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

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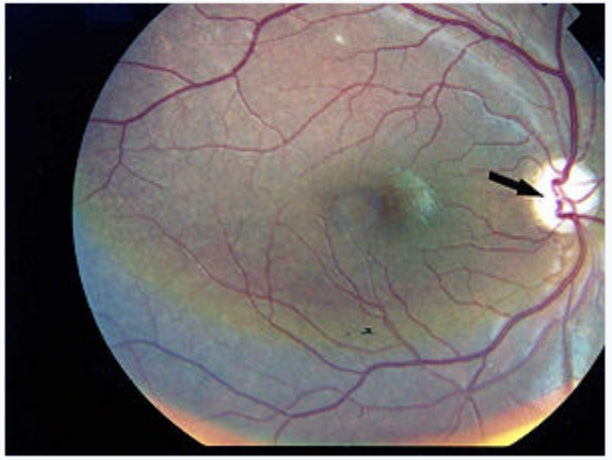
Wolfram Syndrome

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



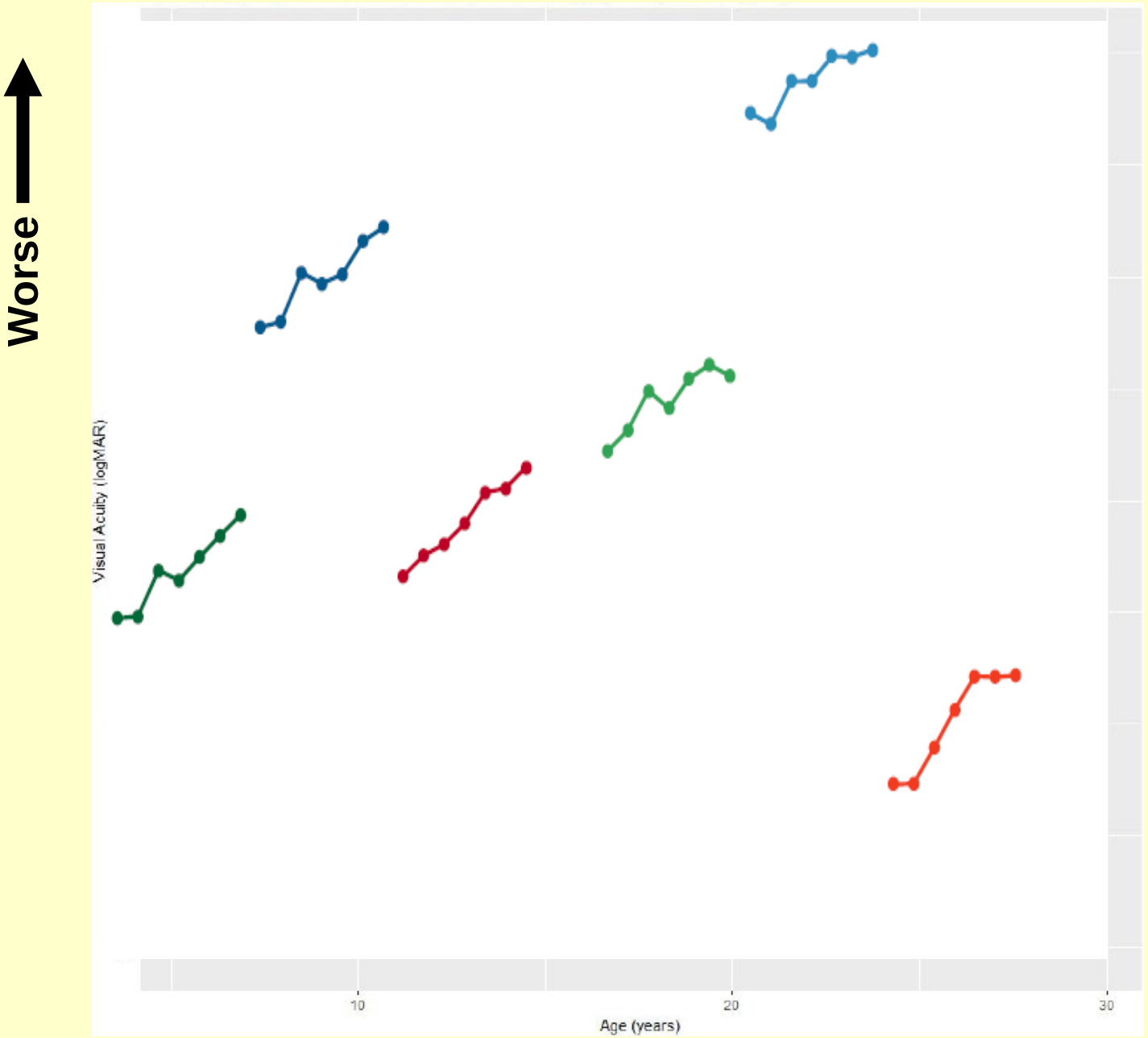
Photographic image of the patient right eye showing optic atrophy without diabetic retinopathy; from Manaviat et al., 2009[1]

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.

Simulated VA in six patients with Wolfram syndrome



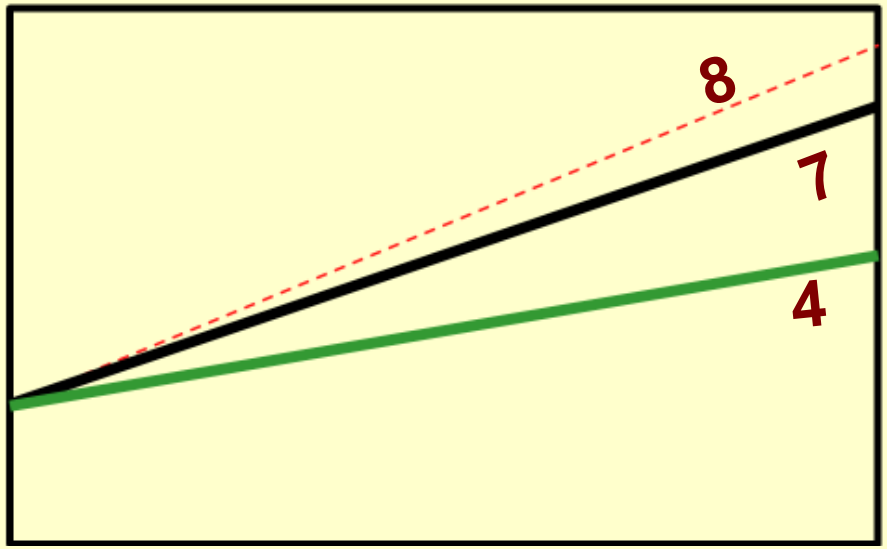
Source: Simulation based on parameters from analysis of Hershey data. Within pt slope = 8 units/year

The Wolfram 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=72 (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

Current RCT design 1:2 N = 72



Placebo effect lowers control treatment

Active treatment effect as expected

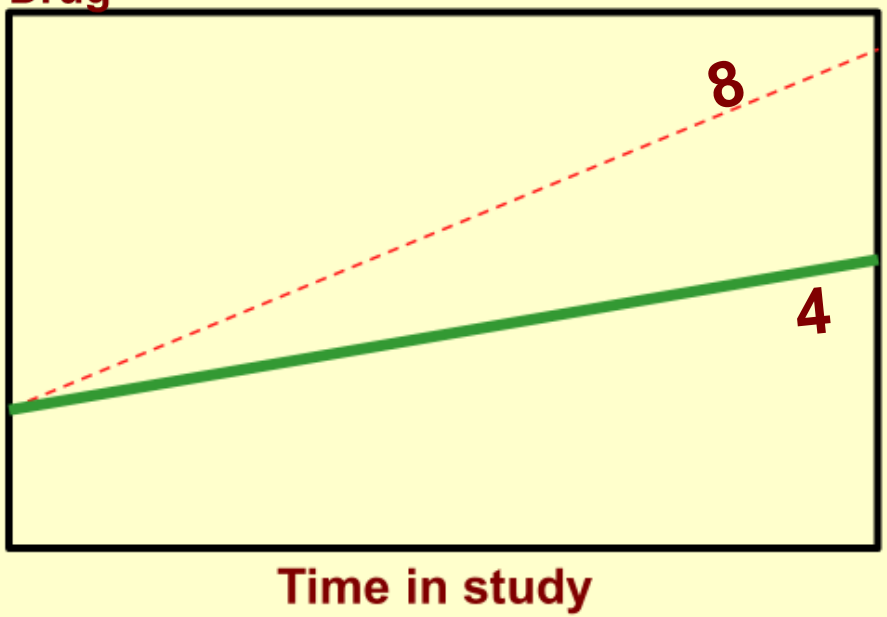
Trial non-significant

Historical

Placebo

Drug

Single arm study Lower total N = 60



Result exactly as was powered for.

Significant

BACKUP SLIDES

PLACEBO'S NEW POWER

What the emergence of the "honest placebo" says about healing in America

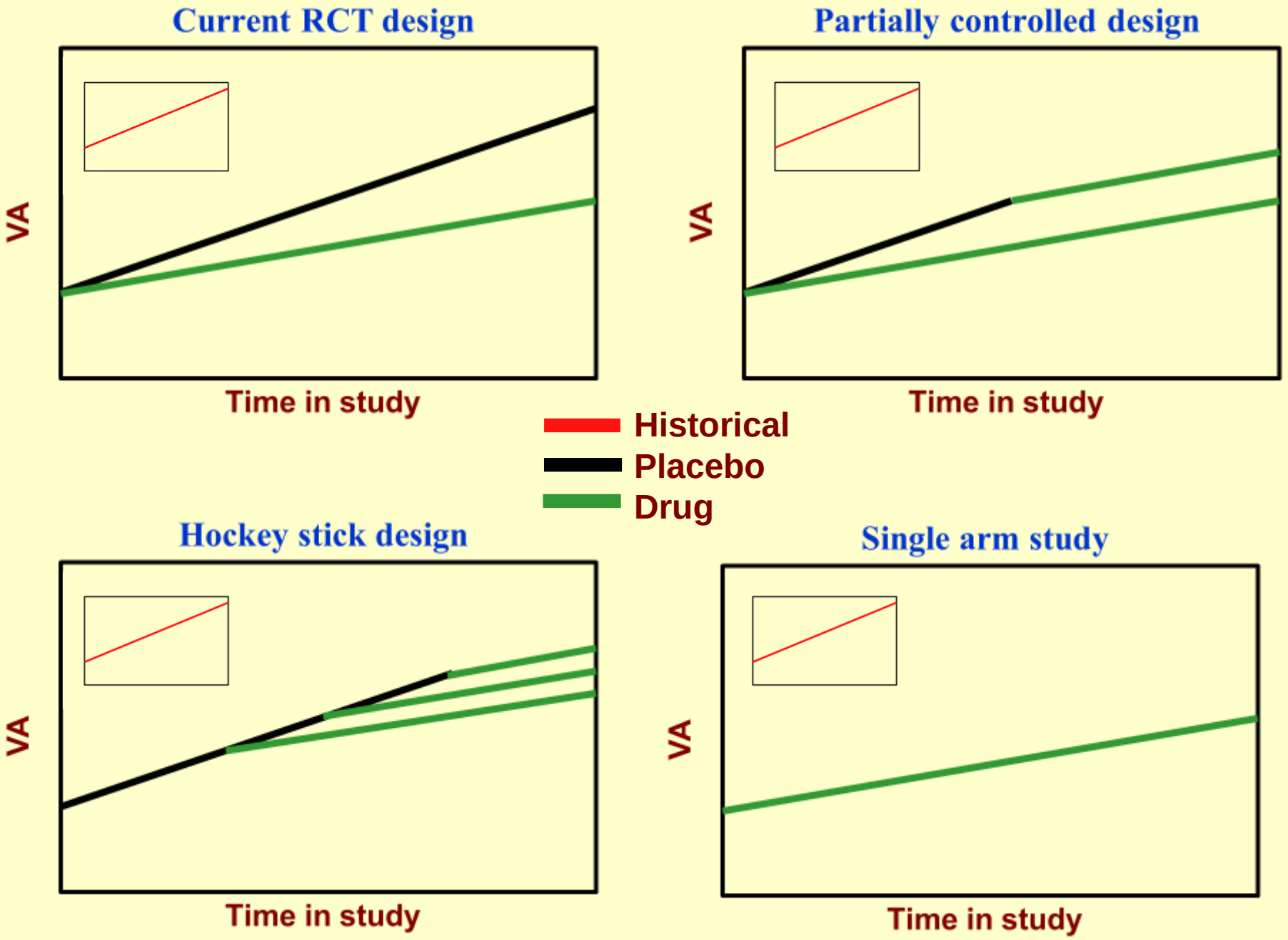
BY ALEXANDRA SIFFERLIN

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
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