Impact of Delayed Outcomes, Accrual Rates, and Prognostic Variables on a Simulated Randomized Trial with Adaptive Enrichment

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Problem Motivation

- Testing treatment effects in two subpopulations and the overall population

1. Outcome measured with delay
2. Use information from prognostic baseline variables and short-term outcomes
3. Use adaptive enrichment designs

- Question:
  How do the prognostic value, delay time and accrual rate affect the performance of trials?

Problem Motivation

- Question:
  How do the prognostic value, delay time and accrual rate affect the performance of trials?
  What happens to **Type I Error, Power, Expected Sample Size, Average Duration** if:

- correlation between baseline variables and primary outcome is different from pilot study?

- change the focus to a sooner-available outcome?

- accrual rate is different from pre-planned?

ADNI Data

- Alzheimer's Disease Neuroimaging Initiative (ADNI): observational longitudinal study of cognitive impairment and progression to Alzheimer's disease
- 286 patients with:
  - **S**: no alleles vs. at least one allele of APOE ε4
  - **W**: 5 variables measured at enrollment
  - **L**: disease progression at 12 months
  - **Y**: disease progression at 24 months
- **A**: treatment assignment (added in the simulation)

Null Hypotheses

- Define three **treatment effects** of interest:

- **Δ_1 = E(Y | A = 1 , S = 1) - E(Y | A = 0 , S = 1)**
  Mean treatment effect for subpopulation 1

- **Δ_2 = E(Y | A = 1 , S = 2) - E(Y | A = 0 , S = 2)**
  Mean treatment effect for subpopulation 2

- **Δ_0 = E(Y | A = 1) - E(Y | A = 0)**
  Mean treatment effect for combined population

- Define three **null hypotheses**:

$$H_{01} : \Delta_1 \leq 0; \quad H_{02} : \Delta_2 \leq 0; \quad H_{00} : \Delta_0 \leq 0$$

Multiple Testing Procedure

$$H_{01} : \Delta_1 \leq 0; \quad H_{02} : \Delta_2 \leq 0; \quad H_{00} : \Delta_0 \leq 0$$

At each analysis:

1. For each $s \in \{0, 1, 2\}$, if $Z_{s,k} > u_{s,k}$, reject H_{0s}.
2. For each subpopulation $s \in \{1, 2\}$, if H_{0s} was rejected or $Z_{s,k} < l_{s,k}$, stop subpopulation s enrollment.
3. If both H_{01} and H_{02} are rejected, reject H_{00}.

c.f. Rosenblum et. al. (2015)

Estimators

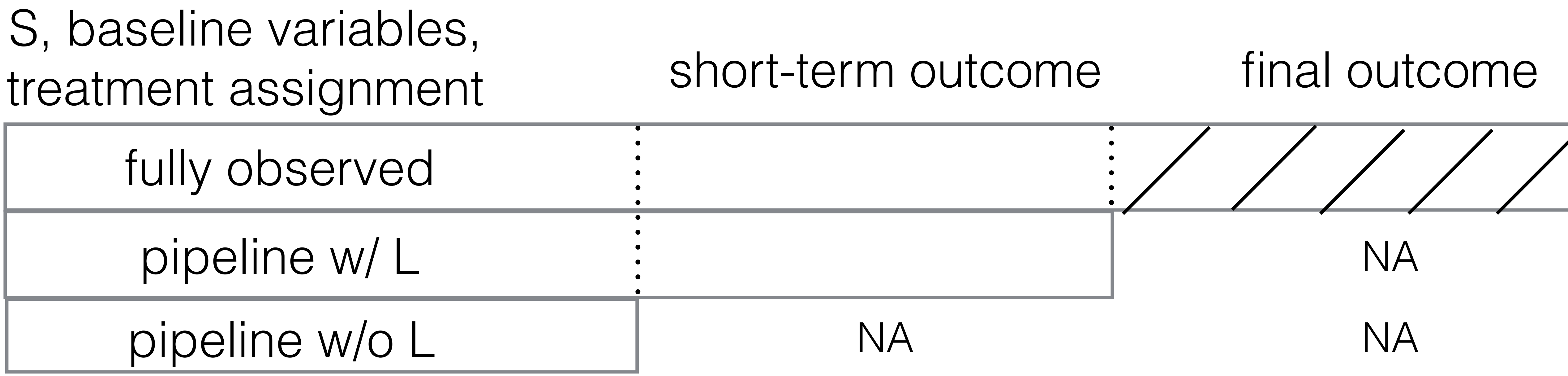
S, baseline variables, treatment assignment	short-term outcome	final outcome
fully observed		
pipeline w/ L		NA
pipeline w/o L	NA	NA

- **Unadjusted estimator**

- **Adjusted estimator**

c.f. van der Laan and Gruber (2012)

Estimators

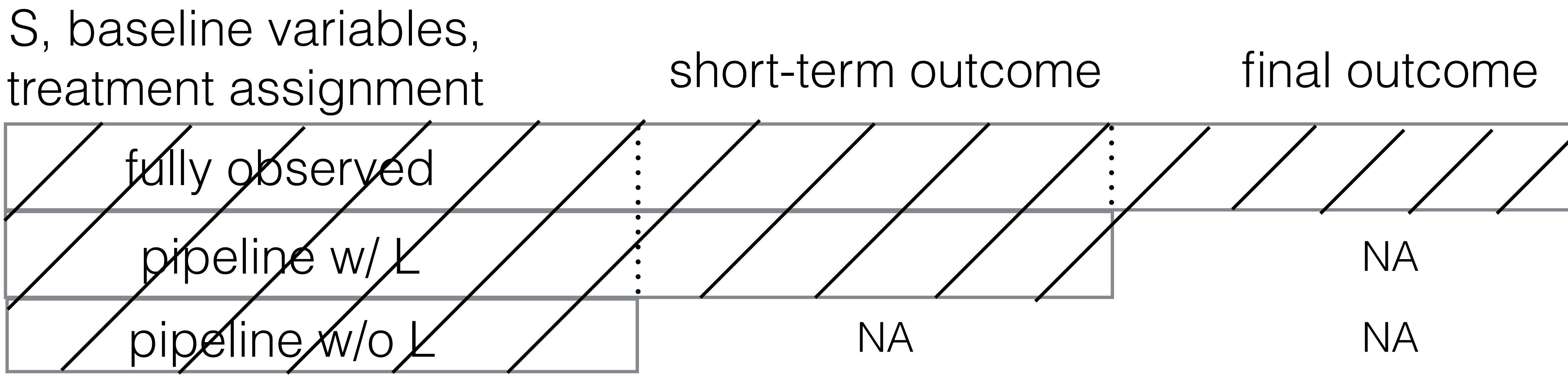


- **Unadjusted estimator** only uses final outcome of fully observed participants

- **Adjusted estimator**

c.f. van der Laan and Gruber (2012)

Estimators



- **Unadjusted estimator** only uses final outcome of fully observed participants

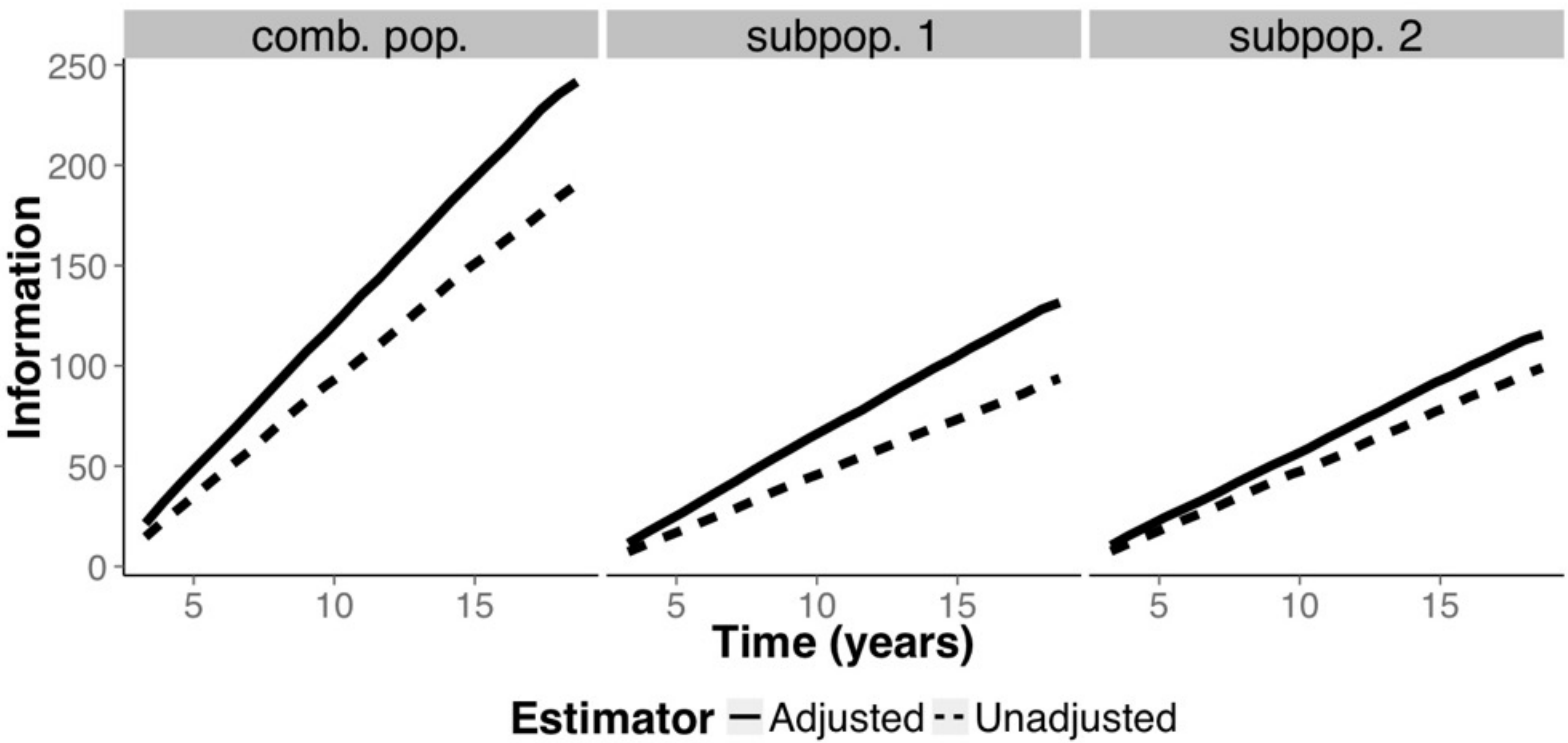
- **Adjusted estimator** also uses baseline variables and short-term outcome, and pipeline data; these variables are only used for improving precision in estimating the treatment effect

- Targeted Maximum Likelihood Estimator: require no parametric assumptions; consistent and asymptotically normal under mild regularity conditions

c.f. van der Laan and Gruber (2012)

Information-based Monitoring

$$\text{information} := 1/\text{Var}(\text{estimator})$$



Goal of Trials

$$H_{01} : \Delta_1 \leq 0; \quad H_{02} : \Delta_2 \leq 0; \quad H_{00} : \Delta_0 \leq 0$$

1. Familywise Type I error $\leq .025$

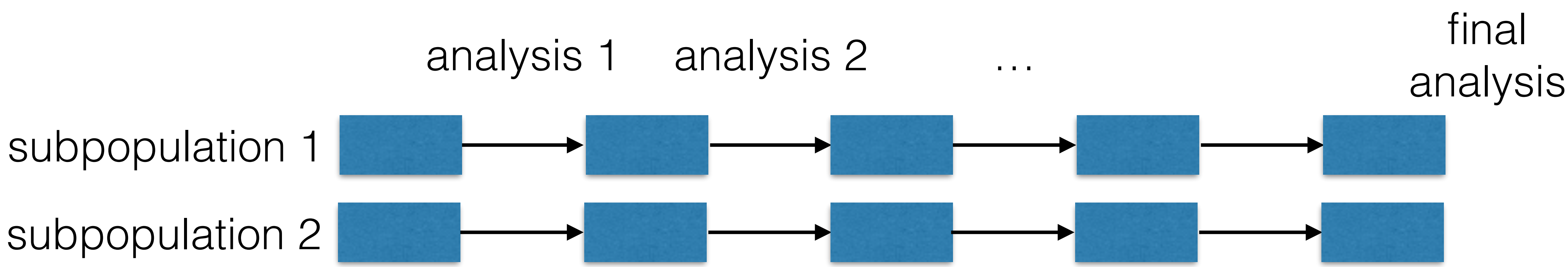
2. $\geq 80\%$ power to:
   (a) reject H_{01} if treatment only benefits Subpop. 1
   (b) reject H_{02} if treatment only benefits Subpop. 2
   (c) reject H_{00} if treatment benefits both Subpop.

Simulation Setup

- Minimize expected sample size for unadjusted estimator, subject to Type I error and Power constraints.

Analysis (k)	1	2	3	4	5
Information threshold for Subpop. 1	13.0	20.2	24.9	40.1	69.1
Information threshold for Subpop. 2	13.4	20.2	25.7	41.1	69.6
Information threshold for Comb. Pop.	27.1	40.8	50.1	80.3	138.5
Type I error spent for H_{01}	0.0007	0.0007	0.0028	0.0015	0.0038
Type I error spent for H_{02}	0.0001	0.0023	0.0012	0.0026	0.0027
Type I error spent for H_{00}	0.0028	0.0006	0.0009	0.0013	0.0012
Futility boundary ($l_{1,k}$)	-4.12	0.40	-1.48	0.94	-
Futility boundary ($l_{2,k}$)	-0.10	0.29	0.42	0.93	-

Example Trial



Analysis (k)	1	2	3	4	End Enroll	5 (final)
Time (years)	3.2	3.8	4.2	5.5	6.1	8.1
CSS (Subpop. 1)	140 (+310)	250 (+300)	300 (+310)	510 (+310)	600 (+310)	910 (+0)
CSS (Subpop. 2)	220 (+360)	330 (+370)	420 (+340)	640 (+320)	710 (+350)	1060 (+0)
CSS (Comb. Pop.)	360 (+670)	580 (+670)	720 (+650)	1150 (+630)	1310 (+660)	1970 (+0)

Result

1. Familywise Type I error ≤ .025
2. ≥ 80% power to:
   (a) reject H_{01} if treatment only benefits Subpop. 1
   (b) reject H_{02} if treatment only benefits Subpop. 2
   (c) reject H_{00} if treatment benefits both Subpop.

Change in trial performance translates to change in Expected Sample Size and Average Duration

Prognostic Value

in baseline variable

$$R^2_W = \frac{\text{Var}\{E(Y \mid W)\}}{\text{Var}(Y)}$$

in short-term outcome

$$R^2_L = \frac{\text{Var}\{E(Y \mid L)\}}{\text{Var}(Y)}$$

Prognostic Value

in baseline variable

$$R_W^2 = \frac{\mathrm{Var}\{E(Y \mid W)\}}{\mathrm{Var}(Y)}$$

in short-term outcome

$$R_L^2 = \frac{\mathrm{Var}\{E(Y \mid L)\}}{\mathrm{Var}(Y)}$$

change

unchanged

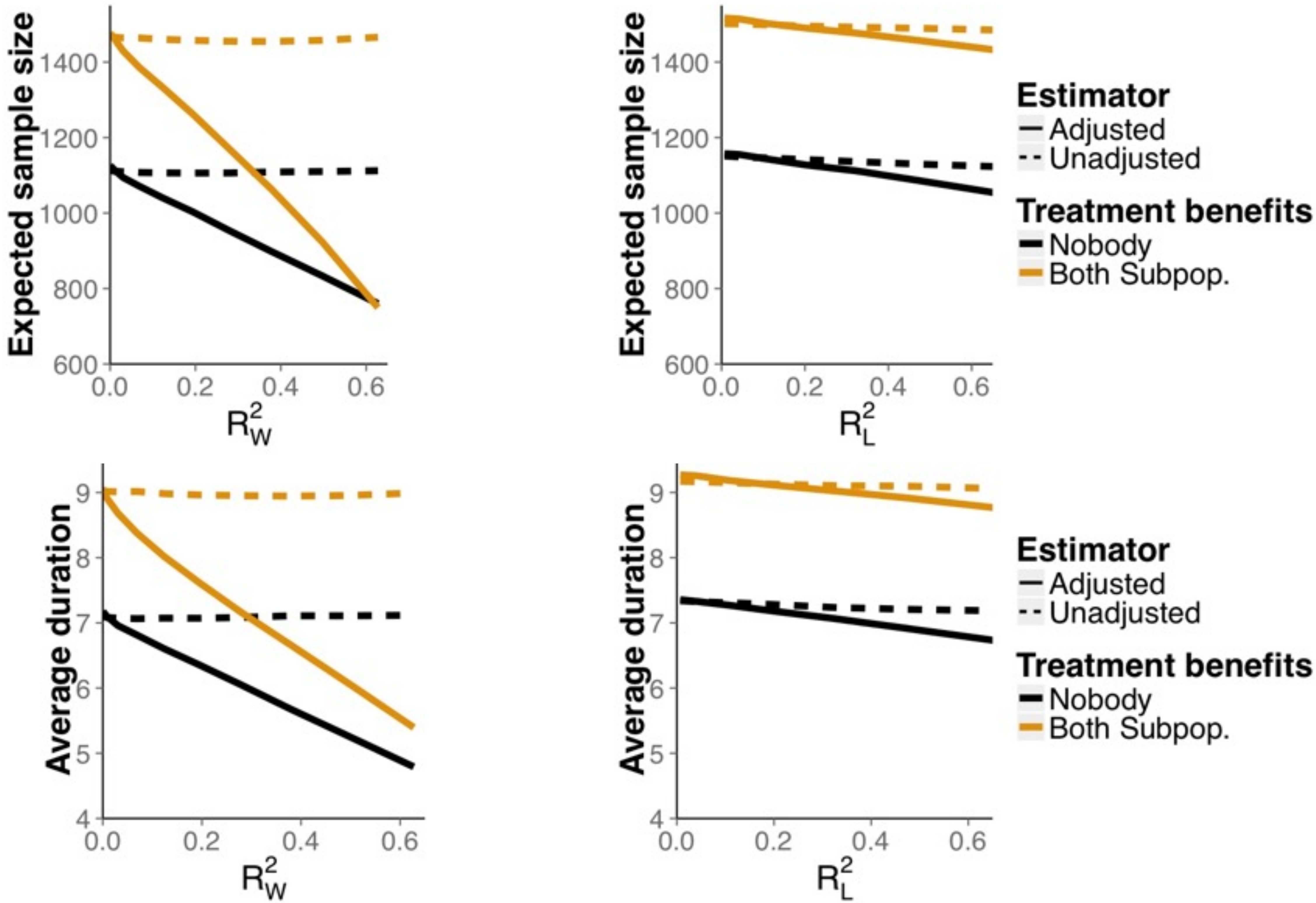
- Performance of unadjusted estimator is unaffected
- Performance of adjusted estimator changes

baseline variable

$$R_W^2 = \frac{\mathrm{Var}\{E(Y \mid W)\}}{\mathrm{Var}(Y)}$$

short-term outcome

$$R_L^2 = \frac{\mathrm{Var}\{E(Y \mid L)\}}{\mathrm{Var}(Y)}$$



baseline variable

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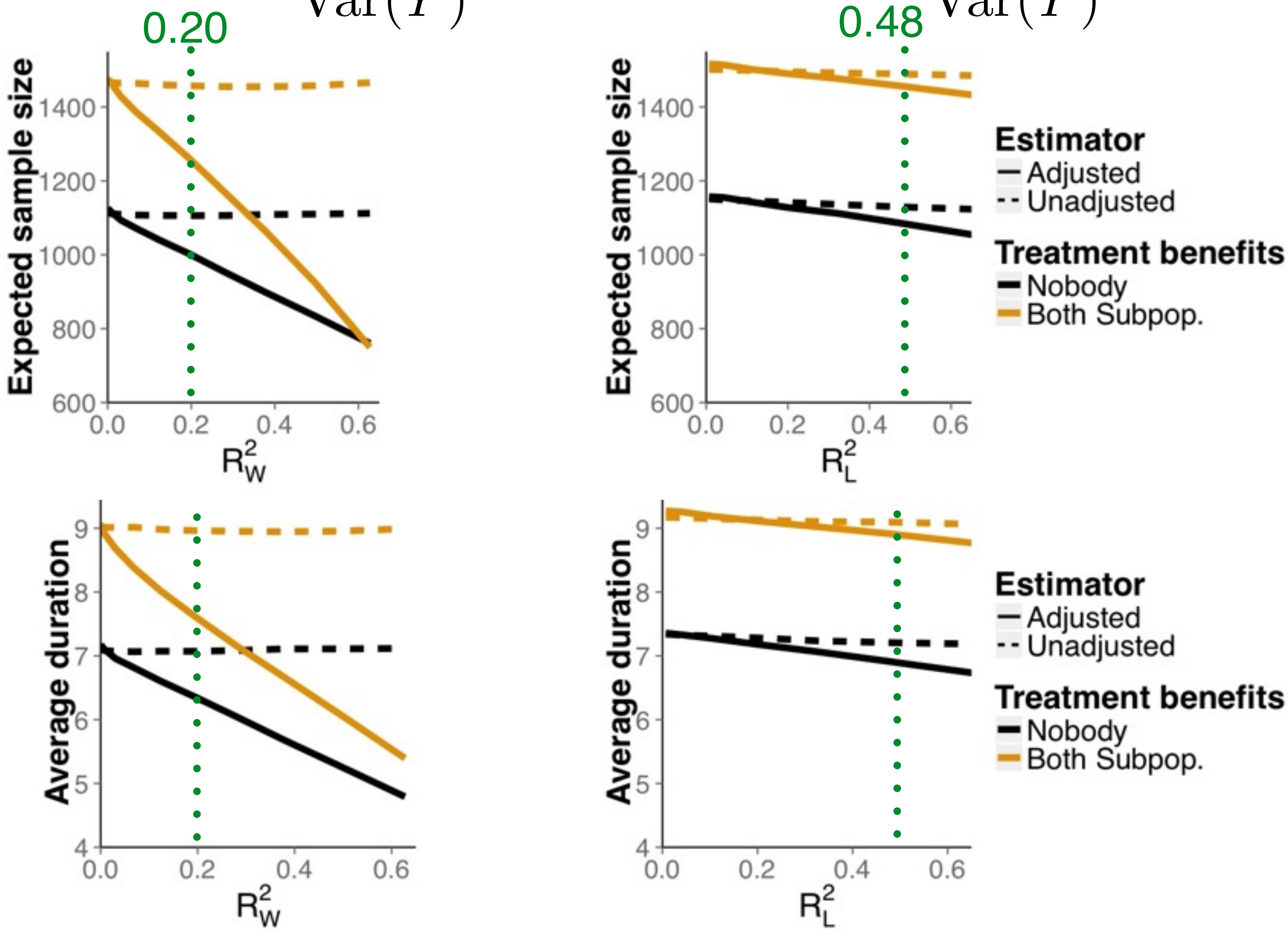
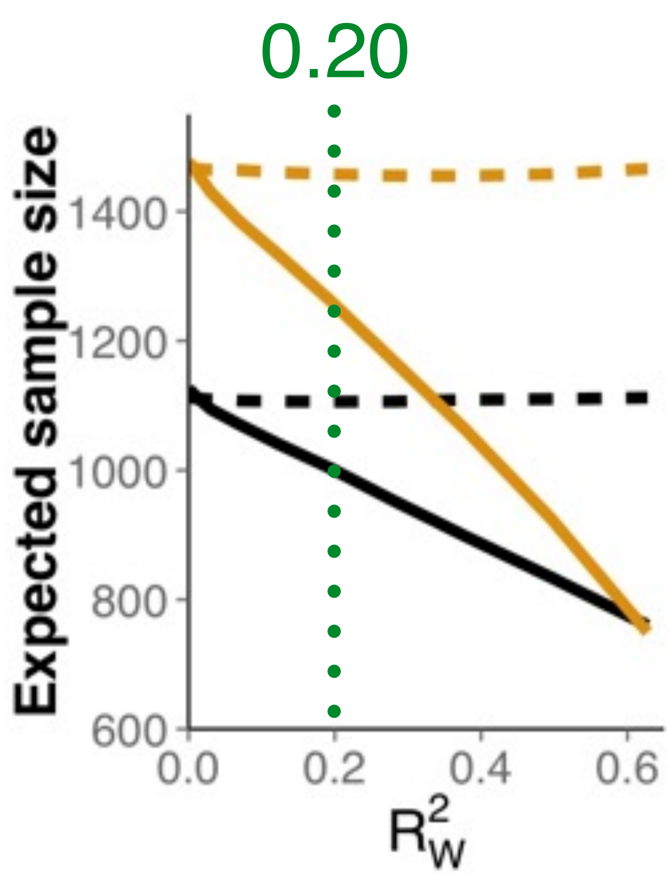


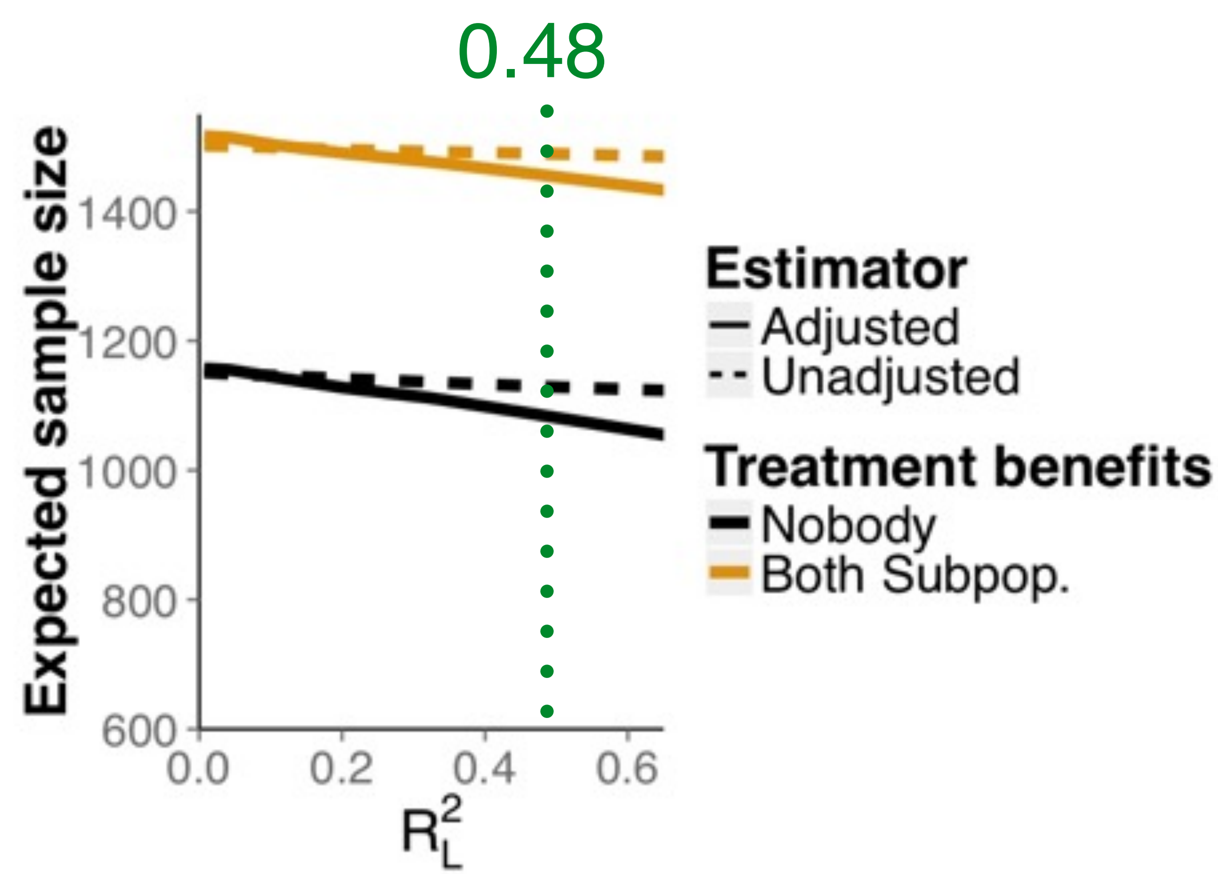
Baseline variable (W)

- Contribution of W proportional to the number of *enrolled patients*
- W improves precision for estimation of *both* E(Y|A=1) and E(Y|A=0)



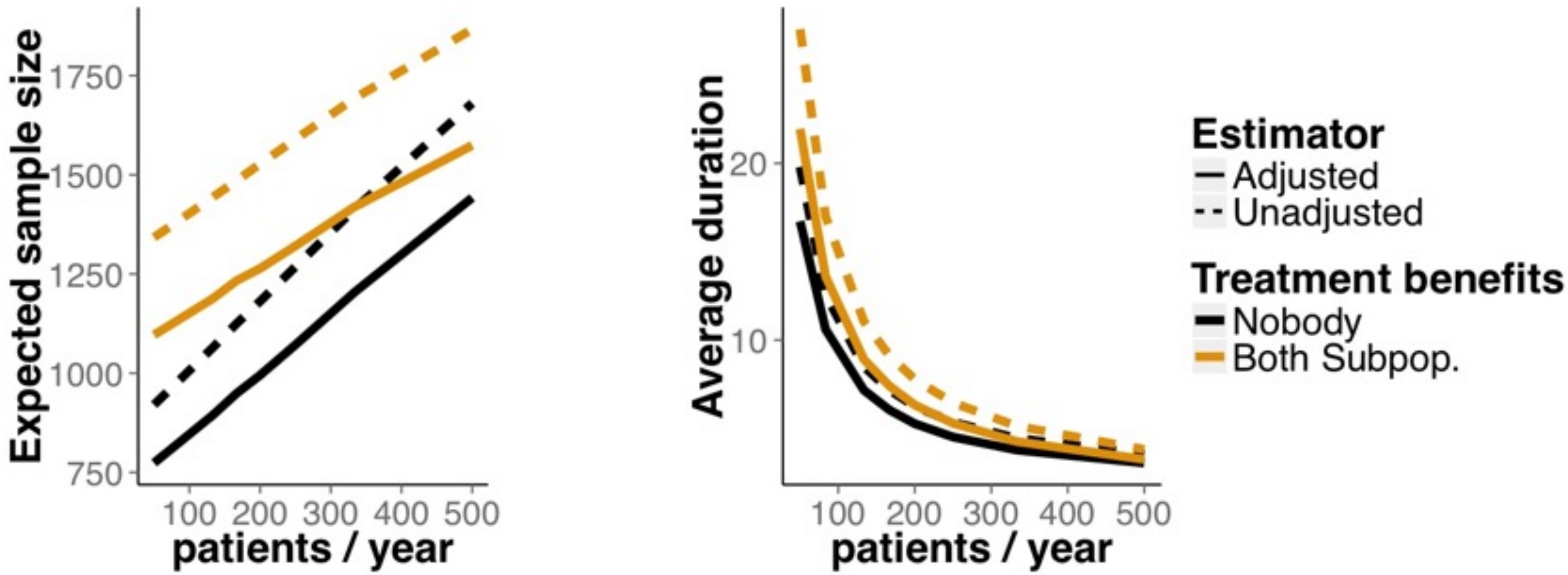
Short-term outcome (L)

- Contribution of L proportional to the number of *pipeline patients*
- L improves precision for estimation of *either* E(Y|A=1) *or* E(Y|A=0) for a participant



Accrual Rate

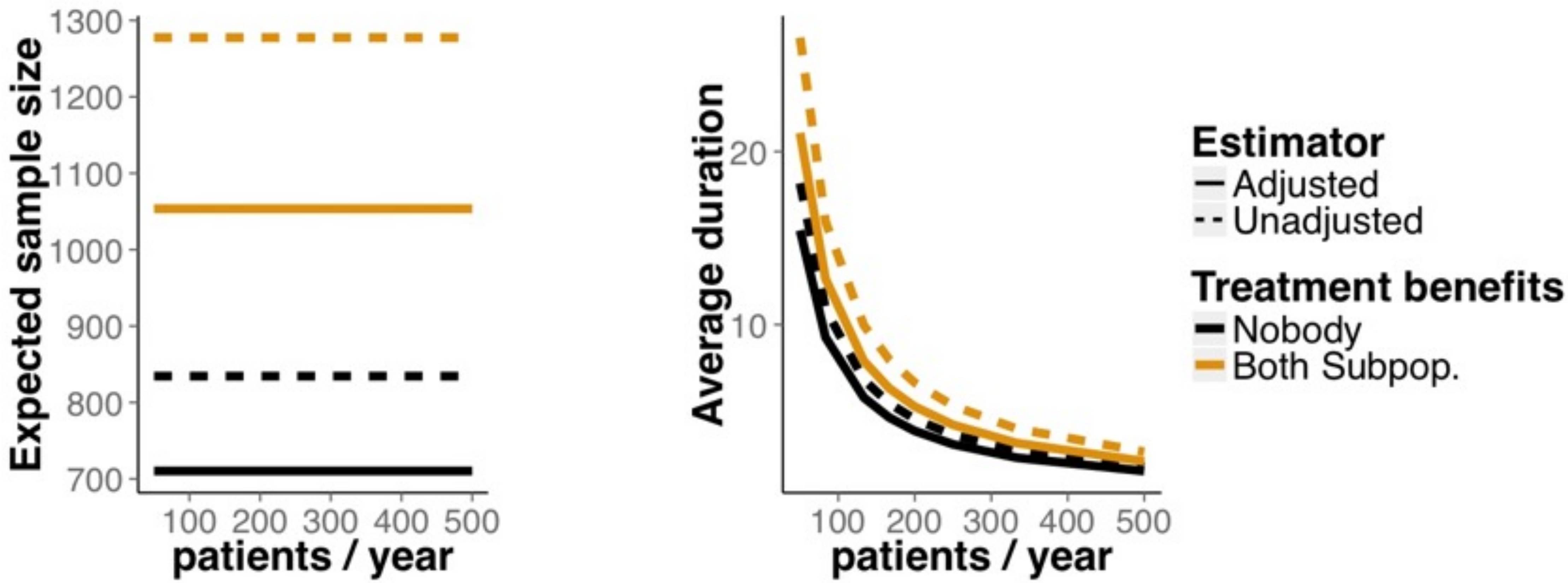
delay of final outcome = 2 years



- Trade-off: faster enrollment, shorter duration, larger sample size

Accrual Rate

delay of final outcome = 0 (immediate)



- Impact of accrual rate is modified by length of the delay

Limitations and Future Research

- Specific to our data generating distribution
- Prognostic values may decrease with longer delay
- Optimize design separately for unadjusted and adjusted estimators
- Incorporate dropout: Adjusted estimator will be consistent as long as Missing At Random

Thank you!

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References:

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- van der Laan, M. J., & Gruber, S. (2012). Targeted minimum loss based estimation of causal effects of multiple time point interventions. *The international journal of biostatistics*

Prognostic Value

in baseline variable

in short-term outcome

change

$$R_W^2 = \frac{\mathrm{Var}\{E(Y \mid W)\}}{\mathrm{Var}(Y)}$$

$$R_L^2 = \frac{\mathrm{Var}\{E(Y \mid L)\}}{\mathrm{Var}(Y)}$$

unchanged

- (S_i, W_i) random sample with replacement
- $A_i \sim \mathrm{Bernoulli}(0.5)$
- $L_i \sim N(\alpha W_i, \eta^2)$
- $Y_i \sim N(\beta W_i + \gamma L_i + \theta A_i, \sigma^2)$