Improving Precision and Power by Adjusting for Prognostic Baseline Variables in Alzheimer's Disease Clinical Trials

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Objectives

There is potential to improve precision and power in randomized trials by appropriately adjusting for baseline variables that are prognostic for the primary outcome.

We provide guidance on two key challenges to appropriately adjusting for baseline variables:

1) How are baseline variables identified, before the trial starts, that are likely to be strongly correlated with the primary outcome?

2) How do we choose a statistical method that has the key statistical properties required by regulators such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA)?

Namely,
- Fully leverages the prognostic information in the identified baseline variables
- Accounts for drop-out that may be differential across treatment groups and correlated with outcomes

We explore solutions to the two challenges by considering planning a trial for preventing progression from mild cognitive impairment to Alzheimer's disease (AD) and utilizing data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study

Trial Design

Consider an intervention trial for preventing progression from mild cognitive impairment to Alzheimer's disease (AD).
- Clinical Dementia Rating Scale (CDR) is administered at baseline and 6, 12 and 18-months post randomization.
- Primary endpoint: Change in CDR Sum of Boxes (CDR_{SB}) comparing 18-months to baseline
- Marginal Treatment Effect: Difference in mean change in CDR_{SB} comparing the intervention and control
- Inclusion/exclusion criteria: 55 to 85 years of age, CDR_{SB} (sums of boxes score) ≤ 2.5, EMCI patients excluded
- Anticipate 20% patient drop-out

Results and Conclusions

Using available observational data or Phase II trial data, simple statistical computations based on the R^2 statistic can be used identify candidate prognostic baseline variables.
- Within the ADNI study, we identified 8 candidate prognostic baseline variables, including two neuroimaging measures
- Assuming no missing data, adjusting for these variables reduces the required sample size by roughly 25% compared to using a standard unadjusted estimator

Novel estimators for the marginal treatment effect have been developed that account for both drop-out and chance imbalances in prognostic baseline variables
- Think ANCOVA with correction for drop-out
- In our example, after accounting for various drop-out models, use of these estimators could *conservatively* yield gains in precision of 5 to 25%.

For trial planning , we recommend:
- A simple approach for identifying a set of candidate prognostic baseline variables, to be pre-specified in the trial
- Use of a statistical method that address both prognostic baseline variables and drop-out

Identification of Prognostic Baseline Variables

Using the inclusion/exclusion criteria, we identified roughly 200 ADNI patients eligible for the trial.

Although the primary endpoint is 18-month change in CDR_{SB},
- Performed our evaluation on 12 and 24-month change in CDR_{SB}
- 18 month CDR_{SB} and neuroimaging variables were available for only a subset of patients

Step 1: Identify a set of candidate baseline variables from the ADNI study. We relied on the expertise of our Alzheimer's Disease and Dementia collaborators.

Step 2: Compute the cross-validated R^2 statistic for each candidate baseline variable.

The reduction in sample size possible when using an adjusted estimator relative to an unadjusted estimator for the marginal treatment effect is: $1 - 1 / R^2$

Step 3: Select a set of the candidate baseline variables based the estimated prognostic ability and clinical relevance. Again, using the cross-validated R^2, estimate the prognostic ability of the set of candidate baseline variables.

Table 1: Assessment of individual candidate baseline variables

	12-month	24-month
CDRSB Baseline	0.0	0.2
Age	0.0	2.0
Female	0.0	0.0
Married	0.0	0.0
Divorced	0.0	0.0
APOE4 (factor)	0.0	0.0
Mini-mental State Exam	7.3	7.2
Logial Memory Delayed Recall Score	7.4	8.3
Modified Hashinski Total Score	0.0	0.0
Geriatric Depression Scale Total	0.5	0.0
Category Fluency (Animals) - Total Correct	1.4	9.1
Trial Making Test Part A - Time to Complete	0.5	3.3
Trails A Errors of Commission	2.5	3.1
Trails A Errors of Ommission	1.9	1.0
Trial Making Test Part B - Time to complete	6.3	6.8
Trails B Errors of Commission	4.4	3.1
Trails B Errors of Omission	2.2	0.3
Aricept use at Baseline	1.2	0.0
ADAS Cog 11 item score	11.3	8.6
ADAS Cog 13 Item score	13.2	12.3
RAVLT Delay	3.9	5.2
RAVLT Recognition	3.2	2.1
Functional Activities Questionnaire	10.1	7.6
Hippocampal Volume	3.7	10.8
Entorhinal Thickness	5.6	12.7

Selected 8 prognostic variables (denote these by W): baseline CDR_{SB}, APOE4 carrier status, Mini-mental State Exam, Logical Memory Delayed Recall Score, Trial Making Test Part B- Time to complete, Functional Activities Questionnaire and two neuroimaging measures: Hippocampal Volume and Entorhinal Thickness.

Adjusting for W, the sample size required to estimate the marginal treatment effect is reduced by roughly 25% compared to that required when using an unadjusted estimator.

NOTE: This evaluation does not account for patient drop-out.

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References

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Available Estimators for Marginal Treatment Effect

The simple unadjusted estimator is the difference in the sample means of the primary endpoint, computed from patients with CDR_{SB} measured at 18-months.

Two important drawbacks:
1. This estimator can be biased if drop-out is differential in the treatment groups and correlated with CDR_{SB}
2. This estimator does not take advantage of chance imbalance in prognostic baseline variables across treatment groups

In recent years, novel estimators have been developed that can address these two important drawbacks.

- Precise, locally efficient, augmented, simple estimator (PLEASE): same statistical properties as ANCOVA and accounts for drop out as a function of W and baseline CDR_{SB}
- Special case of targeted minimum loss estimators (TMLE): same statistical properties as ANCOVA and accounts for drop out as a function of W and outcomes (baseline and intermediate CDR_{SB})

Simulation Study

We simulated hypothetical trials using the ADNI data to:
- Enroll patients with same distribution of W as observed in ADNI
- Preserve the relationship between CDR_{SB} measured over time
- The relationship between CDR_{SB} and W
  (i) is that observed in ADNI
  (ii) is reduced relative to that observed in ADNI

We assumed 20% patient drop-out:
- Completely at random
- Missing at random – baseline: drop-out depends only on W and baseline CDR_{SB}
- Missing at random – intermediate: drop-out depends on W, baseline CDR_{SB} and intermediate CDR_{SB}

Table 2: Comparison of estimators based on observed relationship between CDR_{SB} and W

Drop-out Model	Estimator	Bias	Variance	Relative Variance	MSE	Relative MSE
Completely at Random	Unadjusted	0.00090	0.013	1.00	0.013	1
	PLEASE	0.000093	0.0091	1.47	0.0091	1.47
	TMLE	0.00022	0.0087	1.54	0.0087	1.54
Missing at Random (baseline)	Unadjusted	0.0019	0.014	1.00	0.014	1.00
	PLEASE	0.00073	0.0099	1.41	0.0099	1.41
	TMLE	0.00078	0.0093	1.50	0.0093	1.50
Missing at Random (intermediate)	Unadjusted	0.032	0.014	1.00	0.015	1.00
	PLEASE	0.024	0.0094	1.47	0.010	1.49
	TMLE	0.00034	0.0090	1.55	0.0090	1.66

Table 3: Comparison of estimators based on ***conservative*** estimate of the relationship between CDR_{SB} and W

Drop-out Model	Estimator	Bias	Variance	Relative Variance	MSE	Relative MSE
Completely at Random	Unadjusted	-0.00022	0.014	1.00	0.014	1.00
	PLEASE	0.000089	0.013	1.07	0.013	1.07
	TMLE	-0.00018	0.012	1.14	0.012	1.14
Missing at Random (baseline)	Unadjusted	0.0043	0.014	1.00	0.014	1.00
	PLEASE	0.0012	0.014	1.05	0.014	1.05
	TMLE	0.0012	0.012	1.15	0.012	1.15
Missing at Random (intermediate)	Unadjusted	0.035	0.014	1.00	0.015	1.00
	PLEASE	0.034	0.013	1.07	0.014	1.07
	TMLE	0.00037	0.012	1.15	0.012	1.25

- If drop-out is completely at random, the unadjusted is unbiased but does not take advantage of the prognostic baseline variables
- Conservative precision gains of 5% can be achieved using PLEASE, however, this estimator cannot account for information in the intermediate outcomes and is biased if drop-out depends on intermediate outcomes
- Conservative precision gains of 15-25% can be achieved with the TMLE.