Supplementary Materials for Integrating randomized and observational studies to estimate optimal dynamic treatment regimes by Anna Batorsky, Kevin J. Anstrom, and Donglin Zeng

Supplementary Materials

1 Web Appendix A: Standard Simulation Parameters

Regression Parameters for Standard Simulation Model

Web Table S1 shows the standard simulation parameters for the outcome-generating models for stages 1 and 2 for both the trial and observational study (OS) training set data. The distributions for the variables x_1, x_2, x_3 are described in Section 3.1 of the main text and displayed in Table 1. Additional details about the simulation parameters are documented in the readme file and included in the R scripts provided.

Web Table S1: Standard simulation parameters for outcome-generating models

Variable	Variable Description	Value
$\beta_{0,1}$	Intercept	4.5
$\beta_{1,1}$	Main effect of standardized age, x_{1k}	-1
$\beta_{2,1}$	Main effect of opioid use (baseline)	0.3
$\beta_{3,1}$	Main effect of depression (baseline)	0
$\beta_{4,1}$	Main effect of treatment $A_1 = 1$	0
$\beta_{5,1}$	Interaction of $A_1 = 1$ and $x_{21} = 1$	-1
$\beta_{6,1}$	Interaction of $A_1 = 1$ and $x_{31} = 1$	2
$\beta_{7,1}$	Interaction of $A_1 = 1$ and standardized x_{1k}	-0.3
$\beta_{8,1}$	Interaction of $A_1 = 1$ and standardized x_{1k}^2	-0.6
$\beta_{9,1}$	Interaction of $A_1 = 1$ and standardized x_{1k}^3	-0.01
$\beta_{10,1}$	Interaction of $A_1 = 1$ and unobserved confounder, z	2
$\beta_{0,2}$	Intercept	4.5
$\beta_{1,2}$	Main effect of standardized age, x_{1k}	-1
$\beta_{2,2}$	Main effect of opioid use (3 months)	0.2
$\beta_{3,2}$	Main effect of depression (3 months)	-0.1
$\beta_{4,2}$	Main effect of treatment $A_2 = 1$	1
$\beta_{5,2}$	Interaction of $A_2 = 1$ and $x_{22} = 1$	-1
$\beta_{6,2}$	Interaction of $A_2 = 1$ and $x_{32} = 1$	-1.5
$\beta_{7,2}$	Main effect of response to stage 1 treatment	0.1
$\beta_{8,2}$	Interaction of response to stage 1 treatment and treatment $A_2 = 1$	-0.5
$\beta_{9,2}$	Main effect of $A_1 = 1$ as part of participant history	0.3
$\beta_{10,2}$	Interaction of $A_2 = 1$ and standardized x_{1k}	-0.3
$\beta_{11,2}$	Interaction of $A_2 = 1$ and standardized x_{1k}^2	-0.6
$\beta_{12,2}$	Interaction of $A_2 = 1$ and standardized x_{1k}^3	-0.01
$\beta_{13,2}$	Interaction of $A_2 = 1$ and unobserved confounder, z	2
ϵ_1	Variance of error term in outcome model for stage 1	0.5
ϵ_2	Variance of error term in outcome model for stage 2	1
π_1	Stage 1 randomization probability to treatment $A_1 = 1$	0.5
π_2	Stage 2 randomization probability to treatment $A_2 = 1$	0.5

While x_1 represents age, the value used in the outcome-generating model for each dataset is $[x_1 - \text{mean}(x_1)]/\text{sd}(x_1)$, the standardized age.

The outcome-generating models for the trial, observational study and test set data are shown below:

$$\begin{aligned} Y_1 = \beta_{0,1} + \beta_{1,1}x_{11} + \beta_{2,1}x_{21} + \beta_{3,1}x_{31} + \beta_{4,1}A_1 + \beta_{5,1}x_{21}A_1 + \\ \beta_{6,1}x_{31}A_1 + \beta_{7,1}x_{11}A_1 + \beta_{8,1}x_{11}^2A_1 + \beta_{9,1}x_{x11}^3A_1 + \beta_{10,1}z + \epsilon_1 \end{aligned} \tag{1}$$

$$\begin{aligned} Y_2 = \beta_{0,2} + \beta_{1,2}x_{11} + \beta_{2,2}x_{22} + \beta_{3,2}x_{32} + \beta_{4,2}A_2 + \beta_{5,2}x_{22}A_2 + \\ \beta_{6,2}x_{32}A_2 + \beta_{7,2}Resp + \beta_{8,2}RespA_2 + \beta_{9,2}A_1 + \beta_{10,2}x_{11}A_2 + \\ \beta_{11,2}x_{11}^2A_2 + \beta_{12,2}x_{11}^3A_2 + \beta_{13,2}z + \epsilon_2 \end{aligned} \tag{2}$$

The indicator for responder status (Resp=1 vs 0) was derived as any Y_1 value in the trial or OS data higher than the 60th percentile value of the Y_1 value in the test dataset.

2 Web Appendix B: Sensitivity Analyses

2.1 Addition of Noise Variables

To test performance of the multi-stage augmented Q-learning estimator (MAQE) and standard Q-learning estimator (SQE) when including noise variables (i.e., variables that are in the analysis models but not the outcome-generating models) we created 10 random noise variables with a variety of distributions (Web Table S2) and an additional 10 random noise variables each with a Normal distribution with a mean of 0 and variance of 1.

Web Table S2: Simulation parameters for first 10 noise variables

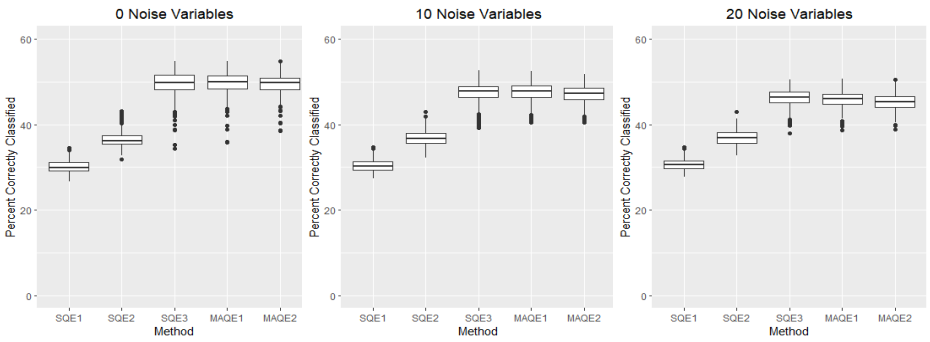
Variable	Distribution	Notes
Noise 1	Normal(0, 5)	
Noise 2	Normal(10, 3)	
Noise 3	Normal(0.5, 0.15)	
Noise 4	Bernoulli(0.4)	
Noise 5	Bernoulli(0.75)	
Noise 6	Uniform(3, 60)	Duration of pain in months, correlated with Age
Noise 7	Normal(10, 2.5)	Pain Catastrophizing Raw Score, correlated with Noise variable 10
Noise 8	Bernoulli(0.5)	Binary probability of high PROMIS Pain Interference score
Noise 9	Bernoulli(0.5)	Binary probability of high PROMIS Physical Function score
Noise 10	Normal(10, 1)	Correlated with Noise variable 7

The first 10 noise variables were included in the outcome models for the estimation of $\widehat{\eta}_{ak}$ and the Q-functions at both stages (results shown in Web Figure S1b), and a separate simulation was performed where all 20 were included (results shown in Web Figure S1c). Selected noise variables are representative of variables or derived variables from the BACPAC Minimum Dataset which may be used in the analysis of BEST. When adding 10 noise variables the decrease in PCC of the SQE3, MAQE1 and MAQE2 is 2.0%, 2.1%, and 2.3%, respectively. When adding 20 noise variables the decrease in PCC of the SQE3, MAQE1 and MAQE2 is 3.4%, 3.8%, and 4.2%, respectively. Given the large number of noise variables added, the reduction in performance is very small, and some decrease in performance would be expected. The decrease in performance between the SQE3 and MAQE is comparable.

2.2 Different Effect Sizes

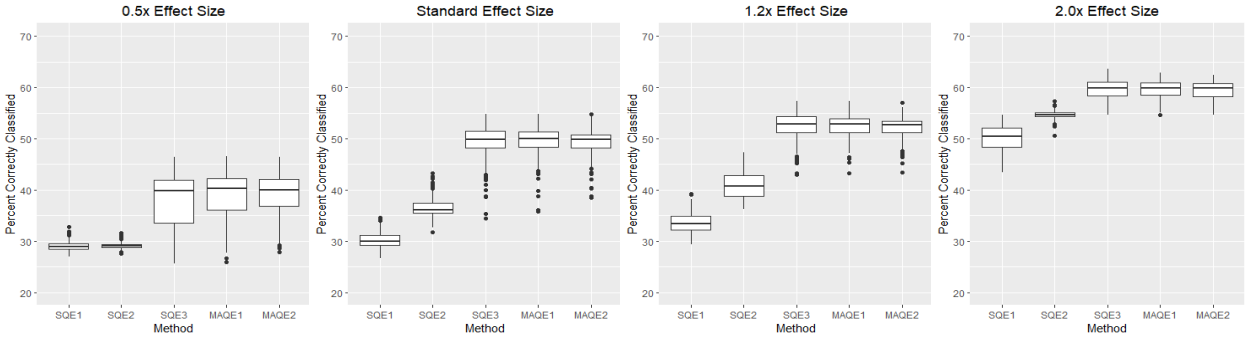
In the following sensitivity analysis we experimented with changing the effect sizes (i.e., the outcome-model parameters) for treatments at both stages, and all covariate interactions with treatments. The parameters in these analyses are 50%, 120% or 200% of the standard parameters listed in Web Table S1.

Web Figure S2 shows that for each set of simulation parameters, the MAQE has comparable performance to the SQE3 as determined by the PCC. As we would expect, as the effect sizes increase, the mean PCC increases, and the variability of the PCC decreases for all estimators. The MAQE demonstrates an improvement in efficiency over the SQE in that it retains a higher PCC when the effect size is reduced.



(a) (b) (c)

Web Figure S1: Percent correctly classified of multi-stage augmented Q-learning estimators (MAQE) and standard Q-learning estimators (SQE) using 0, 10 or 20 noise variables. The MAQE1 uses $w = n/(n+m)$, the MAQE2 uses $w = 0$, the SQE1 uses only OS data, the SQE2 uses combined trial and OS data and the SQE3 uses only trial data.

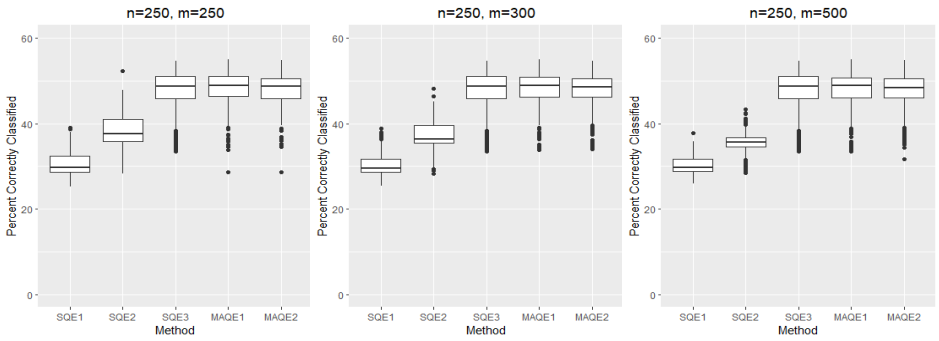


(a) (b) (c) (d)

Web Figure S2: Percent correctly classified of multi-stage augmented Q-learning estimators (MAQE) and standard Q-learning estimators (SQE) using different effect sizes. The MAQE1 uses $w = n/(n+m)$, the MAQE2 uses $w = 0$, the SQE1 uses only OS data, the SQE2 uses combined trial and OS data and the SQE3 uses only trial data.

2.3 Smaller Sample Sizes

In the following sensitivity analysis we experimented with smaller trial and OS sample sizes, where trial size n=250 and OS size m is 250, 300 or 500. Web Figure S3 shows that for each set of sample sizes, the MAQE has comparable performance to the SQE3 as determined by the PCC. As the OS size increases the performance of the SQE1 remains the same, but the performance of the SQE2 decreases due to unobserved confounding in the OS data.



(a) (b) (c)

Web Figure S3: Percent correctly classified of multi-stage augmented Q-learning estimators (MAQE) and standard Q-learning estimators (SQE) using smaller trial and OS sample sizes. The MAQE1 uses $w = n/(n+m)$, the MAQE2 uses $w = 0$, the SQE1 uses only OS data, the SQE2 uses combined trial and OS data and the SQE3 uses only trial data.