A CROSS-VALIDATED TARGETED MAXIMUM LIKELIHOOD ESTIMATOR FOR DATA-ADAPTIVE EXPERIMENT SELECTION APPLIED TO THE AUGMENTATION OF RCT CONTROL ARMS WITH EXTERNAL DATA

ABSTRACT

Augmenting the control arm of a randomized controlled trial (RCT) with external data may increase power at the risk of introducing bias. Existing data fusion estimators generally rely on stringent assumptions or may have decreased coverage or power in the presence of bias. Framing the problem as one of data-adaptive experiment selection, potential experiments include the RCT only or the RCT combined with different candidate real-world datasets. To select and analyze the experiment with the optimal bias-variance tradeoff, we develop a novel experiment-selector cross-validated targeted maximum likelihood estimator (ES-CVTMLE). The ES-CVTMLE uses two bias estimates: 1) a function of the difference in conditional mean outcome under control between the RCT and combined experiments and 2) an estimate of the average treatment effect on a negative control outcome (NCO). We define the asymptotic distribution of the ES-CVTMLE under varying magnitudes of bias and construct confidence intervals by Monte Carlo simulation. In simulations involving violations of identification assumptions, the ES-CVTMLE had better coverage than test-then-pool approaches and an NCO-based bias adjustment approach and higher power than one implementation of a Bayesian dynamic borrowing approach. We further demonstrate the ability of the ES-CVTMLE to distinguish biased from unbiased external controls through a re-analysis of the effect of liraglutide on glycemic control from the LEADER trial. The ES-CVTMLE has the potential to improve power while providing relatively robust inference for future hybrid RCT-RWD studies.

1 Introduction

In 2016, the United States Congress passed the 21st Century Cures Act [14th Congress, 2016] with the aim of improving the efficiency of medical product development. In response, the U.S. Food and Drug Administration established its “Framework for FDA’s Real-World Evidence Program” [FDA, 2018], which considers how data collected outside the scope of the randomized controlled trial (RCT) may be used in the regulatory approval process. One such application is the use of real world healthcare data (RWD) to augment or replace the control arm of an RCT. The FDA has considered the use of such external controls in situations “when randomized trials are infeasible or impractical”, “unethical”, or there is a “lack of equipoise” [Rivera, 2021]. Conducting an adequately-powered RCT may be infeasible when target populations are small, as in the case of rare diseases [Rivera, 2021; Franklin et al., 2020; Jahanshahi et al., 2021]. In other circumstances, research ethics may dictate that a trial control arm consist of the minimum number of patients necessary, as in the case of severe diseases without effective treatments [Rivera, 2021; Ghadessi et al., 2020; Dejardin et al., 2018] or in pediatric approvals of drugs that have previously been shown to be safe and efficacious in adults [Rivera, 2021; Dejardin et al., 2018; Viele et al., 2014]. With the growing availability of observational data from sources such as registries, claims databases, electronic health records, or the control arms of previously-conducted trials, the power of such studies could potentially be improved while randomizing fewer people to control status if we were able to incorporate real-world data in the analysis [Schmidt et al., 2014; Colnet et al., 2021].
Yet combining these data types comes with the risk of introducing bias from multiple sources, including measurement error, selection bias, and confounding. Bareinboim and Pearl (2016) previously defined a structural causal model-based framework for causal inference when multiple data sources are utilized, a setting known as data fusion. Using directed acyclic graphs (DAGs), this framework helps researchers understand what assumptions, testable or untestable, must be made in order to identify a causal effect from the combined data. By introducing observational data, we can no longer rely on randomization to satisfy the assumption that there are no unmeasured common causes of the intervention and the outcome in the pooled data. Furthermore, causal identification of the average treatment effect is generally precluded if the conditional expectations of the counterfactual outcomes given the measured covariates are different for those in the trial compared to those in the RWD (Rudolph and van der Laan, 2017).

Such a difference can occur for a number of reasons, including changes in medical care over time or health benefits simply from being enrolled in a clinical trial (Ghadessi et al., 2020; Viele et al., 2014; Pocock, 1976; Chow et al., 2013). In 1976, Stuart Pocock developed a set of criteria for evaluating whether historical control groups are sufficiently comparable to trial controls such that the suspected bias of combining data sources would be small (Pocock, 1976). We are not limited to historical information, however, but could also incorporate data from prospectively followed cohorts in established health care systems. These and other considerations proposed by subsequent authors are vital when designing a hybrid randomized-RWD study to make included populations similar, minimize measurement error, and measure relevant confounding factors (FDA, 2018; Franklin et al., 2020; Ghadessi et al., 2020).

Despite careful consideration of an appropriate real-world control group, the possibility of bias remains, casting doubt on whether effect estimates from combined RCT-RWD analyses are truly causal. A growing number of data fusion estimators — discussed in Related Literature below — attempt to estimate the bias from including RWD in order to decide whether to incorporate RWD or how to weight RWD in a combined analysis. A key insight from this literature is that there is an inherent tradeoff between maximizing power when unbiased external data are available and maintaining close to nominal coverage across the spectrum of potential magnitudes of RWD bias (Chen et al., 2021; Obert et al., 2022). The strengths and limitations of existing methods led us to consider an alternate approach to augmenting the control arm of an RCT with external data that incorporates multiple estimates of bias to boost potential power gains while providing robust inference despite violations of necessary identification assumptions. Framing the decision of whether to integrate RWD (and by extension, which RWD to integrate) as a problem of data-adaptive experiment selection, we develop a novel cross-validated targeted maximum likelihood estimator for this context that 1) incorporates an estimate of the average treatment effect on a negative control outcome (NCO) into the bias estimate, 2) uses cross-validation to separate bias estimation from effect estimation, and 3) constructs confidence intervals by sampling from the estimated limit distribution of this estimator, where the sampling process includes an estimate of the bias, further promoting accurate inference.

The remainder of this paper is organized as follows. In Section 2, we discuss related data fusion estimators. In Section 3, we introduce the problem of data-adaptive experiment selection and discuss issues of causal identification, including estimation of bias due to inclusion of RWD. In Section 4, we introduce potential criteria for including RWD based on optimizing the bias-variance tradeoff and utilizing the estimated effect of treatment on an NCO. In Section 5, we develop an extension of the cross-validated targeted maximum likelihood estimator (CV-TMLE) (Zheng and van der Laan, 2010; Hubbard et al., 2016) for this new context of data-adaptive experiment selection and define the limit distribution of this estimator under varying amounts of bias. In Section 6, we set up a simulation to assess the performance of our estimator and describe four potential comparator methods: two test-then-pool approaches (Viele et al., 2014), one method of Bayesian dynamic borrowing (Schmidli et al., 2014), and a difference-in-differences (DID) approach to adjusting for bias based on a negative control outcome (Sofier et al., 2016; Shi et al., 2020). We also introduce a CV-TMLE based version of this DID method. In Section 7, we compare the causal coverage, power, bias, variance, and mean squared error of the experiment-selector CV-TMLE to these four methods as well as to a CV-TMLE and t-test for the RCT only. In Section 8, we demonstrate the use of the experiment-selector CV-TMLE to distinguish biased from unbiased external controls in a real data analysis of the effect of liraglutide versus placebo on improvement in glycemic control in the Central/South America subgroup of the LEADER trial.

2 Related Literature

A growing literature highlights different strategies for combined RCT-RWD analyses. One set of approaches, known as Bayesian dynamic borrowing, generates a prior distribution of the RCT control parameter based on external control data, with different approaches to down-weighting the observational information (Pocock, 1976; Ibrahim and Chen, 2000; Hobbs et al., 2012; Schmidli et al., 2014). These methods generally require assumptions on the distributions of the involved parameters, which may significantly impact the effect estimates (Galwey, 2017; Dejardin et al., 2018). While these methods can decrease bias compared to pooling alone, multiple studies have noted either increased type 1 error or decreased power when there is heterogeneity between the historical and RCT control groups (Dejardin et al., 2018; Viele et al., 2014; Galwey, 2017; Cutler, 2011; Harun et al., 2020).
This tradeoff between the ability to increase power with unbiased external data and the ability to control type 1 error across different potential magnitudes of bias has also been noted in the frequentist literature (Chen et al. 2021; Oberst et al. 2022). A simple “test-then-pool” strategy for combining RCT and RWD, described by Viele et al. (2014), involves a hypothesis test that the mean outcomes are equal in the RCT and RWD control arms; datasets are only combined if the null hypothesis of the test is not rejected. However, even when the RCT is small, tests for inclusion of RWD are also underpowered, and so observational controls may be inappropriately included even when the test’s null hypothesis is not rejected (Li et al. 2020). Thus, such approaches are subject to inflated type 1 error in exactly the settings in which inclusion of external controls is of greatest interest.

Subsequently, several estimators that are more conservative in their ability to maintain nominal type 1 error control have been proposed. For example, Rosenman et al. (2020) have built on the work of Green and Strawderman (1991) in adapting the James-Stein shrinkage estimator (Stein, 1956) to weight RCT and RWD effect estimates in order to estimate stratum-specific average treatment effects. Another set of methods aims to minimize the mean squared error of a combined RCT-RWD estimator, with various criteria for including RWD or for defining optimal weighted combinations of RCT and RWD (Yang et al. 2020; Chen et al. 2021; Cheng and Cai 2021; Oberst et al. 2022). These studies reveal the challenge of optimizing the bias-variance tradeoff when bias must be estimated. Oberst et al. (2022) note that estimators that decrease variance most with unbiased RWD also tend to have the largest increase in relative mean squared error compared to the RCT only when biased RWD is considered. Similarly, Chen et al. (2021) show that if the magnitude of bias introduced by incorporating RWD is unknown, the optimal minimax confidence interval length for their anchored thresholding estimator is achieved by an RCT-only estimator, again demonstrating that both power gains and guaranteed type I error control should not be expected. Yang et al. (2020), Chen et al. (2021), and Cheng and Cai (2021) introduce tuning parameters for their estimators to modify this balance. Because no estimator is likely to outperform all others both by maximizing power and maintaining appropriate type 1 error in all settings, different estimators may be beneficial in different contexts where one or the other of these factors is a greater priority. While these methods focus on estimating either the conditional average treatment effect (Yang et al. 2020; Cheng and Cai 2021) or the average treatment effect (Chen et al. 2021; Oberst et al. 2022) in contexts when treatment is available in the external data, in this paper we focus on the setting where a medication has yet to be approved in the real world.

An alternate approach to estimating bias, used mostly for observational data analyses, involves the use of an NCO. Because the treatment does not affect an NCO, evidence of an association between the treatment and this outcome is indicative of bias (Lipsitch et al. 2010). Authors including Sofer et al. (2016), Shi et al. 2020a, and Miao et al. 2020 have developed methods of bias adjustment using an NCO. Yet because there may be unmeasured factors that confound the relationship between the treatment and the true outcome that do not confound the relationship between the treatment and the NCO, an NCO-based bias estimate near zero does not rule out residual bias (Lipsitch et al. 2010).

In summary, methods that estimate bias to evaluate whether to include RWD or how to weight RWD in a combined analysis most commonly rely either on a comparison of mean outcomes or effect estimates between RCT and RWD (e.g. Viele et al. 2014; Schmidli et al. 2014; Yang et al. 2020; Oberst et al. 2022) or on the estimated average treatment effect on an NCO (e.g. Shi et al. 2020b). The latter approach requires additional assumptions regarding the quality of the NCO (Shi et al. 2020b; Lipsitch et al. 2010). Bias estimation is a challenge for both approaches, leading to a tradeoff between the probability that information from unbiased RWD is included and the probability that information from biased RWD is excluded (Chen et al. 2021; Oberst et al. 2022). We discuss both options for bias estimation and our proposal to combine information from both sources below.

### 3 Causal Roadmap for Hybrid RCT-RWD Trials

In this section, we follow the causal inference roadmap described by Petersen and van der Laan (2014) to explain this data fusion challenge. Please refer to Supplementary Table 1 in Appendix 1 for a list of symbols used in this manuscript. For a hybrid RCT-RWD study, let $S$ indicate the experiment being analyzed, where $s_i = 0$ indicates that individual $i$ participated in an RCT, $s_i \in \{1, \ldots, K\}$ indicates that individual $i$ participated in one of $K$ potential observational cohorts, and $S \in \{0, s\}$ indicates an experiment combining an RCT with dataset $s$. We have a binary intervention, $A$, a set of baseline covariates, $W$, and an outcome $Y$. $W$ may affect inclusion in the RCT versus RWD. Assignment to active treatment, $A$, is randomized with probability $p$ for those in the RCT and set to 0 (standard of care) for those in the RWD, because the treatment has yet to be approved. Thus, $A$ is only affected by $S$ and $p$, not directly by $W$ or any exogenous error. $Y$ may be affected by $W$, $A$, and potentially also directly by $S$. The unmeasured exogenous errors $U = (U_W, U_S, U_Y)$ for each of these variables could potentially be dependent. The full data then consist of both endogenous and exogenous variables. Our observed data are $n$ independent and identically distributed observations $O_i = (W_i, S_i, A_i, Y_i)$ with true distribution $P_0$.

A common causal target parameter for RCTs is the average treatment effect (ATE). With multiple available datasets, there are multiple possible experiments we could run to evaluate the ATE for the population represented by that
While these causal gaps are functions of the full and observed data, we can estimate a statistical gap that is only a function of the observed data as

$$\Psi^*_s(P_{U,O}) = E_{W|S \in \{0,s\}}[E(Y^1 - Y^0|W, S \in \{0,s\})]$$

for $$s \in \{0, ..., K\}$$.

### 3.1 Identification

Next, we discuss whether each of the potential causal parameters, $$\Psi^F(P_{U,O})$$, is identifiable from the observed data.

**Lemma 1:** For each experiment with $$S \in \{0,s\}$$, under Assumptions 1 and 2a-b below, the causal ATE, $$\Psi^F(P_{U,O})$$, is identifiable from the observed data by the g-computation formula (Robins [1986]), with statistical estimand

$$\Psi_s(P_0) = E_{W|S \in \{0,s\}}[E_0[Y|A = 1, S \in \{0,s\}, W] - E_0[Y|A = 0, S \in \{0,s\}, W]].$$

(1)

**Assumption 1** (Positivity (e.g., Hernán, [2006]; Petersen et al., [2012])): $$P(A = a|W = w, S \in \{0,s\}) > 0$$ for all $$a \in A$$ and all $$w$$ for which $$P(W = w, S \in \{0,s\}) > 0$$. This assumption is true in the RCT by design and may be satisfied for other experiments by removing RWD controls whose W covariates do not have support in the trial population.

**Assumption 2** (Mean Exchangeability (e.g., Rudolph and van der Laan [2017]; Dahabreh et al., [2019b])): As described by Rudolph and van der Laan [2017] and subsequently named by Dahabreh et al. [2019b].

**Assumption 2a** ("Mean exchangeability in the trial" (Dahabreh et al., [2019b]): $$E[Y^a|W, S = 0, A = a] = E[Y^a|W, S = 0]$$ for every $$a \in A$$. This assumption is also true by the design of the RCT.

**Assumption 2b** ("Mean exchangeability over $$S^*"(Dahabreh et al.,[2019b]):$$E[Y^a|W, S \in \{0,s\}] = E[Y^a|W, S \in \{0,s\}]$$ for every $$a \in A$$. Assumption 2b may be violated if unmeasured factors affect trial inclusion or if being in the RCT directly affects adherence or outcomes (Rudolph and van der Laan [2017]; Dahabreh et al., 2019a). Dahabreh et al. [2019a] note that Assumption 2b is more likely to be true for pragmatic RCTs integrated with RWD from the same healthcare system. Nonetheless, we may not be certain whether Assumption 2b is violated in practice.

### 3.2 Bias Estimation

One approach to concerns about violations of Assumption 2b would be to target a causal parameter that we know is identifiable from the observed data. As noted by Hartman et al. [2015], Balzer [2017], and Dahabreh et al. [2019c], we may consider interventions not only on treatment assignment but also on trial participation. The difference in the outcomes an individual would have had if they had received active treatment and been in the RCT ($Y_{a=1,s=0}$) compared to if they had received standard of care and been in the RCT ($Y_{a=0,s=0}$), averaged over a distribution of covariates that are represented in the trial, gives a causal ATE of A on Y in the population defined by that experiment. Under Assumptions 1 and 2a, this “ATE-RCT” parameter for any experiment, $$\Psi^F_s(P_{U,O}) = E_{W|S \in \{0,s\}}[E(Y^1_{a=1,s=0} - Y^0_{a=0,s=0}|W, S \in \{0,s\})]$$, is equal to the following statistical estimand:

$$\Psi^*_s(P_0) = E_{W|S \in \{0,s\}}[E_0[Y|A = 1, S = 0, W] - E_0[Y|A = 0, S = 0, W]].$$

(2)

Nonetheless, by estimating this parameter, we would not gain efficiency compared to estimating the sample average treatment effect for the RCT only (Balzer et al., 2015).

Another general approach to addressing concerns regarding violations of Assumption 2b would be to estimate the causal gap or bias due to inclusion of external controls. In order to further explore this option, we consider two causal gaps as the difference between one of our two potential causal parameters and the statistical estimand $$\Psi_s(P_0)$$ for a given experiment with $$S \in \{0,s\}$$:

1. **Causal Gap 1:** $$\Psi^F_s(P_{U,O}) - \Psi_s(P_0)$$
2. **Causal Gap 2:** $$\Psi^F_s(P_{U,O}) - \Psi_s(P_0)$$

While these causal gaps are functions of the full and observed data, we can estimate a statistical gap that is only a function of the observed data as

$$\Psi^*_s(P_0) = \Psi^F_s(P_{U,O}) - \Psi_s(P_0)$$

(3)

**Lemma 2:** Causal and Statistical Gaps for an experiment with $$S \in \{0,s\}$$

If Assumption 2b is true, then $$\Psi^F_s(P_{U,O}) = \Psi^*_s(P_{U,O})$$, $$\Psi^*_s(P_0) = 0$$

1. **Causal Gap 1:** $$\Psi^F_s(P_{U,O}) - \Psi_s(P_0) = 0$$
2. **Causal Gap 2:** $$\Psi^F_s(P_{U,O}) - \Psi_s(P_0) = 0$$
\[ \Psi^\#(P_0) \] may thus be used as evidence of whether Assumption 2b is violated. If we were to bias correct our estimate \( \Psi_s(P_0) \) by subtracting \( \Psi^\#(P_0) \), we would again be estimating \( \Psi_s(P_0) \), with no gain in efficiency compared to estimating the sample ATE from the RCT only (Balzer et al., 2015). Nonetheless, the information from estimating \( \Psi^\#(P_0) \) may still be incorporated into an experiment selector, \( s_0^* \), discussed below.

### 4 Potential Experiment Selection Criteria

A natural goal for experiment selection would be to optimize the bias-variance tradeoff for estimating a causal ATE. Such an approach of determining combinations of RCT and RWD that minimize the estimated mean squared error is taken by Yang et al. (2020), Cheng and Cai (2021), Chen et al. (2021), and Oberst et al. (2022). Next, we discuss the challenge of selecting a truly optimal experiment when bias must be estimated from the data. We then introduce a novel experiment selector that incorporates bias estimates based on both the primary outcome and a negative control outcome.

Ideally, we would like to construct a selector that is equivalent to the oracle selector of the experiment that optimizes the bias-variance tradeoff for our target parameter:

\[
 s_0 = \arg\min_s \frac{\sigma^2_{\Psi_s}}{n} + (\Psi^\#(P_0))^2
\]

where

\[
 l(S \in \{0, s\}) \left( \Psi_s(O) - \frac{\sigma^2_{\Psi_s}}{n} \right) = \frac{D_{\Psi_s}(O)}{\frac{r_0(A=1) W S \in \{0, s\})}{r_0(A=1) W S \in \{0, s\}}} - \frac{D_{\Psi_s}(O)}{\frac{r_0(A=0) W S \in \{0, s\})}{r_0(A=0) W S \in \{0, s\}}} (Y - Q^0_s(S \in \{0, s\}, A, W)) + Q^0_s(S \in \{0, s\}, 1, W) - Q^0_s(S \in \{0, s\}, 0, W) - \Psi_s(P_0)
\]

is the efficient influence curve of \( \Psi_s(P_0) \), \( Q^0_s(S \in \{0, s\}, A, W) = E_0[Y|S \in \{0, s\}, A, W] \), and \( g_0(A = a|W, S \in \{0, s\}) = P_0(A = a|W, S \in \{0, s\}) \). Our statistical estimand of interest is then \( \Psi_{s_0}(P_0) \).

The primary challenge is that \( s_0 \) must be estimated. We thus define an empirical bias squared plus variance ("b2v") selector,

\[
 s^*_n = \arg\min_s \frac{\sigma^2_{\Psi_s}}{n} + (\hat{\Psi}^\#(P_n))^2
\]

If, for a given experiment with \( S \in \{0, s\} \), \( \Psi^\#(P_0) \) were given and small relative to the standard error of the ATE estimator for that experiment, nominal coverage would be expected for the causal target parameter. If bias were large relative to the standard error of the ATE estimator for the RCT, then the RWD would be rejected, and only the RCT would be analyzed. One threat to valid inference using this experiment selection criterion is the case where bias is of the same order as the standard error \( \sigma_{\Psi_s}/\sqrt{n} \), risking decreased coverage. We could require a smaller magnitude of bias by putting a penalty term in the denominator of the variance as \( s^*_n = \arg\min_s \frac{\sigma^2_{\Psi_s}}{n + c(n)} + \hat{\Psi}^\#(P_n))^2 \) where \( c(n) \) is either a constant or some function of \( n \). A similar approach is taken by Cheng and Cai (2021) who multiply the bias term by a penalty and determine optimal weights for RCT and RWD estimators via L1-penalized regression. However, finite sample variability may lead to overestimation of bias for unbiased RWD and underestimation of bias in magnitude to \( \sigma_{\Psi_s}/\sqrt{n} \). In order to make \( c(n) \) large enough to prevent selecting RWD that would introduce bias of a magnitude that could decrease coverage for the causal parameter, we would also prevent unbiased RWD from being included in a large proportion of samples.

This challenge exists for any method that bases inclusion of RWD on differences in the mean or conditional mean outcome under control for a small RCT control arm versus a RWD population. It also suggests that having additional knowledge beyond this information may help the selector distinguish between RWD that would introduce varying degrees of bias. Intuitively, if we are not willing to assume mean exchangeability, information available in the RCT alone is insufficient to estimate bias from including real world data in the analysis precisely enough to guarantee inclusion of extra unbiased controls and exclusion of additional controls that could bias the effect estimate; if the RCT contained this precise information about bias, we would be able to estimate the ATE of \( A \) on \( Y \) from the RCT precisely enough to not require the real world data at all. Conversely, if we were willing to assume mean exchangeability, then simply pooling RCT and RWD would provide optimal power gains but also fully relinquish the protection to inference afforded by randomization.
4.1 Additional Knowledge to Improve Experiment Selector

One additional source of information regarding bias is the estimated effect of the treatment on a negative control outcome. An NCO is not affected by the treatment but is affected by unmeasured factors that are associated with both the treatment and the outcome (Lipsitch et al., 2010). A non-zero estimated ATE of treatment on the NCO is therefore either due to finite sample variability or due to these unmeasured common causes. NCOs have been used primarily in observational analyses to detect and/or adjust for unmeasured confounding (Sofer et al., 2016; Miao et al., 2020; Shi et al., 2020a,b). In order to fully adjust for bias using an NCO, we must assume U-comparability: that the unmeasured factors that confound the treatment-outcome relationship are the same as the unmeasured factors that confound the treatment-NCO relationship (Lipsitch et al., 2010). When this assumption is not met, the estimated effect of treatment on the NCO represents some unknown percentage of the total bias that comes from incorporating real-world data.

Again using the g-computation formula (Robins, 1986), we may define an estimand of the ATE of treatment on the NCO as

\[
\Phi_{s}(P_{0}) = E_{W|S=0,s}[E_{0}[NCO|W, A = 1, S \in \{0, s\}] - E_{0}[NCO|W, A = 0, S \in \{0, s\}]].
\]

Then, we could add our estimate \(\hat{\Phi}_{s}(P_{n})\) to our estimate of the bias, with selector "+nco":

\[
s_{n}^{**} = \arg\min_{s} \frac{\sigma_{\hat{\Phi}_{s}}^{2}}{n} + (\hat{\Psi}_{s}(P_{n}) + \hat{\Phi}_{s}(P_{n}))^{2}.
\]

Because \(\Psi_{s=0}(P_{0})\) is deterministically 0 with only RCT data, whereas \(\hat{\Phi}_{s>0}(P_{n})\) may be estimated but with greater variability than \(\hat{\Phi}_{s>0}(P_{n})\) due to the smaller size of the RCT compared to RCT plus RWD, \(s_{n}^{**}\) helps to promote the inclusion of unbiased external controls. If only biased external controls are available, however, \(\hat{\Phi}_{s>0}(P_{0})\) has a larger magnitude for the combined RCT-biased RWD experiment because unmeasured confounding makes this statistical quantity not truly zero. We would expect that including \(\hat{\Phi}_{s}(P_{n})\) in the selector should thereby increase the probability that biased RWD is rejected. Yet we must note that this selector relies on the assumption that the unmeasured factors that affect the treatment-outcome relationship affect the treatment-NCO relationship in the same direction. Otherwise the sum \(\hat{\Psi}_{s}(P_{n}) + \hat{\Phi}_{s}(P_{n})\) will negate some of the true bias from including external controls. This consideration should be made when selecting an appropriate NCO, but is still weaker than assumptions necessary for bias adjustment using an NCO.

We also consider selector "nco only" based only on \(\hat{\Phi}_{s}(P_{0})\):

\[
s_{n}^{***} = \arg\min_{s} \frac{\sigma_{\hat{\Phi}_{s}}^{2}}{n} + (\hat{\Phi}_{s}(P_{n}))^{2}.
\]

Nonetheless, because we cannot learn from the data what percentage of the true bias is accounted for by this estimate, we choose to combine rather than replace our estimate \(\hat{\Psi}_{s}(P_{n})\) with this information. We will compare these options with the originally-proposed selector \(s_{n}^{**}\). The advantage of \(s_{n}^{**}\) compared to introducing a penalty term in the denominator of the selector’s variance term is that the penalty term makes the selector less likely to include any real-world data, while \(s_{n}^{**}\) has the potential to promote inclusion of unbiased RWD while discouraging the inclusion of biased RWD.

5 CV-TMLE for Data-Adaptive Experiment Selection

Now that we have defined potential experiment-selection criteria, we must use the data both to select and analyze the optimal experiment. If we select \(s_{n}^{*}\) in a manner that is not outcome-blind, we should not expect to obtain valid inference if we both select the experiment and evaluate our target parameter based on the same data (Hubbard et al., 2016). Cross-validated targeted maximum likelihood estimation (CV-TMLE) was previously developed as a method to obtain valid inference for other data-adaptive target parameters (Zheng and van der Laan, 2010; Hubbard et al., 2016; van der Laan and Luedtke, 2015). We build on this previous work by developing a CV-TMLE for data-adaptive experiment selection, which poses new challenges for inference, described below.

First, we randomly split the data into \(V\) samples with an experiment-selection set consisting of \((V-1)/V\) of the data and an estimation set consisting of \(1/V\). For each split, \(v\), the estimation set has empirical distribution \(P_{n,v}\) with estimation set subjects assigned \(V_{1} = v\). The experiment-selection set has empirical distribution \(P_{n,v^{-}},\) and therefore the experiment-selection observations have \(V_{1} \neq v\). For each split, the experiment-selection set is used to define a data-adaptive target parameter mapping based on a fold-specific selection criterion, \(s_{n}^{*}(v)\). The fold-specific target parameter then becomes \(\Psi_{s_{n}^{*}(v)}^{F}(P_{U,O})\), the causal ATE of \(A\) on \(Y\) in the experiment selected based on the experiment-selection set for fold \(v\). The overall target parameter, \(\psi_{0}\), and statistical estimand, \(\psi_{n,0}\), are then averages of the fold-specific parameters and estimands:
\[
\psi_0 = \frac{1}{V} \sum_{v=1}^{V} \Psi_{\ast n}^{V}(P_{U,O})
\]
\[
\psi_{n,0} = \frac{1}{V} \sum_{v=1}^{V} \Psi_{s_n}^{V}(P_0)
\]

Our modified ES-CVTMLE estimator for data-adaptive experiment-selection is then:
\[
\psi_n = \frac{1}{V} \sum_{v=1}^{V} \hat{\Psi}_{s_n}^{V}(Q_{n,v}^{0,\ast})
\]

where \(Q_{n,v}^{0,\ast}\) indicates training of initial estimators of the outcome regression \(Q_{n,v}^{0,s}\) and treatment mechanism \(g_{n,v}^a\) on the experiment-selection set for fold \(v\) with TMLE targeting of the initial \(Q_{n,v}^{0,s}\) on separate or pooled estimation sets, as described in Algorithm 1 below. In contrast, as used in the bias estimates, \(Q_{n,v}^{0,\ast}\) indicates training and targeting of the outcome regression using experiment-selection set data for fold \(v\). All bias and ATE estimates are obtained using TMLE, which is a doubly-robust plug-in estimator that targets initial model fits to optimize the bias-variance tradeoff for the target parameter (van der Laan and Rubin, 2006; van der Laan and Rose, 2011). In the case of the ATE, TMLE is asymptotically unbiased if either the outcome regression or the treatment mechanism are estimated consistently and is asymptotically efficient if both are estimated consistently (van der Laan and Rose, 2011). A detailed description of targeted maximum likelihood estimation of the bias term \(\hat{\Psi}_{\ast}^{\#}(P_n)\) may be found in Appendix 2. The empirical selectors, based on experiment-selection set data for each fold, are then
\[
s_{\ast n}(v) = \arg \min_s \frac{\sigma_{\ast n}^2}{\partial_{\ast n}^2}(\hat{\Psi}_s(Q_{n,v}^{0,\ast}, Q_{n,v}^{s,\ast}))^2
\]
\[
s_{\ast \ast n}(v) = \arg \min_s \frac{\sigma_{\ast n}^2}{\partial_{\ast n}^2}(\hat{\Psi}_s(Q_{n,v}^{0,\ast}, Q_{n,v}^{s,\ast}) + \hat{\Phi}_s(Q_{NCO}^{\ast}))^2
\]

where \(Q^s = E[Y|S \in \{0, s\}, S, A, W], Q_{NCO}^{\ast} = E[NCO|S \in \{0, s\}, A, W]\), and
\[
D_{\hat{\Psi}_{s,n,v}}^{\ast}(O, V) = \frac{I(S \in \{0, s\}, V \neq v)}{P_n(S \in \{0, s\}, V \neq v)} \left( \frac{I(A=1)}{g_{n,v}^a(A=1|W, S \in \{0, s\})} - \frac{I(A=0)}{g_{n,v}^a(A=0|W, S \in \{0, s\})} \right) (Y - Q_{n,v}^{0,s}\ast(S \in \{0, s\}, A, W)) + Q_{n,v}^{0,s}\ast(S \in \{0, s\}, 1, W) - Q_{n,v}^{0,s}\ast(S \in \{0, s\}, 0, W) - \hat{\Psi}_s(Q_{n,v}^{0,\ast})
\]

Algorithm 1 describes the overall estimation process for the experiment-selector CV-TMLE.
Algorithm 1 CV-TMLE for Data-Adaptive Experiment Selection

1: To ensure Assumption 1, trim data so no W values are not represented in RCT.
2: Divide \( O^n = (O_1, ..., O_n) \) into V folds stratified on S with experiment-selection set \( O^n_v = \{O_i : i = 1, ..., n, V_i \neq v\} \) and estimation set \( O^n_v = \{O_i : i = 1, ..., n, V_i = v\} \).
3: For \( v \in \{1, ..., V\} \),
   1. For all \( I(S \in \{0, s\}) \) subsets of \( O^n_v \) experiment-selection sets
      - Estimate: \( Q^{(0,s)}_{n,v}, Q^{(0,s)}_{n,v}, Q_{n,v}^{NCO}, g_{n,v}^{P}, \hat{g}_{n,v}^{P}, \frac{\sigma_{\hat{g}_{n,v}^{P}}}{n} \)
      - Use TMLE to estimate \( \hat{\Psi}(Q^{(0,s),*}_{n,v}, Q_{n,v}^{*,*}) \)
      - Select experiment based on \( s_n^*(v) \), or \( s_n^*(v) \)
4: For all \( O^n_v \) estimation sets
   - For all \( S \in \{0, s\} \)
     1. Pool all \( S \in \{0, s\} \) subsets of \( O^n_v \) across all \( v \)
     2. Estimate coefficient for TMLE update \( \epsilon_s \) using logistic regression of binary or scaled-continuous \( Y \) on
        \[
        H^*_s(A, W) = \frac{I(A = 1)}{g_{n,v}^{P}(A = 1|S \in \{0, s\}, W)} - \frac{I(A = 0)}{g_{n,v}^{P}(A = 0|S \in \{0, s\}, W)}
        \]
        with offset \( \text{logit}(Q^{(0,s)}_{n,v}) (S \in \{0, s\}, A, W) \) pooled across all \( v \) based on initial regressions trained in experiment-selection sets.
   - For all \( v \in \{1, ..., V\} \)
     1. Select the \( I(S \in \{0, s_n^*(v)\}) \) subset of \( O^n_v \)
     2. Use \( \epsilon_{s_n^*(v)} \) to obtain targeted estimates
        \[
        \Psi_{n} = \frac{1}{V} \sum_{v=1}^{V} \hat{\Psi}_{s_n^*(v)}(Q^{(0,s_n^*(v))}_{n,v})
        \]

\( g^* = P(S = 0|S \in \{0, s\}, A = 0, W) \)
\( \epsilon_{s_n^*(v)} \): An alternative method that may be more stable in the context of practical positivity violations is to “target the weights” (Robins et al., 2007; Rotnitzky et al., 2012; Tran et al., 2019) by using clever covariate \( H_s^*(A, W) = I(A = 1) - I(A = 0) \) and weights \( \frac{g_{n,v}^{P}(A = 1|S \in \{0, s\}, W)}{g_{n,v}^{P}(A = 0|S \in \{0, s\}, W)} \).
\( \Psi_{s_n^*(v)} \): Re-scale \( Q^{(0,s_n^*(v))}_{n,v} \) to the original outcome scale if using scaled-continuous \( Y \)

5.1 Asymptotic Distribution of the Experiment-Selector CV-TMLE

Next, we examine the asymptotic distribution of the ES-CVTMLE. Unlike the CV-TMLE for data-adaptive target parameter estimation developed by Zheng and van der Laan (2010), the limit distribution of the ES-CVTMLE depends on the amount of bias introduced by a given real-world dataset. The finite sample challenge for selecting an optimal experiment depends on the magnitude of this true bias relative to the standard error of the ATE estimator, which in turn depends on the sample size. As noted by Yang et al. (2020) for their elastic integrative analysis estimator, in order to understand the behavior of a selector in the context of this finite sample estimation challenge, we must understand the behavior of the selector when the bias is not fixed but rather dependent on the sample size. To accomplish this goal, define \( P(n, n) \) as the true data distribution dependent on \( n \). In order to define the limit distribution, let us also define the following quantities.
Next we consider the distribution of the standardized selectors, which are random variables that depend on the distribution of $Z^#(s,v^c)$ or $Z^{#+\Phi}(s,v^c)$. Multiplying the selector by $n$ and adding and subtracting the true value of the bias yields a standardized selector

$$s^*_n(v^c) = \text{argmin}_{s} \sigma^2_{D_{\Psi^#,v^c}} + (Z^#(s,v^c) + \sqrt{n}(\Psi^#(P_{0,n})))^2$$

$$s^{**}_n(v^c) = \text{argmin}_{s} \sigma^2_{D_{\psi^#,v^c}} + (Z^{#+\Phi}(s,v^c) + \sqrt{n}(\Psi^#(P_{0,n}) + \Phi_{s}(P_{0,n})))^2$$

Let $s^*_n = (s^*_n(v^c) : v)$ and $s^{**}_n = (s^{**}_n(v^c) : v)$ represent the multivariate standardized selectors applied across all experiment-selection sets. Let $P^*_{n,v^c}$ denote training of initial estimators of the outcome regression $Q^{(0,s)}_{n,v^c}$ and treatment mechanism $g^0_{n,v^c}$ on experiment selection sets with TMLE targeting on separate or pooled estimation sets to generate $Q^{(0,s),*}_{n,v^c}$ for fold $v$. Let $P^*_{n,v^c}$ denote training and TMLE targeting of the relevant outcome regressions for each bias parameter on experiment selection sets for fold $v$.

**Theorem 1:** Under conditions of convergence of second-order remainders, consistency of EIC estimation, and a Donsker class condition for bias term estimation specified in Appendix 3, $s^*_n(v^c)$ and $s^{**}_n(v^c)$ approximate the limit processes $\bar{s}^*(v^c)$ and $\bar{s}^{**}(v^c)$ such that

$$\bar{s}^*(v^c) \sim \text{argmin}_{s} \sigma^2_{D_{\Psi^#,v^c}} + (Z^#(s,v^c) + \sqrt{n}(\Psi^#(P_{0,n})))^2$$

$$\bar{s}^{**}(v^c) \sim \text{argmin}_{s} \sigma^2_{D_{\psi^#,v^c}} + (Z^{#+\Phi}(s,v^c) + \sqrt{n}(\Psi^#(P_{0,n}) + \Phi_{s}(P_{0,n})))^2$$

and the standardized experiment-selector CV-TMLE,

$$\sqrt{n}(\psi_n - \psi_{n,0}) = H(\Psi^#, Z, \Psi^#(P_{0,n}))) + o_P(1)$$

or

$$\sqrt{n}(\psi_n - \psi_{n,0}) = H(Z^{#+\Phi}, Z, \Psi^#(P_{0,n}), \Phi(P_{0,n})) + o_P(1)$$
converges to a mixture of normal distributions defined by the sampling process depicted in Definition 1 below. The Proof of Theorem 1 may be found in Appendix 3.

**Definition 1. Limit Distribution for Experiment-Selector CV-TMLE**

Across all $s = 0, ..., K$ and $v = 1, ..., V$, define the stacked vector of standardized experiment-selection set bias estimators and estimation set bias estimators as

$$\tilde{Z} = (Z^#, Z) \sim N(\tilde{\Sigma})$$

where $\tilde{\Sigma}$ is depicted in Figure 1, and

$$\tilde{Z} = (Z^# + \Phi, Z) \sim N(\tilde{\Sigma})$$

The limit distribution for the experiment-selector CV-TMLE is then defined by sampling from $\tilde{Z}$, calculating $s^*$ or $\tilde{s}^*$, and finally calculating

$$H(Z^#, Z, \Psi^#(P_{0,n})) = \frac{1}{V} \sum_{v=1}^{V} (Z(s^*(v^c), v))$$

or $H(Z^# + \Phi, Z, \Psi^#(P_{0,n}), \Phi(P_{0,n})) = \frac{1}{V} \sum_{v=1}^{V} (Z(\tilde{s}^*(v^c), v))$.

### 5.1.1 Asymptotic Distribution of Selector Under Varying Magnitudes of Bias

| Magnitude of Bias | Limit Distribution of Selector |
|-------------------|---------------------------------|
| **Small**         | $\sqrt{n}\Psi^#(P_{0,n}) \xrightarrow{p} 0$ |
|                   | $\hat{S}^*(v^c) \sim \arg\min_s \sigma_{D_{\Psi^#}(s,v^c)}^2 + (Z^#(s, v^c))^2$ |
| **Intermediate**  | $\sqrt{n}\Psi^#(P_{0,n}) \xrightarrow{p} C$ |
| where $C$ is a constant | $\hat{S}^*(v^c) \sim \arg\min_s \sigma_{D_{\Psi^#}(s,v^c)}^2 + (Z^#(s, v^c) + C)^2$ |
| **Large**         | $\sqrt{n}\Psi^#(P_{0,n}) \xrightarrow{p} \infty$ |
|                   | $\hat{S}^*(v^c) = 0$ |

As shown in Table 1, although the random selector depends on $\Psi^#(P_{0,n})$, it converges to a limit distribution that does not depend on $n$, and which is known if bias is small, known up to a constant if bias is intermediate, and degenerate, selecting 0 with probability 1, if bias is large. To obtain inference for the experiment-selector CV-TMLE, we use Monte Carlo simulation to generate 1000 samples from the estimated limit distribution and define 95% confidence intervals based on the quantiles $q^{0.975}$ of these samples as $\psi_n + (\frac{0.025}{\sqrt{n}}, \frac{0.075}{\sqrt{n}})$.

In the case where RCT-only is selected in all experiment-selection sets, we use influence curve-based variance estimates consistent with a standard CV-TMLE procedure, with confidence intervals estimated as $\psi_n \pm 1.96 \times (\frac{1}{\sqrt{n}} \sum_{v=1}^{V} \frac{\delta^2(S^0_{s=0,n,v})}{\eta^2_{s=0,n,v}})^{1/2}$ (Zheng and van der Laan, 2010; Hubbard et al., 2016) where

$$\delta^2(S^0_{s=0,n,v}) = I(A = 1) - \frac{I(A = 0)}{Q_{n,v}(1, W, S = 0)} - I(A = 1) - \frac{Q_{n,v}(1, W, S = 0)}{Q_{n,v}(0, W, S = 0)}(Y - Q_{n,v}(1, W, S = 0)) + Q_{n,v}(1, W, S = 0) - Q_{n,v}(0, W, S = 0) - \hat{\Psi}_{s=0}(P_{n,v})$$

In Table 1, assume $\sqrt{\tilde{N}^#(P_{0,n})}$, which is known if bias is small, known up to a constant if bias is intermediate, and degenerate, selecting 0 with probability 1, if bias is large. To obtain inference for the experiment-selector CV-TMLE, we use Monte Carlo simulation to generate 1000 samples from the estimated limit distribution and define 95% confidence intervals based on the quantiles $q^{0.975}$ of these samples as $\psi_n + (\frac{0.025}{\sqrt{n}}, \frac{0.075}{\sqrt{n}})$.
estimated among RCT estimation set observations for fold $v$. We use plug-in estimates for the relevant components of
the efficient influence curves and for the bias terms in the selector. Because we overestimate bias for truly unbiased
RWD, we expect the confidence intervals to be conservative in this case. Nonetheless, as shown through simulations
below, this method of determining confidence intervals provides close to nominal coverage with both intermediate and
large magnitudes of bias.

6 Simulations

The following simulation compares the ES-CVTMLE to an RCT-only t-test and an RCT-only CV-TMLE using the tmle
R package (Gruber and Van Der Laan, 2012), as well as four other data fusion methods described below across several
magnitudes of external data bias and when the U-comparability assumption needed for bias adjustment with an NCO is
false.

6.1 Data Generation

We generate a small RCT (S=0) of 150 observations with probability of randomization to $A = 1$ of 0.67. The goal is to
mimic a situation where, for ethical reasons, it is desirable to randomize more participants to active treatment. We also
simulate three candidate real-world datasets $S \in \{1, 2, 3\}$ of 500 observations each, all with $A = 0$. Thus, no treatment
is available outside the trial. Dataset $S = 1$ has the same data-generating distribution as the RCT except that all $A = 0$,
so any apparent bias in $S = 1$ is due to finite sample variability. There are two unmeasured bias variables $B_1$ and $B_2$
that are deterministically 0 in $S = 0$ and $S = 1$ and are generated as follows in $S \in \{2, 3\}$. For this simulation, biased
RWD could be included if it is approximately

$$\sqrt{\frac{\sigma_{D_{2}\in(0.2)_{n, c}}}{n}} \approx B = 0.21.$$ 

We then generate $B_1$ and $B_2$ as normally distributed random variables such that average total bias in $S = 2$ is $B$ (intermediate bias) and in $S = 3$ is $5 + B$ (large bias). The outcome, $Y$ is a function of both $B_1$ and $B_2$, while the NCO is only a function of
$B_1$, so the U-comparability assumption is not true. Appendix 4 contains further details regarding the data generating
process and specifications for TMLE-based estimators used in this simulation.

6.2 Comparators

For each combination of $S = 0$ with one of $S \in \{1, 2, 3\}$, we compare our ES-CVTMLE with potential selectors
$s^*$ (b2v), $s^{**}$ (+nco), and $s^{***}$ (nco only) to four other data fusion estimators. These comparators were selected
because they were developed for the context of augmenting a control arm of an RCT with external control data, they are
commonly referenced, and they include methods for confidence interval construction. We introduce new versions of
the test-then-pool approach originally described by Viele et al. (2014) and the NCO-based difference-in-differences
approach described by Sofer et al. (2016) and Shi et al. (2020b), where our modifications use CV-TMLE estimators of
the relevant parameters.

6.2.1 Test-then-Pool

For the “test-then-pool” approach described by Viele et al. (2014), a hypothesis test is conducted for a difference in
the mean outcome of the trial controls and the mean outcome of the external controls. RCT and real-world data are
combined if the null hypothesis is not rejected; if the null hypothesis is rejected, then the RCT data are analyzed without
integration of RWD (Viele et al., 2014). The original test-then-pool used an unadjusted estimator of the difference in
mean outcome under treatment and control (Viele et al., 2014). For the sake of comparison with other TMLE-based estimators, we include here both the method previously described, together with a minor extension that incorporates adjustment for baseline covariates for the sake of efficiency. For the unadjusted version, both the hypothesis test for
including RWD and the treatment effect estimate are obtained using Welch’s t-test with unequal variances. For the adjusted
version, we first use CV-TMLE to estimate the ATE of S on Y among those with $A = 0$ and decide to pool RCT and
RWD if the 95% confidence interval for this estimate includes zero. We then obtain an estimate of the ATE of A on
Y in the pooled or RCT-only sample, again using CV-TMLE. While the “test-then-pool” approach has been criticized
for inappropriately including biased data due to low power of the test (Li et al., 2020), a byproduct of this limitation
is that the estimator is able to achieve large power gains when unbiased external controls are available. It is thus an
interesting comparator as a high-risk, high-reward strategy for data fusion.

6.2.2 Meta-Analytic-Predictive Priors

For comparison to a method of Bayesian Dynamic Borrowing, we use the RBest R package (Weber et al., 2021)
based on the approach described by Schmidli et al. (2014). As described by Schmidli et al. (2014) but modified for consistency with the above
notation, \( \theta_s = \Psi_s^{\delta, n, BDB} (P) \) is the mean outcome of controls in experiment \( S \in \{0, s\} \). The prior distribution of \( \theta_s \) is assumed to be Normal(\( \mu, \tau^2 \)). \( \tau \) is an estimate of the between-study heterogeneity that determines how much external control information is borrowed. For a continuous outcome, Weber et al. (2021) recommend a Half-Normal(0, \( \sigma^2/2 \)) prior distribution for \( \tau \), where \( \sigma \) is the standard deviation of the outcome estimated from external studies. Because the choice of the prior distribution of \( \tau \) can impact results, Schmidli et al. (2014) recommend conducting sensitivity analyses with different parameterizations of this distribution.

A sampling distribution of \( \theta_s \) is generated using a Markov Chain Monte Carlo algorithm and approximated with a mixture of conjugate prior distributions (Schmidli et al. 2014). To protect against non-exchangeability between external and trial controls, RBesT also provides a function to add a unit information prior component to this mixture (Schmidli et al. 2014; Weber et al. 2021). The weight of that vague prior must be specified by the researchers based on their beliefs regarding how likely the available control groups are to be exchangeable (Schmidli et al. 2014), with a suggested weight of 0.2 (Weber et al. 2021). The control target parameter is estimated as the mean of the posterior distribution \( \hat{\theta}_s | O^n \). The posterior distribution of the treatment target parameter is estimated as a mixture of conjugate distributions based on a weakly informative unit-information prior (Weber et al. 2021).

### 6.2.3 Negative Control Outcome (Difference-in-Differences Approach)

Because our methods incorporate information from a negative control outcome, we also compare simulation results to a simple bias adjustment approach that is also based on an NCO. Multiple authors have noted that under the following assumptions, adjustment for bias using an NCO can be accomplished using a difference-in-differences approach (Sofer et al. 2016; Shi et al. 2020b). The first assumption is U-comparability, which states that all of the unmeasured factors that affect the A-Y relationship are the same as the unmeasured factors that affect the A-NCO relationship (Lipsitch et al. 2010). The second is “additive equi-confounding”, which states that the unmeasured confounding has the same effect (on the additive scale) on the primary outcome as on the NCO (Sofer et al. 2016; Shi et al. 2020b). Under these assumptions, an estimator for the average treatment effect of A on Y for a given the experiment with \( S \in \{0, s\} \) may be defined as \( \hat{\Psi}_s^{DID} (P_s) = \hat{\Psi}_s (P_s) - \hat{\Psi}_s (P_0) \) (Sofer et al. 2016; Shi et al. 2020b). For a consistent comparison with the rest of our methods, we use CV-TMLE to estimate both parameters. The efficient influence curve of \( \hat{\Psi}_s^{DID} \) is then \( D_s^{DID} = D_s^\psi - D_s^\psi \).

### 7 Simulation Results

Table 2 shows the bias, variance, mean of the estimated variance, mean squared error (MSE), 95% confidence interval coverage, and power to detect the causal ATE (using \( \alpha = 0.05 \)) across 1000 iterations of this simulation. The standard CV-TMLE analyzed using the RCT data alone had nominal coverage of 0.95 and power of 0.64. The RCT-only CV-TMLE had higher power than any of the unadjusted estimators, with the RCT t-test having coverage of 0.96 and power of 0.24.

The test-then-pool approaches were able to increase power as high as 0.93 for the TMLE-based test-then-pool when unbiased RWD were available. However, as bias in the RWD increased, the coverage suffered, dropping as low as 0.79 for the TMLE-based test-then-pool with \( S = 2 \) and 0.76 for the t-test based test-then-pool with \( S = 3 \). Test-then-pool is thus a high-risk, high-reward approach to integrating observational and RCT data.

Because the U-comparability assumption is not true, the two methods that rely only on a bias estimate of the ATE of A on the NCO also exhibited decreased coverage. Bias in the NCO-based difference-in-differences approach increased as the bias in the available RWD increased, leading to coverage of 0.84 for the most biased RWD dataset (\( S=3 \)). When we only considered the estimated ATE of A on NCO in the experiment-selector CV-TMLE \( (s_{n}^{*} (nco \ only)) \), coverage dropped as low as 0.87, which was lower coverage than when we also included \( \hat{\Psi}_s^{*} \) as an estimate of bias in the selector (discussed below).

With default specifications, RBesT (Weber et al. 2021) maintained coverage 0.94-0.97. Yet because this method does not adjust for covariates, power remained similar to the t-test, with higher power achieved by considering RWD with intermediate bias (power 0.32) than by considering unbiased RWD (power 0.29). Thus, while RBesT resulted in close to nominal coverage, this method had lower power than alternative estimators, including an adjusted CV-TMLE using only the RCT data. MSE was higher for the RBesT estimator than for any of the ES-CVTMLE estimators across all tested magnitudes of external bias.

Next, we examine the experiment-selector CV-TMLEs with the b2v and +nco selectors. With \( S = 3 \), these ES-CVTMLEs with selector \( s_{n}^{*} (b2v) \) or \( s_{n}^{*} (nco) \) were approximately equivalent to the RCT-only CV-TMLE from the tmle R package. This makes sense because data with bias this large was rejected, in which case the ES-CVTMLE algorithm is equivalent to a traditional CV-TMLE from the RCT only. When unbiased external controls were available,
coverage was 0.96 for $s_n^*$ \textbf{(b2v)} and $s_n^{**}$ \textbf{(nco)}, suggesting somewhat conservative confidence intervals consistent with the fact that estimated bias is included in the limit distribution sampling procedure despite truly being zero. Power increased compared to the RCT-only CV-TMLE in either case but was lower with $s_n^*$ \textbf{(b2v)} at 0.74, compared to 0.83 for $s_n^{**}$ \textbf{(nco)}, demonstrating the utility of including information from the estimated ATE of A on the NCO in the selector for incorporating truly unbiased external controls. With $S = 2$ (intermediate bias), coverage was 0.95 for $s_n^*$ \textbf{(b2v)} and 0.92 for $s_n^{**}$ \textbf{(nco)}, demonstrating that the experiment-selector CV-TMLE is able to maintain coverage close to 0.95 even with this challenging amount of bias and an imperfect NCO.

In this simulation, the ES-CVTMLE MSE was lower with either of the \textbf{b2v} or \textbf{nco} selectors compared to the RCT-only CV-TMLE when considering $S = 1$ and lower or the same when considering $S = 2$ or $S = 3$. Of all the compared estimators, the ES-CVTMLE with the $s_n^*$ \textbf{(b2v)} selector provided the largest power gains with unbiased RWD while maintaining 95% coverage across all tested magnitudes of bias. However, the ES-CVTMLE with the $s_n^{**}$ \textbf{(nco)} selector is the estimator that decreased MSE the most when unbiased RWD were available without increasing MSE when considering RWD with intermediate or large bias. If we were running this simulation to choose an estimator for a proposed trial in a context when excessive randomization to control is considered unethical but we still desire a fairly precise estimate of the true causal effect of interest from a well-powered multisite and multi-region RCT.

Table 2: Results of Simulation - 1000 Iterations

| Estimator (RWD) | Bias | Variance | Mean Est. Var. | MSE | Coverage | Power |
|-----------------|------|----------|----------------|-----|----------|-------|
| RCT T-Test      | 0.005| 0.206    | 0.219          | 0.206| 0.96     | 0.24  |
| RCT CV-TMLE     | 0.014| 0.065    | 0.070          | 0.065| 0.95     | 0.64  |
| ES-CVTMLE $s_n^*$ \textbf{(b2v)} (S=1) | 0.003| 0.054    | 0.058          | 0.054| 0.96     | 0.74  |
| ES-CVTMLE $s_n^*$ \textbf{(b2v)} (S=2) | -0.026| 0.065  | 0.061          | 0.065| 0.95     | 0.71  |
| ES-CVTMLE $s_n^*$ \textbf{(b2v)} (S=3) | 0.005| 0.065    | 0.071          | 0.065| 0.95     | 0.64  |
| ES-CVTMLE $s_n^{**}$ \textbf{(nco)} (S=1) | 0.005| 0.045    | 0.044          | 0.045| 0.96     | 0.83  |
| ES-CVTMLE $s_n^{**}$ \textbf{(nco)} (S=2) | -0.028| 0.059   | 0.052          | 0.060| 0.92     | 0.76  |
| ES-CVTMLE $s_n^{**}$ \textbf{(nco)} (S=3) | 0.005| 0.065    | 0.071          | 0.065| 0.95     | 0.64  |
| ES-CVTMLE $s_n^{**}$ \textbf{(nco only)} (S=1) | 0.004| 0.028    | 0.034          | 0.028| 0.97     | 0.92  |
| ES-CVTMLE $s_n^{**}$ \textbf{(nco only)} (S=2) | -0.152| 0.036   | 0.038          | 0.059| 0.87     | 0.95  |
| ES-CVTMLE $s_n^{**}$ \textbf{(nco only)} (S=3) | -0.037| 0.089   | 0.068          | 0.090| 0.91     | 0.67  |
| TTP (CV-TMLE) (S=1) | 0.004| 0.037    | 0.029          | 0.037| 0.93     | 0.93  |
| TTP (CV-TMLE) (S=2) | -0.113| 0.059   | 0.033          | 0.072| 0.79     | 0.87  |
| TTP (CV-TMLE) (S=3) | 0.004| 0.065    | 0.070          | 0.065| 0.95     | 0.64  |
| Diff-in-Diff (NCO) (S=1) | 0.008| 0.052    | 0.054          | 0.052| 0.95     | 0.73  |
| Diff-in-Diff (NCO) (S=2) | -0.040| 0.054   | 0.054          | 0.056| 0.94     | 0.79  |
| Diff-in-Diff (NCO) (S=3) | -0.227| 0.054   | 0.054          | 0.105| 0.84     | 0.94  |
| TTP (T-Test) (S=1) | -0.001| 0.122    | 0.090          | 0.122| 0.93     | 0.53  |
| TTP (T-Test) (S=2) | -0.132| 0.147   | 0.095          | 0.164| 0.88     | 0.70  |
| TTP (T-Test) (S=3) | -0.128| 0.359   | 0.182          | 0.376| 0.76     | 0.35  |
| RBesT (Weber et al. \textbf{2021}) (S=1) | -0.005| 0.152    | 0.183          | 0.152| 0.97     | 0.29  |
| RBesT (Weber et al. \textbf{2021}) (S=2) | -0.052| 0.157   | 0.185          | 0.159| 0.96     | 0.32  |
| RBesT (Weber et al. \textbf{2021}) (S=3) | -0.116| 0.213   | 0.222          | 0.227| 0.94     | 0.31  |

Notes: Mean. Est. Var.: Mean of variance estimates. S=1: unbiased RWD. S=2: RWD with intermediate bias. S=3: RWD with large bias. Power: Probability that confidence interval < 0 across 1000 iterations. TTP: Test-then-Pool. $s_n^* = \arg\min_s \frac{s^2}{n} + (\hat{\Psi}_s(P_n))^2$, $s_n^{**} = \arg\min_s \frac{s^2}{n} + (\hat{\Psi}_s(P_n) + \Phi_s(P_n))^2$, $s_n^{***} = \arg\min_s \frac{s^2}{n} + (\phi_s(P_n))^2$

8 Real Data Application

Ultimately, the goal of the experiment-selector CV-TMLE is to facilitate integration of RCT and real-world data in order to boost RCT power without introducing bias. As an initial test case for this method, we have chosen an example where we have a fairly precise estimate of the true causal effect of interest from a well-powered multisite and multi-region RCT. We use these data to create a hypothetical scenario in which RCT data are only available from a subset of participants
from one region — resulting in an under-powered trial — but candidate control arm-only data are available from other regions (mimicking RWD of varying quality). We use this scenario to evaluate the ability of our proposed methods and others to recover the initial RCT effect estimate.

To create such a scenario, we use de-identified data from the LEADER trial (Clinical Trial NCT01179048). Initially reported by [Marso et al., 2016], this study evaluated the effect of an injectable (subcutaneous) glucagon-like peptide-1 receptor agonist, liraglutide, on a primary combined outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. The sample size for LEADER was 9340 patients. Because this trial was designed to evaluate relatively long-term and rare outcomes, the sample size was large enough to estimate the effect of liraglutide versus placebo (both added to standard of care therapy with oral antihyperglycemic drugs (OADs) and/or insulin) on glycemic control (measured by hemoglobin A1c ($HbA_{\text{1c}}$)) with great precision.

LEADER encouraged trial clinicians to optimize standard of care diabetes regimens beyond the addition of liraglutide or placebo in order to achieve a target $HbA_{\text{1c}}$ of $\leq 7\%$ for all trial participants [Zinman et al., 2018]. We thus would expect not only to see a difference in change in $HbA_{\text{1c}}$ between the liraglutide and placebo arms but also to see a change in $HbA_{\text{1c}}$ from baseline in the placebo arm due to modifications in patients’ baseline diabetes regimens. We would expect the major driver of change in $HbA_{\text{1c}}$ in the placebo arm to be $HbA_{\text{1c}}$ at baseline.

As shown in Figure 2, change in $HbA_{\text{1c}}$ differed by study region, with the largest average changes in both the liraglutide and placebo arms taking place in the Central and South American groups. Average baseline $HbA_{\text{1c}}$ was also higher in Central/South America (9.29) compared to Europe (8.31). If we were to mimic a small RCT by taking a limited sample of patients from Central and South America and then augment the control arm with external controls from Central and South America, we would expect those individuals who were randomized to placebo from within the same region to be unbiased controls. However, if we were to augment the small Central/South America RCT with external controls from Europe, and if we treated baseline $HbA_{\text{1c}}$ as an unmeasured factor that causes the differences in placebo group outcomes by region, we would expect the following. The treatment arm would only contain subjects from Central and South America, with a relatively large average decrease in $HbA_{\text{1c}}$. The addition of European controls to the placebo arm would lead to a smaller average change in $HbA_{\text{1c}}$ among all controls, leading to an overestimate of the effect of liraglutide compared to placebo on glycemic control compared to the effect estimate from the full Central/South America LEADER subset.

This set-up implies the following directed acyclic graph:
Based on our data set-up, region (Central/South America or Europe) affects treatment because members of the Central/South America group may receive liraglutide or placebo, and participants from Europe may only receive placebo. As we have noted, region also affects change in $HbA_{1c}$ in the placebo arm. Because average baseline $HbA_{1c}$ was higher and average improvement in $HbA_{1c}$ was larger for the Central/South America compared to European subgroups, this suggests that on average, baseline diabetes regimens may have been less adequate in the Central/South America LEADER sample. In reviews of barriers and facilitators for diabetes management in Latin America, Blasco-Blasco et al. (2020) and Avilés-Santa et al. (2020) cite access to healthcare, limitations in health system resources, and social determinants of health as challenges that impede optimal glycemic control for many people. While these factors vary by country, differences in such underlying barriers between the Central/South American and European subgroups of LEADER could explain at least part of the noted difference in average baseline $HbA_{1c}$.

We also have access to the following baseline covariates, $W$: age, sex, smoking status (never, former, or current), diabetes duration, whether the patient is insulin naive at baseline, eGFR, and BMI. Based on this DAG, we would expect baseline $HbA_{1c}$ and $W$ to block all paths from region to the outcome, other than the path through treatment, but we will treat $HbA_{1c}$ as unmeasured.

The last ingredient for our analysis is an appropriate negative control. As shown in our causal graph, we may hypothesize that regional differences in health care for patients with metabolic syndrome causing inadequate control of $HbA_{1c}$ may also lead to inadequate control of cholesterol. This hypothesis is supported by Venkitachalam et al. (2012)'s finding that both country-level health systems factors and economic development metrics were significantly associated with prevalence of elevated cholesterol among patients with a history of hyperlipidemia from thirty-six countries. If this hypothesis is true, baseline cholesterol may serve as a negative control variable given that it would be associated with unmeasured factors hypothesized to cause differences in the placebo arm change in $HbA_{1c}$ by region while not being affected by liraglutide administered post-baseline. Note also that we expect improvements in the adequacy of the baseline medication regimen to lead to smaller improvements in $HbA_{1c}$ during the trial and also to be associated with lower levels of baseline cholesterol. By defining our outcome as improvement in $HbA_{1c}$, we satisfy our goal of defining a negative control variable that should be affected by the unmeasured bias in the same direction as the true outcome.

Our observed data thus consist of $O = (S, W, C, A, Y)$, where the $W$ covariates are defined above, $C$ is baseline cholesterol level in mmol/L, $A$ is a binary indicator of liraglutide versus placebo, and $Y$ is improvement in $HbA_{1c}$ from baseline to study month 12. $S$ is an indicator of study: 1 for the Central/South American “RCT” sample (random sample of 150 participants), 2 for extra controls from Central/South America (random sample of 500 participants not included in study 1), and 3 for extra controls from Europe (random sample of 500 participants). For clarity, we will refer to study 1 as C/S, a combination of studies 1 and 2 as C/S+, and a combination of studies 1 and 3 as Eu+. In order to demonstrate the case where we would like to increase the number of patients receiving the intervention of interest in our “RCT”, we select $S = 1$ participants with a probability of 0.67 of having been in the liraglutide arm and 0.33 of having been in the placebo arm.
Overall missingness for change in \( HbA_1c \) was 6\%. Missingness for baseline cholesterol, which was treated as an outcome for the estimate of the ATE of \( A \) on negative control in the selector but was treated as a baseline variable in the TMLE for the ATE of \( A \) on \( Y \), was 2\%. Outcome missingness was handled with inverse probability weights, consistent with the \textit{tmle} package (Gruber and Van Der Laan, 2012). Specifically, we define a binary variable \( \Delta \) that indicates an outcome was not missing. Clever covariates for all TMLEs were then modified to include the missingness indicator in the numerator and missingness mechanism in the denominator. For example, the clever covariate for the ATE was modified as \( H(A, W) = \frac{\Delta(2A - 1)}{g(A = 1|A, W)g(A|W)} \). Missingness for baseline covariates, which was less than 0.1\% for all \( W \) variables, was imputed using the \textit{R} package \textit{mice: Multivariate Imputation by Chained Equations} (van Buuren and Groothuis-Oudshoorn, 2011) separately for each study.

Our desired target causal parameter is the average treatment effect of liraglutide versus placebo on improvement in \( HbA_1c \) from baseline to 12 months in Central/South America. Due to randomization within the LEADER trial, this target parameter should be identifiable from dataset C/S and C/S+ but not from Eu+ without adjustment for baseline \( HbA_1c \). We compare the following estimators: a CV-TMLE from the \textit{tmle} package (Gruber and Van Der Laan, 2012) using C/S only, the experiment-selector CV-TMLE considering C/S+ or considering Eu+, the \textit{RBesT} package (Weber et al., 2021) considering C/S+ or considering Eu+, and a t-test using C/S only. To further demonstrate what could happen if the ATE were estimated from data that includes biased controls without any evaluation of whether bias is present, we also include standard CV-TMLEs based on the C/S+ and Eu+ datasets. We run this analysis 100 times with different random seeds.

For the TMLEs, we use the following specifications. We employ a discrete Super Learner for all outcome regressions with a library consisting of linear regression (Enea, 2022), lasso regression (via \textit{R} package \textit{glmnet} (Friedman et al., 2010)), and multivariate adaptive regression splines (Milborrow, 2021). When considering only \( S = 1 \), we use the true randomization probability of 0.67 for \( P(A = 1) \). When external controls are considered, we use a discrete Super Learner with library consisting of logistic regression and lasso regression for the treatment mechanism. Because missingness was low, for the missingness mechanism we use a linear model adjusting only for treatment unless the number of missing observations is less than five, in which case we employ an intercept only adjustment. We also use the \textit{tmle} package defaults of fitting a CV-TMLE, using a logistic fluctuation, and targeting the weights, as described above.
8.1 Results of Analysis of LEADER Data

Figure 4: Estimated ATE of Liraglutide v. Placebo on Improvement in $HbA_1c$ by Estimator

Boxplots of ATE and Relative confidence interval (CI) width with medians labeled. Relative width of CI compared to RCT CV-TMLE from sample C/S. Full C/S: Full Central/South America sample from LEADER trial (sample size 1182). C/S: Central/South American sample “RCT” (sample size 150). C/S+: C/S plus 500 additional controls from Central/South America. Eu+: C/S + 500 additional controls from Europe. ES-CV-TMLE: Experiment-selector CV-TMLE. CV-TMLE: Standard CV-TMLE from tmle package [Gruber and Van Der Laan 2012].
We introduce a novel cross-validated targeted maximum likelihood estimator that aims to select the experiment (RCT or RCT plus external controls) that optimizes the bias-variance tradeoff for the causal average treatment effect. To address the challenge that the selector may remain random asymptotically with small to intermediate magnitudes of external bias, we develop an algorithm for confidence interval construction that samples from the estimated limit distribution and that includes an estimate of the bias in this sampling process. Through simulations, we demonstrate that we are able to improve power compared to a standard CV-TMLE from the RCT only when unbiased external controls are available and maintain coverage close to $\alpha = 0.05$ with intermediate to large magnitudes of bias. In an analysis of the ATE of liraglutide versus placebo on improvement in 12 month $HbA_1c$ from the LEADER trial, we also demonstrate the ability of the experiment-selector CV-TMLE to include external controls and narrow confidence intervals when additional unbiased controls are available and to reject biased external controls in the majority of iterations, maintaining similar confidence interval widths and point estimates compared to the sample “RCT” sample when biased Eu+ controls are considered.

## 9 Discussion

We introduce a novel cross-validated targeted maximum likelihood estimator that aims to select the experiment (RCT or RCT plus external controls) that optimizes the bias-variance tradeoff for the causal average treatment effect. To address the challenge that the selector may remain random asymptotically with small to intermediate magnitudes of external bias, we develop an algorithm for confidence interval construction that samples from the estimated limit distribution and that includes an estimate of the bias in this sampling process. Through simulations, we demonstrate that we are able to improve power compared to a standard CV-TMLE from the RCT only when unbiased external controls are available and maintain coverage close to $\alpha = 0.05$ with intermediate to large magnitudes of bias. In an analysis of the ATE of liraglutide versus placebo on improvement in 12 month $HbA_1c$ from the LEADER trial, we also demonstrate the ability of the experiment-selector CV-TMLE to include external controls and narrow confidence intervals when additional unbiased controls are available and to reject biased external controls in the majority of iterations, maintaining similar confidence interval widths and point estimates compared to the sample “RCT” sample when biased Eu+ controls are considered.

The purpose of the experiment-selector CV-TMLE is to provide an estimator that is robust to varying magnitudes of bias from a combined RCT-RWD analysis when, as may frequently happen in partially observational studies, we are not certain whether the randomization assumption or U-comparability assumptions are true. Many existing methods rely explicitly on these assumptions. Others either rely on a comparison of mean outcomes or effect estimates for RCT versus external participants or evaluate the effect of treatment on an NCO (Shi et al., 2020b), but not both. Because bias must be estimated from the data, attempts to optimize the bias-variance tradeoff may either inadvertently exclude truly unbiased external data or include external data with a magnitude of bias that may impact causal coverage. By including an estimate of the ATE of treatment on a negative control outcome in our selector, we are able to more frequently include truly unbiased external controls.
controls in our analysis. Yet we do not require the NCO to be perfect and show improved coverage compared to an
NCO-based bias-adjustment approach when the U-comparability assumption does not actually hold. We thus aim to
improve on existing methods by incorporating information from both an estimated causal gap and from a negative
control outcome to maximize our ability to select an optimal experiment for analyzing a causal ATE. Another advantage
of the experiment-selector CV-TMLE is that it attempts to learn how much external information to include only from
the data, rather than requiring a researcher to specify a level of confidence in the external controls as is required in some
Bayesian dynamic borrowing approaches (Schmidli et al., 2014) or to specify the value of a tuning parameter as is
required by some frequentist approaches (Chen et al., 2021; Yang et al., 2020).

The largest limitation of the experiment-selector CV-TMLE is that, because we cannot guarantee 95% coverage, the
performance may depend on characteristics of the proposed analysis. Once again, this limitation is not unique to
our estimator, as other data fusion estimators have demonstrated either increases in type 1 error or relative MSE or
decreases in power with differing magnitudes of external data bias (Dejardin et al., 2018; Viele et al., 2014; Chen
et al., 2021; Oberst et al., 2022; Galwey, 2017; Cuffe, 2011; Harun et al., 2020; Yang et al., 2020; Cheng and Cai,
2021). Yet because of this limitation, it would be important to conduct an outcome-blind simulation that is as true to
a proposed study as possible, prior to implementing this estimator in a different context. Outcome-blind simulations
can address differences in estimator performance for differing study characteristics and estimator specifications, such
as different RCT and RWD sample sizes, the relative predictiveness of the covariates for the outcome, the candidate
algorithms, the number of cross-validation folds, and the outcome type. For example, it is possible that for a given
study design, the optimal bias-variance tradeoff across varying magnitudes of potential bias could actually be achieved
by adding a smaller number of external controls than are available. A future version of the selector could consider
adding different numbers of external controls based on, for example, increasing numbers of propensity-score matched
external participants. In future work, we also intend to evaluate the experiment-selector CV-TMLE in a wider variety
of contexts, including extending the methods to include time-to-event outcomes.

This real data analysis allowed the opportunity to test the experiment-selector CV-TMLE in a setting where we
understand the “unmeasured” factors causing external controls to be biased or unbiased. In the future, we intend to
test this method when attempting to combine real electronic health records data with a small RCT sample, again with
the aim of replicating the full trial results. While this approach may prove viable in some settings, we suggest that in
order to optimize the probability both that RWD is included and that bias is truly minimal, in many cases a preferable
approach will be to prospectively specify a hybrid RCT-RWD study, allowing protocols and measurements to be made
as similar as possible. We do not intend these methods to be a replacement for a traditional randomized controlled trial
when it is feasible to run one for the sake of evaluating the efficacy of a new drug that has yet to be approved. Yet
we hope that the experiment-selector CV-TMLE may ultimately be able to provide evidence to support conclusions
from under-powered RCTs conducted for rare diseases, to allow randomization of more patients to the intervention
arm for medications evaluated for severe diseases with few treatment options, and to contribute robust evidence to the
evaluation of previously approved drugs for new populations and indications.

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10 Appendix

10.1 Appendix 1: Table of Symbols

| Symbol | Meaning |
|--------|---------|
| S      | Variable indicating experiment (RCT or RCT+RWD) |
| A      | Intervention |
| W      | Covariates |
| Y      | Outcome |
| X      | Endogenous variables |
| U      | Exogenous variables |
| $O^n$  | Observed data $O^n = (O_1, ..., O_n)$ |
| $P_{U,O}$ | True distribution of full data (endogenous and exogenous variables) |
| $P_{0}$ | True distribution of observed data |
| $P_{s}$ | Empirical distribution of observed data |
| $P_{n,v}$ | Empirical distribution of estimation set for cross-validation fold $v$ |
| $P_{n,v^c}$ | Empirical distribution of experiment-selection set (fold $v$) |
| $P_{0,n}$ | True data distribution dependent on $n$ |
| $P_{x,n,v}$ | Indicates training of initial estimators for outcome regression and treatment mechanism on experiment-selection set for fold $v$ with TMLE targeting on separate or pooled estimation set(s) |
| $P_{x,n,v^c}$ | Indicates training and TMLE targeting of estimator for outcome regression on experiment-selection set for fold $v$ |
| $Q_{n,v}^{[0,s]}$ | Indicates updated $Q$ after training of initial estimators for outcome regression $Q_{n,v}$ and treatment mechanism on experiment-selection set for fold $v$ with TMLE targeting on separate or pooled estimation set(s) |
| $Q_{n,v}^{NCO}$ | Indicates updated $Q$ after training and TMLE targeting of estimator for outcome regression on experiment-selection set for fold $v$ |
| $\phi^*$ | Indicates updated $Q$ after training and TMLE targeting of estimator for outcome regression on experiment-selection set for fold $v$ |
| $g^*$ | $P(S = 0|S \in \{0, s\}, A = 0, W)$ ("Selection Mechanism") |
| $g^a$ | $P(A = a|S \in \{0, s\}, W)$ ("Treatment Mechanism") |
| $\Psi_{U,O}^F(P_{U,O})$ | $E_{W|S \in \{0, s\}}[E[Y^1 - Y^0| W, S \in \{0, s\}]]$ ("ATE") |
| $\Psi_{S}(P_{0})$ | $E_{W|S \in \{0, s\}}[E[Y|A = 1, S \in \{0, s\}] - E_{W}[Y|A = 0, S \in \{0, s\}, W]]$ |
| $\tilde{\Psi}_{S}^F(P_{U,O})$ | $E_{W|S \in \{0, s\}}[E[Y=1,s=O - Y_s=s=0| W, S \in \{0, s\}]]$ ("ATE-RCT") |
| $\Psi_{S}^F(P_{0})$ | $E_{W|S \in \{0, s\}}[E_0[Y|A = 1, S = 0, W] - E_0[Y|A = 0, S = 0, W]]$ |
| $\Phi_{S}(P_{0})$ | $E_{W|S \in \{0, s\}}[E_0[NCO|A = 1, S \in \{0, S\}, W] - E_0[NCO|A = 0, S \in \{0, s\}, W]]$ |
| $s^*_n$ | $\arg\min_s\frac{\sigma_{\phi^*}}{n} + (\tilde{\Psi}_{S}^F(P_{0}))^2$ (Bias$^2$ + variance selector "b2v") |
| $s^{**}_n$ | $\arg\min_s\frac{\sigma_{\phi^*}}{n} + (\Psi_{S}^F(P_{0}) + \tilde{\Phi}_{S}(P_{0}))^2$ (Selector including ATE on NCO "+nco") |
| $s^{***}_n$ | $\arg\min_s\frac{\sigma_{\phi^*}}{n} + (\tilde{\Phi}_{S}(P_{0}))^2$ (Bias only estimated as ATE on NCO "nco only") |

NCO: Negative control outcome. ATE: Average treatment effect. ATE-RCT: Average treatment effect if participants were in RCT.

Table 3: Table of Symbols

| Symbol | Meaning |
|--------|---------|
| s      | Variable indicating experiment (RCT or RCT+RWD) |
| A      | Intervention |
| W      | Covariates |
| Y      | Outcome |
| X      | Endogenous variables |
| U      | Exogenous variables |
| $O^n$  | Observed data $O^n = (O_1, ..., O_n)$ |
| $P_{U,O}$ | True distribution of full data (endogenous and exogenous variables) |
| $P_{0}$ | True distribution of observed data |
| $P_{s}$ | Empirical distribution of observed data |
| $P_{n,v}$ | Empirical distribution of estimation set for cross-validation fold $v$ |
| $P_{n,v^c}$ | Empirical distribution of experiment-selection set (fold $v$) |
| $P_{0,n}$ | True data distribution dependent on $n$ |
| $P_{x,n,v}$ | Indicates training of initial estimators for outcome regression and treatment mechanism on experiment-selection set for fold $v$ with TMLE targeting on separate or pooled estimation set(s) |
| $P_{x,n,v^c}$ | Indicates training and TMLE targeting of estimator for outcome regression on experiment-selection set for fold $v$ |
| $Q_{n,v}^{[0,s]}$ | Indicates updated $Q$ after training of initial estimators for outcome regression $Q_{n,v}$ and treatment mechanism on experiment-selection set for fold $v$ with TMLE targeting on separate or pooled estimation set(s) |
| $Q_{n,v}^{NCO}$ | Indicates updated $Q$ after training and TMLE targeting of estimator for outcome regression on experiment-selection set for fold $v$ |
| $\phi^*$ | Indicates updated $Q$ after training and TMLE targeting of estimator for outcome regression on experiment-selection set for fold $v$ |
| $g^*$ | $P(S = 0|S \in \{0, s\}, A = 0, W)$ ("Selection Mechanism") |
| $g^a$ | $P(A = a|S \in \{0, s\}, W)$ ("Treatment Mechanism") |
| $\Psi_{U,O}^F(P_{U,O})$ | $E_{W|S \in \{0, s\}}[E[Y^1 - Y^0| W, S \in \{0, s\}]]$ ("ATE") |
| $\Psi_{S}(P_{0})$ | $E_{W|S \in \{0, s\}}[E_0[Y|A = 1, S \in \{0, s\}] - E_{W}[Y|A = 0, S \in \{0, s\}, W]]$ |
| $\tilde{\Psi}_{S}^F(P_{U,O})$ | $E_{W|S \in \{0, s\}}[E[Y=1,s=O - Y_s=s=0| W, S \in \{0, s\}]]$ ("ATE-RCT") |
| $\Psi_{S}^F(P_{0})$ | $E_{W|S \in \{0, s\}}[E_0[Y|A = 1, S = 0, W] - E_0[Y|A = 0, S = 0, W]]$ |
| $\Phi_{S}(P_{0})$ | $E_{W|S \in \{0, s\}}[E_0[NCO|A = 1, S \in \{0, S\}, W] - E_0[NCO|A = 0, S \in \{0, s\}, W]]$ |
| $s^*_n$ | $\arg\min_s\frac{\sigma_{\phi^*}}{n} + (\tilde{\Psi}_{S}^F(P_{0}))^2$ (Bias$^2$ + variance selector "b2v") |
| $s^{**}_n$ | $\arg\min_s\frac{\sigma_{\phi^*}}{n} + (\Psi_{S}^F(P_{0}) + \tilde{\Phi}_{S}(P_{0}))^2$ (Selector including ATE on NCO "+nco") |
| $s^{***}_n$ | $\arg\min_s\frac{\sigma_{\phi^*}}{n} + (\tilde{\Phi}_{S}(P_{0}))^2$ (Bias only estimated as ATE on NCO "nco only") |
10.2 Appendix 2: Estimation of Bias

In order to estimate the bias, $\Psi_s^\#(P_n)$, we will use targeted maximum likelihood estimation (van der Laan and Rubin, 2006). The efficient influence curve (EIC) for $\Psi_s^\#(P_n)$ is

$$D_{\Psi_s^\#}(O) = \frac{I(\{S \in \{0,s\}\})}{P_n(\{S \in \{0,s\}\})} I(A=0)(Y - Q^0_{s,n}(S = 0, A, W)) + Q^0_{s,n}(S = 0, A, W) - \Psi_s^\#(P_n)$$

where $g_n^s(A = 0 | S = 0, W)$ is the probability that $A = 0$ given $S = 0, W$, and $Q^0_{s,n}(S = 0, A, W) = E_0[Y | S = 0, A, W]$. TMLE involves fitting initial estimates of the treatment mechanism, $g_n^s$, and outcome regression, $Q^0_{s,n}$, with the SuperLearner ensemble machine learning algorithm (van der Laan et al., 2007). The initial estimate is then targeted using a parametric working model (van der Laan and Rose, 2011):

$$\text{logit}(Q^0_{s,n}(s, A, W)) = \text{logit}(Q^0_{s,n}(S = 0, A, W)) + \epsilon_n H^*_s,s(n, A, W)$$

where $H^*_s,s(n, A, W) = I(A = 0, s, W) g_n^s(A = 0 | S = 0, W) P_n(\{S = 0\})$ using the same $\epsilon_n$. The final estimate of the mean outcome under control in the combined dataset is then

$$\hat{\Psi}_s^\#(P_n) = \frac{1}{n} \sum_{i=1}^n I(S_i = 0, W_i) Q^0_{s,n}(S_i = 0, 0, W_i)$$

An alternate option that may be more stable in the context of near-violations of the positivity assumption is to move the denominator of the cleaver covariate to the denominator of the weights for the regression training the TMLE coefficient (Robins et al., 2007; Rotnitzky et al., 2012; Tran et al., 2019). For this option of "targeting the weights", we perform a logistic regression of binary or scaled-continuous $Y$ on $H^*_s,s(n, A, W) = I(A = 0, s, W)$ with offset $\text{logit}(Q^0_{s,n}(S = 0, A, W))$ and weights $I(A = 0, s, W) g_n^s(A = 0 | S = 0, W) P_n(\{S = 0\})$ among observations with $S = 0$. Initial estimates are then updated as $Q^0_{s,n}(s, A, W) = \text{logit}^{-1}(\text{logit}(Q^0_{s,n}(S = 0, A, W)) + \epsilon_n)$.

We can also use TMLE to estimate $\tilde{\Psi}_s^\#(P_n) = E(W | S = 0, E_0[Y | A = 0, S = 0, W])$, with EIC

$$D_{\tilde{\Psi}_s^\#}(O) = \frac{I(S \in \{0,s\})}{P_n(S \in \{0,s\})} I(A=0)\tilde{g}_n^s(A = 0, S = 0, W) E_0(Y - Q^0_n(S = 0, A, S, W)) + Q^0_n(S = 0, A, S, W) - \tilde{\Psi}_s^\#(P_n)$$

where $\tilde{Q}_n(S = 0, A, S, W) = E_0[Y | S = 0, A, S, W]$. We use the same procedure as above with clever covariate $H^*_n,n(S = 0, A, S, W) = I(S = 0, A = 0) g_n^s(A = 0 | S = 0, W) P_n(S \in \{0,s\})$ to obtain a targeted estimate $Q^\#_n(S = 0, A, S, W)$. Our updated estimate

$$\tilde{\Psi}_s^\#(P_n) = \frac{1}{n} \sum_{i=1}^n I(S_i = 0, W_i) Q^\#_n(S_i = 0, 0, W_i)$$

Then, our TMLE estimate of the bias

$$\hat{\Psi}_s^\#(P_n) = \tilde{\Psi}_s^\#(P_n) - \hat{\Psi}_s^\#(P_n)$$

10.3 Appendix 3: Proof of Theorem 1

Conditions for Theorem 1:
1. Convergence of Second-Order Remainers

(a) Second-order remainder for ES-CVTMLE: \[
\frac{1}{\sqrt{n}} \sum_{v=1}^{V} (R_s(P_{n,v}, P_0)) = o_P((nS_{n(0,s)})^{-1/2}).
\]

(b) Second-order remainder for \(Z_{n}(s,v)\): \[
R_{s}^{(s)}(P_{n,v}, P_0) = \psi_{s}^{(s)}(P_{n,v}) + D_{n,v}^{(s)}(P_{n,v}, P_0)
\]

(c) Second-order remainder for \(Z_{n}^{#}(s,v)\): \[
R_{s}^{(s)}(P_{n,v}, P_0) = \psi_{s}^{(s)}(P_{n,v}) + D_{n,v}^{(s)}(P_{n,v}, P_0)
\]

2. Consistency of EIC Estimation: For each \(s \in \{0, ..., K\}, v \in \{1, ..., V\}, P_{0}\) is \(\hat{\Phi}_{s}(P_{n,v})\), \(\hat{\Phi}_{s}(P_{n,v})\) and \(\hat{\Phi}_{s}(P_{n,v})\)

3. Donnder Class Condition for Bias Term Estimation: \{\(D_{n,v}^{(s)}(P_{n,v}) : P \in M\) and \(D_{n,v}^{(s)}(P_{n,v}) : P \in M\) are \(P_{D_{n,v}}\)-Donnder, where \(M\) defines the set of possible distributions \(P\) (van der Laan and Rose, 2011).

Proof of Theorem 1:

\[
\sqrt{n}(\psi_{s} - \psi_{s,0}) = \frac{1}{\sqrt{n}} \sum_{v=1}^{V} (\psi_{s}^{(s)}(P_{n,v}) - \psi_{s}^{(s)}(P_{0})) =
\]

\[
\sqrt{n}(\sum_{v=1}^{V} (P_{n,v} - P_0))D_{n,v}^{(s)}(P_{n,v}, P_0) + (P_{n,v} - P_0)(D_{n,v}^{(s)}(P_{n,v}) - D_{n,v}^{(s)}(P_{0})) + R_{s}^{(s)}(P_{n,v}, P_0)
\]

by assumption of Conditions 1 and 2. Define

\[
Z_{n}^{(s)}(s,v) = \sqrt{n}(P_{n,v} - P_0)D_{n,v}^{(s)}(P_0)
\]

By the Central Limit Theorem, across all \(s\) and \(v\), the vector \(Z_{n}^{(s)}(s,v) \sim N(0, \Sigma^{(s)}P_{0})\)

In order to understand the behavior of \(\sqrt{n}(\psi_{s} - \psi_{s,0})\), we must also understand the behavior of \(\frac{1}{\sqrt{n}} (\hat{\Phi}_{s}(P_{n,v}) - \psi_{s}^{(s)}(P_{0}))\), which depends on the behavior of either \(Z_{n}^{(s)}(s,v)\) or \(Z_{n}^{#}(s,v)\) or \(Z_{n}^{#}(s,v)\).

For the standardized bias terms estimated on experiment-selection sets,

\[
Z_{n}^{(s)}(s,v) = \frac{1}{\sqrt{n}}(\hat{\Phi}_{s}(P_{n,v}) - \psi_{s}^{(s)}(P_{0}))
\]

\[
= \frac{1}{\sqrt{n}}((P_{n,v} - P_0)D_{n,v}^{(s)}(P_{n,v}, P_0) + (P_{n,v} - P_0)(D_{n,v}^{(s)}(P_{n,v}) - D_{n,v}^{(s)}(P_{0})) + R_{s}^{(s)}(P_{n,v}, P_0))
\]

by assumption of Conditions 1, 2, and 3. If \(\hat{\Phi}_{s}\) is included in the bias estimation, then \(D_{n,v}^{(s)}(P_{n,v}, P_0) + D_{n,v}^{(s)}(P_{n,v}, P_0)\).

By the Central Limit Theorem, \(Z_{n}^{#}(s,v)\) and \(Z_{n}^{#}(s,v)\) also converge to normal distributions. Across all \(s\) and \(v\).
We also simulate two covariates, $W_1$ and $W_2$, as

$$Z_n^\# = (Z_n^\#(s, v^c) : s, v) \sim \mathcal{N}(\theta, \Sigma^\#)$$
$$Z_n^\# + \Phi = (Z_n^\# + \Phi(s, v^c) : s, v) \sim \mathcal{N}(0, \Sigma^\# + \Phi)$$
$$\tilde{Z} = (Z^\#, Z^1) \sim \mathcal{N}(\theta, \tilde{\Sigma})$$

or $\tilde{Z} = (Z^\# + \Phi, Z^1) \sim \mathcal{N}(0, \tilde{\Sigma})$

where $\tilde{\Sigma}$ is defined in Section 5.1. The limit distribution of the experiment-selector CV-TMLE is then defined by sampling from $\tilde{Z}$, calculating

$$\tilde{s}^*(v^c) = \arg\min_s \sigma^2_{D_{\Psi, v^c}^s} + (Z^\#(s, v^c) + \sqrt{n}\Psi^\#(P_0))^2$$

or

$$\tilde{s}^{**}(v^c) = \arg\min_s \sigma^2_{D_{\Psi, v^c}^s} + (Z^\# + \Phi(s, v^c) + \sqrt{n}(\Psi^\#(P_0) + \Phi_s(P_0)))^2$$

and finally calculating

$$\sqrt{n}(\psi_n - \psi_{n,0}) = \frac{1}{\sqrt{n}} \sum_{v=1}^V (P_{n,v} - P_0) D_{\Psi, (v^c)}^s(P_0) + o_P(1) = \frac{1}{V} \sum_{v=1}^V (Z^1(\tilde{s}^*(v^c), v)) + o_P(1)$$

or

$$\sqrt{n}(\psi_n - \psi_{n,0}) = \frac{1}{\sqrt{n}} \sum_{v=1}^V (P_{n,v} - P_0) D_{\Psi, (v^c)}^{**}(P_0) + o_P(1) = \frac{1}{V} \sum_{v=1}^V (Z^1(\tilde{s}^{**}(v^c), v)) + o_P(1)$$

$\sqrt{n}(\psi_n - \psi_{n,0})$ thus converges to a mixture of normal distributions.

### 10.4 Appendix 4: Data Generating Process for Simulation

As described in Section 6.1, four datasets were simulated as follows: 1) an “RCT” dataset of 150 observations with $S = 0$, $A = 1$ randomized with probability 0.67, and bias terms $B_1$ and $B_2$ equal to zero, 2) a “real-world” dataset of 500 observations with $S = 1$, $A = 0$, and bias terms $B_1$ and $B_2$ equal to zero, 3) “RWD” of 500 observations with $S = 2$, $A = 0$, and $B_1 + B_2 \approx B$, and 4) “RWD” of 500 observations with $S = 3$, $A = 0$, and $B_1 + B_2 \approx 5 \times B$. For this simulation, biased RWD could be included if it is approximately $\sqrt{\frac{\sigma^2_{D_{\Psi, v^c}^s} - \sigma^2_{D_{\Psi, (v^c), n,v^c}}}{n}} = B = 0.21$.

We generate $B_1$ and $B_2$ as described below:

| Dataset | $B_1$ | $B_2$ |
|---------|-------|-------|
| $S = 0$ | 0     | 0     |
| $S = 1$ | 0     | 0     |
| $S = 2$ | $N(\frac{3}{4}B, 0.02^2)$ | $N(\frac{1}{4}B, 0.02^2)$ |
| $S = 3$ | $N(\frac{3}{4} \times 5 \times B, 0.02^2)$ | $N(\frac{1}{4} \times 5 \times B, 0.02^2)$ |

We also simulate two covariates, $W_1$ and $W_2$, as $N(0, 1)$. The outcome $Y$ and NCO are then simulated as

$$Y = -3 + 2 \times W_1 + W_2 - 0.6 \times A + B_1 + B_2 + U_Y$$
$$NCO = -2 + W_1 + 2 \times W_2 + B_1 + U_{nco}$$

with $U_Y \sim N(0, 1.5^2)$ and $U_{nco} \sim N(0, 1.5^2)$. The true causal ATE of $A$ on $Y$ in this simulation is $-0.6$. The NCO is affected by $B_1$ but not $B_2$, and so the U-comparability and additive equi-confounding assumptions do not completely hold in this case.

For the TMLE-based methods used in the simulation, we use linear regression for the outcome regression and a candidate library for the treatment mechanism consisting of lasso regression (Friedman et al., 2010) or the mean. We use 10-fold cross-validation and target the weights as described above. When only $S = 0$ data is considered, we use the true randomization probability for $g(A|W)$.

### 10.5 Appendix 5: References for Appendices

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