Improving Precision in Clinical Trials with Repeated Outcome Measurements

Clinical Pharmacology Research in Progress

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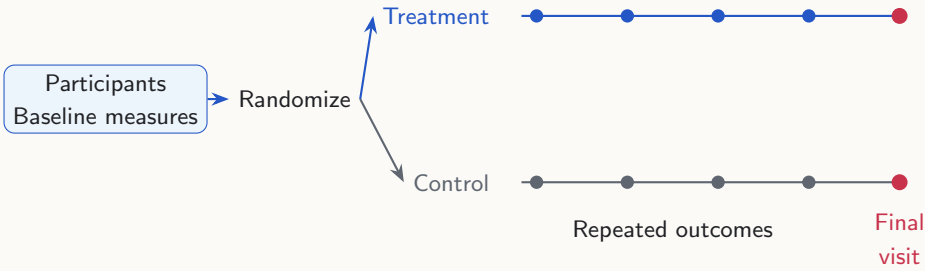
Roadmap

1. **Background**
2. Borrowing Information Across Visits
3. Numerical Study
4. Discussion

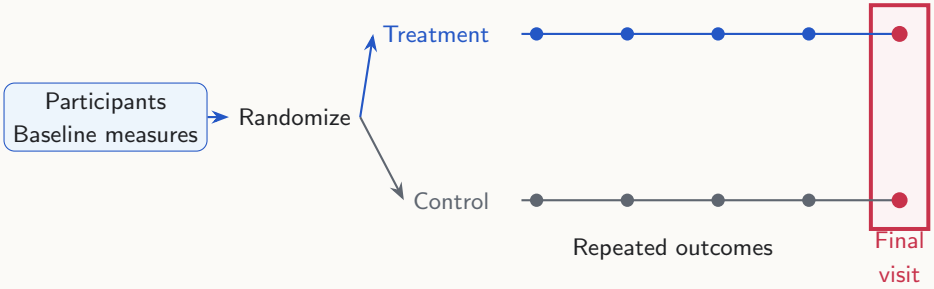
Randomized Trials with Repeated Outcomes

Common structure in randomized trials: assign participants to treatment or control, then measure outcomes repeatedly over follow-up



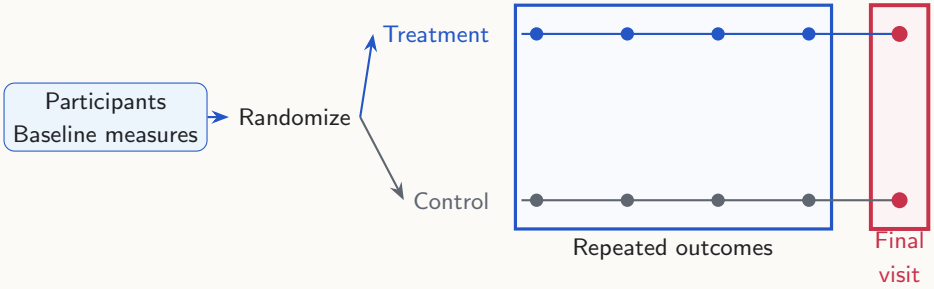
Randomized Trials with Repeated Outcomes

Although outcomes are measured repeatedly, the primary study endpoint is often the average treatment effect **at the final visit**



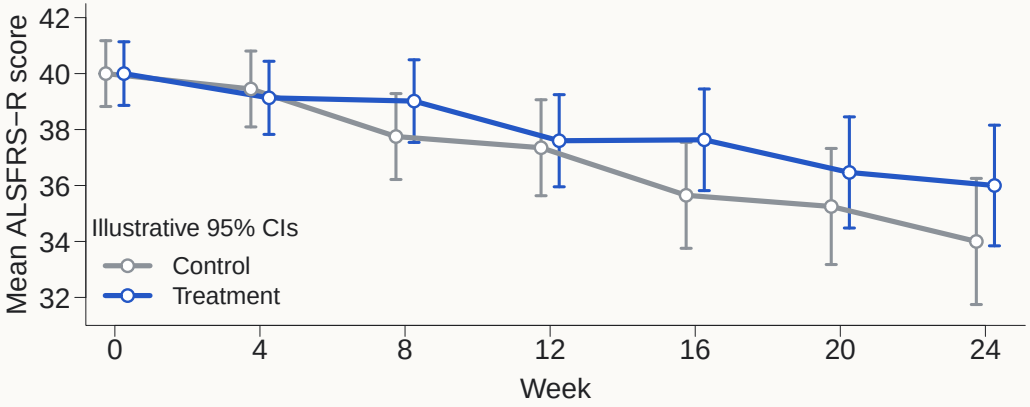
Randomized Trials with Repeated Outcomes

High-level question: Can we use the earlier outcomes to estimate the **final treatment effect** more precisely?



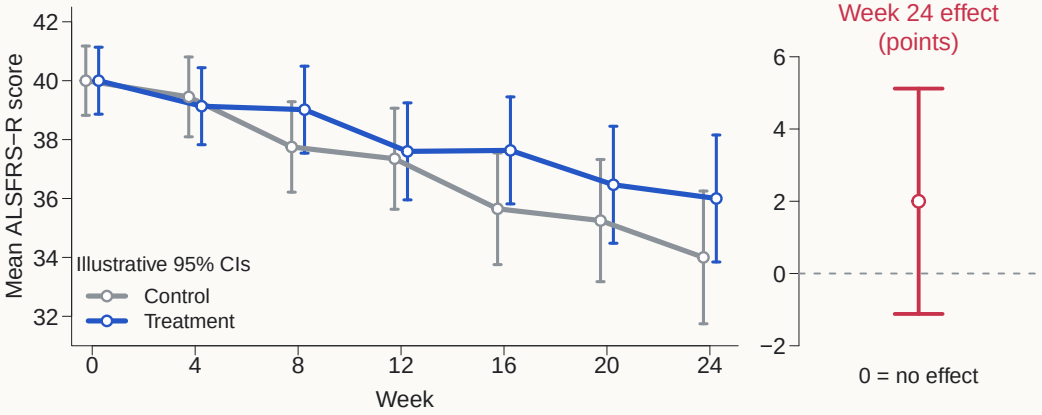
Motivation: ALS Trials

Motivating example The HEALEY ALS platform trial



Motivation: ALS Trials

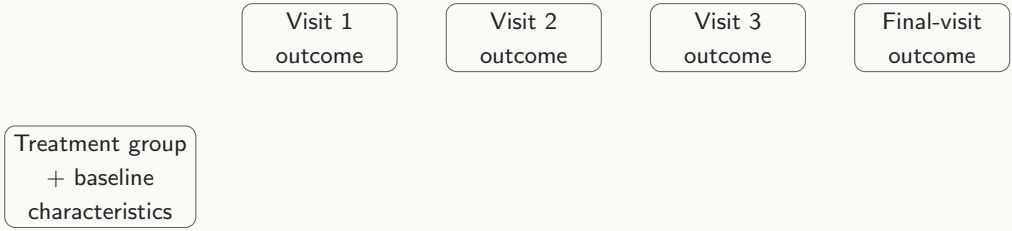
Big-picture goal: estimate the difference in average function **at week 24** more precisely, by leveraging information from previous visits



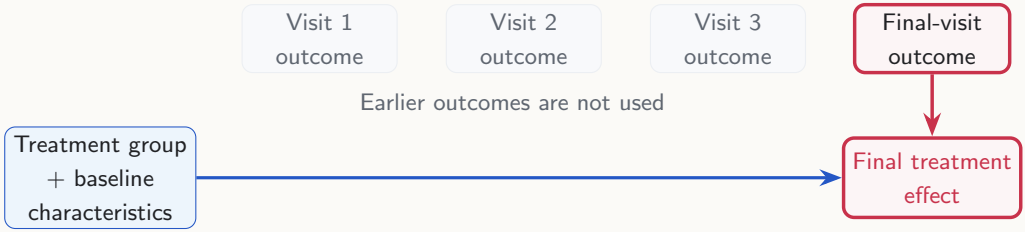
Common Analyses of Trial Outcomes

Standard methods may leave information in the **intermediate outcomes** unused when estimating the **final treatment effect**

Common Analyses of Trial Outcomes

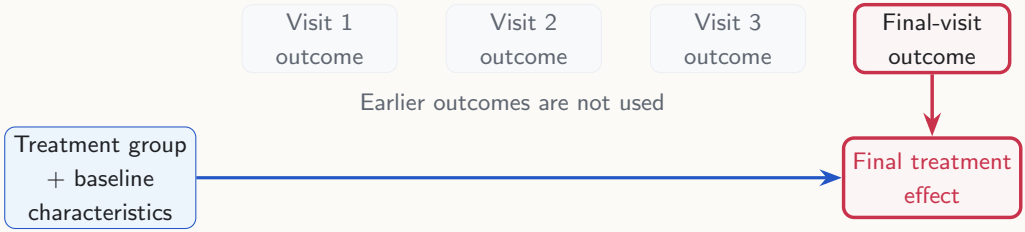


Common Analyses of Trial Outcomes



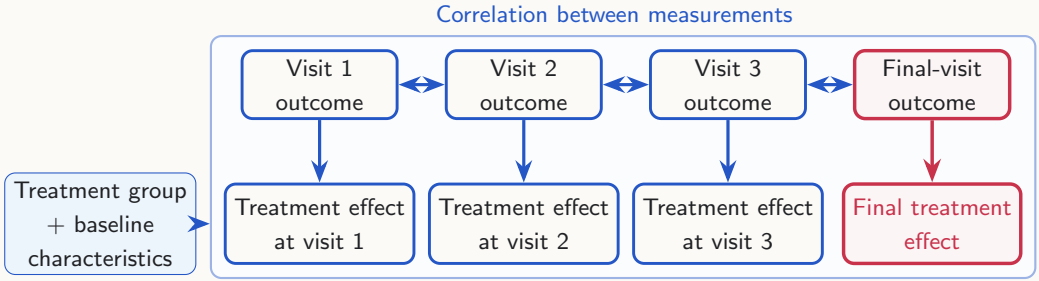
Analysis of covariance (ANCOVA) compares final outcomes, adjusting for baseline characteristics

Common Analyses of Trial Outcomes



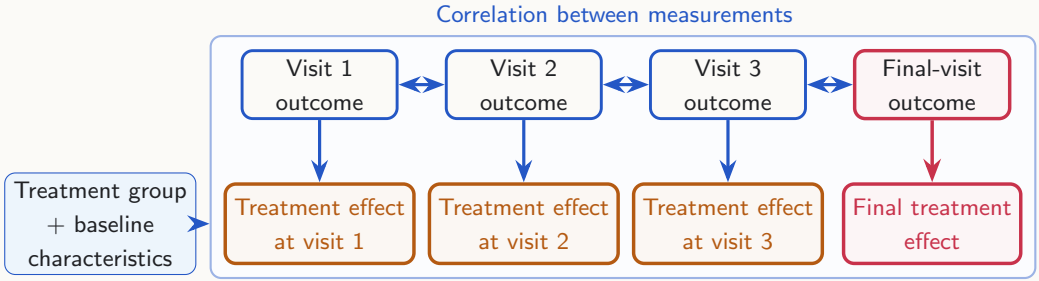
Randomization protects this comparison in large samples, even if the working regression is wrong

Common Analyses of Trial Outcomes



A **mixed model for repeated measures (MMRM)** analyzes outcomes together and accounts for their correlation

Common Analyses of Trial Outcomes



Accounting for **correlation** does not necessarily use all the information in **how treatment effects change across visits**

Goal of This Project

Goal: introduce a statistical approach to **improve efficiency** using repeated outcome measurements

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Main idea: adapt ideas from the **external controls literature** to **borrow information across time points**

- **Borrow from earlier visits** to improve precision of the **final treatment-effect estimate**
- Adapt the amount of borrowing to **limit bias** when the assumed relationships are wrong

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Motivation: Borrowing from External Controls

The notion of borrowing information to improve statistical precision is central to the external controls literature

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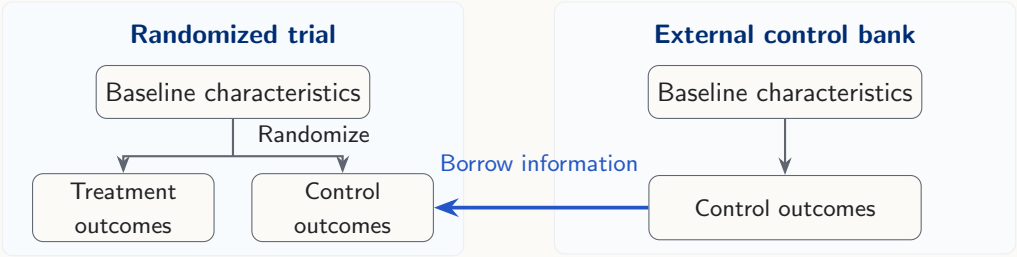

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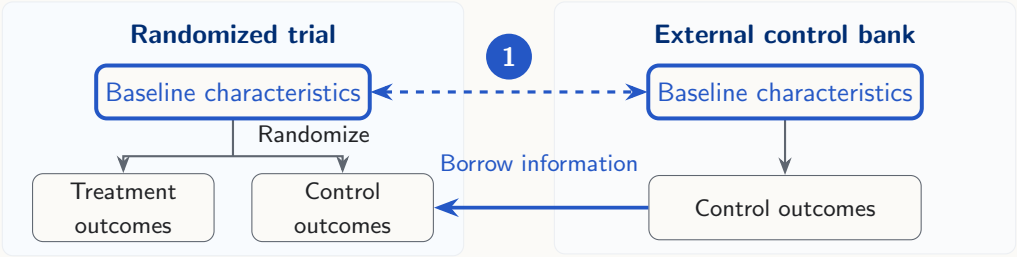

1. **Comparable baseline populations**, possibly after adjustment

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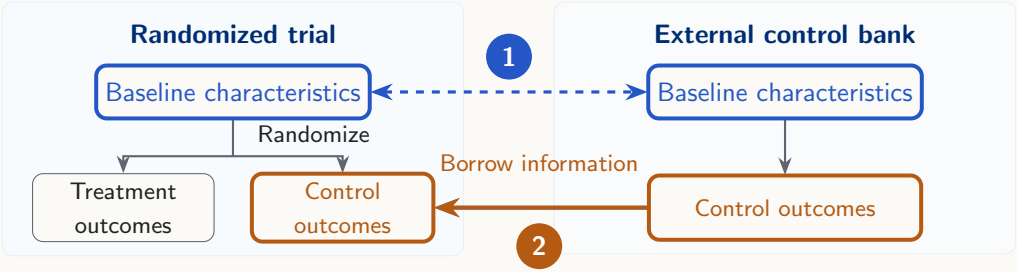


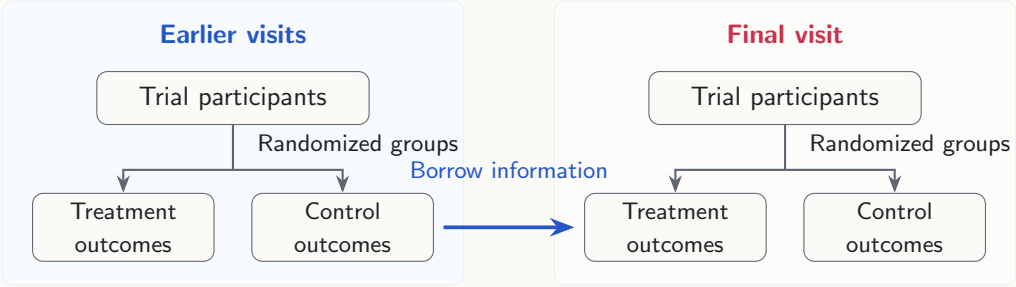
1. **Comparable baseline populations**, possibly after adjustment

2. **Comparable control-outcome distributions** across studies, after adjustment—or a credible model linking them

Borrowing Across Visits

Our analogue: borrow from **earlier visits** in the same trial to improve precision at the **final visit**

Borrowing Across Visits



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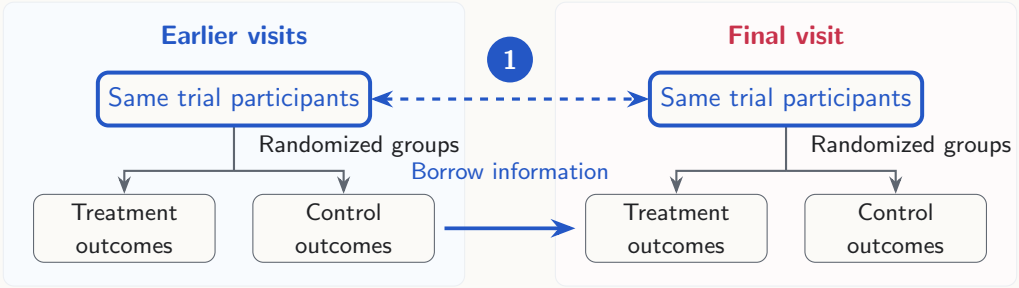
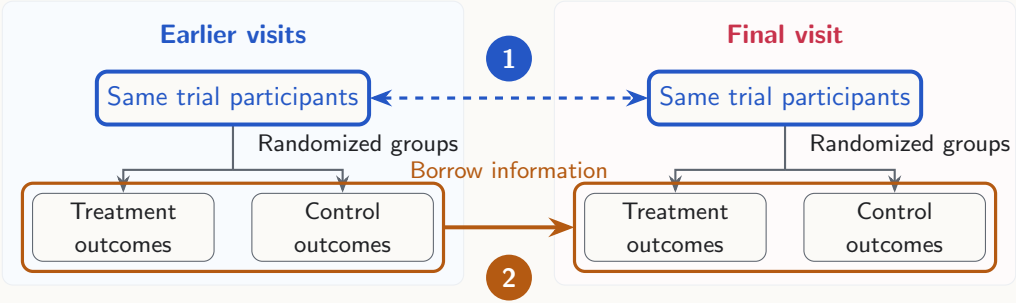


1. **Same participants** at every visit, with complete follow-up

Borrowing Across Visits



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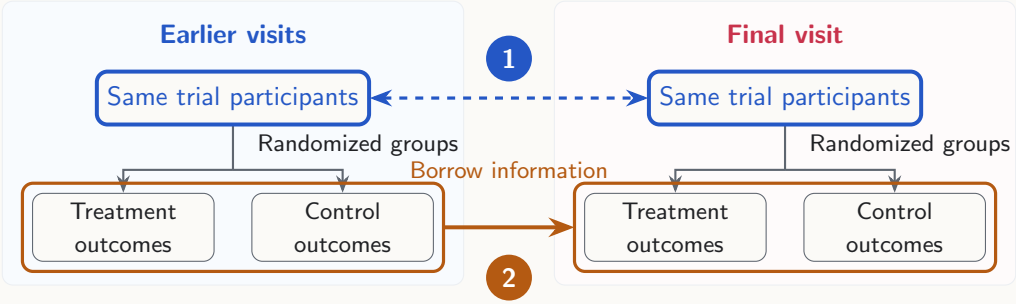
Borrowing Across Visits



1. **Same participants** at every visit, with complete follow-up

2. **Outcomes change over time**: we need a model linking outcomes across visits

Idea: model the trend in treatment effects over time

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   - **Gaining Precision through Assumed Effect Trajectories**
   - Allowing for Incorrect Trend Assumptions
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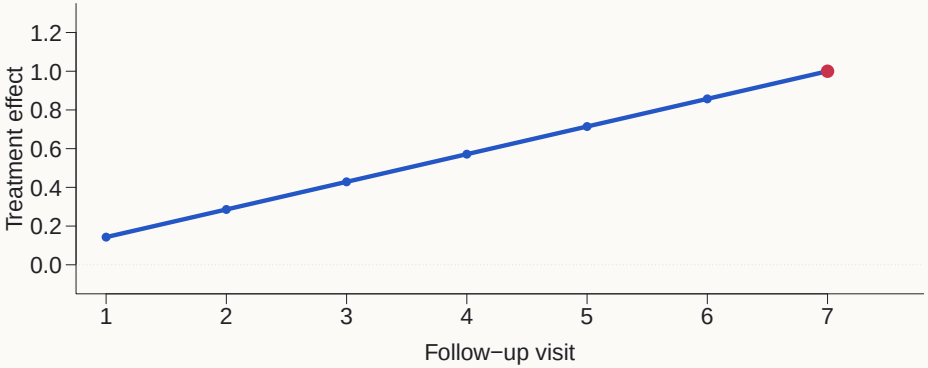
Plausible Treatment-Effect Trajectories

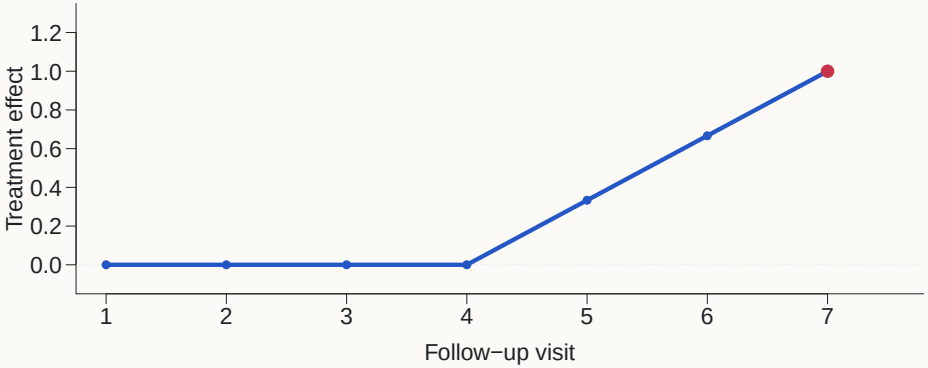
In practice and across applications, there are many possible trajectories for the true underlying treatment effects that we aim to estimate...

Here, the benefit increases linearly during follow-up



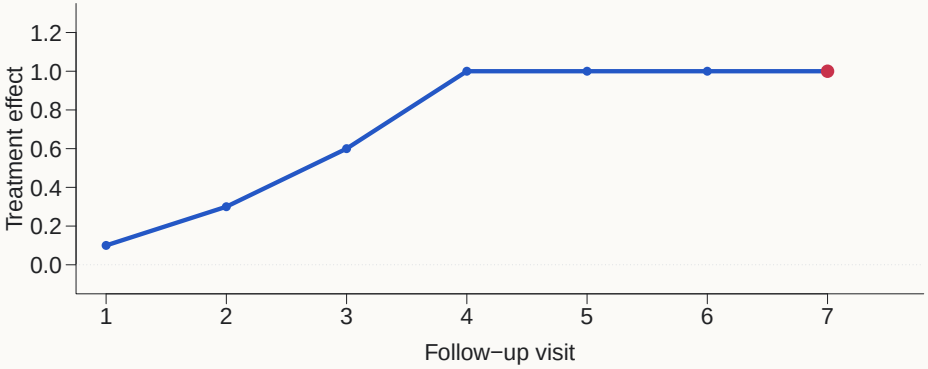
Plausible Treatment-Effect Trajectories

Or a **delayed benefit**, followed by a linearly increasing effect



Plausible Treatment-Effect Trajectories

Or an initial increase, followed by a **plateau**



Plausible Treatment-Effect Trajectories

Of course, the true trajectory is unknown

- In many applications, it may be plausible to expect certain shapes

Idea: use a **trajectory model** for the true treatment effects to borrow information across visits



Borrowing Under a Linear Trend

To see how assumed structure can help, consider a scenario where we **correctly assume** that the true treatment-effect trend is **linear**

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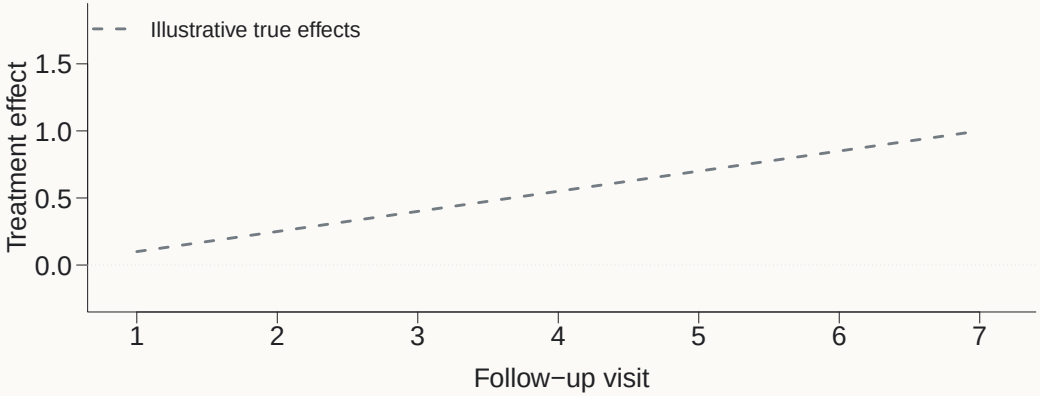

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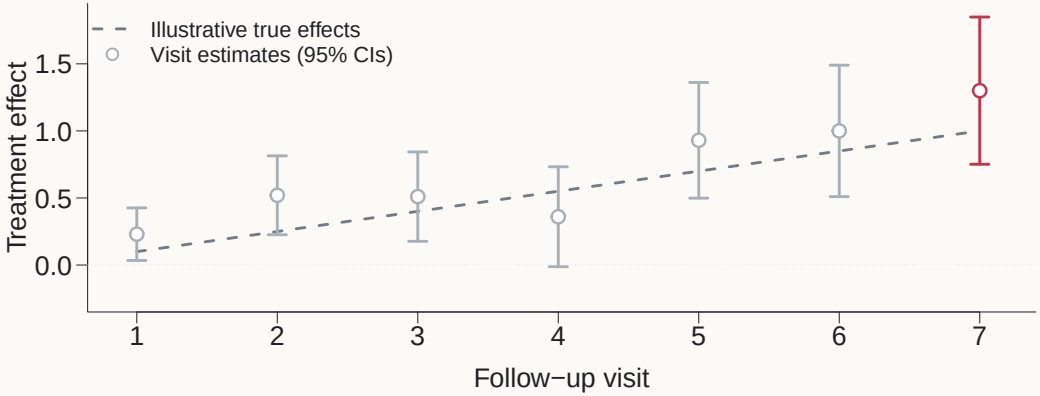

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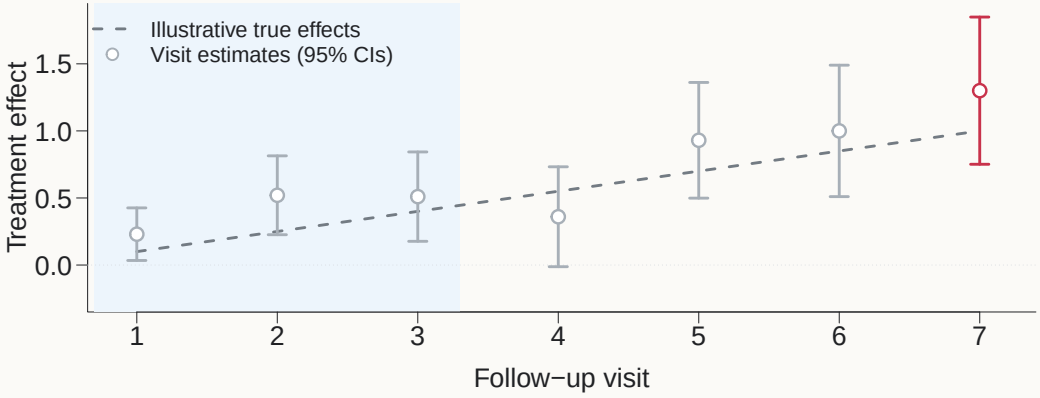
To see how assumed structure can help, consider a scenario where we **correctly assume** that the true treatment-effect trend is **linear**

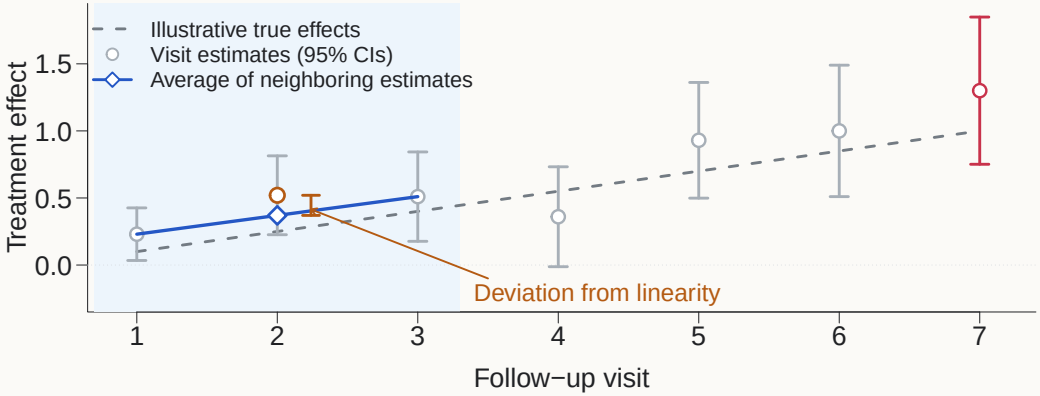
First consider the relationship among visits 1–3



Borrowing Under a Linear Trend

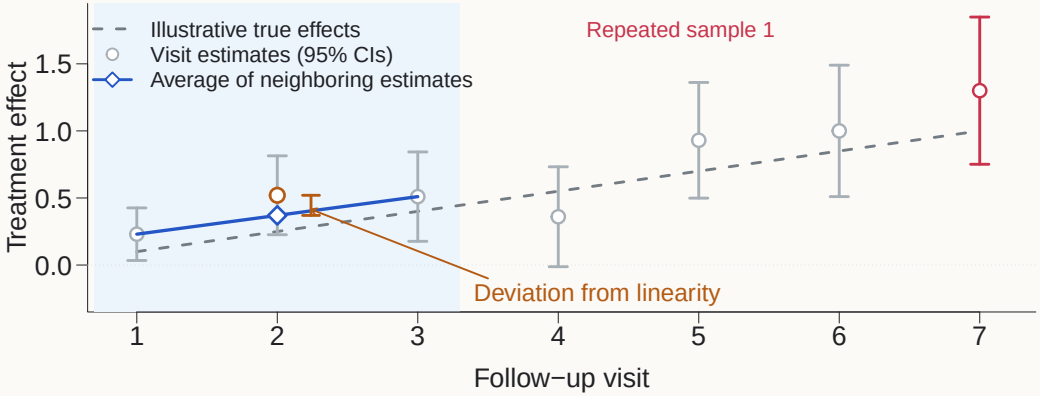
Under linearity, the true effect at visit 2 equals the average of the true effects at visits 1 and 3

$$\text{deviation} = \text{visit-2 estimate} - \frac{\text{visit-1 estimate} + \text{visit-3 estimate}}{2}$$



Variation Across Repeated Trials

Notice that in repeated samples, the estimates themselves will vary



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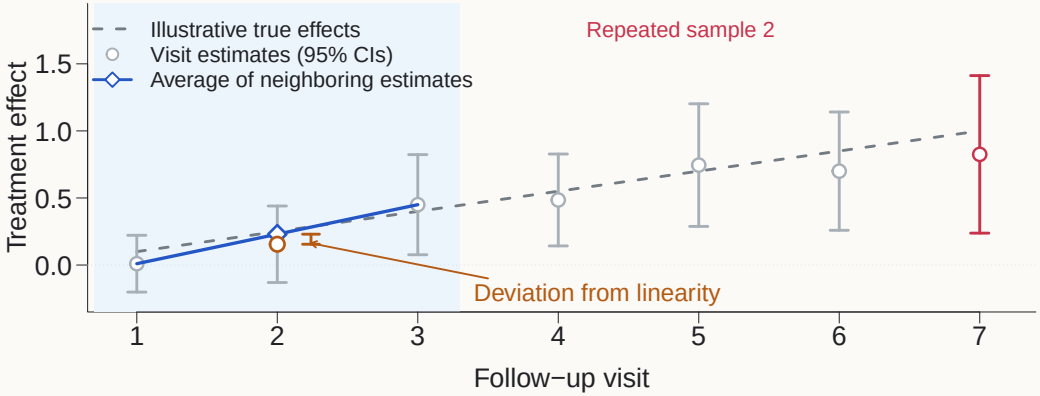

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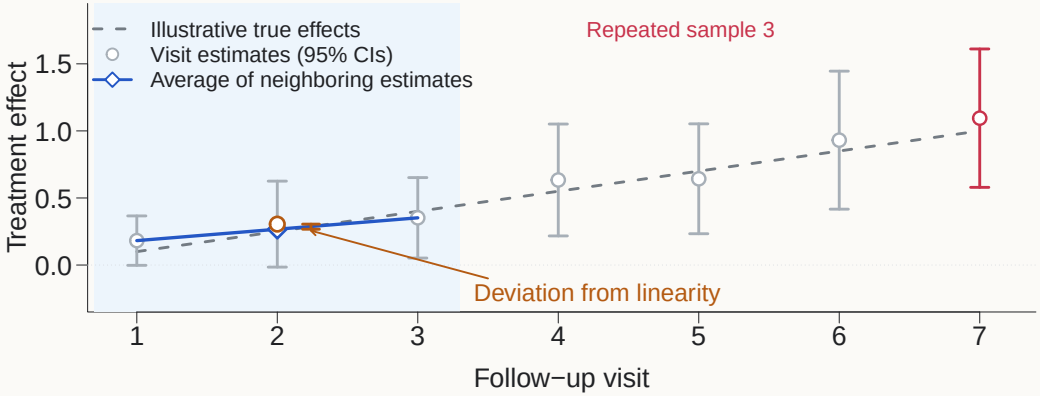

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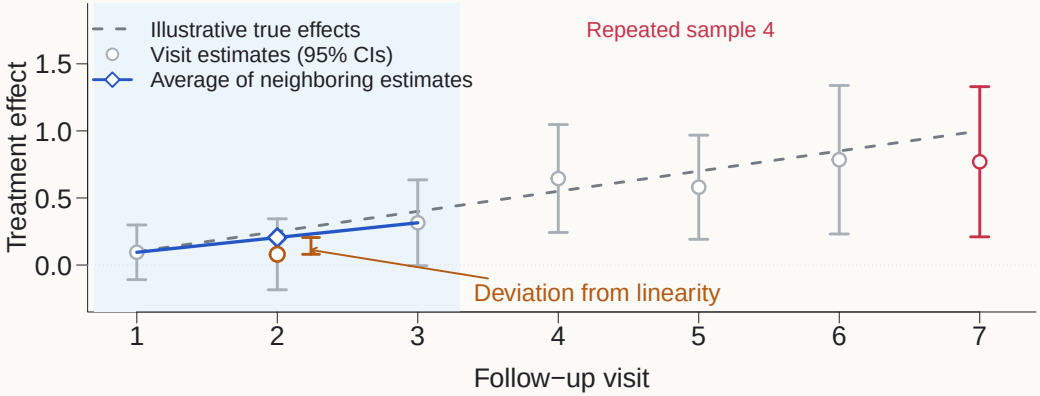

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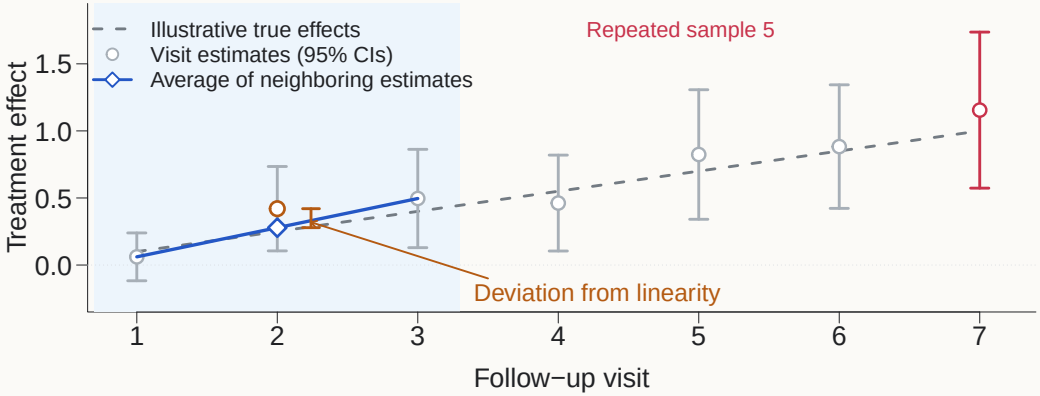
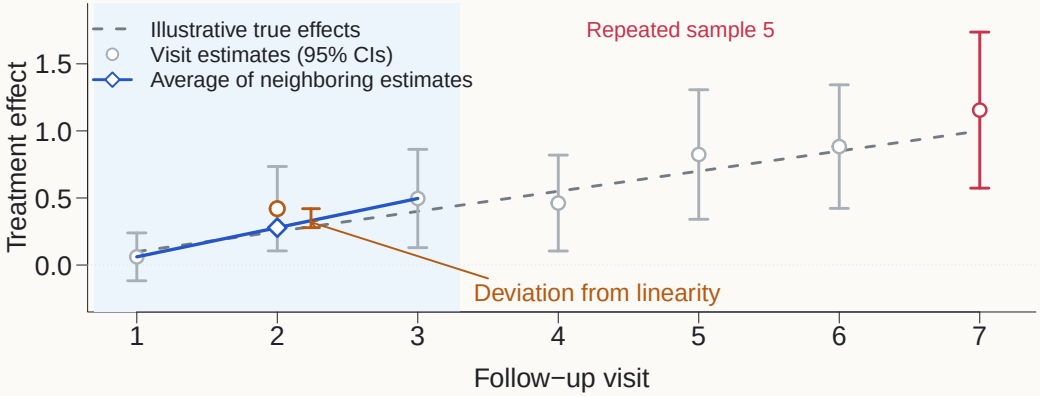


Variation Across Repeated Trials

Under linearity, we know the deviations average to **zero**

They will also tend to be correlated with the sampling error in the final estimate

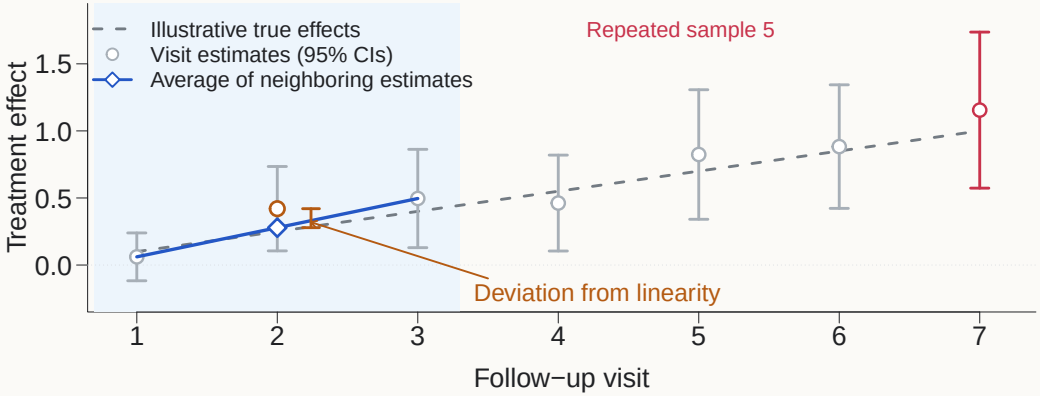


Variation Across Repeated Trials

In this example, the correlation is **positive**:

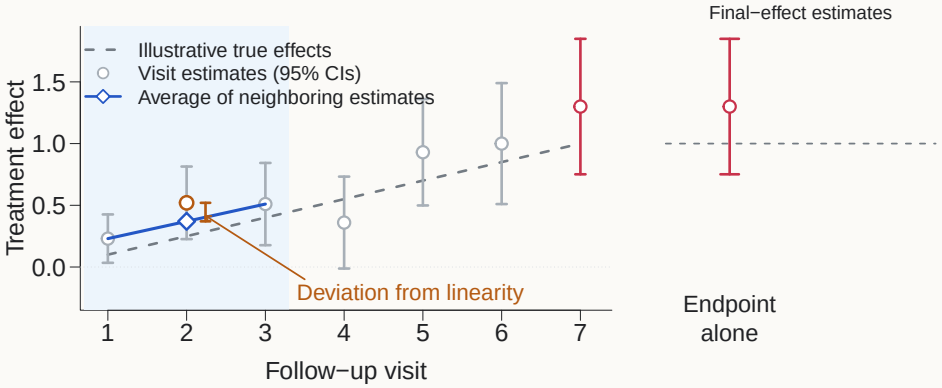
Deviation above zero $\longrightarrow$ final estimate tends to be too high

Deviation below zero $\longrightarrow$ final estimate tends to be too low



Adjusting the Final Estimate

$$\text{adjusted estimate} = \text{endpoint estimate} - b \times \text{deviation}$$



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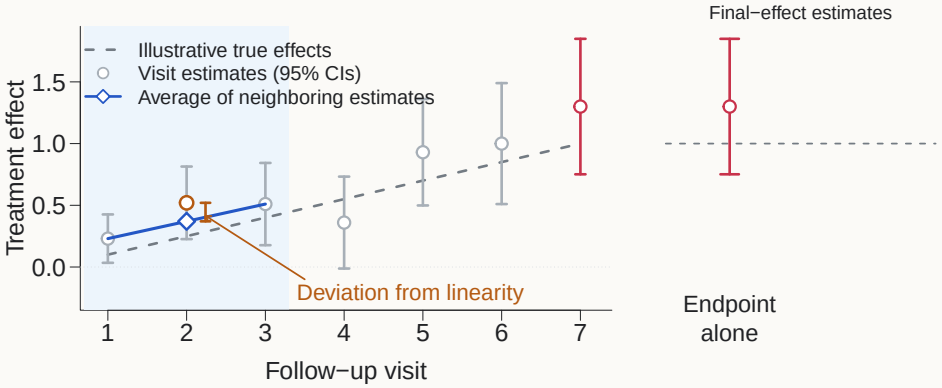
The borrowing coefficient b uses the correlation and variability of the deviation and final estimate, which can be estimated from the trial data



Adjusting the Final Estimate

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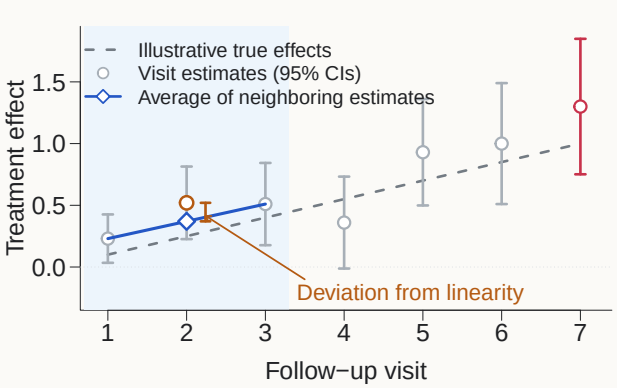
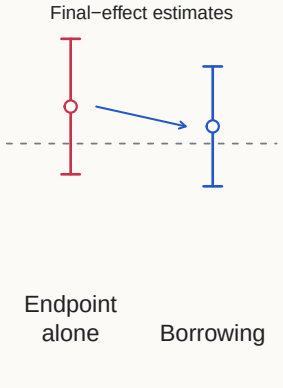
Use the deviation to **remove some of the final estimate's sampling variability**

Under the working relationship, the correction averages to zero

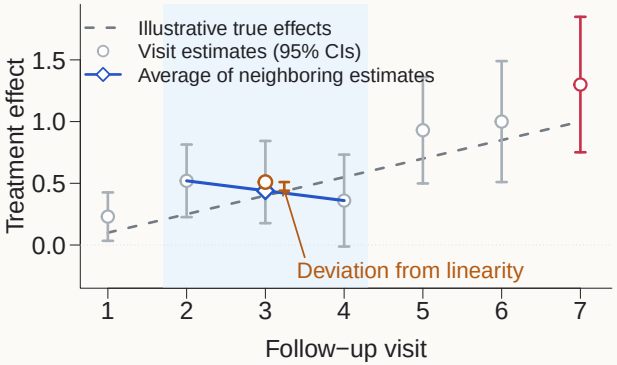


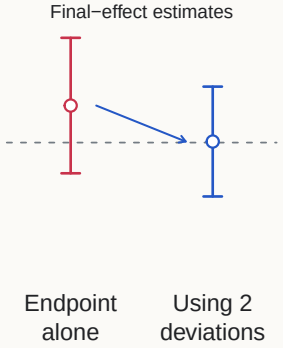


Adjusting the Final Estimate

$$\text{adjusted estimate} = \text{endpoint estimate} - b_1\,\text{deviation}_1 - b_2\,\text{deviation}_2$$

Combine deviations from several parts of follow-up





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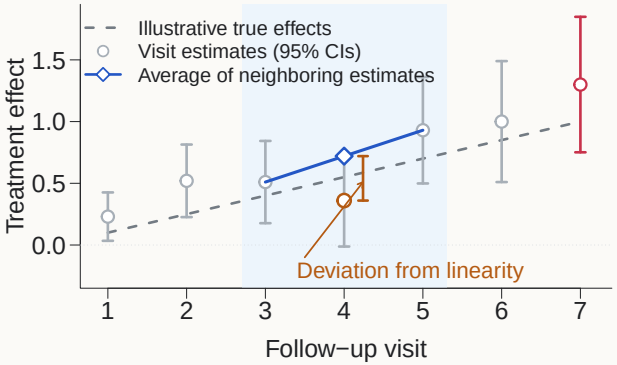

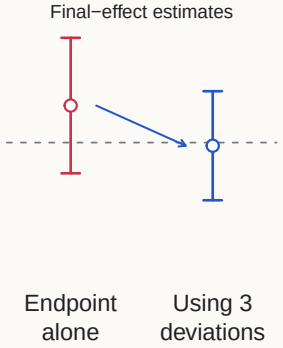

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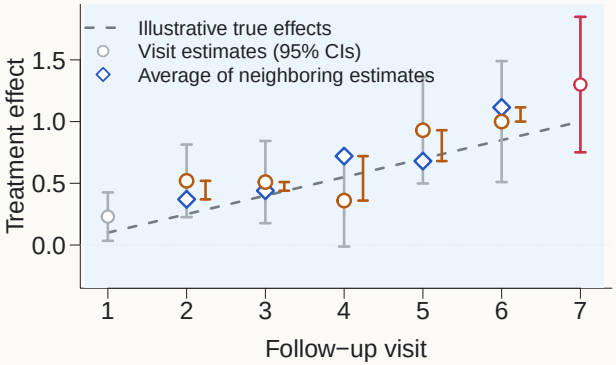
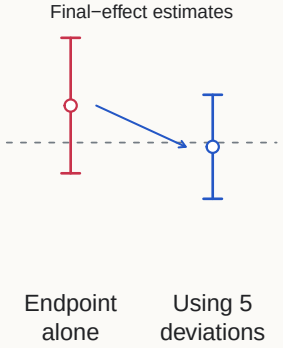




Borrowing From Working Relationships

Stepping back, our idea has three key parts:

1. If the assumed effect trajectory is correct, this implies deviations that average to zero
2. These deviations will tend to be correlated with sampling error in the final estimate, implying we can partially "correct" this sampling error
3. Borrowing strength controls the size of the adjustment

Roadmap

1. Background

2. **Borrowing Information Across Visits**

   Gaining Precision through Assumed Effect Trajectories

   Allowing for Incorrect Trend Assumptions

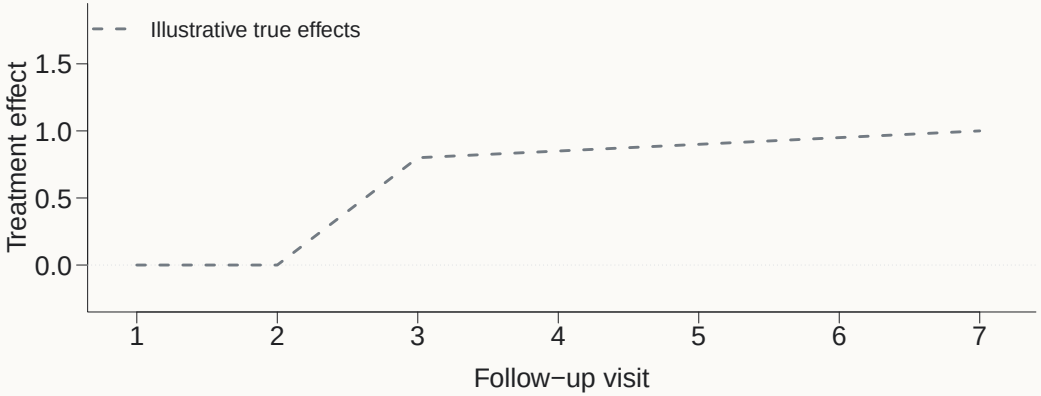
3. Numerical Study

4. Discussion

Allowing the Relationships to Be Wrong

Suppose we assume a **linear trend** in the true treatment effects

In reality, the trend is **partly nonlinear**



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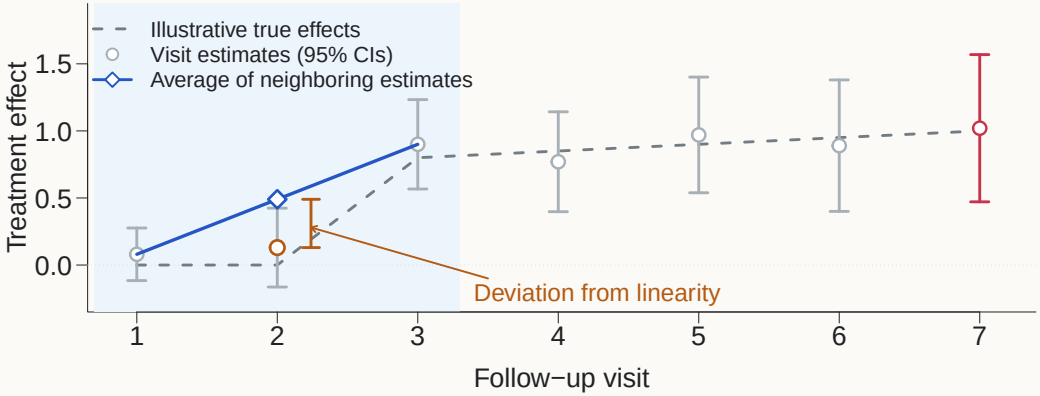

Allowing the Relationships to Be Wrong

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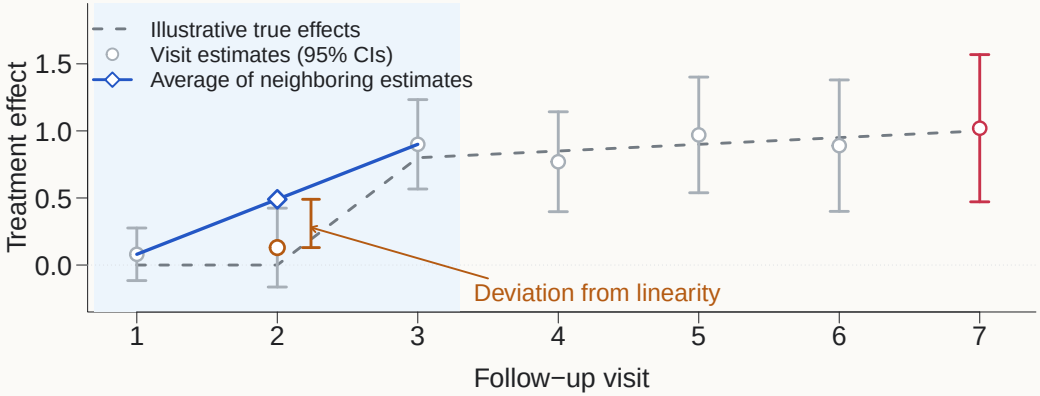
Borrowing under this incorrect linearity assumption can **introduce bias**

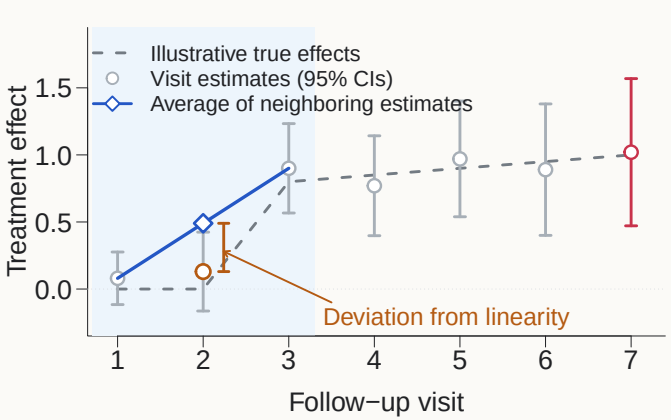


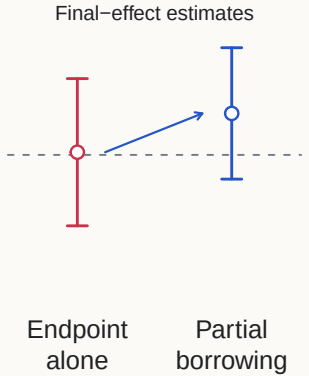
Allowing the Relationships to Be Wrong

$$\text{adjusted estimate} = \text{endpoint estimate} - b \times \text{deviation}$$

Idea: use a penalty to control how much to borrow

Partial borrowing moves b toward zero, making a smaller adjustment

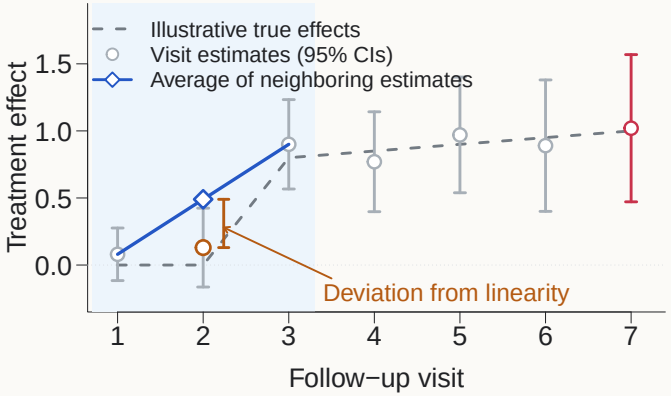


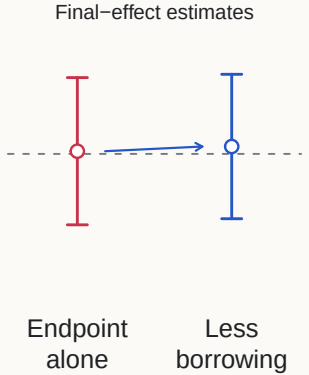


Allowing the Relationships to Be Wrong

$$\text{adjusted estimate} = \text{endpoint estimate} - b \times \text{deviation}$$

With b closer to zero, the estimate stays closer to endpoint ANCOVA





Roadmap

1. Background
2. Borrowing Information Across Visits
3. **Numerical Study**
4. Discussion

Simulations: Setup

Goal: assess the performance of our borrowing approach, in an "ideal" and "challenging" scenario

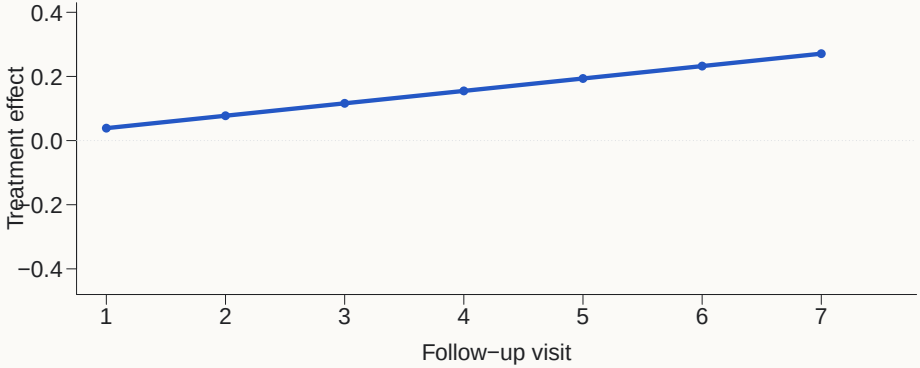
We simulate hypothetical trial datasets with 7 visits, and $n = 500$ participants

Compare three analyses

- Endpoint ANCOVA
- Unpenalized borrowing
- Penalized borrowing

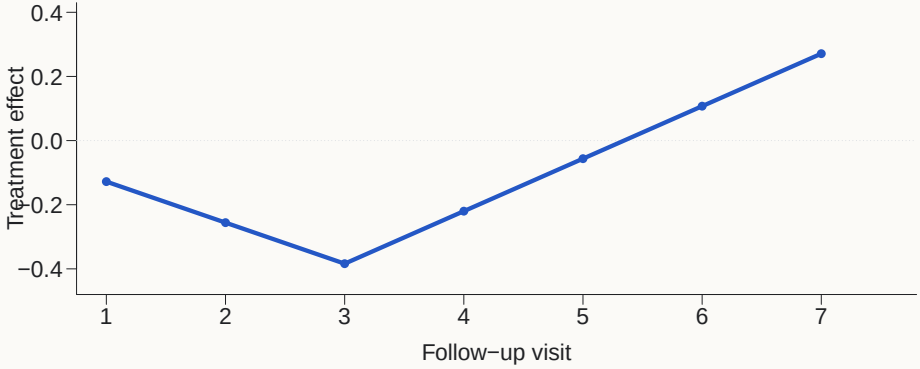
Simulations: Two Treatment-Effect Trajectories

A **linear trend** in the true treatment effects

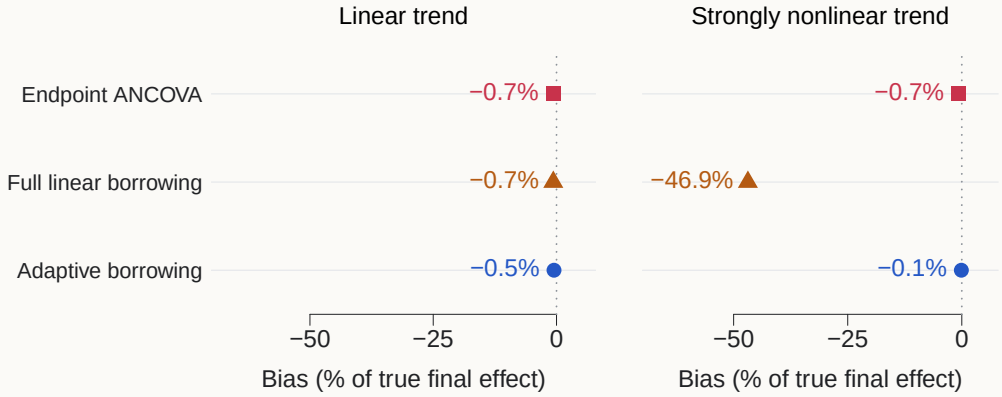


Simulations: Two Treatment-Effect Trajectories

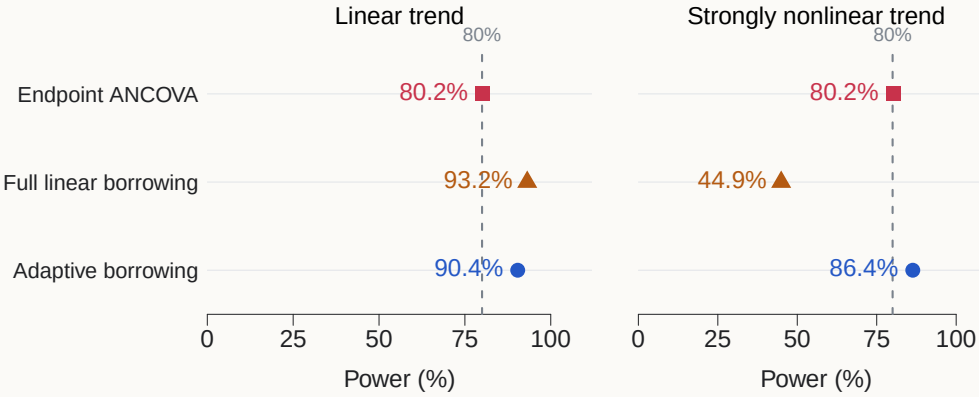
A **strongly nonlinear trend**, with the same final effect



Simulations: Percent Bias



Simulations: Power



Roadmap

1. Background
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Discussion

Goal: use **repeated outcome measurements** to improve precision of the **final treatment-effect estimate**

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Main idea: adapt ideas from the **external controls literature** to **borrow information across time points**

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Goal: use **repeated outcome measurements** to improve precision of the **final treatment-effect estimate**

> **Main idea**: adapt ideas from the **external controls literature** to **borrow information across time points**

Future work

- Refine how we choose **borrowing strength**
- Improve **confidence intervals** in small trials

Appendix: Additional Simulation Results

Proposed method: sample-size comparison in the localized-kink setting

	MSE: 0	0.25	0.50	Coverage: 0	0.25	0.50
100	0.830	0.854	0.934	95.2%	94.9%	94.5%
250	0.776	0.900	0.916	95.4%	93.7%	94.0%
500	0.763	0.926	0.850	94.8%	93.0%	94.8%
1000	0.738	0.908	0.812	95.7%	94.1%	96.6%

Rows give sample size; columns give departure magnitude

Relative MSE uses endpoint ANCOVA; coverage is for nominal 95% intervals

10,000 repetitions for $n = 500$; 1,000 for the other sample sizes

Appendix: Additional Simulation Results

Simulation details

- Seven visits, six baseline covariates, 1:1 randomization
- Residual correlation 0.3; final treatment effect fixed at 0.271; chosen in an independent pilot for approximately 80% endpoint ANCOVA power
- Additive ANCOVA omits nonlinear treatment-effect heterogeneity
- Current method uses stabilized joint covariance, LOO CV, and jackknife SEs
- Endpoint ANCOVA uses HC3 with a t reference; borrowing intervals use the jackknife with a normal reference

Power uses two-sided nominal 95% intervals; it is not adjusted for differences in false-positive rates

Appendix: Sources and Clinical Scope

Clinical motivation

Writing Committee for the HEALEY ALS Platform Trial (2025)

Pridopidine in Amyotrophic Lateral Sclerosis: The HEALEY ALS Platform Trial

JAMA 333:1128–1137

The published regimen used a 24-week joint function/survival analysis

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ANCOVA and repeated outcomes

Wang et al. (2019), Analysis of covariance in randomized trials

Schuler, Mixed models for repeated measures and time-by-covariate interactions

All teaching trajectories are hypothetical; all performance results are simulations

Appendix: External Controls and the Analogy

FDA (February 2023), draft guidance: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

The guidance discusses baseline prognosis, treatment setting, time zero, outcome measurement, and analysis assumptions

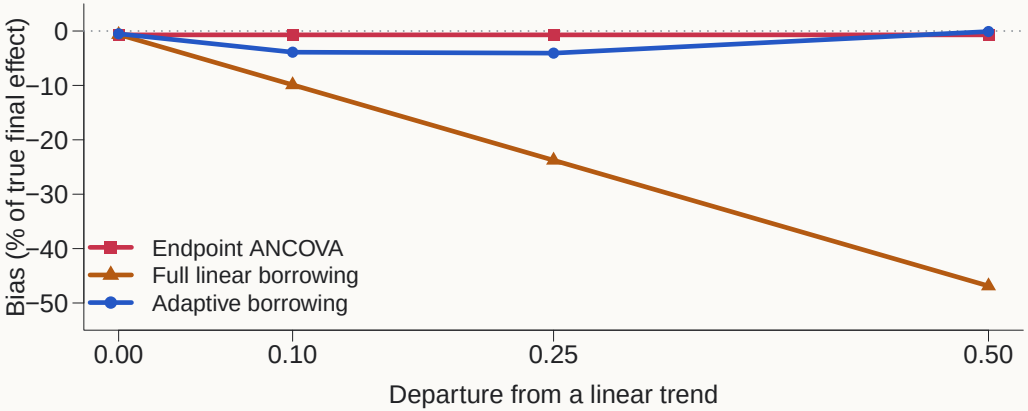
Hobbs et al. (2011), Hierarchical commensurate and power prior models

Gaussian commensurate models motivate the analogy between agreement penalties and borrowing strength

Our analogue uses repeated randomized comparisons in one population, with complete follow-up in the setting presented here

We assume relationships among marginal treatment effects, rather than equality of full outcome distributions

Appendix: Results Across All Departures



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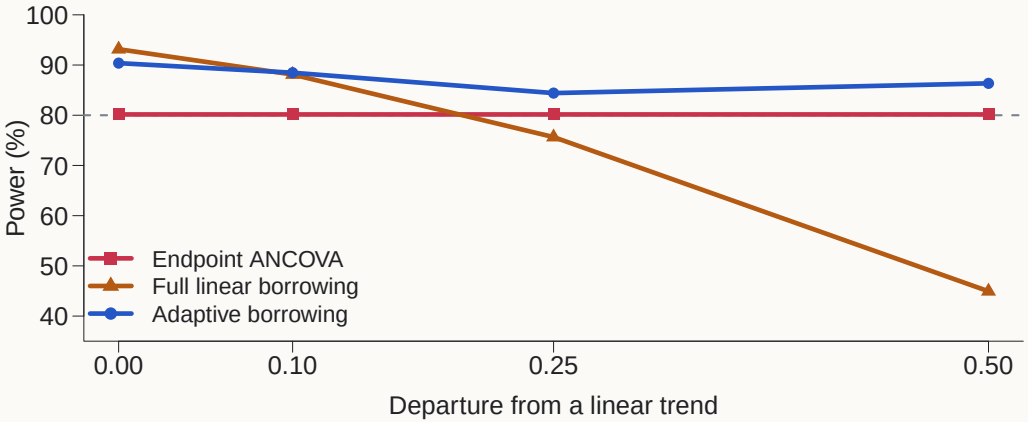

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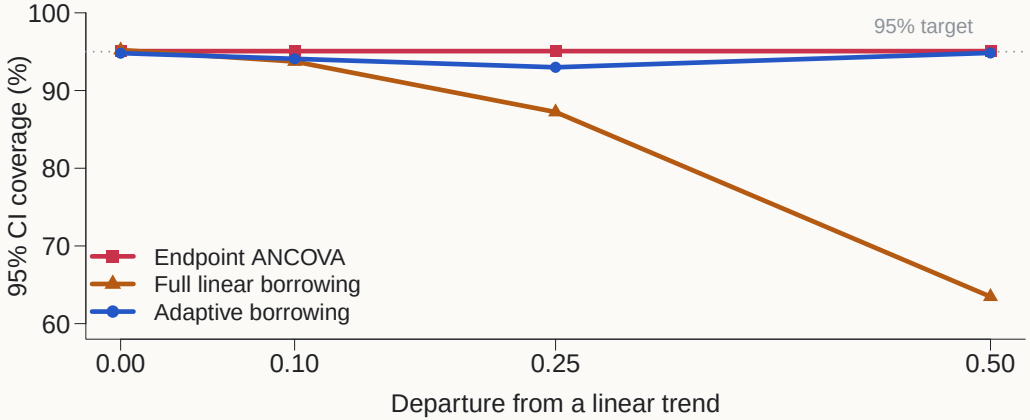
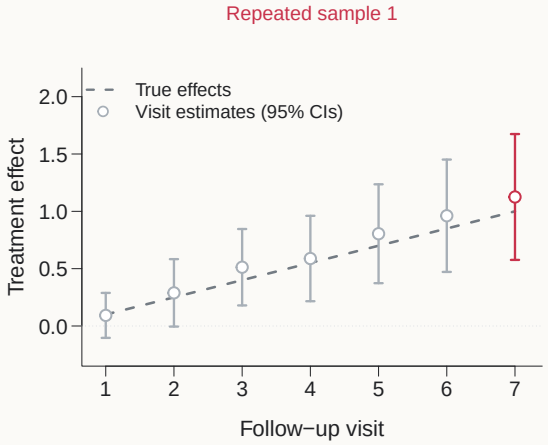
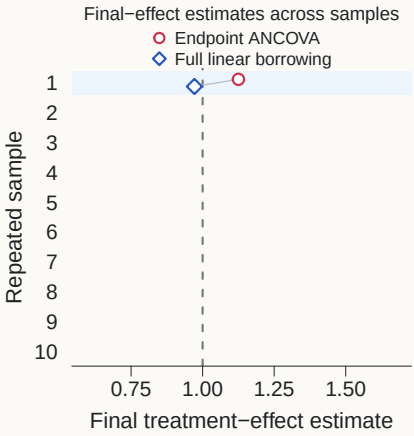


Appendix: Variability Across Repeated Trials

Ten illustrative samples with the **same true linear trajectory**

Compare **endpoint ANCOVA** with **full linear borrowing**





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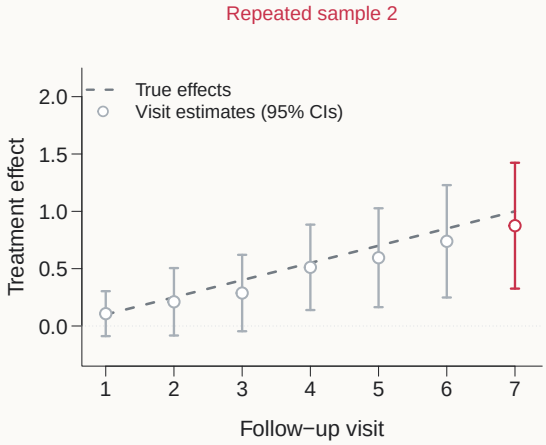

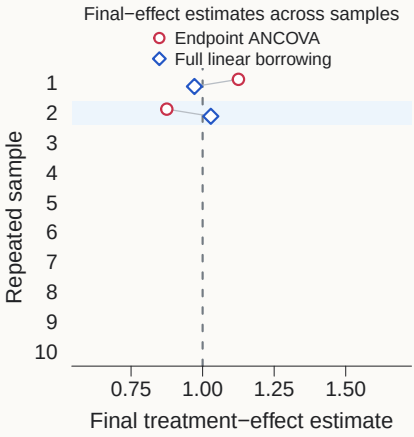

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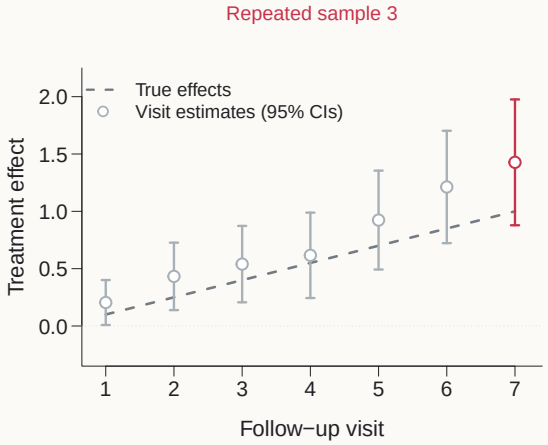

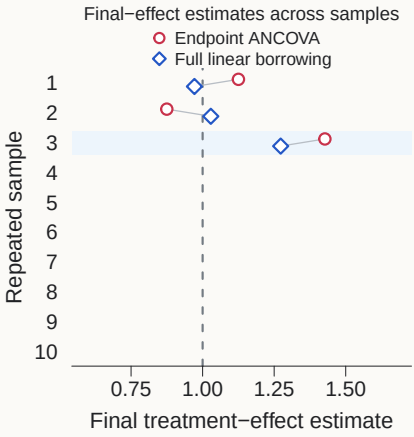

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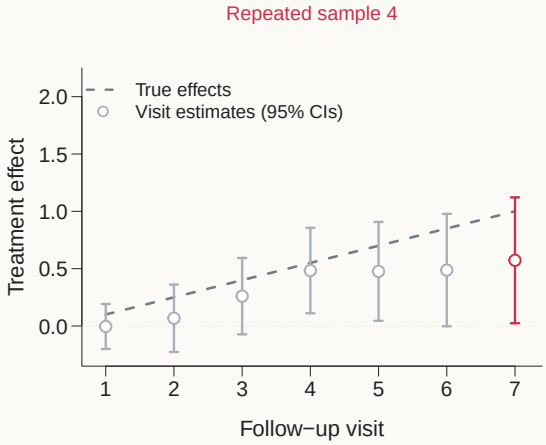

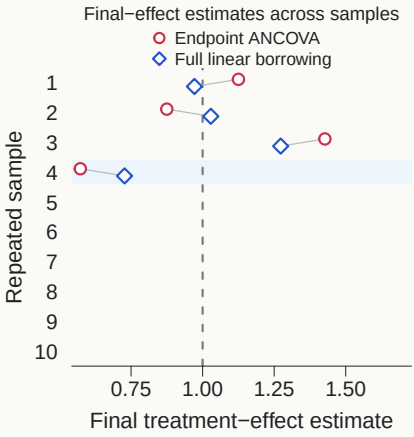

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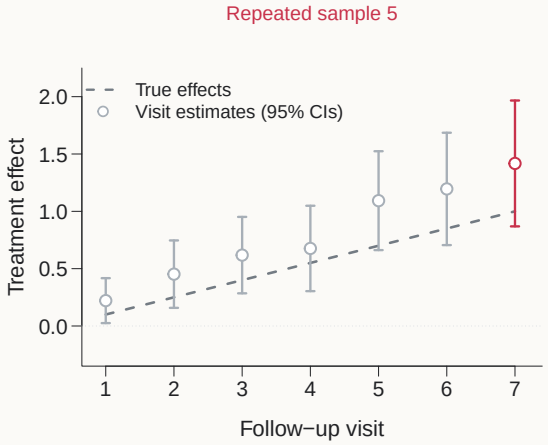

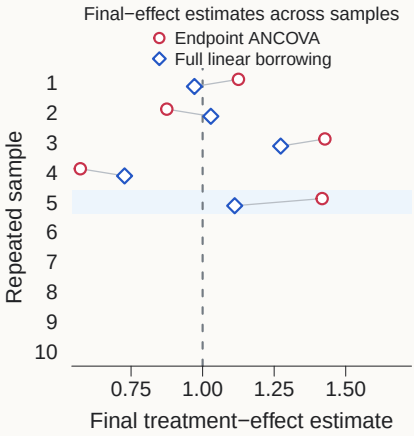

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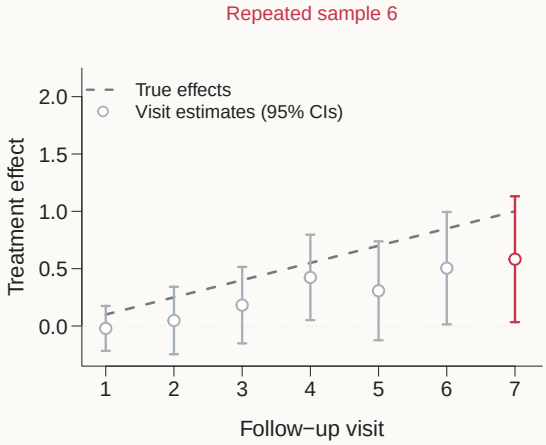

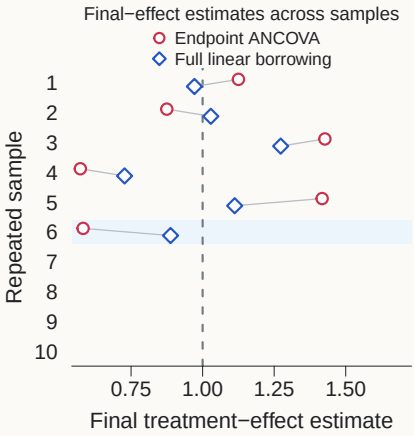

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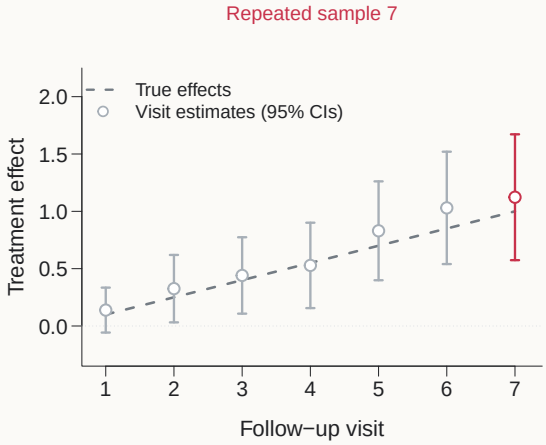

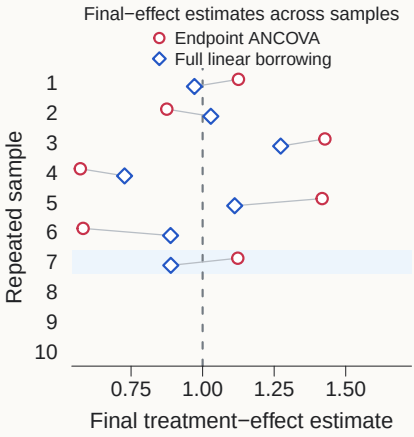

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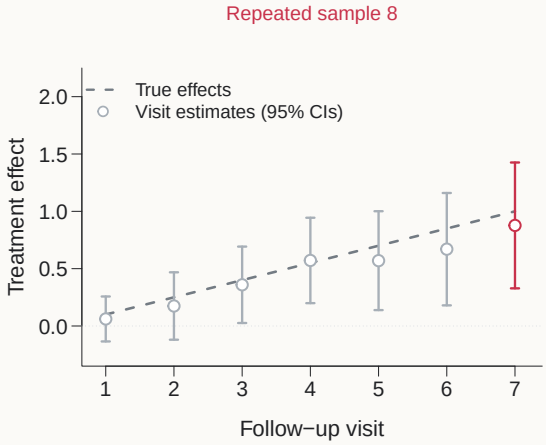

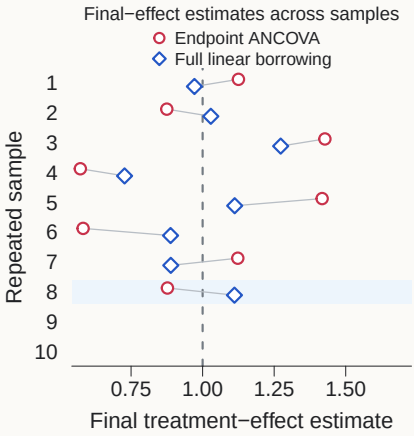

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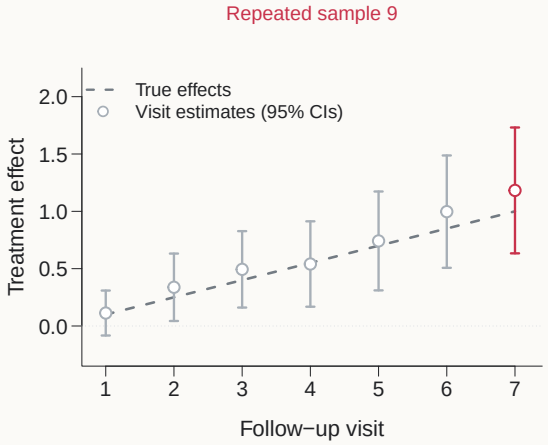

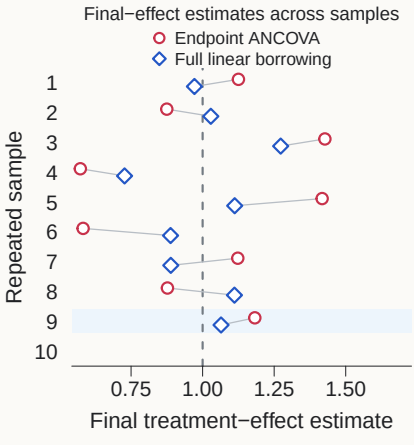

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