Sensitivity of Trial Performance to Delayed Outcomes, Accrual Rates, and Prognostic Variables based on a Simulated Randomized Trial with Adaptive Enrichment

Tianchen Qian, Elizabeth Colantuoni, Aaron Fisher, Michael Rosenblum

Department of Biostatistics, Johns Hopkins University Bloomberg School of Public Health

Summary

Research Question: In adaptive enrichment trial designs, how do prognostic baseline variables and short-term outcomes, accrual rate, and delayed outcomes impact power, sample size and duration?

- We use a targeted maximum likelihood estimator (TMLE) to adjust for prognostic covariates, and combine it with a new multiple testing procedure. This method is **guaranteed to strongly control the familywise type I error rate**, asymptotically.
- Compared to the unadjusted estimator, adjusting for prognostic baseline variables and short-term outcomes **increase power** and **reduce sample size and duration** of the trial. The adjustment is most valuable when the variables are highly correlated with final outcome, when the delay to observe final outcome is long, and when accrual rate is fast.

Our **motivating clinical application is a trial of a new treatment for preventing Alzheimer's disease progression**.

- We use a data set of 286 patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The primary outcome is the Clinical Dementia Rating Sum of Boxes (CDRsb) measured 2 years from enrollment.
- In simulation studies, compared to the standard unadjusted estimator, by using the adjusted estimator that leverages prognostic covariates, we **simultaneously increased the power by 10%, reduced sample size by 3%, and reduced duration by 0.6 years**.

Adaptive Enrichment Design

- Adaptive enrichment designs involve **preplanned rules for modifying enrollment criteria** based on accrued data in an ongoing trial.
- We consider two prespecified subpopulations (defined by ApoE4 genotype) that partition the overall population.
- At each interim analysis, for each subpopulation a decision is made of whether to continue accrual or stop.
- Randomization is 1:1 to treatment or control throughout the trial.
- Strong familywise Type I error control guaranteed by [2].

Cumulative Sample Size as number with final outcome observed (+ pipeline*)

Interim Analysis (k)	1	2	3	4	5
Cum.S.S. Subpop. 1	184 (+368)	368 (+368)	552 (+368)	768 (+216)	984 (+0)
Cum.S.S. Subpop. 2	314 (+628)	628 (+314)	942 (+0)	942 (+0)	942 (+0)
Cum.S.S. Comb. Pop.	498 (+996)	996 (+682)	1494 (+368)	1710 (+216)	1926 (+0)
Futility Boundary ($l_{1,k}$)	0.25	0.24	0.23	0.23	-
Futility Boundary ($l_{2,k}$)	0.41	0.39	∞	-	-

Efficacy boundaries calculated using the covariances of the test-statistics for each simulated trial; see [1].

* Number of pipeline is calculated assuming $d_L = 1$ year.

Denote by Δ_1, Δ_2, and Δ_0 the average treatment effect in subpopulation 1, subpopulation 2, and the combined population, respectively. We test the following null hypotheses:

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

We simulate the trials under a) both H_{01} and H_{02} are true; b) only H_{02} is true; c) only H_{01} is true; d) neither H_{01} nor H_{02} is true.

Notation

Each participant i has data vector $\mathbf{D}_i = (S_i, W_i, A_i, L_i, Y_i)$:

- S_i: subpopulation (no ApoE4 $\epsilon 4$ alleles / at least one allele)
- W_i: baseline variables (baseline CDR, age, $A\beta_{42}$, ADA scale, MMSE score)
- A_i: binary treatment indicator
- L_i: short-term outcome, with delay d_L from enrollment (CDRsb at 1 year);
- Y_i: primary outcome, with delay d_Y from enrollment (CDRsb at 2 year)

Baseline variables and short-term outcomes only used as potentially prognostic variables for final outcome. No assumptions made on relationship among these variables. (We do not assume short-term outcome is surrogate.)

Our simulations are based on data generated from linear models that were initially fit to the ADNI data. We use the R^2 to measure the prognostic value in the baseline variables and the short-term outcome, defined as follows:

$$R^2_W = \frac{\mathrm{Var}\{E(Y \mid W)\}}{\mathrm{Var}(Y)}, \qquad R^2_L = \frac{\mathrm{Var}\{E(Y \mid L)\}}{\mathrm{Var}(Y)}.$$

In the ADNI data, $R^2_W \approx 0.2$ and $R^2_L \approx 0.3$.

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Adjusted Estimator: TMLE

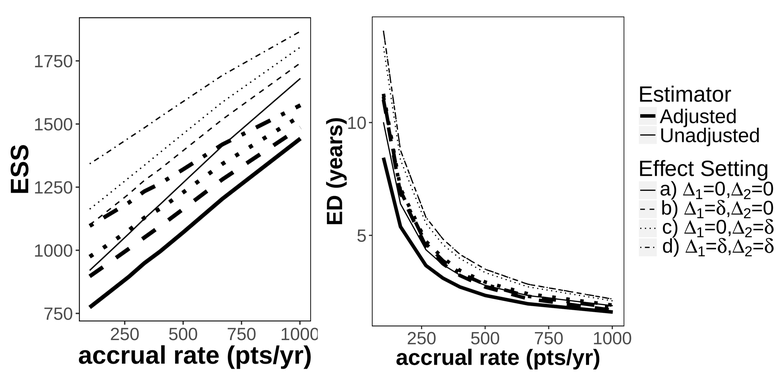
We use the Targeted Maximum Likelihood Estimator (TMLE) [3] to adjust for prognostic baseline variables and short-term outcomes. The advantages of using TMLE in a randomized trial are as follows.

- Guaranteed to strongly control the familywise Type I error rate, using the testing procedure based on corresponding Wald statistics. (Assuming outcome data missing completely at random, or missing at random with correctly modeled missingness probability.)
- Improve power, reduce sample size, and reduce trial duration compared to the unadjusted estimator.
- Available in R package ltmle.

Impact of Accrual Rate

We assume constant rate for continuous accrual throughout the trial. **Faster accrual rate** leads to the following.

- **More pipeline participants** at each stage; hence **larger expected sample size**.
- **Shorter trial duration** as information accrues faster.
- Power of both estimators are almost unchanged.

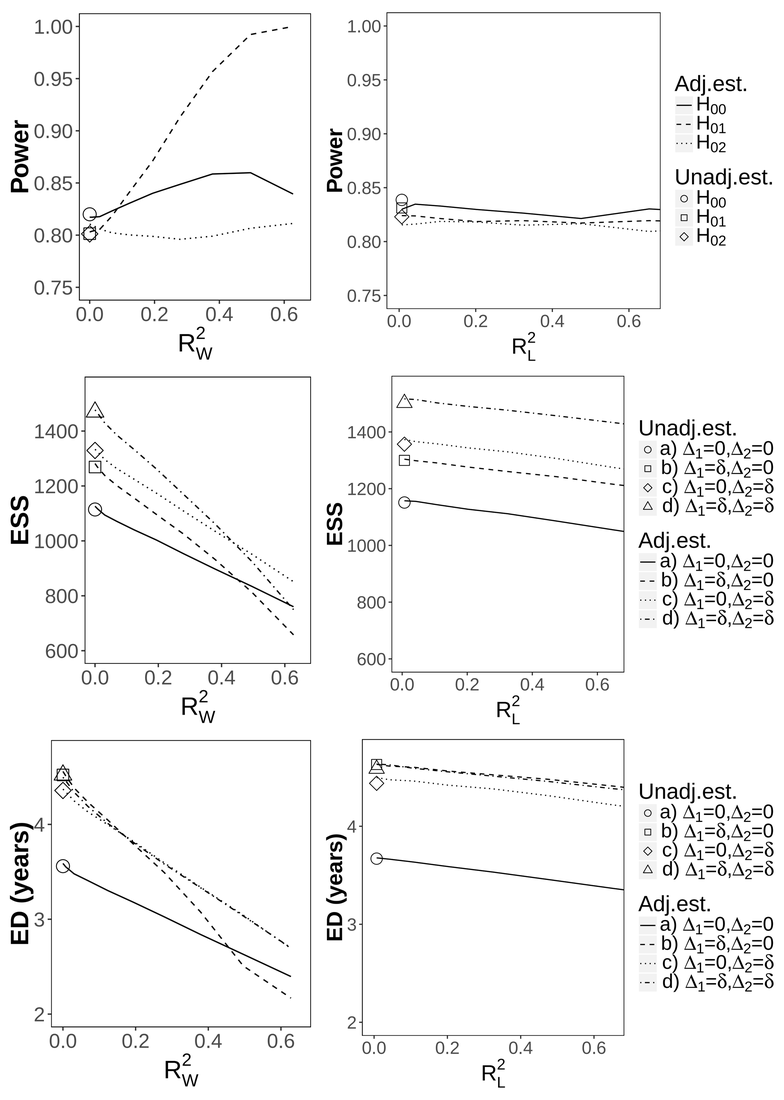


Impact of accrual rate on expected sample size (ESS) and expected duration (ED).

Impact of Prognostic Covariates

A Prognostic baseline variable is more valuable than an equally prognostic short-term outcome in terms of:

- **Increasing power** of the trial;
- **Reducing expected sample size** of the trial;
- **Reducing expected duration** of the trial.



Impact of prognostic value on power, expected sample size (ESS), expected duration (ED). Performance of the unadjusted estimator does not depend on R^2_W or R^2_L, and is marked next to the vertical axis.

Contact Information

- Email: tqian2@jhu.edu
- Phone: +1 (609) 216-4600
- Link to this poster: `https://goo.gl/DiYD4u`
- Link to the corresponding working paper: `http://biostats.bepress.com/jhubiostat/paper277/`

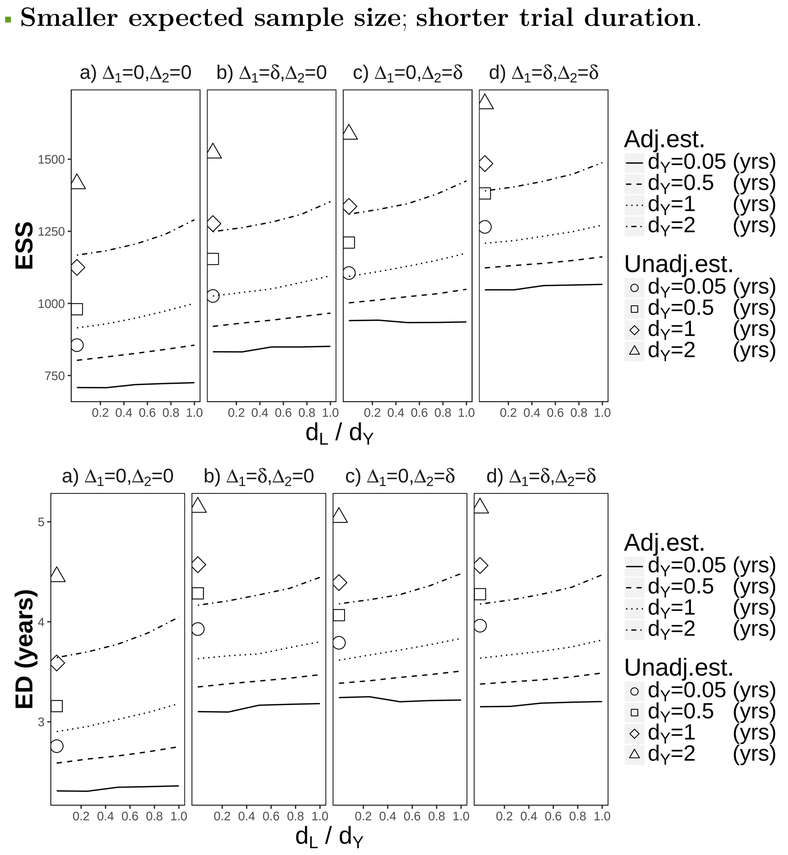
Impact of Outcome Delay Time

Fixing delay to final outcome d_Y, **shorter delay to short-term outcome** d_L will result in the following.

- Slightly **higher power of the adjusted estimator**; power of unadjusted estimator is unchanged;
- **Smaller expected sample size**; **shorter trial duration**.

Fixing delay to short-term outcome d_L, **shorter delay to final outcome** d_Y will result in the following.

- Power of both estimators unchanged;
- **Smaller expected sample size**; **shorter trial duration**.



Impact of delay time to final outcome (d_Y) and to short-term outcome (d_L) on expected sample size (ESS) and expected duration (ED). Horizontal axis is the ratio of the delays to short-term outcome and to final outcome. Performance of the unadjusted estimator does not depend on d_L or d_Y, and is marked next to the vertical axis.

Practical Implication

When using adjusted estimators such as TMLE to adjust for prognostic baseline variables and short-term outcomes, compared to the unadjusted estimator, the performance of the adaptive enrichment randomized trial is impacted by design characteristics in the following way. The trial has:

Increased power and estimation precision when:

- prognostic baseline variables and short-term outcomes are available;
- the delay to short-term outcome is short.

Reduced expected sample size when:

- prognostic baseline variables and short-term outcomes are available;
- the delay to short-term outcome is short.
- the delay to final outcome is short.
- the accrual rate is slow.

Shorter expected duration when:

- prognostic baseline variables and short-term outcomes are available;
- the delay to short-term outcome is short.
- the delay to final outcome is short.
- the accrual rate is fast.

Future Research

- To analyze the impact of subpopulation proportion on trial performance.
- To consider random enrollment process. Make the correlation between variables dependent on the length of delay.
- To implement information-based design (instead of pre-set sample size at each stage). We conjecture this will further reduce expected sample size.

References

[1] Qian, T., E. Colantuoni, A. Fisher, and M. Rosenblum. Sensitivity of trial performance to delay outcomes, accrual rates, and prognostic variables based on a simulated randomized trial with adaptive enrichment. *Johns Hopkins University, Dept. of Biostatistics Working Papers, Working Paper 277*.

[2] Rosenblum, M., T. Qian, Y. Du, H. Qiu, and A. Fisher (2016). Multiple testing procedures for adaptive enrichment designs: combining group sequential and reallocation approaches. *Biostatistics 17*(4), 650–662.

[3] van der Laan, M. J. and S. Gruber (2012). Targeted minimum loss based estimation of causal effects of multiple time point interventions. *The international journal of biostatistics 8*(1).