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
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
Historical Placebo Drug

Current RCT design 1:2 N = 72

Placebo effect lowers control treatment
Active treatment effect as expected
Trial non-significant

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

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<th>fast track</th>
<th>breakthrough therapy</th>
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Table 1. Recommendations to improve the design and analyses of clinical trials.

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

Current RCT design

Partially controlled design

HAckey stick design

Single arm study