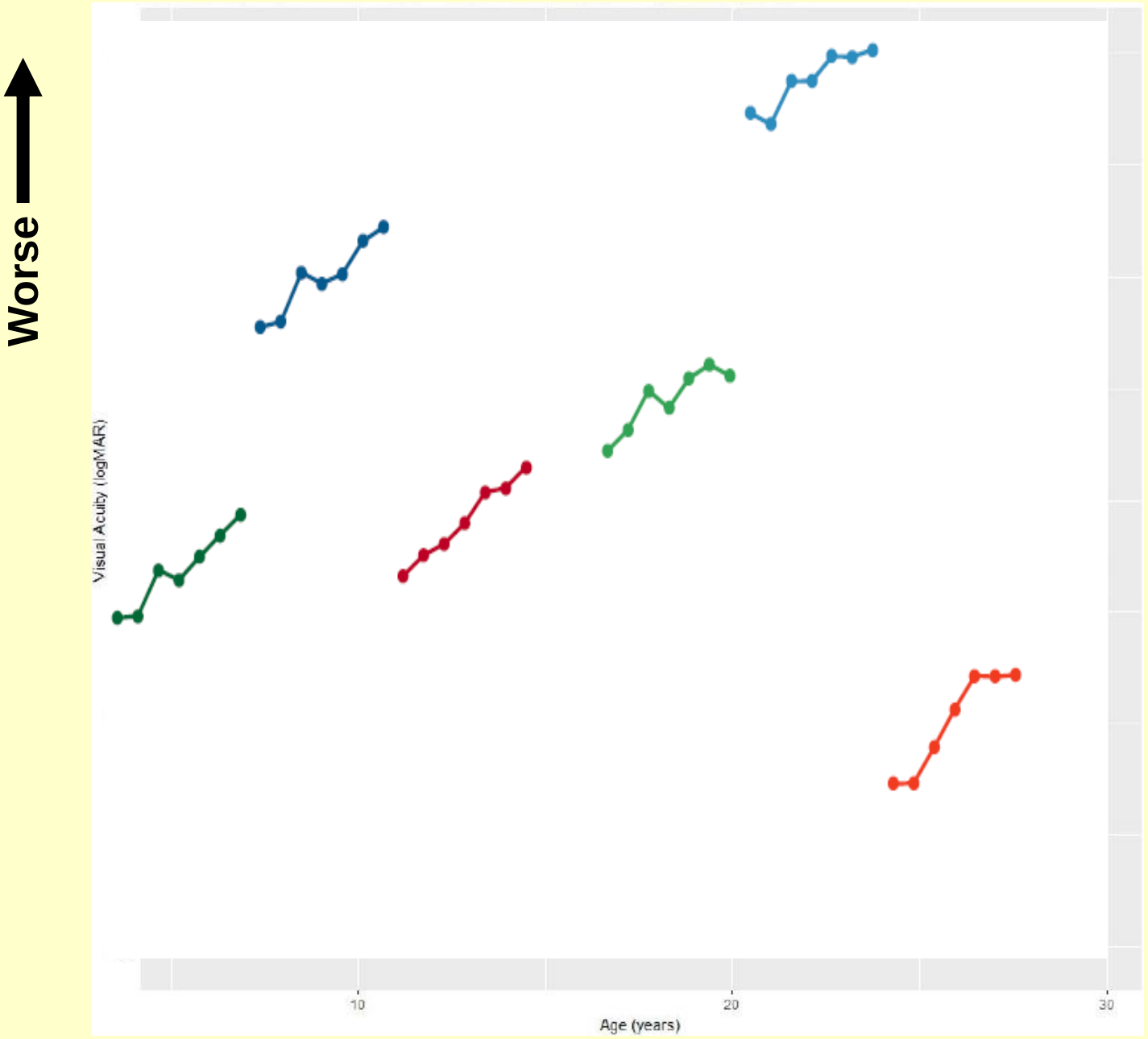


Partially controlled design

Talk outline

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

Simulated VA in six patients with Wolfram syndrome



Source: Simulation based on parameters from Hershey data. Within patient slope = 8 units/year

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

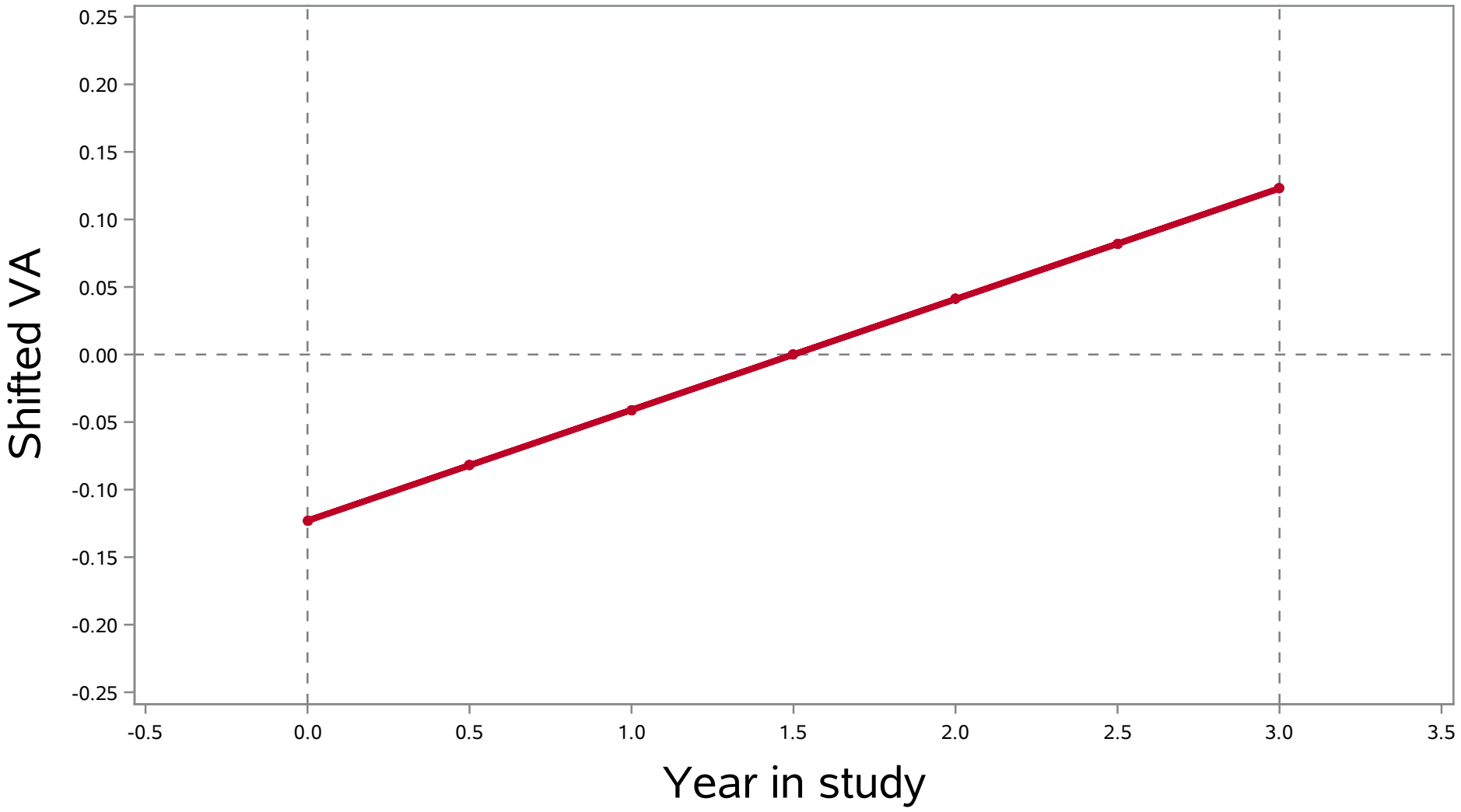


Figure 2: What is the current design and what is the model?

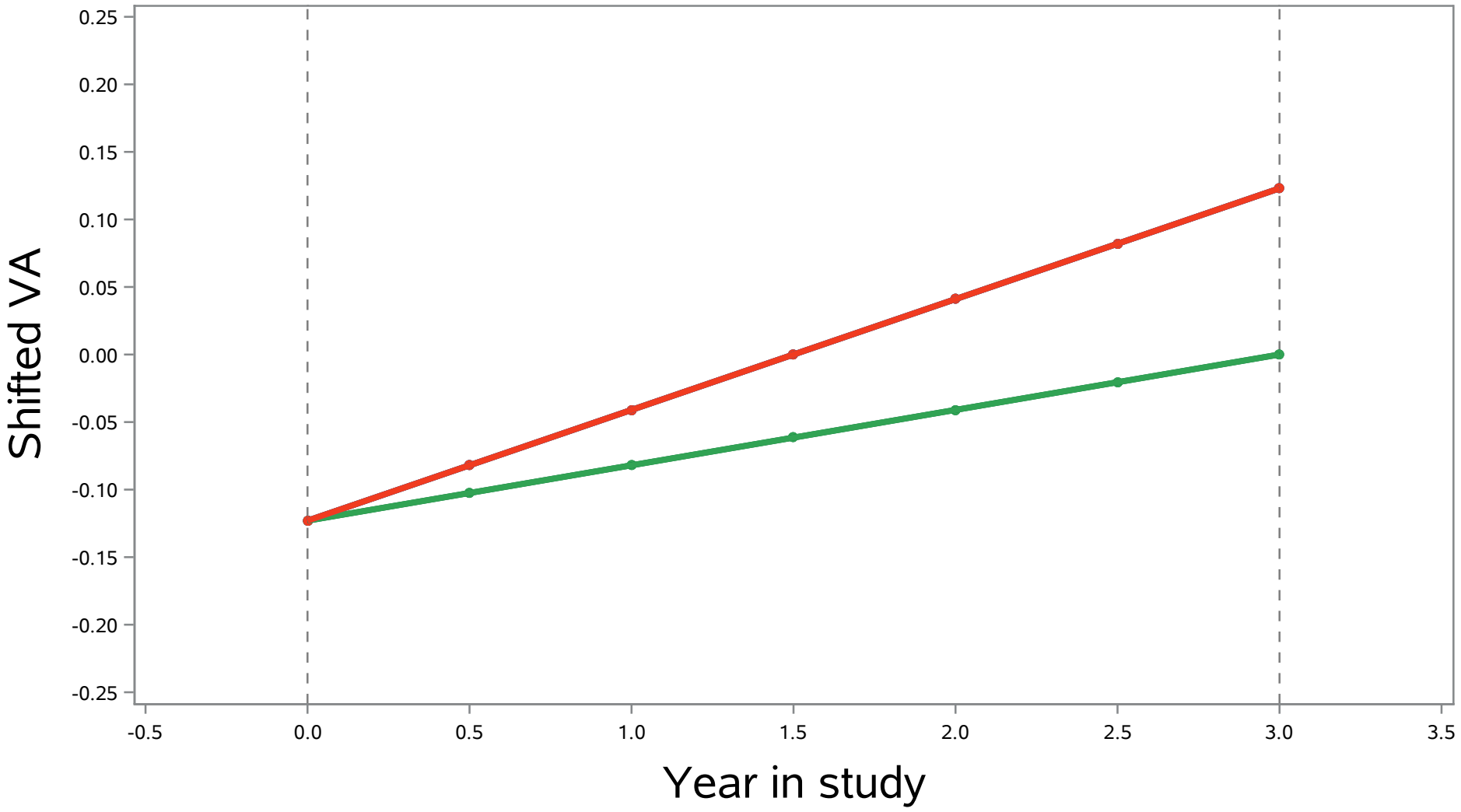


Figure 3: What is the proposed design and what is the model?

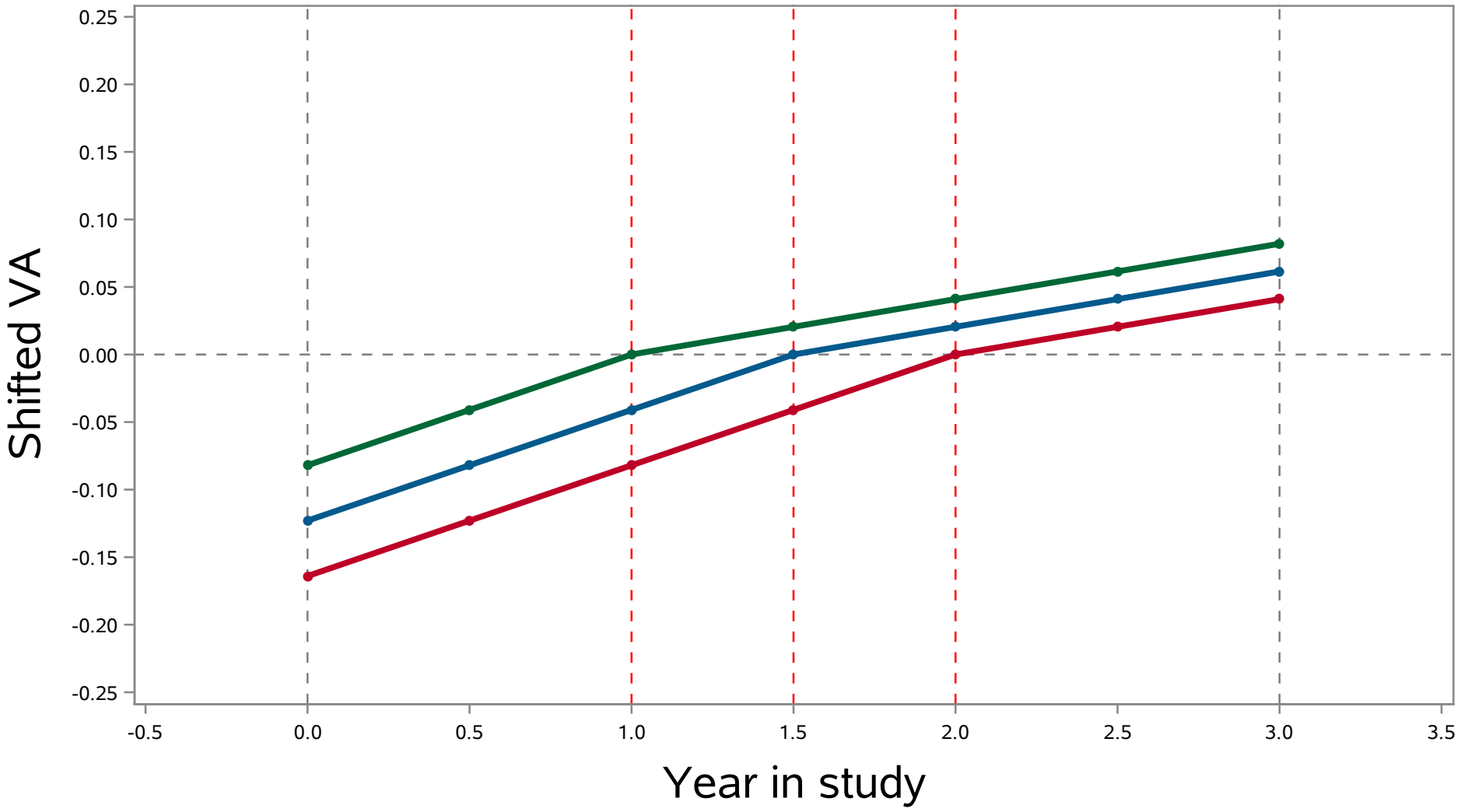


Figure 4: What is the proposed design and what is the model?

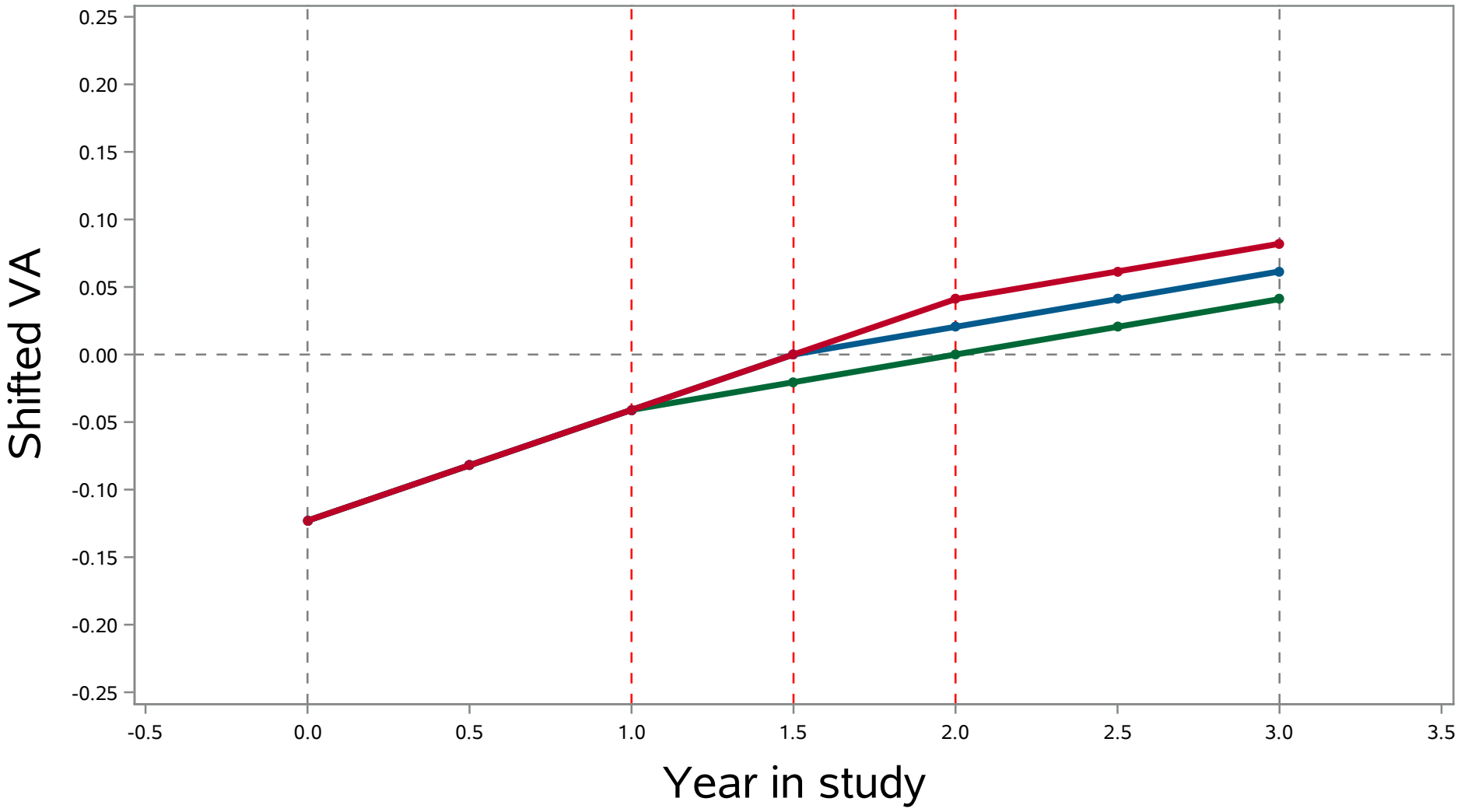


Figure 5: Simulated data shifted to study year over three years

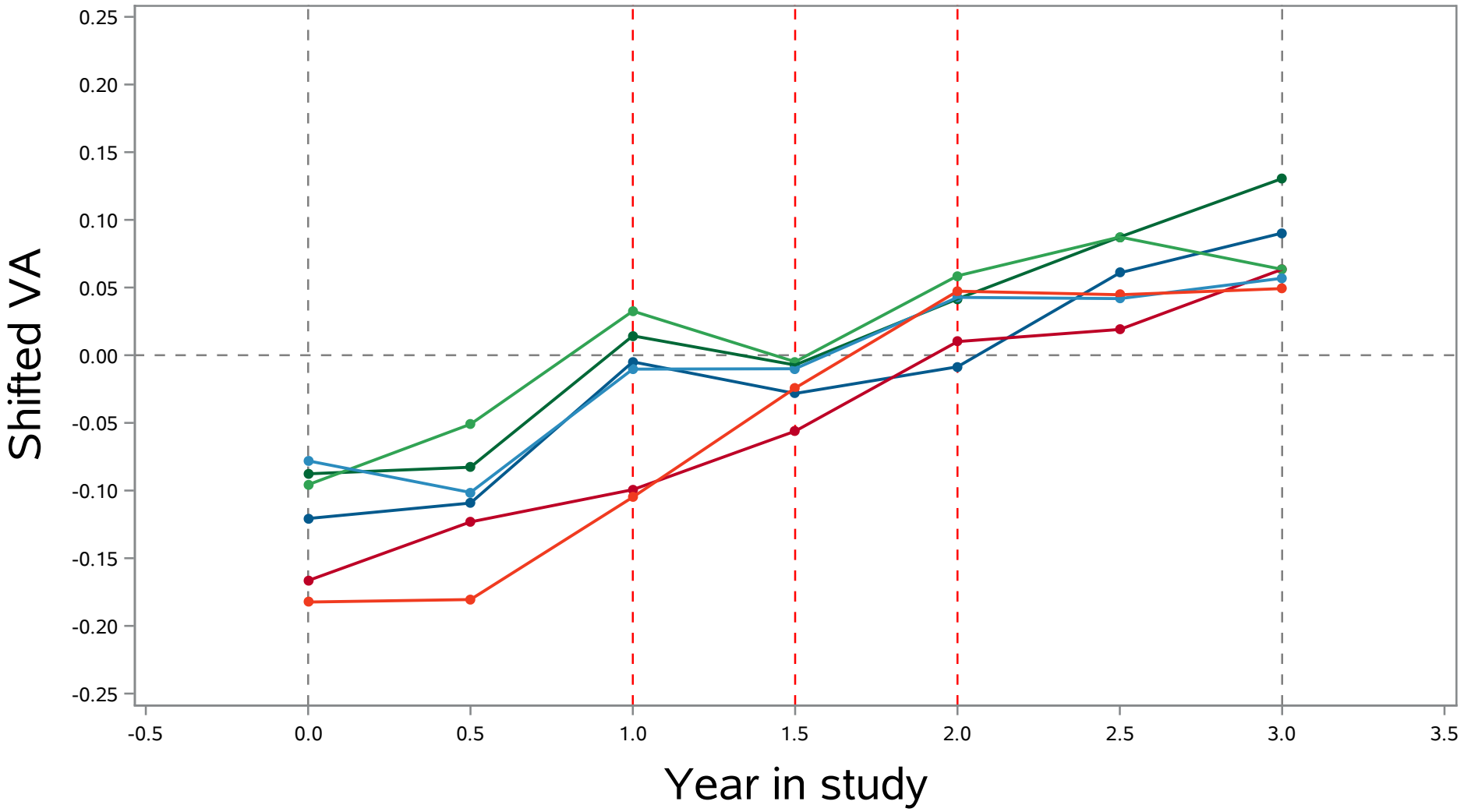


Figure 6: Simulated data shifted to year of treatment with underlying model

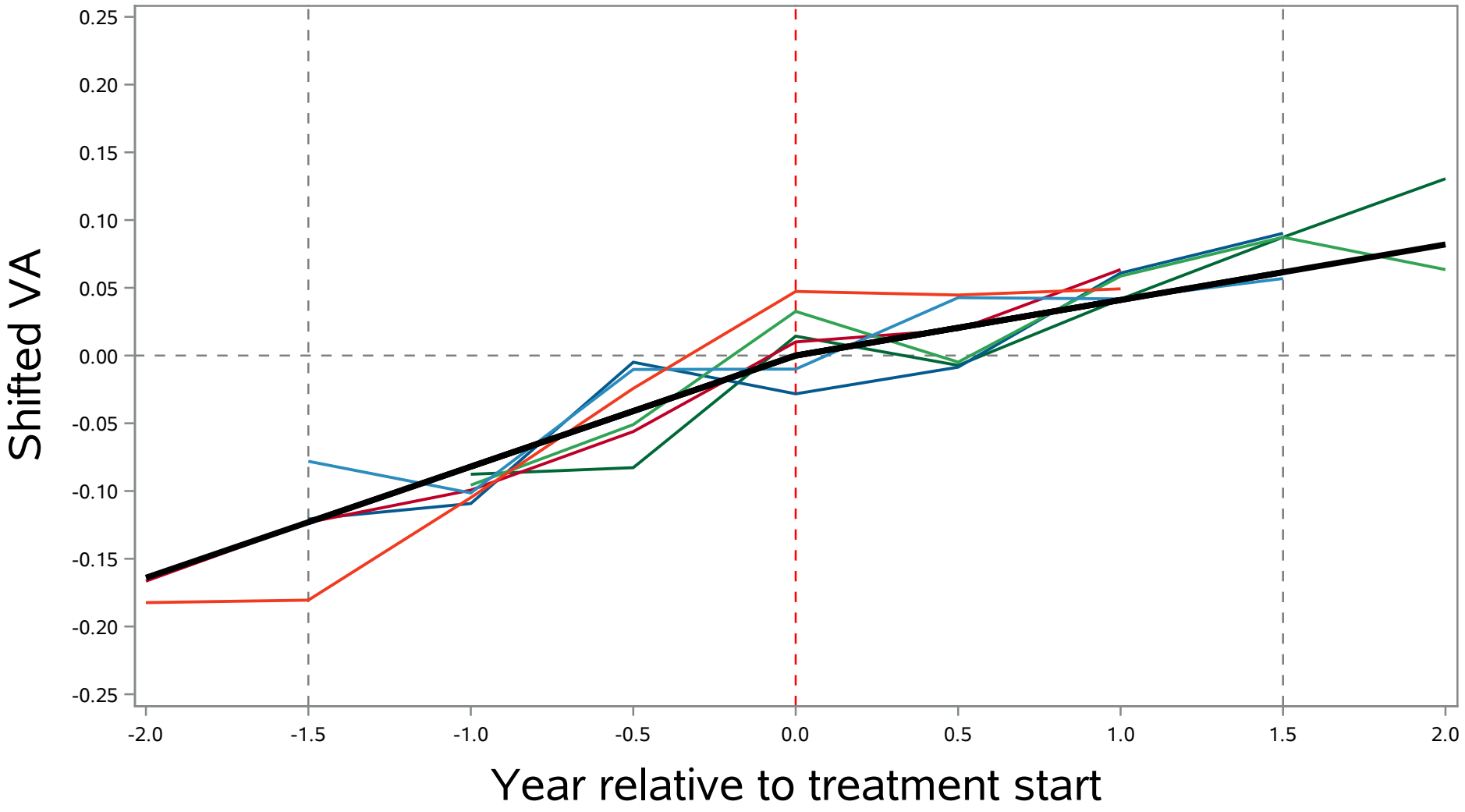


Figure 7: Simple hockey/broken stick model fit

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

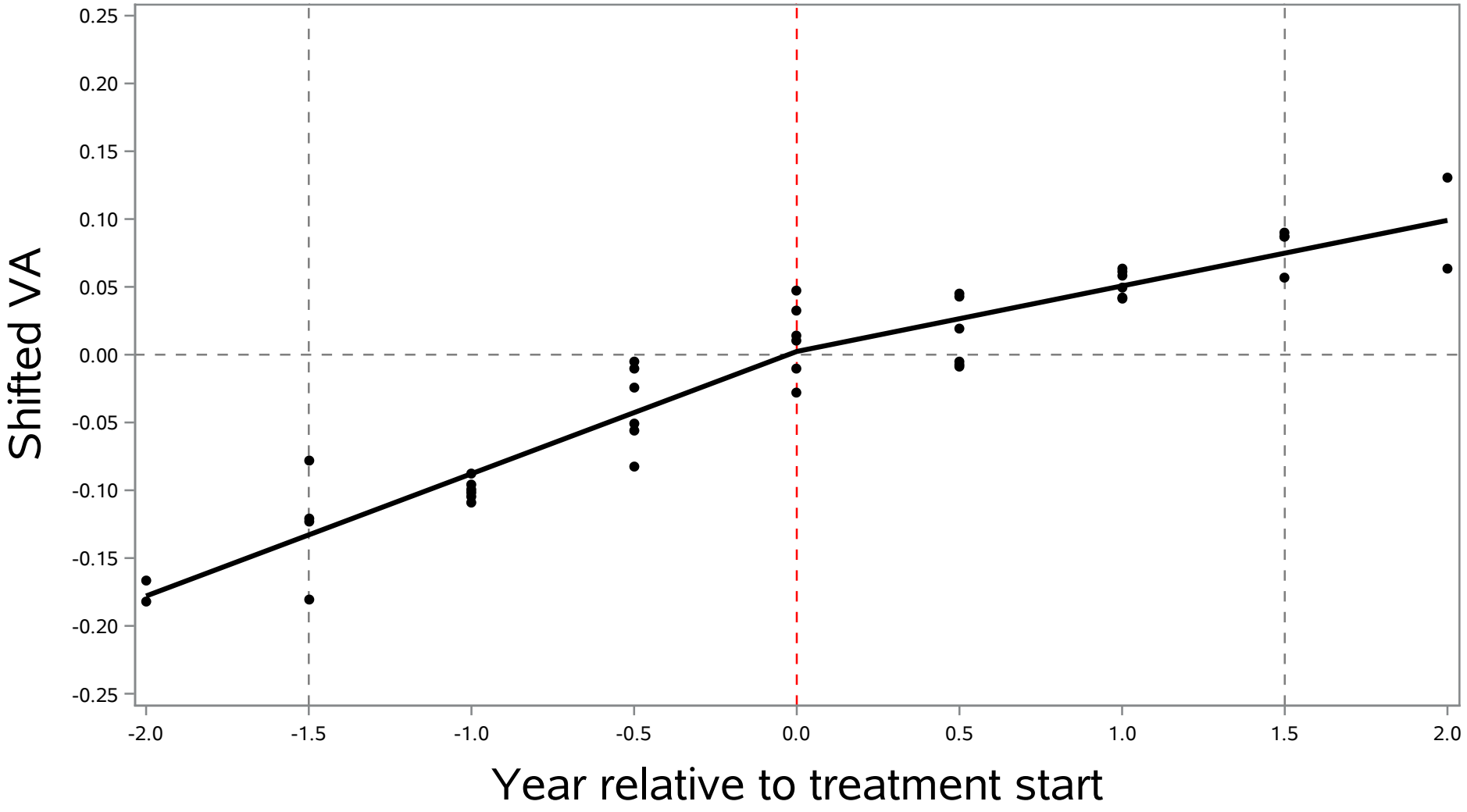


Figure 8: RC broken stick model with per patient predicted lines (random effect)

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

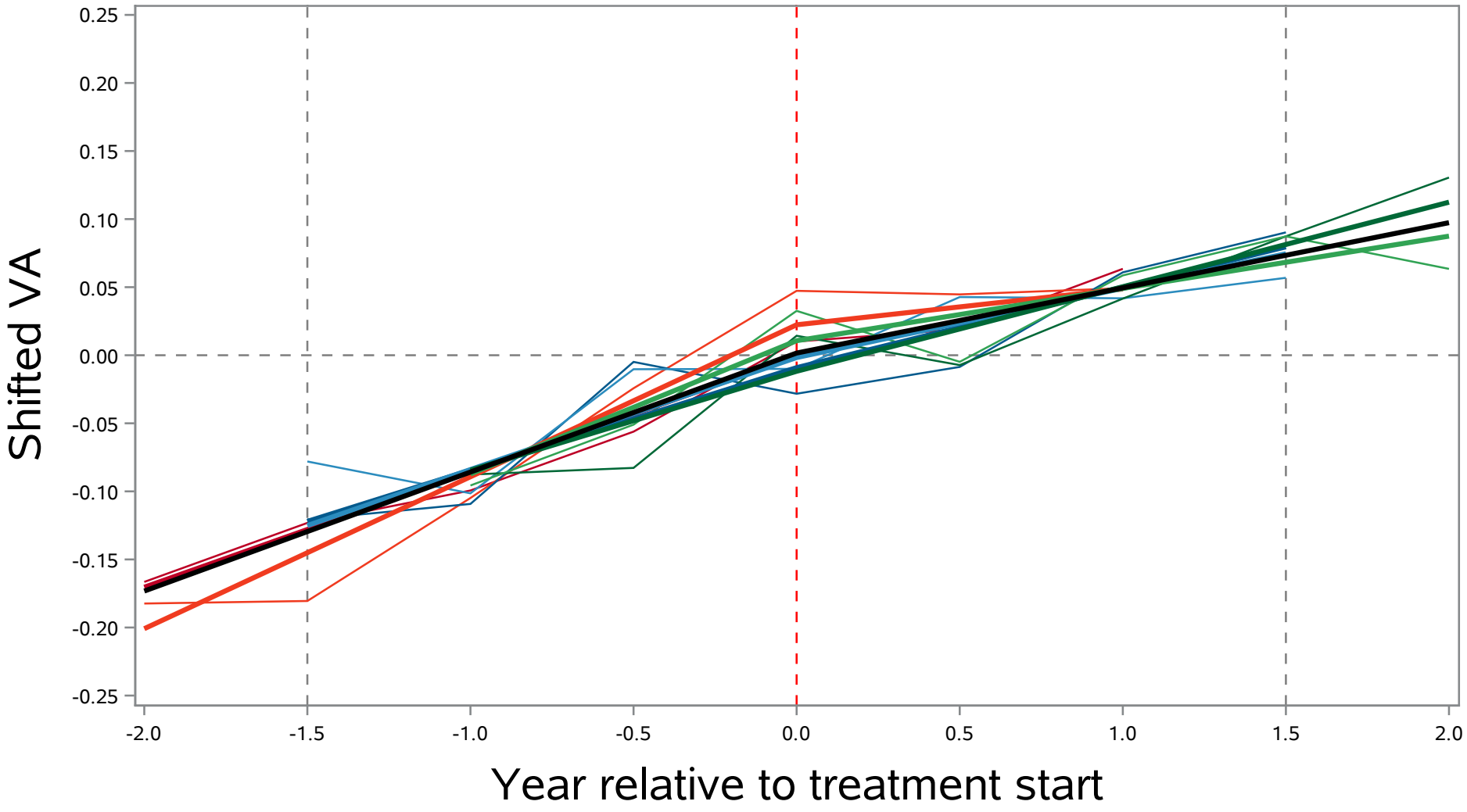


Figure 9: RC broken stick model standardized to same initial slope

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

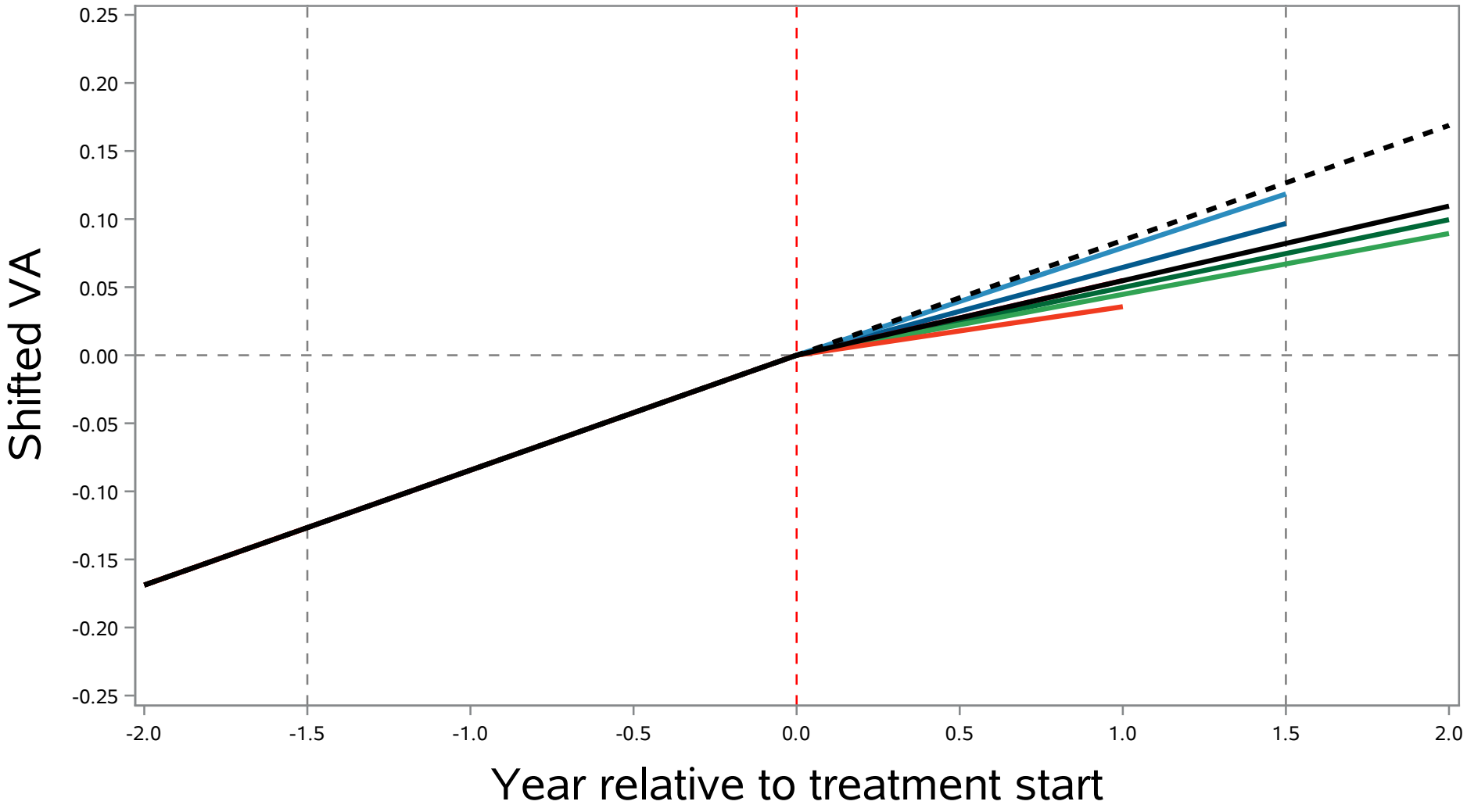
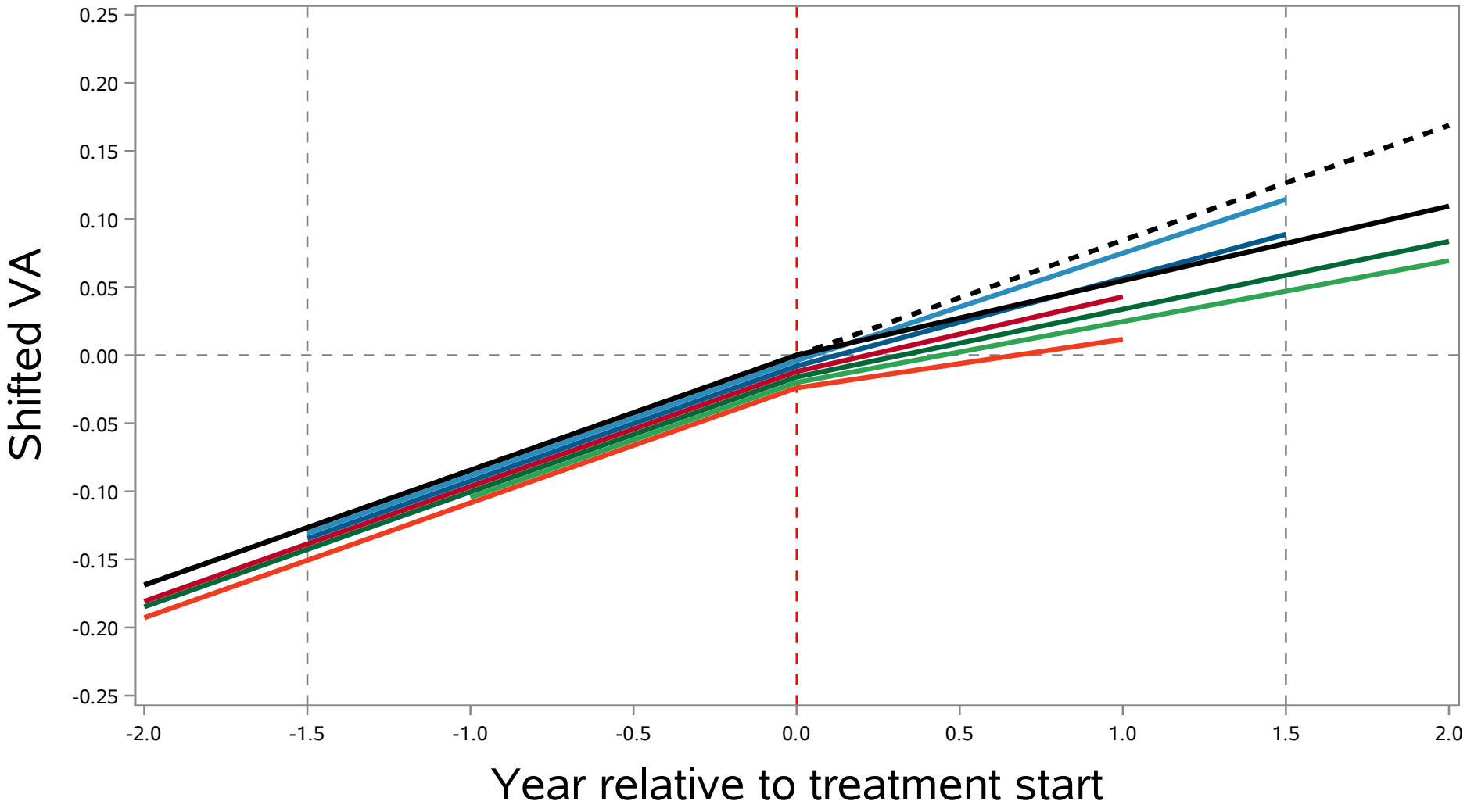


Figure 10: RC broken stick model standardized to same initial slope, with jitter

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

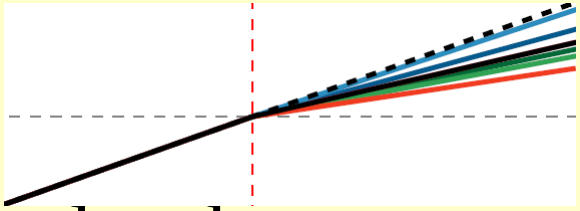


Talk outline

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

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
- (Available and valid data history helps)

Simulations?

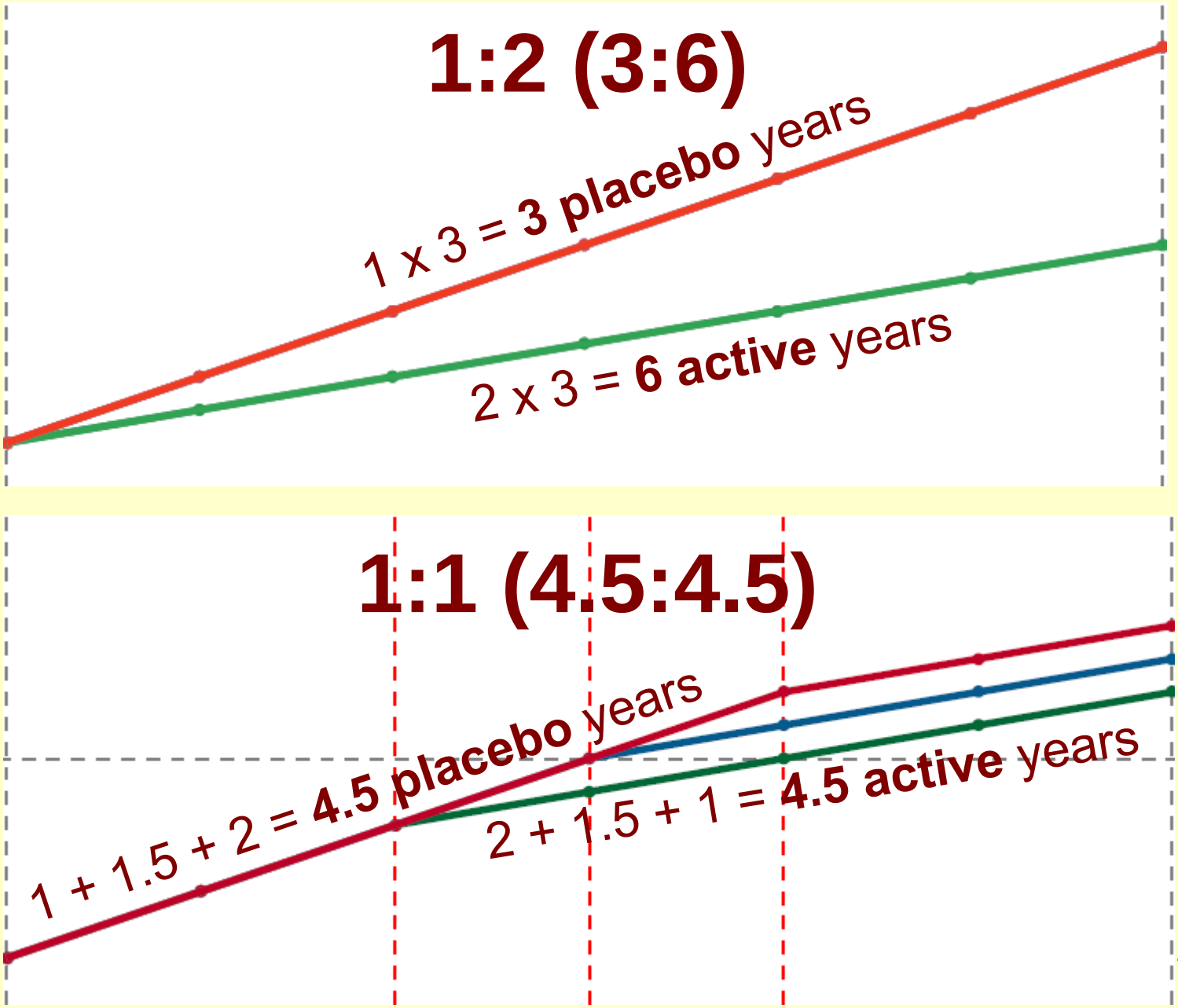
Why?

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)



Thank you for your attention!

QUESTION:
Is adherence to placebo control sometimes doing a disservice to both current and future patients?

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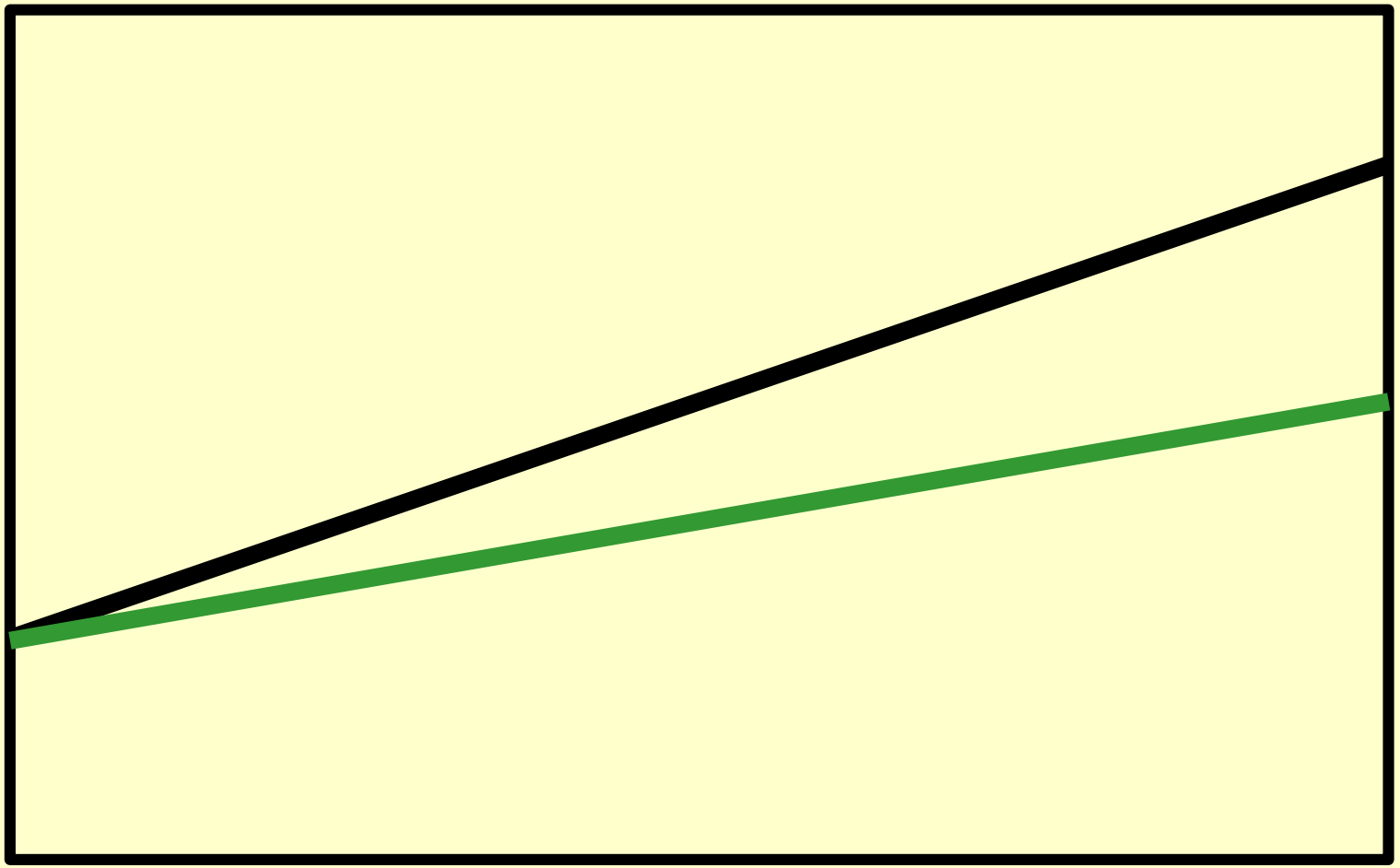
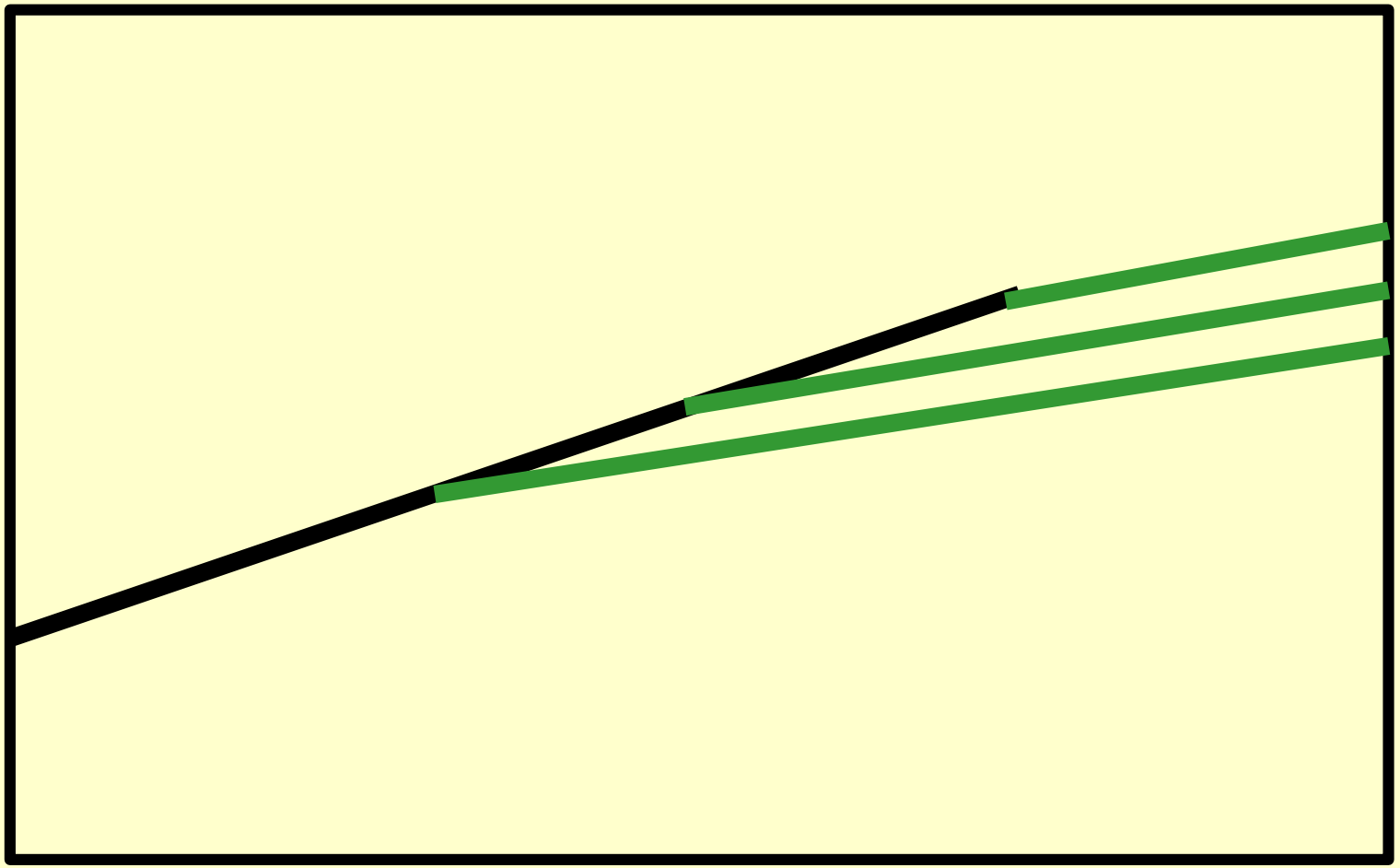
3rd EFSPI Workshop on Regulatory Statistics
Basel, 25 September 2018

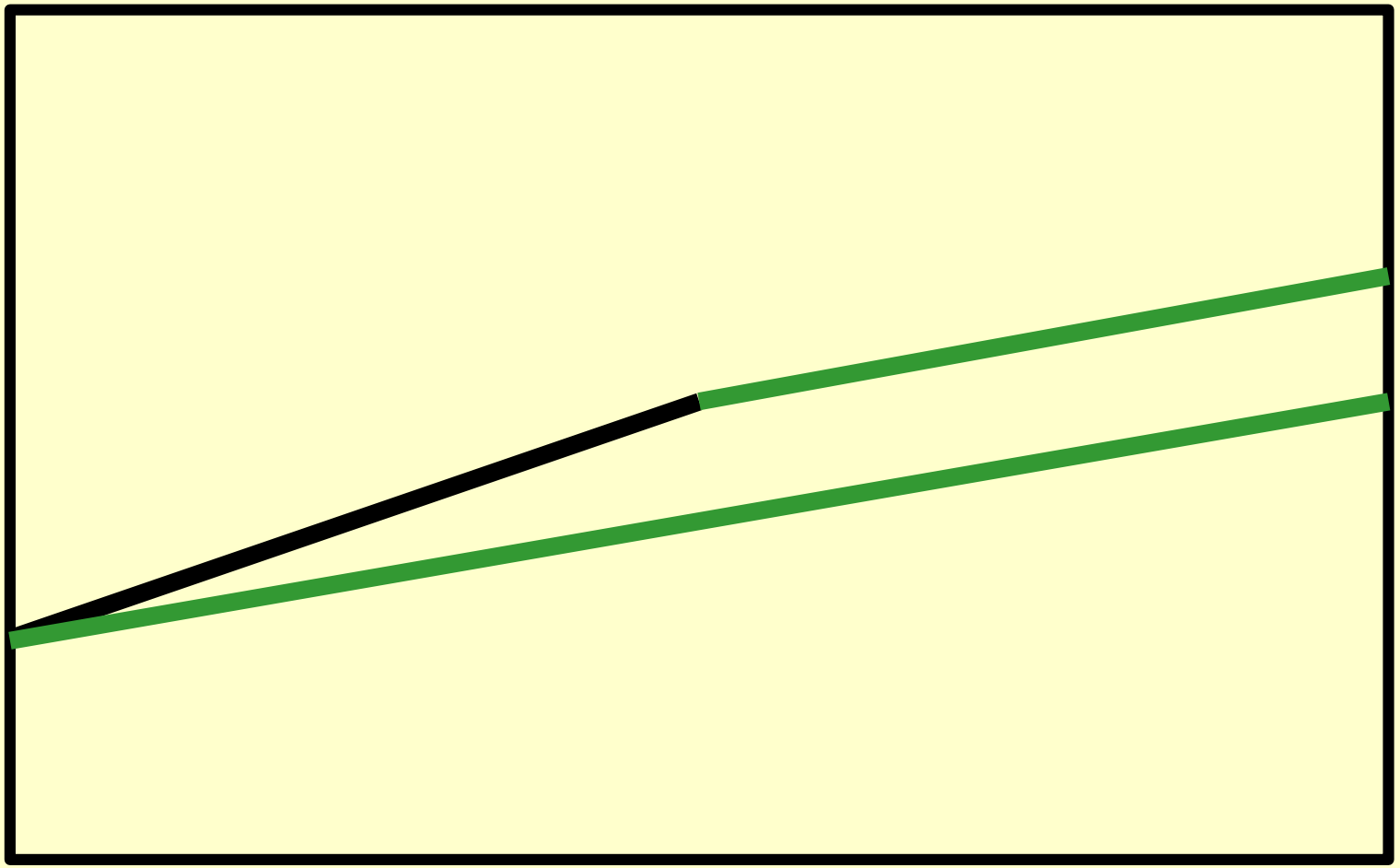
Current RCT design



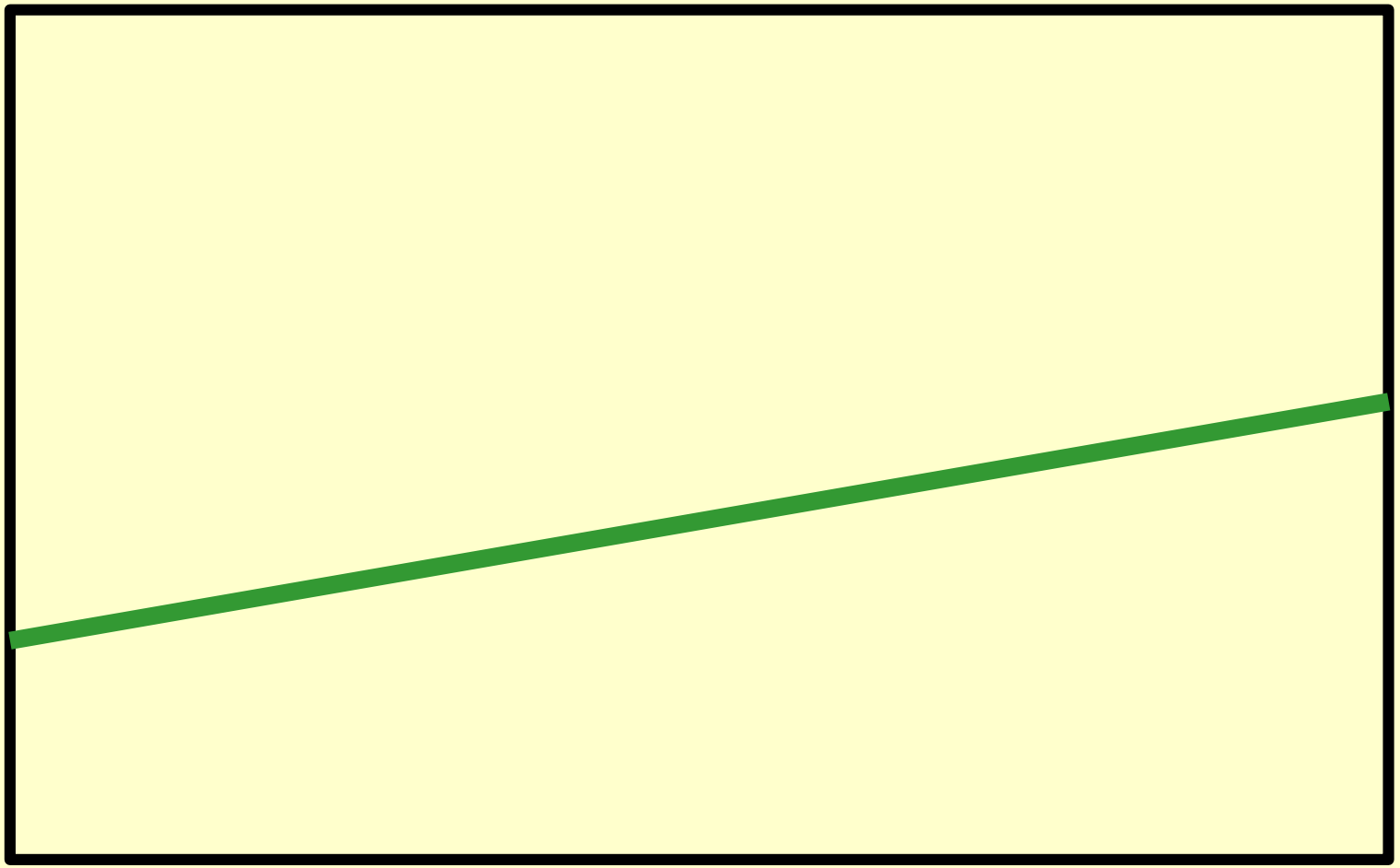
Hockey stick design



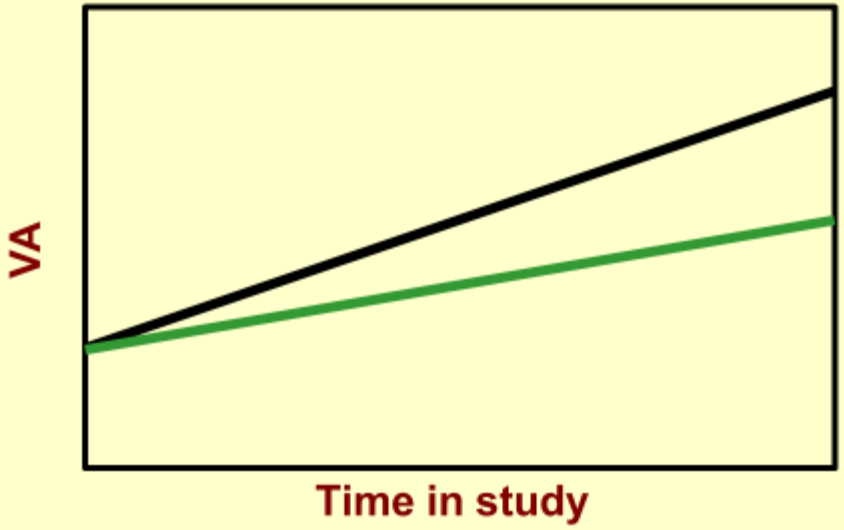
Partially controlled design



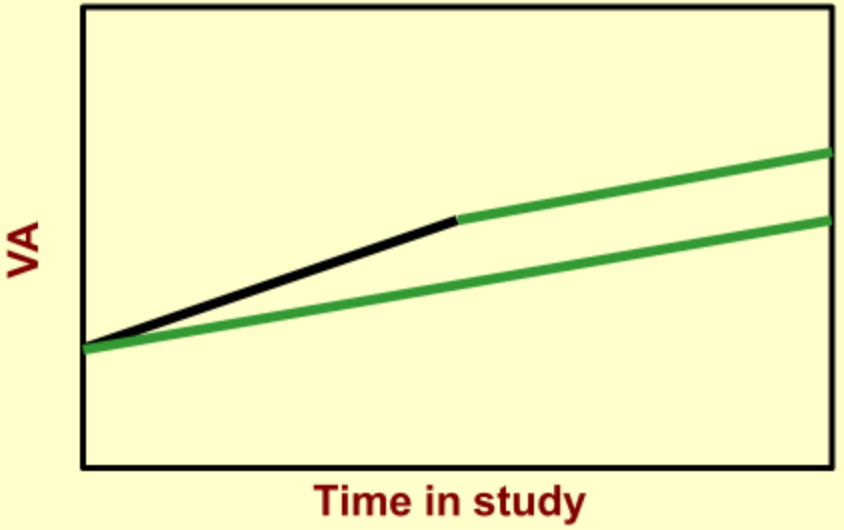
Single arm study



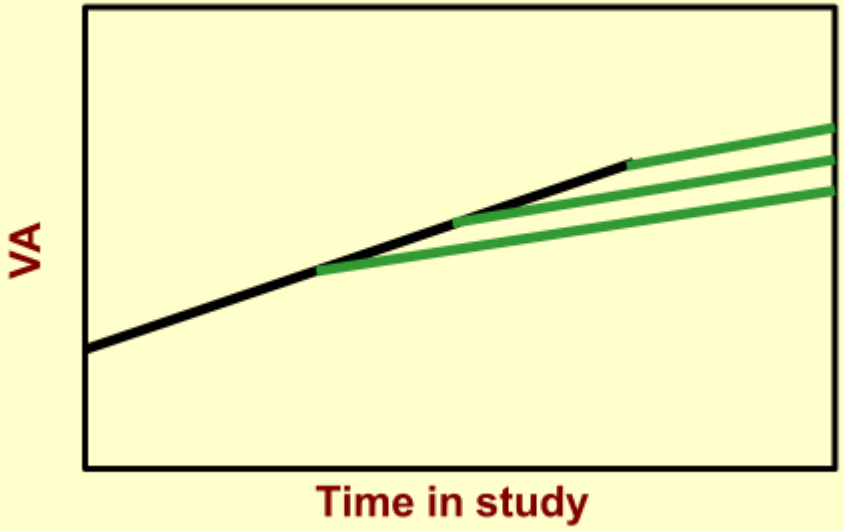
Current RCT design



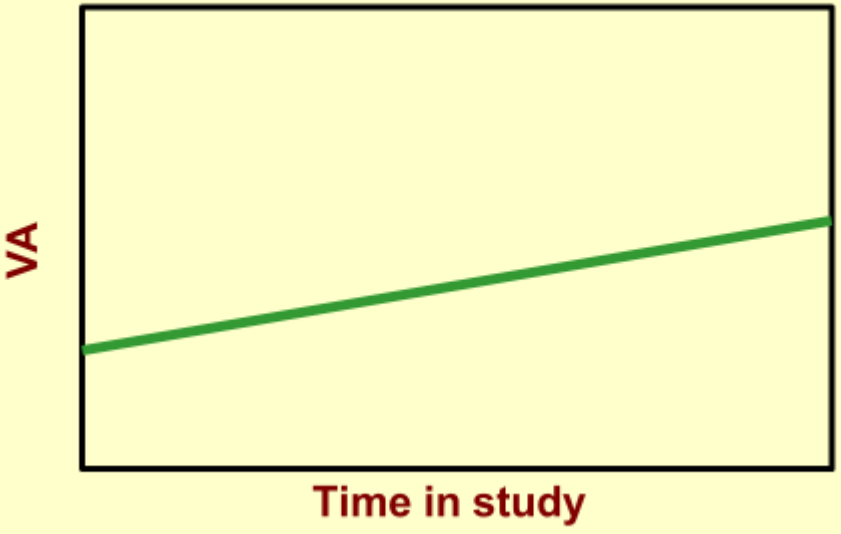
Partially controlled design

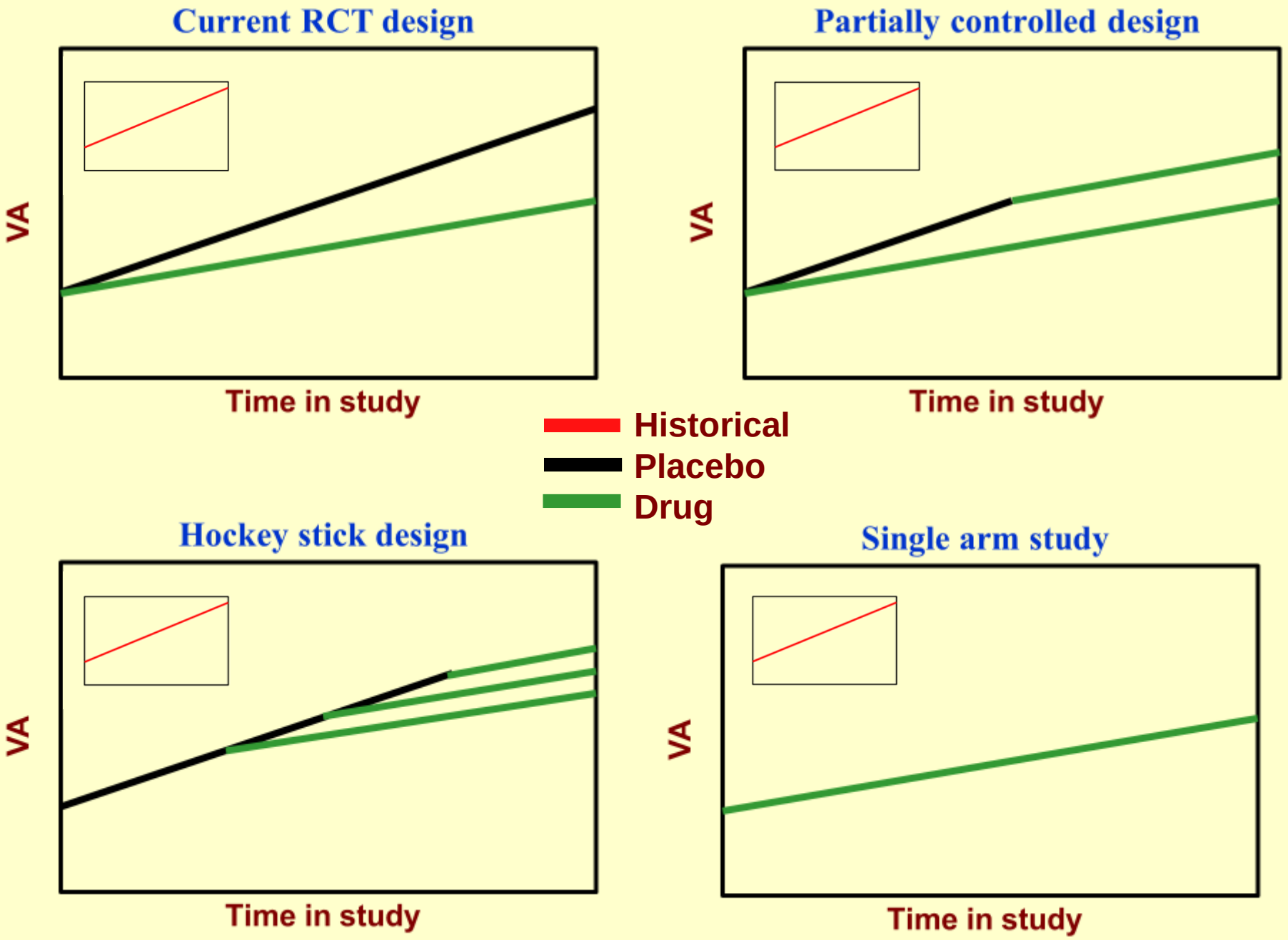


Hockey stick design



Single arm study




Current RCT design
VA
Time in study
Partially controlled design
VA
Time in study
Historical
Placebo
Drug
Hockey stick design
VA
Time in study
Single arm study
VA
Time in study

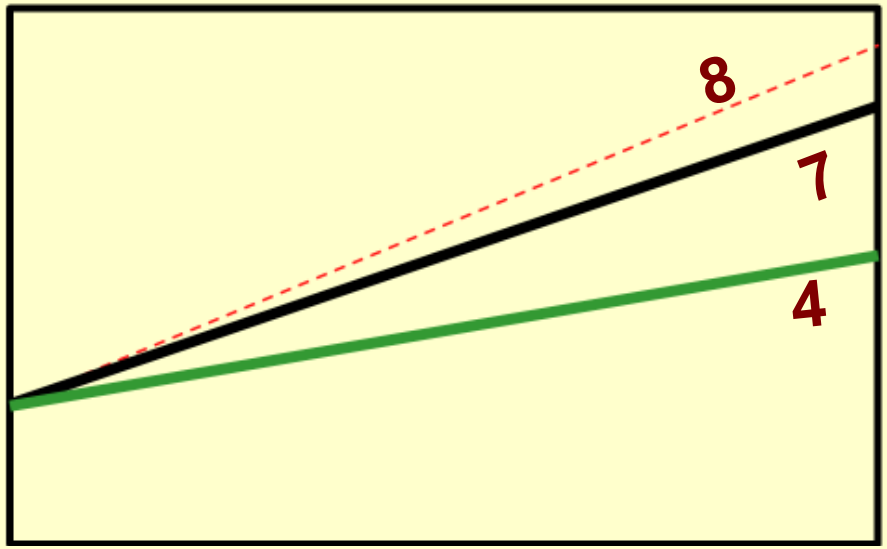
Comparison of FDA's Expedited Programs for Serious Conditions

	Fast Track	Breakthrough Therapy	Accelerated Approval	Priority Review

Table 1. Recommendations to improve the design and analyses of clinical trials.

Area	Investigators and regulators should
Single-arm trials	- Identify the circumstances where the use of single-arm trials may be warranted - When use is justified, consider multiple sources of historical control data - Ensure the comparability between patients in single-arm studies and potential historical controls - Provide cautious (non-causal) interpretations of the findings from single-arm studies - Ensure postmarket evidence generation requirements include randomized controlled trials

Current RCT design 1:2 N = 72



Placebo effect lowers control treatment

Active treatment effect as expected

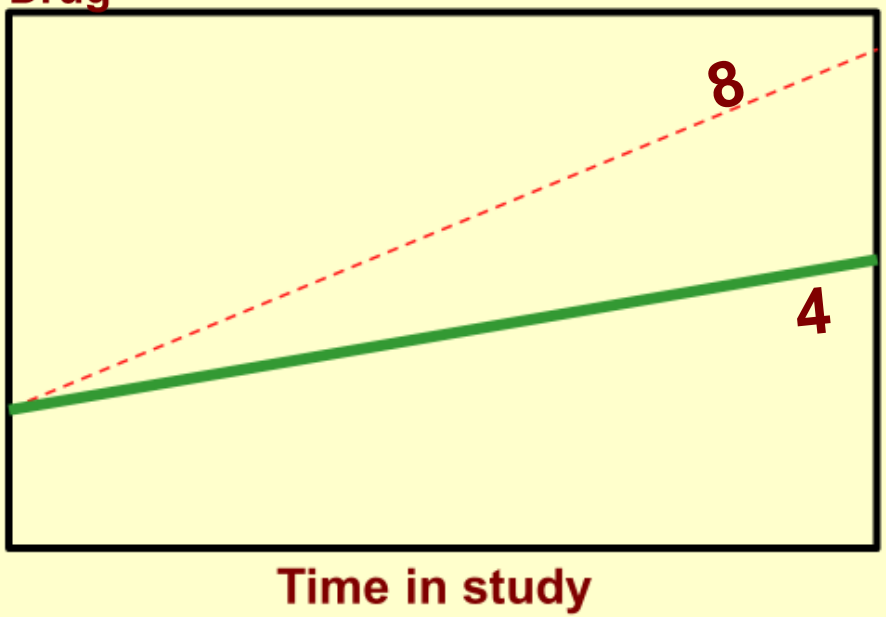
Trial non-significant

Historical

Placebo

Drug

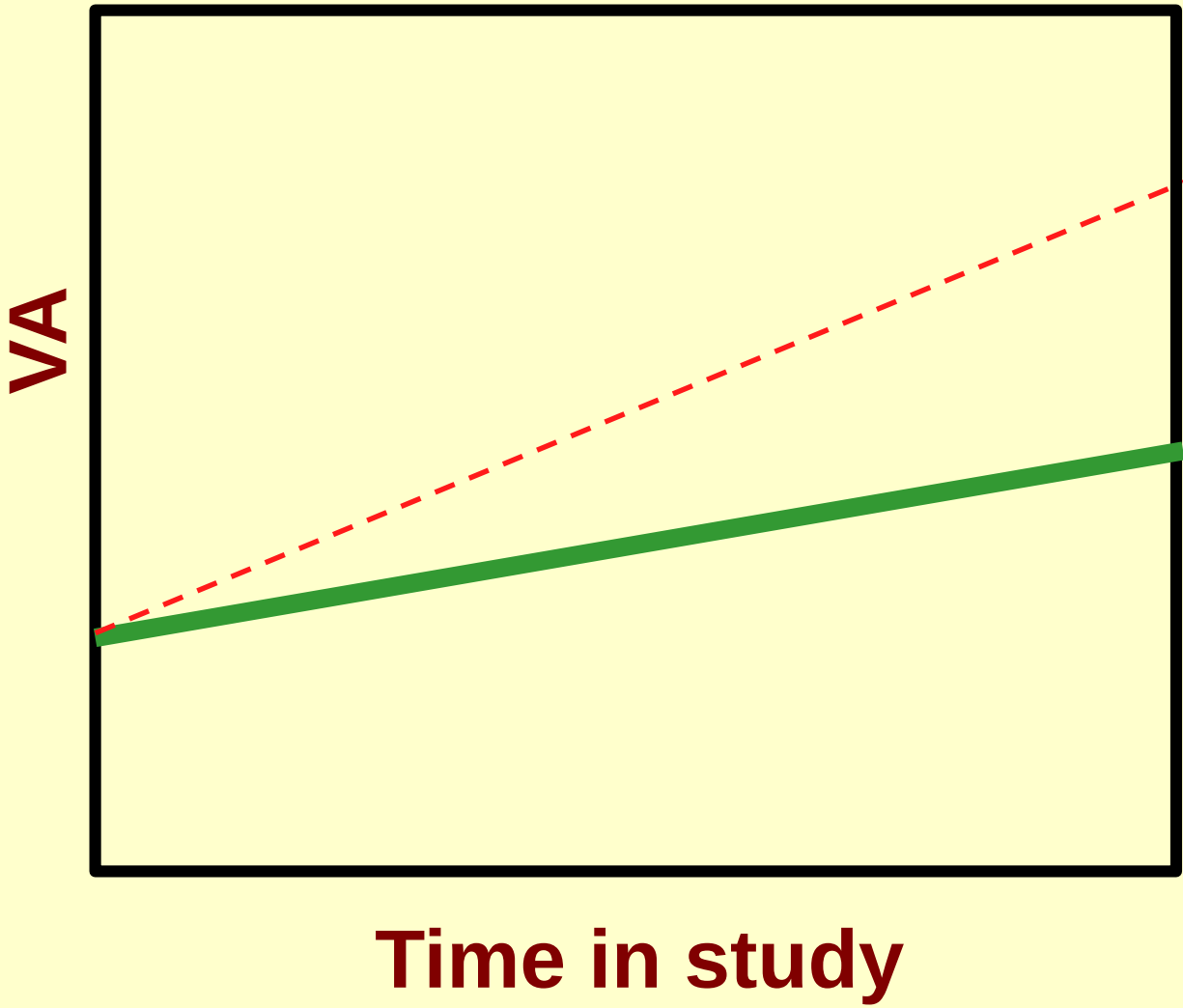
Single arm study Lower total N = 60



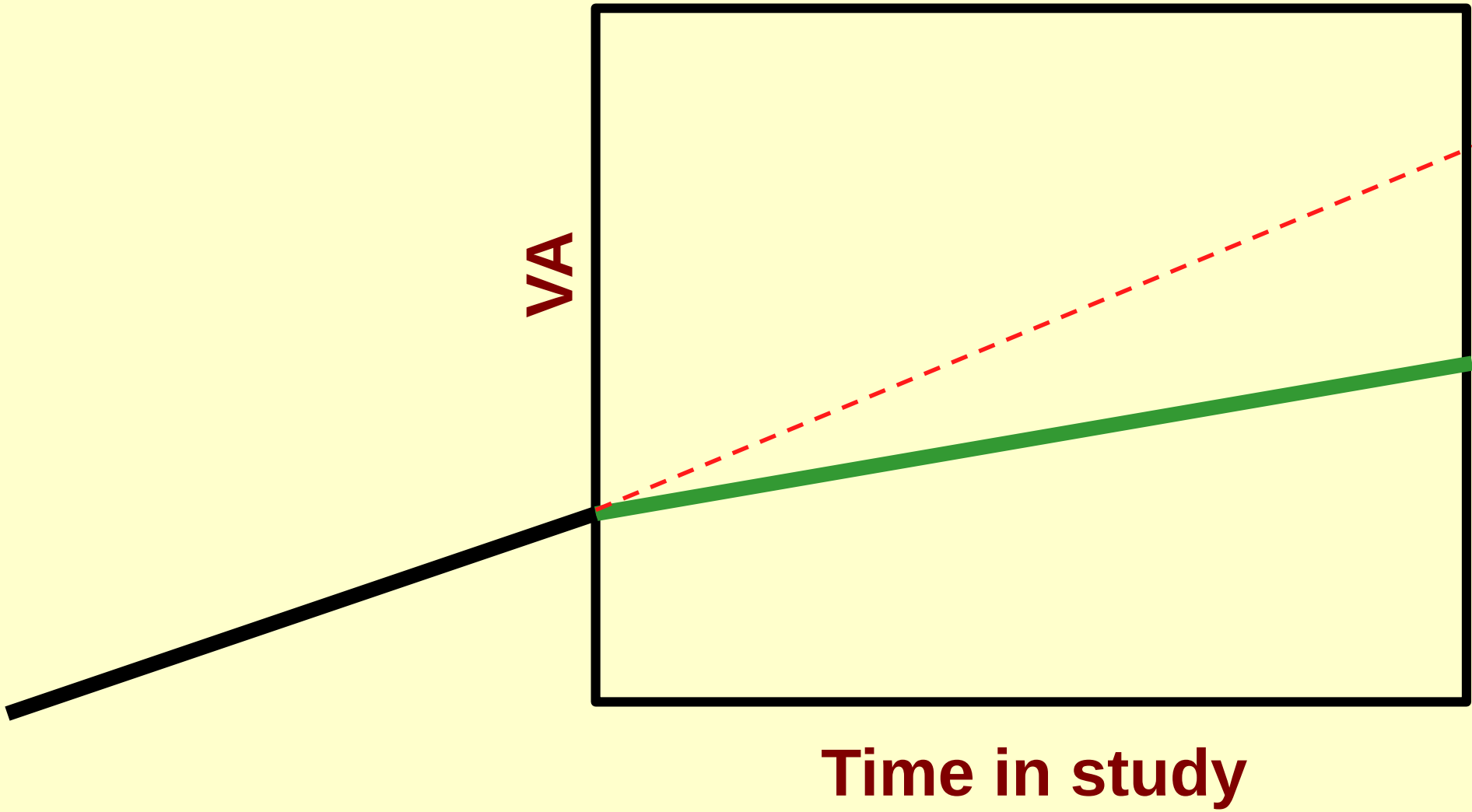
Result exactly as was powered for.

Significant

Single arm study



Single arm study



Thank you for your continued attention!

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This presentation has been brought