Biometrics 000, 000–000 DOI: 000
000 0000

Web-based Supplementary Materials for "Sequential Multiple Assignment Randomization Trials with EnRichment Design"

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This paper has been submitted for consideration for publication in *Biometrics*

Web Appendix A: Derivation of Asymptotic Variance for $\widehat{\mu}(d_1, d_2)$

If we introduce the empirical measure $\mathbf{P}_n$ for the SMART population and $\mathbf{P}_m$ for the enrichment population, then the estimator can be written as

$$\begin{aligned}\widehat{\mu}(d_1,d_2) &= \left\{\mathbf{P}_n\left[Z\frac{I(A_1=d_1(S),A_2=d_2(S,A_1))}{p(A_1|S)p(A_2|S,A_1)}+(1-Z)\frac{I(A_1=d_1(S))}{p(A_1|S)}\right]\right\}^{-1} \\ &\quad\times\left\{\mathbf{P}_n\left[Z\frac{I(A_1=d_1(S),A_2=d_2(S,A_1))}{p(A_1|S)p(A_2|S,A_1)}Y\right]+\mathbf{P}_n\left[(1-Z)\frac{I(A_1=d_1(S))}{p(A_1|S)}\right.\right. \\ &\left.\left.\frac{n\widetilde{\mathbf{P}}_n\left\{\widetilde{Z}\widetilde{Y}I(\widetilde{A}_1=A_1,\widetilde{A}_2=d_2(S,A_1),\widetilde{S}=s)\right\}+m\widetilde{\mathbf{P}}_m\left\{\widetilde{Y}I(\widetilde{A}_1=A_1,\widetilde{A}_2=d_2(S,A_1),\widetilde{S}=S)\right\}}{n\widetilde{\mathbf{P}}_n\left\{\widetilde{Z}I(\widetilde{A}_1=A_1,\widetilde{A}_2=d_2(S,A_1),\widetilde{S}=S)\right\}+m\widetilde{\mathbf{P}}_m\left\{I(\widetilde{A}_1=A_1,\widetilde{A}_2=d_2(S,A_1))\right\}}\right]\right\}. \quad (1)\end{aligned}$$

First, since $\widehat{Y}(s,a_1,a_2)\to E[Y|S=s,A_1=a_1,A_2=a_2]$ by assumption (b), $\widehat{\mu}(d_1,d_2)$ converges to $\mu(d_1,d_2)$ which is equal to the same expression as (1) if we replace $\mathbf{P}_n$ and $\mathbf{P}_m$ by their expectations, denoted by $\mathbf{P}_s$ and $\mathbf{P}_e$, respectively. Therefore, using the linear expansion and microscopic arguments, we obtain

$$\begin{aligned}&\widehat{\mu}(d_1,d_2)-\mu(d_1,d_2) \\ =\;&(\mathbf{P}_n-\mathbf{P}_s)\left[Z\frac{I(A_1=d_1(S),A_2=d_2(S,A_1))}{p(A_1|S)p(A_2|S,A_1)}(Y-\mu(d_1,d_2))\right. \\ &\left.+(1-Z)\frac{I(A_1=d_1(S))}{p(A_1|S)}E[Y-\mu(d_1,d_2)|S,A_1,A_2=d_2(S,A_1)]\right] \\ &+(\mathbf{P}_n-\mathbf{P}_s)\left[ZY\widetilde{\mathbf{P}}_s\left\{(1-\widetilde{Z})\frac{I(\widetilde{A}_1=d_1(\widetilde{S}))}{p(\widetilde{A}_1|\widetilde{S}_1)}\right.\right. \\ &\left.\left.\times\frac{I(S=\widetilde{S},A_1=\widetilde{A}_1,A_2=d_2(\widetilde{S},\widetilde{A}_1))}{\alpha(\widetilde{S},\widetilde{A}_1)\pi_1(\widetilde{S},\widetilde{A}_1,d_2(\widetilde{S},\widetilde{A}_1),)+\beta\pi_3(\widetilde{S},\widetilde{A}_1,d_2(\widetilde{S},\widetilde{A}_1))}\right\}\right] \\ &-(\mathbf{P}_n-\mathbf{P}_s)\left[Z\widetilde{\mathbf{P}}_s\left\{(1-\widetilde{Z})\frac{I(\widetilde{A}_1=d_1(\widetilde{S}))}{p(\widetilde{A}_1|\widetilde{S}_1)}\right.\right. \\ &\left.\left.\times\frac{E[Y|\widetilde{A}_1,\widetilde{A}_2=d_2(\widetilde{S},\widetilde{A}_1),\widetilde{S}]I(S=\widetilde{S},A_1=\widetilde{A}_1,A_2=d_2(\widetilde{S},\widetilde{A}_1))}{\alpha(\widetilde{S},\widetilde{A}_1)\pi_1(\widetilde{S},\widetilde{A}_1,d_2(\widetilde{S},\widetilde{A}_1))+\beta\pi_3(\widetilde{S},\widetilde{A}_1,d_2(\widetilde{S},\widetilde{A}_1))}\right\}\right] \\ &+\beta(\mathbf{P}_m-\mathbf{P}_e)\left[Y\widetilde{\mathbf{P}}_s\left\{(1-\widetilde{Z})\frac{I(\widetilde{A}_1=d_1(\widetilde{S}))}{p(\widetilde{A}_1|\widetilde{S}_1)}\right.\right. \\ &\left.\left.\times\frac{I(S=\widetilde{S},A_1=\widetilde{A}_1,A_2=d_2(\widetilde{S},\widetilde{A}_1),)}{\alpha(\widetilde{A}_1,\widetilde{S})\pi_1(\widetilde{S},\widetilde{A}_1,d_2(\widetilde{S},\widetilde{A}_1))+\beta\pi_3(\widetilde{S},\widetilde{A}_1,d_2(\widetilde{S},\widetilde{A}_1))}\right\}\right]\end{aligned}$$

$$-\beta\left(\mathbf{P}_m-\mathbf{P}_e\right)\left[\widetilde{\mathbf{P}}_s\left\{(1-\widetilde{Z})\frac{I(\widetilde{A}_1=d_1(\widetilde{S}))}{p(\widetilde{A}_1|\widetilde{S}_1)}\right.\right.$$
$$\left.\left.\times\frac{E[Y|\widetilde{S},\widetilde{A}_1,\widetilde{A}_2=d_2(\widetilde{S},\widetilde{A}_1),]I(A_1=\widetilde{A}_1,A_2=d_2(\widetilde{S},\widetilde{A}_1),S=\widetilde{S})}{\alpha(\widetilde{A}_1,\widetilde{S})\pi_1(\widetilde{S},\widetilde{A}_1,d_2(\widetilde{S},\widetilde{A}_1),)+\beta\pi_3(\widetilde{S},\widetilde{A}_1,d_2(\widetilde{S},\widetilde{A}_1))}\right\}\right]$$
$$+o_p(n^{-1/2}).$$

By introducing $r(s,a_1)=q(a_1|s)q(s)/[p(a_1|s)p(s)]$, we note

$$\frac{\pi_2(a_1,a_2,s)}{\alpha(a_1,s)\pi_1(s,a_1,a_2)+\beta\pi_3(s,a_1,a_2)}=\frac{1}{p(a_2|s,a_1)}\frac{I(a_2=d_2(s,a_1))}{\alpha(s,a_1)+\beta r(s,a_1)}.$$

Hence, we can further simplify the expansion to

$$\begin{aligned}
&\widehat{\mu}(d_1,d_2)-\mu(d_1,d_2)\\
=\;&(\mathbf{P}_n-\mathbf{P}_s)\left[Z\frac{I(A_1=d_1(S),A_2=d_2(S,A_1))}{p(A_1|S)p(A_2|S,A_1)}(Y-\mu(d_1,d_2))\right.\\
&\left.+(1-Z)\frac{I(A_1=d_1(S))}{p(A_1|S)}E[Y-\mu(d_1,d_2)|S,A_1,A_2=d_2(S,A_1)]\right]\\
&+(\mathbf{P}_n-\mathbf{P}_s)\left[\frac{(1-\alpha(S,A_1))Z\left(Y-E[Y|A_1,A_2,S]\right)}{\alpha(S,A_1)+\beta r(S,A_1)}\frac{I(A_1=d_1(S),A_2=d_2(S,A_1))}{p(A_1|S)p(A_2|S,A_1)}\right]\\
&+\beta\left(\mathbf{P}_m-\mathbf{P}_e\right)\left[\frac{(1-\alpha(S,A_1))\left(Y-E[Y|A_1,A_2,S]\right)}{\alpha(S,A_1)+\beta r(S,A_1)}\frac{I(A_1=d_1(S),A_2=d_2(S,A_1))}{p(A_1|S)p(A_2|S,A_1)}\right].
\end{aligned}$$

As a result, the asymptotic variance of $\widehat{\mu}(d_1,d_2)$ is V/n as defined in section 3.

$$\begin{aligned}
V\;\equiv\;&Var_s\left(Z\frac{I(A_1=d_1(S),A_2=d_2(S,A_1))}{p(A_1|S)p(A_2|S,A_1)}\right.\\
&\times\left\{(Y-\mu(d_1,d_2))+\frac{1-\alpha(S,A_1)}{\alpha(S,A_1)+\beta r(S,A_1)}(Y-E[Y|S,A_1,A_2])\right\}\\
&\left.+(1-Z)\frac{I(A_1=d_1(S))}{p(A_1|S)}E[Y-\mu(d_1,d_2)|S,A_1,A_2=d_2(S,A_2)]\right)\\
&+\beta Var_e\left(\frac{(1-\alpha(S,A_1))\left(Y-E[Y|A_1,A_2,S]\right)}{\alpha(S,A_1)+\beta r(S,A_1)}\frac{I(A_1=d_1(S),A_2=d_2(S,A_1))}{p(A_1|S)p(A_2|S,A_1)}\right),
\end{aligned}$$

where Var_s and Var_e denote the variance in the SMART and enrichment population respectively. We thus conclude that $\sqrt{n}(\widehat{\mu}(d_1,d_2)-\mu(d_1,d_2))$ converges in distribution to $N(0,V)$.

Clearly, a consistent estimator for V is given by

$$\begin{aligned}\widehat{V} &= \mathbf{P}_n \Bigg[Z \frac{I(A_1 = d_1(S), A_2 = d_2(S, A_1))}{p(A_1|S)p(A_2|S, A_1)} (Y - \widehat{\mu}(d_1, d_2)) \\ &\quad + (1 - Z) \frac{I(A_1 = d_1(S))}{p(A_1|S)} (\widehat{Y}(A_1, d_2(S, A_1), S) - \widehat{\mu}(d_1, d_2)) \\ &\quad + \frac{(1 - \widehat{\alpha}(S, A_1))Z \left(Y - \widehat{Y}(A_1, A_2, S)\right)}{\widehat{\alpha}(S, A_1) + \beta \widehat{r}(S, A_1)} \frac{I(A_1 = d_1(S), A_2 = d_2(S, A_1))}{p(A_1|S)p(A_2|S, A_1)} \Bigg]^2 \\ &\quad + \beta \mathbf{P}_m \left[\frac{(1 - \widehat{\alpha}(S, A_1)) \left(Y - \widehat{Y}(A_1, A_2, S)\right)}{\widehat{\alpha}(S, A_1) + \beta \widehat{r}(S, A_1)} \frac{I(A_1 = d_1(S), A_2 = d_2(S, A_1))}{p(A_1|S)p(A_2|S, A_1)} \right]^2,\end{aligned}$$

where $\widehat{\alpha}(s, a_1)$ and $\widehat{r}(s, a_1)$ are the empirical estimates of $\alpha(s, a_1)$ and $r(s, a_1)$ respectively.

Web Appendix B: Derivation of Simplified Formula for Comparative Efficiency (2)

From the notation in the main manuscript, one have the relative efficiency is

$$\rho = V_0/V = \frac{E_s\left[\frac{(\nu(S)-\mu(d_1,d_2))^2+\sigma(S)^2}{p_1(S)p_2(S)}\right]}{E_s\left[\left(\frac{\alpha}{p_1(S)p_2(S)}+\frac{1-\alpha}{p_1(S)}\right)(\nu(S)-\mu(d_1,d_2))^2+\frac{\sigma(S)^2}{p_1(S)p_2(S)}\frac{\alpha(1+\beta\omega(S))^2+\beta(1-\alpha)^2\omega(S)}{(\alpha+\beta\omega(S))^2}\right]}.$$

Substituting the simplified assumptions into the formula: $p_1(S) = p_1$, $p_2(S) = p_2$ and $\omega(s) \approx 1$, one has

$$\rho \approx \frac{E_s\left[(\nu(S)-\mu(d_1,d_2))^2+\sigma(S)^2\right]}{E_s\left[(\alpha+p_2(1-\alpha))(\nu(S)-\mu(d_1,d_2))^2+\sigma(S)^2\frac{\alpha(1+\beta)^2+\beta(1-\alpha)^2}{(\alpha+\beta)^2}\right]}.$$

Since we assume $\gamma \approx E\sigma(s)^2/E(\nu(s)-\mu(d_1,d_2))^2$, one can devide by $E_s(\nu(s)-\mu(d_1,d_2))^2$ on the denominator and nominator, then the relative efficiency is in the form of (2).

$$\rho \approx \frac{1+\gamma}{(\alpha+p_2(1-\alpha))+\gamma\frac{\alpha(1+\beta)^2+\beta(1-\alpha)^2}{(\alpha+\beta)^2}} = \frac{1+\gamma}{1-(1-\alpha)(1-p_2)+\gamma\frac{\alpha(1+\beta)^2+\beta(1-\alpha)^2}{(\alpha+\beta)^2}}.$$

Web Appendix C: Sensitivity Analysis for Assumption (C.2)

We conducted sensitivity analysis for the non-informative drop out assumption in C.2: *The dropout is independent of* $\{Y(a_1, a_2)\}$ *given* (S, A_1). The simulation setting for treatment, the covariates and outcome, was identical to scenario 1 in Section 4.1 and the value of the same DTR was estimated. The completion rate α was simulated to be associated with the outcome Y, so that the non-informative drop out assumption does not hold. The non-drop-out status denoted by Z in the main paper was generated from a logistic model with probability $\frac{1}{1+\exp(-aY)}$ for the n patients in the SMART sample, where a can be viewed as a sensitivity parameter representing strength of informative dropout as a violation of assumption (C.2). The sample size was $n = 800$ and there were 500 replications.

The results for varying a and β are presented in Table 1 and Figure 1. When $a = 0$, Y is independent of drop out with the completion rate fixed at $\alpha = 0.5$, which is the same scenario as in Section 4.1. As a increases from 0 to 0.8, the estimated value of the DTR has larger bias, and the coverage rate for the 95% confidence interval decreases from 95% to around 55% as shown in Figure 1. For all choices of enrichment ratio β, the coverage rate are similar. The results show that for a weaker informative ($a < 0.2$) of assumption (C.2), the coverage probability is maintained at about 85%. However, stronger informative dropout may affects inference and warrants a different analysis strategy to account for informative missing.

[Table 1 about here.]

[Figure 1 about here.]

Web Appendix D: Sensitivity Analysis for Assumption (C.3)

We conducted sensitivity analysis for assumption C.3: "The mean of Y given (S, A_1) in the enrichment group is the same as that in the original SMART population". The simulation

setting is the same as scenario 1 in Section 4.1 except that the outcome in the enrichment sample is

$$Y = S_2 + (1 + a)A_2(1 - S_1) + I(S_1 = 1, A_1 = 1, A_2 = -1) + e,$$

which differs from the SMART population. Here a can be viewed as a sensitivity parameter representing strength of violation of assumption (C.3).

Similar to the previous sensitivity analysis, the results for varying a and β with $n = 800$ and 500 replications are presented in Table 2 and Figure 2. When $a = 0$, the outcome Y in the SMART and enrichment sample are generated from the same model, and thus assumption C.3 holds. When a increases from 0 to 0.8, the 95% CI coverage rate for the value of a DTR decreases gradually depending on the enrichment ratio β. When $\beta = 2$, the coverage probability decreases fastest. When $\beta = 0.5$, the coverage probability decreases slower and is still maintained at 78% for $a = 0.6$. The results show that when the enrichment ratio β is not high ($\beta = 0.5$), the validity of inference is not sensitive to assumption (C.3) in this setting.

[Table 2 about here.]

[Figure 2 about here.]

Web Appendix E: Learning the Optimal DTR from SMARTer

Here we demonstrate how to use data collected from the SMARTer find optimal DTR. Using a two-stage design as an example, first one can find the optimal second stage treatment using the subjects randomized at the second stage, which includes n_1 group 1 patients and the m group 3 enrichment patients. We identify this optimal second stage treatment as: $d_2^*(S, A_1) = \arg\max_{a_2}\{E(Y|S, A_1, A_2 = a_2)\}$. In this step, one can also obtain an estimation formula for $g(s, a_1) = \widehat{E}(Y|S = s, A_1 = a_1, A_2 = d_2^*(s, a_1))$ either from a parametric or nonparametric model. Second, treating the predicted value $\widehat{E}(Y|A_2 = d_2^*(S, A_1), A_1, S)$ as the outcome for the n patients in stage 1, one can fit a regression model on (S, A_1) so as to determine the optimal first stage treatment as $d_1^*(S) = \arg\max_{a_1}\{E(\widehat{E}(Y|A_2 = d_2^*(S, A_1), A_1, S)|S, A_1 = a_1)\}$. A simulation study is included in Web Appendix B to demonstrate the feasibility.

We conducted a simple simulation study, where the outcomes are generated as $R_1 = 1 + \beta_1 A_1 * S_1 + \epsilon_1$; $R_2 = \beta_2 A_2 * R_1 + \epsilon_2$, where $\beta_1 = \beta_2 = 1$, S_1 is generated from a standard normal distribution, and the errors are independent normal random variables with $\epsilon_1 \sim \mathcal{N}(0, 4)$ and $\epsilon_2 \sim \mathcal{N}(0, 4)$. In addition, we also simulate 4 independent noise covariates from standard normal distribution. We consider different dropout rates in the first stage and set the enrichment rate $\beta = 1$. From the results presented in Figure 3, we observe that as the dropout rate increases, SMARTer shows increasingly greater value function than the analysis which only uses the participants staying in the SMART. Most interestingly, when all patients drops out ($\alpha = 0$), by enrolling the same number of enrichment patients, the SMARTer can still generate an optimal rule with high value function.

[Figure 3 about here.]

Web Appendix F: R code and Software

We provide the R code in a zip file, which contains the sample size computations for simulations presented in tables 1,2,3 in section 4, an illustration of sample size caculation for the real data example presented in table 4 in section 5, and the sensitivity analysis in table 1 and 2 of Web Appendix C and D. The readers can refer to the R code for empirical computation of variance for SMARTer estimates and the sample size calculation. For more detailed description of the code, please refer to the README file. We also have published a R package 'DTRlearn' (Liu et al., 2015), which contains the Q-learning algorithm mentioned in Web appendix E to estimate the best DTR.

References

Liu, Y., Wang, Y., and Zeng, D. (2015). *DTRlearn: Learning Algorithms for Dynamic Treatment Regimes*. R package version 1.2.

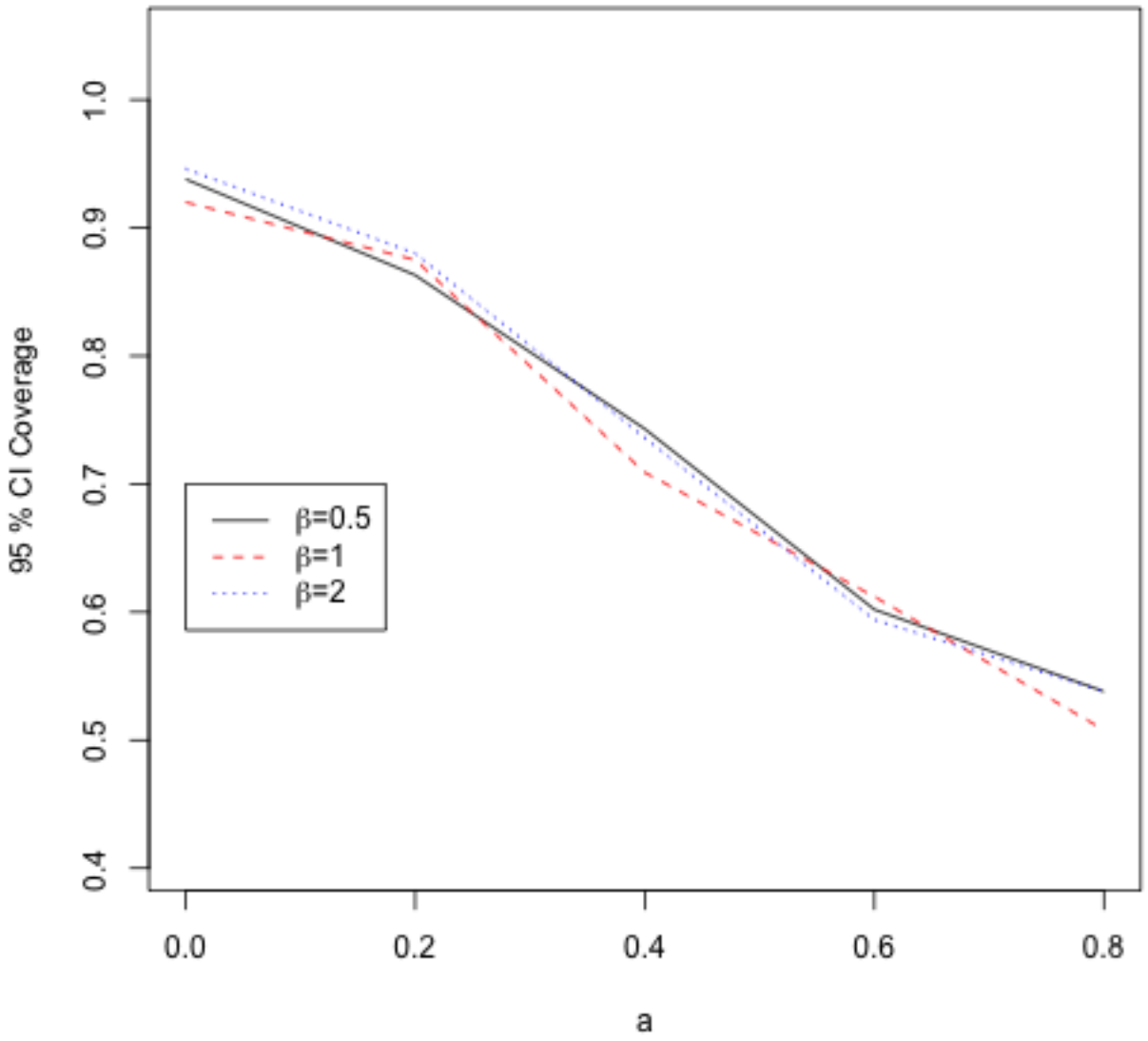

Figure 1: Sensitivity Analysis for Assumption C.2: 95% Coverage Rate for varying sensitivity parameter a

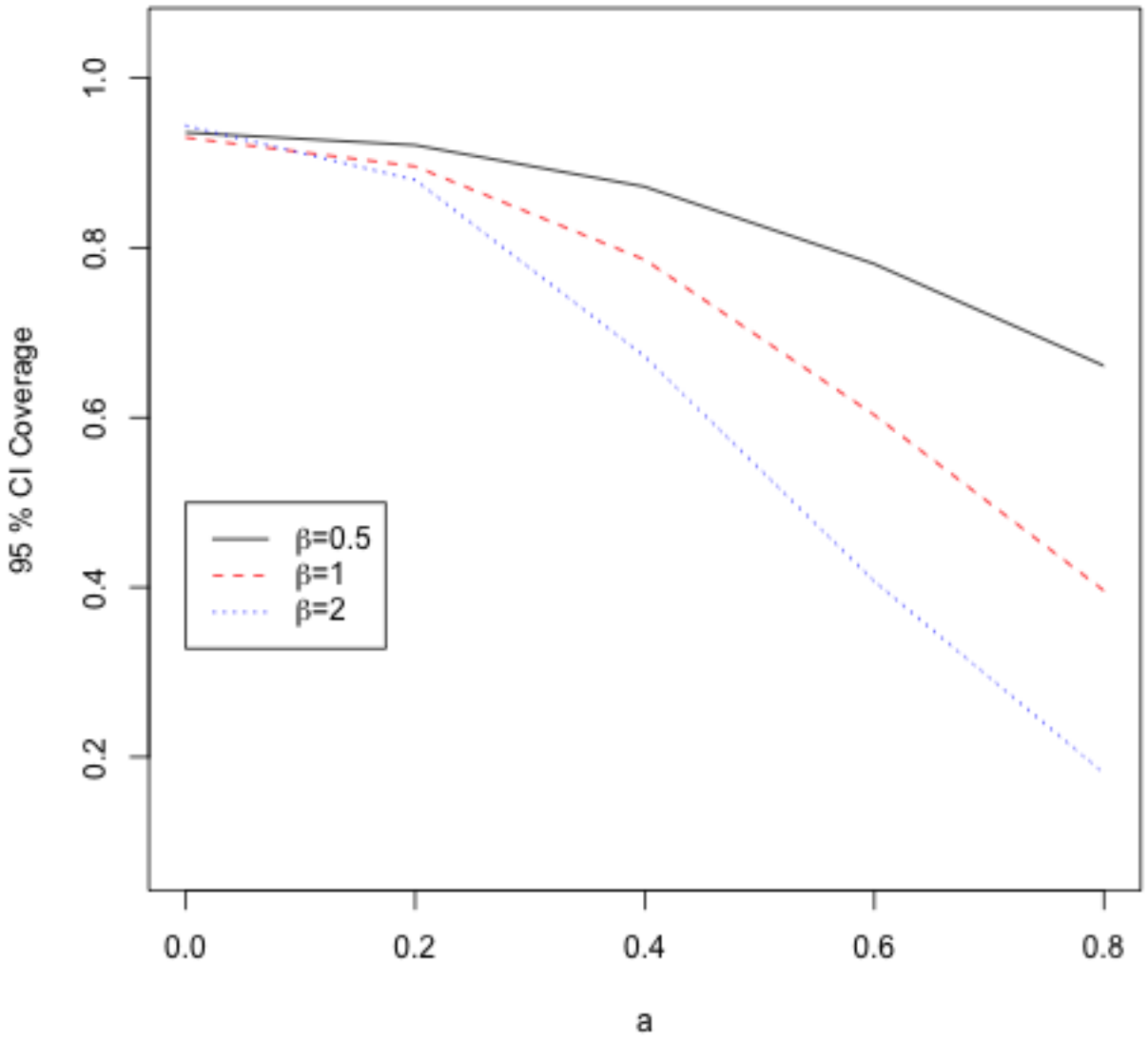

Figure 2: Sensitivity Analysis for Assumption C.3: 95% Coverage Rate for varying sensitivity parameter a

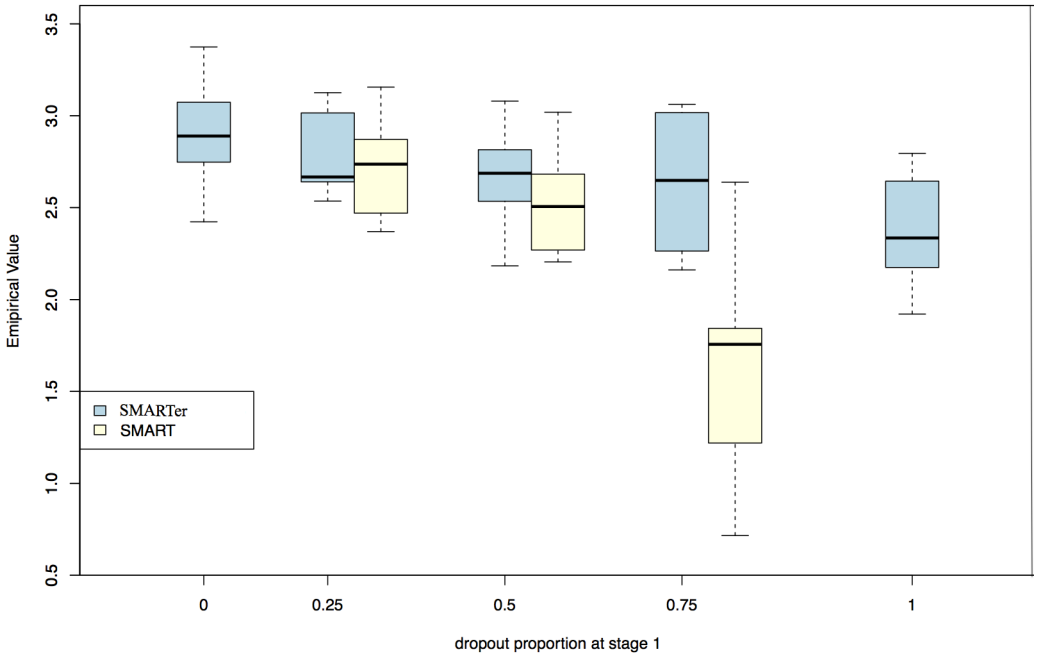

Figure 3: Estimated average outcome (value function) comparing SMARTER with SMART. The optimal value is 4.0.

Table 1: Sensitivity Analysis for Assumption C.2

a	β	Estimate	Estimated SE	empirical SD	95% CI coverage	$\widehat{\rho}$
0	0.5	1.667	0.084	0.087	0.938	0.848
0	1	1.667	0.073	0.079	0.920	1.028
0	2	1.668	0.069	0.072	0.946	1.262
0.2	0.5	1.734	0.083	0.083	0.868	0.907
0.2	1	1.730	0.079	0.074	0.880	1.163
0.2	2	1.725	0.070	0.071	0.881	1.251
0.4	0.5	1.782	0.087	0.080	0.755	0.983
0.4	1	1.776	0.078	0.072	0.717	1.204
0.4	2	1.768	0.074	0.070	0.739	1.283
0.6	0.5	1.810	0.085	0.078	0.619	1.033
0.6	1	1.804	0.081	0.070	0.625	1.271
0.6	2	1.794	0.073	0.068	0.603	1.362
0.8	0.5	1.824	0.087	0.076	0.579	1.098
0.8	1	1.819	0.079	0.069	0.529	1.341
0.8	2	1.807	0.076	0.067	0.554	1.411

Note: Parameter a measures the association between the non-drop-out indicator Z and the outcome, where Z is Bernoulli distributed with probability $\frac{1}{1+\exp(-aY)}$; $\beta = m/n$ is the ratio of sample size between enrichment and SMART group; $\widehat{\rho}$ is the empirical efficiency; the enrichment population and the SMART sample have the same distribution $q = (1/3, 1/3, 1/3)$ for S_1 taking values on $(0, 1, 2)$, and $q(A_1|S_1) = 1/2$.

Table 2: Sensitivity Analysis for Assumption C.3

a	β	Estimate	Estimated SE	empirical SD	95% CI coverage	$\widehat{\rho}$
0.0	0.5	1.667	0.084	0.087	0.936	0.848
0.0	1	1.667	0.076	0.079	0.930	1.028
0.0	2	1.668	0.070	0.072	0.944	1.262
0.2	0.5	1.697	0.084	0.086	0.921	0.849
0.2	1	1.711	0.076	0.077	0.896	1.050
0.2	2	1.719	0.070	0.069	0.880	1.314
0.4	0.5	1.731	0.084	0.087	0.872	0.840
0.4	1	1.756	0.077	0.078	0.786	1.032
0.4	2	1.772	0.071	0.070	0.672	1.272
0.6	0.5	1.764	0.085	0.087	0.781	0.827
0.6	1	1.800	0.078	0.079	0.603	1.007
0.6	2	1.825	0.072	0.072	0.407	1.221
0.8	0.5	1.798	0.086	0.088	0.661	0.810
0.8	1	1.844	0.079	0.080	0.396	0.976
0.8	2	1.879	0.073	0.074	0.181	1.164

Note: a is a parameter in the difference for the outcome generating schemes between the enrichment sample and the SMART sample: $Y = S_2 + (1+a)A_2(1-S_1) + I(S_1 = 1, A_1 = 1, A_2 = -1) + e$ for the enrichment sample, and $Y = S_2 + A_2(1-S_1) + I(S_1 = 1, A_1 = 1, A_2 = -1) + e$ for the SMART sample; $\beta = m/n$ is the ratio of sample size between enrichment and SMART group; $\widehat{\rho}$ is the empirical efficiency; the enrichment population and the SMART sample have the same distribution $q = (1/3, 1/3, 1/3)$ for S_1 taking values on $(0, 1, 2)$, and $q(A_1|S_1) = 1/2$.