Supplementary material for

Extending inferences from a randomized trial to a new target population

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A Nested trial designs

In this section of the Appendix, we collect results on the identification and estimation of potential (counterfactual) outcome means in the target population of non-participants in nested-trial designs. In these designs, the randomized trial is embedded in a cohort (e.g., a cohort of trial eligible individuals, including those who were offered and refused participation in the trial). We address non-nested trial designs in Appendix Section B.

Throughout, X are baseline covariates; S is a binary indicator for trial participation ($S = 1$ for participants in the randomized trial; $S = 0$ for non-participants); A is the assigned treatment; and Y is the outcome of interest.

A.1 Identification in nested trial designs

A.1.1 Identifiability conditions

We now discuss sufficient conditions for identifying the mean of the potential outcomes under each treatment a in the target population, $\mathrm{E}[Y^a|S=0]$.

(1) Consistency of potential outcomes: for every i, if $A_i = a$, then $Y_i = Y_i^a$.

(2) Conditional exchangeability in mean over A in the randomized population: $\mathrm{E}[Y^a|X=x, S=1, A=a] = \mathrm{E}[Y^a|X=x, S=1]$ for every x with positive joint density $f_{X,S}(x, S=1)$.

(3) Positivity of treatment assignment: $\Pr[A=a|X=x, S=1] > 0$, for every a and every x with positive joint density $f_{X,S}(x, S=1) > 0$.

(4) Conditional exchangeability in mean over S: $\mathrm{E}[Y^a|X=x, S=1] = \mathrm{E}[Y^a|X=x, S=0]$, for every a and every x with positive joint density $f_{X,S}(x, S=0)$.

(5) Positivity of trial participation: $\Pr[S = 1|X = x] > 0$, for every x with positive joint density $f_{X,S}(x, S = 0) > 0$.

A.1.2 Identification by the g-formula

Under the identifiability conditions above, the potential outcome mean in the target population is identified:

$$\begin{aligned} \mathrm{E}[Y^a|S=0] &= \mathrm{E}\left[\mathrm{E}[Y^a|X,S=0]\middle|S=0\right] \\ &= \mathrm{E}\left[\mathrm{E}[Y^a|X,S=1]\middle|S=0\right] \\ &= \mathrm{E}\left[\mathrm{E}[Y^a|X,S=1,A=a]\middle|S=0\right] \\ &= \mathrm{E}\left[\mathrm{E}[Y|X,S=1,A=a]\middle|S=0\right]. \end{aligned} \tag{A.1}$$

Thus, the observed data functional

$$\mu(a) \equiv \mathrm{E}\left[\mathrm{E}[Y|X,S=1,A=a]\middle|S=0\right]$$

has a causal interpretation as the potential outcome mean among non-participants, $\mathrm{E}[Y^a|S = 0]$, provided the identifiability conditions hold.

A.1.3 Identification by inverse odds weighting

We will now show that $\mu(a)$ has an inverse odds (IO) weighting re-expression.

$$\begin{aligned}
\mu(a) &= \mathrm{E}\left[\,\mathrm{E}[Y|X,S=1,A=a]\big|S=0\right] \\
&= \frac{1}{\Pr[S=0]}\,\mathrm{E}\left[(1-S)\,\mathrm{E}[Y|X,S=1,A=a]\right] \\
&= \frac{1}{\Pr[S=0]}\,\mathrm{E}\left[\,\Pr[S=0|X]\,\mathrm{E}[Y|X,S=1,A=a]\right] \\
&= \frac{1}{\Pr[S=0]}\,\mathrm{E}\left[\frac{\Pr[S=0|X]\,\mathrm{E}[I(S=1,A=a)Y|X]}{\Pr[S=1|X]\,\Pr[A=a|X,S=1]}\right] \\
&= \frac{1}{\Pr[S=0]}\,\mathrm{E}\left[\,\mathrm{E}\left[\frac{I(S=1,A=a)Y\,\Pr[S=0|X]}{\Pr[S=1|X]\,\Pr[A=a|X,S=1]}\Big|X\right]\right] \\
&= \frac{1}{\Pr[S=0]}\,\mathrm{E}\left[\frac{I(S=1,A=a)Y\,\Pr[S=0|X]}{\Pr[S=1|X]\,\Pr[A=a|X,S=1]}\right].
\end{aligned} \tag{A.2}$$

Note that the above derivation only requires the positivity conditions but does not require any of the identifiability conditions that involve potential (counterfactual) outcomes. Thus, under positivity,

$$\mu(a) = \frac{1}{\Pr[S=0]}\,\mathrm{E}\left[\frac{I(S=1,A=a)Y\,\Pr[S=0|X]}{\Pr[S=1|X]\,\Pr[A=a|X,S=1]}\right], \tag{A.3}$$

even if $\mu(a)$ does not have a causal interpretation.

Last, it is useful to note that under positivity,

$$\begin{aligned}
\mathrm{E}\left[\frac{I(S=1,A=a)\,\Pr[S=0|X]}{\Pr[S=1|X]\,\Pr[A=a|X,S=1]}\right] &= \mathrm{E}\left[\frac{\Pr[S=0|X]\,\mathrm{E}[I(S=1,A=a)|X]}{\Pr[S=1|X]\,\Pr[A=a|X,S=1]}\right] \\
&= \mathrm{E}\left[\,\Pr[S=0|X]\right] \\
&= \Pr[S=0].
\end{aligned} \tag{A.4}$$

Using (A.3) and (A.4) we obtain another IO weighting re-expression for $\mu(a)$,

$$\mu(a) = \left\{ \mathrm{E}\left[\frac{I(S=1, A=a)\Pr[S=0|X]}{\Pr[S=1|X]\Pr[A=a|X, S=1]} \right] \right\}^{-1} \mathrm{E}\left[\frac{I(S=1, A=a)Y\Pr[S=0|X]}{\Pr[S=1|X]\Pr[A=a|X, S=1]} \right]. \tag{A.5}$$

A.2 Identification under conditional exchangeability in measure

Suppose that we replace the assumption of conditional exchangeability in mean over S (i.e., assumption **(4)**, above) with the following assumption of conditional exchangeability in measure:

(4′) Conditional exchangeability in measure over S: $\mathrm{E}[Y^a - Y^{a'}|X = x, S = 1] = \mathrm{E}[Y^a - Y^{a'}|X = x, S = 0]$, for every pair of treatments a, a' and every x with positive joint density $f_{X,S}(x, S = 0) > 0$.

The assumption of conditional exchangeability in measure is weaker than the assumption of conditional exchangeability in mean, in the sense that conditional exchangeability in mean implies conditional exchangeability in measure, but the converse is not true.

We will now show that the average treatment effect among non-participants, $\mathrm{E}[Y^a - Y^{a'}|S = 0]$ is identifiable under exchangeability in measure (i.e., under assumptions **(1)** through **(3)**, **(4′)**, and **(5)**).

$$
\begin{aligned}
\mathrm{E}[Y^a - Y^{a'}|S=0] &= \mathrm{E}\left[\mathrm{E}[Y^a - Y^{a'}|X, S=0]\middle|S=0\right] \\
&= \mathrm{E}\left[\mathrm{E}[Y^a - Y^{a'}|X, S=1]\middle|S=0\right] \\
&= \mathrm{E}\left[\mathrm{E}[Y^a|X, S=1] - \mathrm{E}[Y^{a'}|X, S=1]\middle|S=0\right] \\
&= \mathrm{E}\left[\mathrm{E}[Y^a|X, S=1, A=a] - \mathrm{E}[Y^{a'}|X, S=1, A=a']\middle|S=0\right] \\
&= \mathrm{E}\left[\mathrm{E}[Y|X, S=1, A=a] - \mathrm{E}[Y|X, S=1, A=a']\middle|S=0\right].
\end{aligned} \tag{A.6}
$$

This result reflects the intuition that we should be able to transport average treatment effects if conditioning on X captures all effect modifiers that are differentially distributed between trial participants and non-participants on the absolute difference scale.

Under exchangeability in measure we can identify average treatment effects but we cannot identify the individual potential outcome means. Because these means are of inherent scientific and policy interest, in the remainder of this appendix we focus on them.

A.3 Estimation in nested trial designs

In nested trial designs, the data consist of realizations of $(X_i, S_i, S_i \times A_i, S_i \times Y_i)$, $i = 1, \ldots, n$, where n is the total number of individuals in a cohort (consisting of both trial participants and non-participants) and we define $n_{\text{RCT}} = \sum_{i=1}^{n} S_i$ and $n_{\text{obs}} = \sum_{i=1}^{n}(1 - S_i)$.

OM: Using the identification result in (A.1) we obtain the outcome model-based estimator,

$$
\widehat{\mu}_{\text{OM}}(a) = \left\{ \sum_{i=1}^{n}(1 - S_i) \right\}^{-1} \sum_{i=1}^{n}(1 - S_i) g_a(X_i; \widehat{\theta}), \tag{A.7}
$$

where $g_a(X;\widehat{\theta})$ is an estimator for $\mathrm{E}[Y|X, S=1, A=a]$.

Suppose that $g_a(X;\widehat{\theta})$ has a well-defined limit, $g_a(X;\theta^*)$. When the model for the expectation of the outcome is correctly specified,

$$g_a(X;\widehat{\theta}) \xrightarrow{p} g_a(X;\theta^*) = \mathrm{E}[Y|X, S=1, A=a],$$

so that

$$\begin{aligned}
\widehat{\mu}_{\mathrm{OM}}(a) &\xrightarrow{p} \frac{\mathrm{E}\left[\,\mathrm{E}[Y|X, S=1, A=a](1-S)\right]}{\Pr[S=0]} \\
&= \frac{\mathrm{E}\left[\,\mathrm{E}[Y|X, S=1, A=a]\middle|S=0\right]\Pr[S=0]}{\Pr[S=0]} \\
&= \mu(a).
\end{aligned}$$

IOW1: The first IO weighting estimator we consider is based on (A.3),

$$\widehat{\mu}_{\mathrm{IOW1}}(a) = \left\{\sum_{i=1}^{n}(1-S_i)\right\}^{-1}\sum_{i=1}^{n}\widehat{w}_a(X_i, S_i, A_i)Y_i, \tag{A.8}$$

where

$$\widehat{w}_a(X_i, S_i, A_i) = I(S_i=1, A_i=a) \times \frac{1-p(X_i;\widehat{\beta})}{p(X_i;\widehat{\beta})e_a(X_i;\widehat{\gamma})},$$

$p(X;\widehat{\beta})$ is an estimator for $\Pr[S=1|X]$, and $e_a(X;\widehat{\gamma})$ is an estimator for $\Pr[A=a|X, S=1]$.

Because the treatment assignment mechanism in the trial is known by design, we can always use an estimator $e_a(X;\widehat{\gamma})$ based on a parametric model $e_a(X;\gamma)$ for $\Pr[A=a|X, S=$

1] that has well-defined limit $e_a(X;\gamma^*)$, such that

$$e_a(X;\widehat{\gamma}) \xrightarrow{p} e_a(X;\gamma^*) = \Pr[A=a|X,S=1].$$

This would certainly be the case when using, for example, a correctly specified logistic regression model for the probability of treatment in the trial with parameters estimated via standard maximum likelihood methods.

Suppose that $p(X;\widehat{\beta})$ also has a well-defined limit $p(X;\beta^*)$. When the model for the probability of trial participation is also correctly specified,

$$p(X;\widehat{\beta}) \xrightarrow{p} p(X;\beta^*) = \Pr[S=1|X],$$

so that

$$\begin{aligned}\widehat{\mu}_{\text{IOW1}}(a) &\xrightarrow{p} \frac{1}{\Pr[S=0]}\,\mathrm{E}\left[\frac{I(S=1,A=a)Y\Pr[S=0|X]}{\Pr[S=1|X]\Pr[A=a|X,S=1]}\right] \\ &= \mu(a).\end{aligned}$$

The equality holds because

$$\begin{aligned}\mathrm{E}\left[\frac{I(S=1,A=a)Y\Pr[S=0|X]}{\Pr[S=1|X]\Pr[A=a|X,S=1]}\right] &= \mathrm{E}\left[\frac{\Pr[S=0|X]\,\mathrm{E}[I(S=1,A=a)Y|X]}{\Pr[S=1|X]\Pr[A=a|X,S=1]}\right] \\ &= \mathrm{E}\left[\Pr[S=0|X]\,\mathrm{E}[Y|X,S=1,A=a]\right] \\ &= \mathrm{E}\left[(1-S)\,\mathrm{E}[Y|X,S=1,A=a]\right] \\ &= \mathrm{E}\left[\mathrm{E}[Y|X,S=1,A=a]\big|S=0\right]\Pr[S=0] \\ &= \mu(a)\Pr[S=0].\end{aligned}$$

IOW2: We obtain another IO weighting estimator using the identification result in (A.5),

$$\widehat{\mu}_{\text{IOW2}}(a) = \left\{ \sum_{i=1}^{n} \widehat{w}_a(X_i, S_i, A_i) \right\}^{-1} \sum_{i=1}^{n} \widehat{w}_a(X_i, S_i, A_i) Y_i, \tag{A.9}$$

with $\widehat{w}_a(X_i, S_i, A_i)$ defined as for IOW1.

When the model for the probability of trial participation is correctly specified, IOW2 converges in probability to the same limit as IOW1, because

$$\begin{aligned} \frac{1}{n} \sum_{i=1}^{n} \widehat{w}_a(X_i, S_i, A_i) &\xrightarrow{p} \mathrm{E}\left[\frac{\big(1 - p(X; \beta^*)\big) I(S = 1, A = a)}{p(X; \beta^*) e_a(X; \gamma^*)} \right] \\ &= \mathrm{E}\left[\frac{\Pr[S = 0|X] I(S = 1, A = a)}{\Pr[S = 1|X] \Pr[A = a|X, S = 1]} \right] \\ &= \Pr[S = 0], \end{aligned}$$

where the first equality follows from correct model specification and the second equality follows from the result in (A.4).

Influence function: Write the observed data functional as $\mu_p(a) = \mathrm{E}_p\big[\mathrm{E}_p[Y|X, A = a, S = 1]\big|S = 0\big]$, where p emphasizes the dependence on the law of the observed data. The first order influence function for $\mu_p(a)$ is

$$\begin{aligned} M^1_{p_0}(a) = \frac{1}{\Pr_{p_0}[S = 0]} \Bigg\{ I(S = 1, A = a) \frac{\Pr_{p_0}[S = 0|X]}{\Pr_{p_0}[S = 1, A = a|X]} \Big\{ Y - \mathrm{E}_{p_0}[Y|X, S = 1, A = a] \Big\} \\ + (1 - S) \Big\{ \mathrm{E}_{p_0}[Y|X, S = 1, A = a] - \mu_{p_0}(a) \Big\} \Bigg\}, \end{aligned}$$

where the 0 subscript indicates the "true" law. Of note, this result suggests that, unless one is willing to make assumptions beyond the identifiability conditions in Subsection A.1.1,

estimators of $\mathrm{E}[Y^a|S=0]$ do not need treatment and outcome data from the sample of the target population (i.e., individuals with $S=0$) (see [1] for a similar observation).

The influence function $M_{p_0}^1(a)$ implies the following *generic* in-sample one-step augmented IO weighting estimator for $\mu_p(a)$:

$$\widehat{\mu}(a) = \frac{1}{n\widehat{\Pr}[S=0]} \sum_{i=1}^{n} \left\{ I(S_i=1, A_i=a) \frac{1-\widehat{p}(X_i)}{\widehat{p}(X_i)\widehat{e}_a(X_i)} \Big\{ Y_i - \widehat{g}_a(X_i) \Big\} + (1-S_i)\widehat{g}_a(X_i) \right\},$$

where $\widehat{\Pr}[S=0]$ is the estimated proportion of non-participants, and $\widehat{p}(X)$, $\widehat{e}_a(X)$, and $\widehat{g}_a(X)$ are generic estimators for $\Pr[S=1|X]$, $\Pr[A=a|X,S=1]$, and $\mathrm{E}[Y|X,S=1,A=a]$, respectively. We refer to this estimator as "generic" because we have not specified the way the working models for the conditional probability of trial participation or the conditional outcome mean are estimated.

DR1: The first doubly robust estimator in the main text of the tutorial,

$$\widehat{\mu}_{\mathrm{DR1}}(a) = \left\{ \sum_{i=1}^{n} (1-S_i) \right\}^{-1} \sum_{i=1}^{n} \left\{ \widehat{w}_a(X_i, S_i, A_i) \Big\{ Y_i - g_a(X_i; \widehat{\theta}) \Big\} + (1-S_i) g_a(X_i; \widehat{\theta}) \right\}, \quad \text{(A.10)}$$

is obtained from the generic augmented Io estimator, using parametric models to estimate conditional probabilities and conditional expectations.

Double robustness of DR1: Provided the limits of the working models exist (even if the

models are misspecified), DR1 converges to

$$\widehat{\mu}_{\text{DR1}}(a) \xrightarrow{p} \frac{1}{\Pr[S=0]}\Bigg\{\mathrm{E}\left[\frac{1-p(X;\beta^*)}{p(X;\beta^*)e_a(X;\gamma^*)}I(S=1,A=a)Y\right] - \mathrm{E}\left[\frac{1-p(X;\beta^*)}{p(X;\beta^*)e_a(X;\gamma^*)}I(S=1,A=a)g_a(X;\theta^*)\right] + \mathrm{E}\left[(1-S)g_a(X;\theta^*)\right]\Bigg\}.$$

We now consider two cases with respect to potential misspecification of the working models for the probability of treatment and the expectation of the outcome.

Case 1: $p(X;\beta)$ ***correctly specified;*** $g_a(X;\theta)$ ***incorrectly specified:*** following the argument for estimator IOW1, the first term in the bracketed part of the above expression converges to $\mathrm{E}\left[\mathrm{E}[Y|X,S=1,A=a]\middle|S=0\right]\Pr[S=0] = \mu(a)\Pr[S=0]$; by iterated expectation, the sum of the other two terms converges to 0.

Case 2: $g_a(X;\theta)$ ***correctly specified;*** $p(X;\beta)$ ***incorrectly specified:*** following the argument for the OM estimator, the last term in the bracketed part of the above expression converges to $\mathrm{E}\left[\mathrm{E}[Y|X,S=1,A=a]\middle|S=0\right]\Pr[S=0] = \mu(a)\Pr[S=0]$; by iterated expectation, the sum of the other two terms converges to 0.

DR2: The second augmented IO weighting estimator was defined as

$$\widehat{\mu}_{\text{DR2}}(a) = \left\{\sum_{i=1}^{n}\widehat{w}_a(X_i,S_i,A_i)\right\}^{-1}\sum_{i=1}^{n}\widehat{w}_a(X_i,S_i,A_i)\left\{Y_i - g_a(X_i;\widehat{\theta})\right\} + \left\{\sum_{i=1}^{n}(1-S_i)\right\}^{-1}\sum_{i=1}^{n}(1-S_i)g_a(X_i;\widehat{\theta}). \tag{A.11}$$

When the model for the probability of trial participation is correctly specified, DR2 converges

in probability to the same limit as DR1 because of the result in (A.4). When the model for the expectation of the outcome is correctly specified, DR2 converges in probability to the same limit as DR1 because, by iterated expectation, the first term in equation (A.11) converges to 0.

DR3: The third augmented IO weighting estimator is

$$\widehat{\mu}_{\text{DR3}}(a) = \left\{ \sum_{i=1}^{n} (1 - S_i) \right\}^{-1} \sum_{i=1}^{n} (1 - S_i) g_a(X_i; \widehat{\theta}_{\text{w}}), \tag{A.12}$$

where $\widehat{\theta}_{\text{w}}$ is the vector of estimated parameters from a weighted outcome regression with weights $\widehat{w}_a(X_i, S_i, A_i)$. The consistency and double robustness properties of DR3 follow from properties of quasi-likelihood estimation in linear exponential families [2] and weighted optimization arguments [3].

A.4 Asymptotic distribution

Using results from our earlier work [4], we now give the asymptotic distribution of the generic estimator $\widehat{\mu}(a)$.

We define

$$\widehat{\eta} = \left\{ \frac{1}{n} \sum_{i=1}^{n} I(S_i = 0) \right\}^{-1},$$

so that $\widehat{\eta} \xrightarrow{p} \eta^* = \Pr[S = 0]^{-1}$. We can now re-write the generic doubly robust estimator as

$$\widehat{\mu}(a) = \frac{\widehat{\eta}}{n} \sum_{i=1}^{n} \left\{ I(S_i = 1, A_i = a) \frac{1 - \widehat{p}(X_i)}{\widehat{p}(X_i)\widehat{e}_a(X_i)} \left\{ Y_i - \widehat{g}_a(X_i) \right\} + (1 - S_i)\widehat{g}_a(X_i) \right\}, \tag{A.13}$$

where the estimators $\widehat{p}(X)$, $\widehat{e}_a(X)$, and $\widehat{g}_a(X)$ have corresponding large-sample limits $p^*(X)$, $e_a^*(X)$, and $g_a^*(X)$ (assumed to exist).

For general functions $\eta', g_a'(X), p'(X)$, and $e_a'(X)$, we define

$$H\big(\eta', g_a'(X), p'(X), e_a'(X)\big) = \eta'\left\{ I(S=1, A=a)\frac{1-p'(X)}{p'(X)e_a'(X)}\Big\{Y - g_a'(X)\Big\} + (1-S)g_a'(X)\right\}.$$

Following [5], for any function q and random variable W, we define $\mathbb{P}_n(q) = n^{-1}\sum_{i=1}^{n} q(W_i)$ and $\mathbb{G}_n(q) = \sqrt{n}\Big(\mathbb{P}_n(q) - \mathrm{E}\left[q(W)\right]\Big)$. Using this notation,

$$\widehat{\mu}(a) = \mathbb{P}_n H\big(\widehat{\eta}, \widehat{g}_a(X), \widehat{p}(X), \widehat{e}_a(X)\big).$$

Suppose that the following assumptions hold:

1. The sequence $H\big(\widehat{\eta}, \widehat{g}_a(X), \widehat{p}(X), \widehat{e}_a(X)\big)$ and the limit $H\big(\eta^*, g_a^*(X), p^*(X), e_a^*(X)\big)$ belong to a Donsker class.

2. $\Big|\Big|H\big(\widehat{\eta}, \widehat{g}_a(X), \widehat{p}(X), \widehat{e}_a(X)\big) - H\big(\eta^*, g_a^*(X), p^*(X), e_a^*(X)\big)\Big|\Big|_2 \xrightarrow{p} 0.$

3. $\mathrm{E}\left[\Big(H\big(\eta^*, g_a^*(X), p^*(X), e_a^*(X)\big)\Big)^2\right] < \infty.$

4. At least one of the following two conditions holds: $\widehat{p}(X) \xrightarrow{p} \Pr[S=1|X]$, or $\widehat{g}_a(X) \xrightarrow{p} \mathrm{E}[Y|X, S=1, A=a]$.

5. The estimator $\widehat{e}_a(X)$ is $\sqrt{n}$-consistent.

Under these assumptions, $\widehat{\mu}(a) \xrightarrow{p} \mu(a) = \mathrm{E}\left[\,\mathrm{E}[Y|X, S=1, A=a]\big|S=0\right]$ and

$$\sqrt{n}\big(\widehat{\mu}(a) - \mu(a)\big) = \mathbb{G}_n\Big(H\big(\eta^*, g_a^*(X), p^*(X), e_a^*(X)\big)\Big) + R + o_P(1), \tag{A.14}$$

where

$$R \leq \sqrt{n} O_P\Big(\big|\big|\widehat{p}(X) - \Pr[S=1|X]\big|\big|_2 \big|\big|\widehat{g}_a(X) - \mathrm{E}[Y|X, S=1, A=a]\big|\big|_2\Big).$$

The right hand-side of expression (A.14) describes how the asymptotic distribution of $\widehat{\mu}(a)$ depends on the estimators $\widehat{p}(X)$ and $\widehat{g}_a(X)$.

The first term is asymptotically normal with variance of the limiting distribution equal to $\mathrm{E}\left[\left\{H\big(\eta^*, g_a^*(X), p^*(X), e_a^*(X)\big) - \mu(a)\right\}^2\right]$.

The second term of (A.14) drives the behavior of the estimator. In particular, if $\widehat{p}(X)$ and $\widehat{g}_a(X)$ are both consistent estimators of $\Pr[S=1|X]$ and $\mathrm{E}[Y|X, S=1, A=a]$, respectively, and converge to their limiting values at rates fast enough for the second term of (A.14) to be $o_P(1)$, then $\widehat{\mu}(a)$ is $\sqrt{n}$-consistent, asymptotically normal, and semiparametric efficient. That is to say, $\sqrt{n}\big(\widehat{\mu}(a) - \mu(a)\big) \xrightarrow{d} \mathcal{N}(0, \sigma^2)$, with

$$\begin{aligned}
\sigma^2 &= \mathrm{E}\left[\big(M_{p_0}^1(a)\big)^2\right] \\
&= \frac{1}{\big(\Pr_{p_0}[S=0]\big)^2}\left\{\mathrm{E}_{p_0}\left[\frac{\big(1 - \Pr_{p_0}[S=1|X]\big)^2 \operatorname{Var}_{p_0}[Y|X, S=1, A=a]}{\Pr_{p_0}[S=1|X]\Pr_{p_0}[A=a|X, S=1]}\right]\right. \\
&\qquad \left. + \mathrm{E}_{p_0}\left[(1-S)\Big(\mathrm{E}_{p_0}[Y|X, S=1, A=a] - \mu(a)\Big)^2\right]\right\}.
\end{aligned} \tag{A.15}$$

For example, that will be the case if both $\widehat{p}(X)$ and $\widehat{g}_a(X)$ are obtained from correctly spec-

ified parametric models. Note, however, that these desirable properties hold even when each of the estimators $\widehat{p}(X)$ and $\widehat{g}_a(X)$ converges at rate slower than the parametric $\sqrt{n}$-rate, for example, if both $\widehat{p}(X)$ and $\widehat{g}_a(X)$ are obtained using correctly specified generalized additive models [6, 7]. In order to use even more flexible estimation approaches (e.g., "machine learning" methods), the Donsker requirement can be relaxed by cross-fitting [8].

The asymptotic representation (A.14) shows that the rate of convergence of $\widehat{\mu}(a)$ is

$$||\widehat{\mu}(a) - \mu(a)||_2 = O_P\left(\frac{1}{\sqrt{n}} + \left|\left|\widehat{p}(X) - \Pr[S = 1|X]\right|\right|_2 \left|\left|\widehat{g}_a(X) - \mathrm{E}[Y|X, S = 1, A = a]\right|\right|_2\right).$$

It follows that if the combined rate of convergence for the estimators $\widehat{g}_a(X)$ and $\widehat{p}(X)$ is equal to $\sqrt{n}$, the estimator $\widehat{\mu}(a)$ is still $\sqrt{n}$ convergent, but no longer efficient. This is the case when one of the estimators is obtained by using a correctly specified generalized linear model and the other estimator is misspecified.

B Non-nested trial designs

As we have noted in the main text, the potential outcome mean in the target population of non-participants is of interest in both nested and non-nested trial designs (e.g., composite dataset designs). For simplicity, in the main text, we focused on identification and estimation in the context of nested trial designs. In this section of the Appendix, we discuss the sampling model underlying non-nested designs and show that, with minor modifications, identification and estimation results for nested trial designs can be extended to non-nested trial designs.

B.1 Sampling properties of the non-nested trial design

To understand the sampling model underlying composite dataset designs, consider the following setup: the research question of interest defines an actual population of individuals to whom the treatments of interest would be applied. We view this actual population as a simple random sample from an (infinite) superpopulation.[1]

In this setup, a non-nested trial design can be viewed as a biased sampling design where (1) all randomized individuals are sampled into the study, but (2) only a simple random sample of non-participants are sampled and (3) the sampling probability of non-participants is unknown.

Let D be an indicator for selection into the study ($D = 1$ for individuals contributing data; $D = 0$ for individuals not contributing data), the above sampling scheme can be formalized as follows: individuals in the actual population are sampled with sampling probabilities that

[1] From this perspective, the nested trial design can be viewed as taking a census of the actual population or as sampling that actual population with a sampling scheme that allows the identification of the marginal and conditional probability of trial participation in the superpopulation (see [9] and [10] for details).

depend on their trial participation status:

$$\Pr[D = 1|X, S = 1, A, Y] = 1;$$

$$\Pr[D = 1|X, S = 0, A, Y] = \Pr[D = 1|S = 0] = u,$$

where u is an *unknown* positive constant. Note that these sampling conditions imply that

$$D \perp\!\!\!\perp (X, A, Y)|S.$$

Readers familiar with cumulative incidence case-referent (case-control) studies with a secondary study base will be able to appreciate the parallel [11, 12]: the actual population is a cohort defined by the trial eligibility criteria; the trial participants are "cases" all of whom are sampled; and the non-participants are "controls," only some of whom are sampled, with unknown sampling probability.

B.2 Identification in non-nested trial designs

B.2.1 Identification by the g-formula

To see that $\mathrm{E}[Y^a|S = 0]$ is identifiable in composite dataset designs recall that, under the identifiability conditions in the main text,

$$\begin{aligned} \mu(a) &\equiv \mathrm{E}\left[\mathrm{E}[Y|X, S = 1, A = a]\middle|S = 0\right] \\ &= \int \mathrm{E}[Y|X = x, S = 1, A = a] dF_{X|S}(x|S = 0). \end{aligned} \tag{B.1}$$

Clearly, $\mathrm{E}[Y|X = x, S = 1, A = a]$ is identifiable in non-nested designs because all

randomized individuals are sampled into the study. The distribution $F_{X|S}(x|S=0)$ is also identifiable because, by the sampling properties of the design, $F_{X|S}(x|S=0) = F_{X|S,D}(x|S=0, D=1)$. Thus, under the sampling properties of the non-nested trial design, all the components of the integral in (B.1) are identifiable, and we have

$$\begin{aligned}\mu(a) &= \mathrm{E}\left[\,\mathrm{E}[Y|X, S=1, A=a]\big|S=0, D=1\right] \\ &= \int \mathrm{E}[Y|X=x, S=1, A=a] dF_{X|S,D}(x|S=0, D=1).\end{aligned} \tag{B.2}$$

B.2.2 Identification by IO weighting

We now consider identification using an IO weighting approach. Clearly, quantities involved in expression (A.3) are not identifiable in non-nested trial designs: for example, the marginal probability of not participating in the trial, $\Pr[S=0]$, and the inverse of the conditional odds of not participating in the trial, $\dfrac{\Pr[S=0|X]}{\Pr[S=1|X]}$, are not identifiable in non-nested designs. We will show, however, that replacing these quantities with the corresponding quantities that are identifiable under the biased sampling model results in an odds weighting re-expression that is equal to $\mu(a)$. Specifically, we will show that,

$$\mu(a) = \frac{1}{\Pr[S=0|D=1]}\,\mathrm{E}\left[\frac{I(S=1, A=a)Y\,\Pr[S=0|X, D=1]}{\Pr[S=1|X, D=1]\,\Pr[A=a|X, S=1]}\Big|D=1\right]. \tag{B.3}$$

The identifiability of all terms in right-hand-side of the above expression is fairly obvious, since all quantities are conditional on being sampled in the data ($D=1$). To see that the

identity holds, first note that

$$\begin{aligned}&\frac{1}{\Pr[S=0|D=1]}\,\mathrm{E}\left[\frac{I(S=1,A=a)Y\,\Pr[S=0|X,D=1]}{\Pr[S=1|X,D=1]\,\Pr[A=a|X,S=1]}\Big|D=1\right]\\&\quad=\frac{1}{\Pr[S=0,D=1]}\,\mathrm{E}\left[\frac{I(S=1,A=a)Y\,\Pr[S=0|X,D=1]}{\Pr[S=1|X,D=1]\,\Pr[A=a|X,S=1]}\right].\end{aligned}\tag{B.4}$$

where we have just multiplied and divided by $\Pr[D=1]$ and then used the fact that $I(S=1,D=1)=I(S=1)$ because all randomized individuals are sampled. Next, note that

$$\begin{aligned}\frac{\Pr[S=0|X,D=1]}{\Pr[S=1|X,D=1]}&=\frac{\Pr[S=0,D=1|X]}{\Pr[S=1,D=1|X]}\\&=\frac{\Pr[S=0|X]\,\Pr[D=1|X,S=0]}{\Pr[S=1|X]\,\Pr[D=1|X,S=1]}\\&=\frac{\Pr[S=0|X]}{\Pr[S=1|X]}\times\Pr[D=1|S=0],\end{aligned}\tag{B.5}$$

where the last equality follows because $D \perp\!\!\!\perp X|S=0$ and $\Pr[D=1|S=1]=1$, by design.

Combining (B.4) and (B.5), and using the result in (A.3), we obtain

$$\begin{aligned}&\frac{1}{\Pr[S=0|D=1]}\,\mathrm{E}\left[\frac{I(S=1,A=a)Y\,\Pr[S=0|X,D=1]}{\Pr[S=1|X,D=1]\,\Pr[A=a|X,S=1]}\Big|D=1\right]\\&\quad=\frac{\Pr[D=1|S=0]}{\Pr[S=0,D=1]}\,\mathrm{E}\left[\frac{I(S=1,A=a)Y\,\Pr[S=0|X]}{\Pr[S=1|X]\,\Pr[A=a|X,S=1]}\right]\\&\quad=\frac{1}{\Pr[S=0]}\,\mathrm{E}\left[\frac{I(S=1,A=a)Y\,\Pr[S=0|X]}{\Pr[S=1|X]\,\Pr[A=a|X,S=1]}\right]\\&\quad=\mu(a).\end{aligned}\tag{B.6}$$

A similar argument shows that a normalized version of the identification result is avail-

able. Specifically, that

$$\mu(a) = \left\{ \mathrm{E}\left[\frac{I(S=1, A=a)\Pr[S=0|X, D=1]}{\Pr[S=1|X, D=1]\Pr[A=a|X, S=1]} \Big| D=1 \right] \right\}^{-1} \times \mathrm{E}\left[\frac{I(S=1, A=a) Y \Pr[S=0|X, D=1]}{\Pr[S=1|X, D=1]\Pr[A=a|X, S=1]} \Big| D=1 \right]. \tag{B.7}$$

To see this, starting from the right-hand-side,

$$\begin{aligned}
&\left\{ \mathrm{E}\left[\frac{I(S=1, A=a)\Pr[S=0|X, D=1]}{\Pr[S=1|X, D=1]\Pr[A=a|X, S=1]} \Big| D=1 \right] \right\}^{-1} \times \\
&\qquad \mathrm{E}\left[\frac{I(S=1, A=a) Y \Pr[S=0|X, D=1]}{\Pr[S=1|X, D=1]\Pr[A=a|X, S=1]} \Big| D=1 \right] \\
&= \left\{ \mathrm{E}\left[\frac{I(S=1, A=a)\Pr[S=0|X, D=1]}{\Pr[S=1|X, D=1]\Pr[A=a|X, S=1]} \right] \right\}^{-1} \times \\
&\qquad \mathrm{E}\left[\frac{I(S=1, A=a) Y \Pr[S=0|X, D=1]}{\Pr[S=1|X, D=1]\Pr[A=a|X, S=1]} \right] \\
&= \left\{ \mathrm{E}\left[\frac{I(S=1, A=a)\Pr[S=0|X]}{\Pr[S=1|X]\Pr[A=a|X, S=1]} \right] \right\}^{-1} \times \\
&\qquad \mathrm{E}\left[\frac{I(S=1, A=a) Y \Pr[S=0|X]}{\Pr[S=1|X]\Pr[A=a|X, S=1]} \right] \\
&= \mu(a),
\end{aligned} \tag{B.8}$$

where the first equality follows from multiplying and dividing by $\Pr[D=1]$ and using the fact that the event $(S=1, D=1)$ is equivalent to the event $(S=1)$; the second from the result in (B.5); and third from the result in (A.5).

Another way to verify the result in (B.7) is to combine the result in (B.6) with the identity

$$\Pr[S=0|D=1] = \mathrm{E}\left[\frac{I(S=1, A=a)\Pr[S=0|X, D=1]}{\Pr[S=1|X, D=1]\Pr[A=a|X, S=1]} \Big| D=1 \right].$$

B.3 Non-nested trial designs as biased sampling designs

Before discussing the efficient influence function for $\mu(a)$ under the non-nested trial design, we examine the biased sampling model induced by the non-nested trial design.

Density under the biased sampling model. In the context of the analyses described in the tutorial, the sampling model for the observable data is

$$p(x, s, a, y) = p(s)p(x|s)p(a|x, s)p(y|x, s, a).$$

The non-nested design described in sub-section B.1 induces a biased sampling model [13],

$$q(x, s, a, y) = q(s)p(x|s)p(a|x, s)p(y|x, s, a).$$

Notice that the only difference between $q(x, s, a, y)$ and $p(x, s, a, y)$ is the substitution of $q(s)$ for $p(s)$ in the former, reflecting that all trial participants but only a subset of the non-participants are sampled. The terms for $p(x|s)$, $p(a|x, s)$, and $p(y|x, s, a)$ remain the same reflecting the sampling properties of the design.

Connection with the identification results in Subsection B.2 The ratio

$$\frac{p(x, s, a, y)}{q(x, s, a, y)} = \frac{p(s)}{q(s)},$$

suggests that inferences about the non-biased model could in principle be obtained under the biased sampling model by using weights equal to $\frac{p(S)}{q(S)}$, if the marginal probability of

trial participation was known. Of course, direct use of such weighting is not possible in the non-nested trial design, because $p(S)$ is not known and cannot be estimated in this design. Nevertheless, the functional $\mu(a)$ is identifiable in any design that can identify $p(x|s=0)$ and $p(y|x,s=1,a)$. That is precisely the case for non-nested trial designs, because the needed densities are components of $q(x,s,a,y)$. Furthermore, the IO weighting identification results in Subsection B.2 can also be directly related to the biased sampling model because $\frac{p(S)}{q(S)} \propto \frac{1}{\Pr[D=1|S]}$.

B.4 Estimation in non-nested trial designs

In non-nested trial designs, the data available for analysis are a combination of data from the randomized trial and data from a simple random sample from the target population. Specifically, the data available from the randomized trial are realizations of $(X_i, S_i=1, A_i, Y_i)$, $i=1,\ldots,n_{\text{RCT}}$; the data from the sample of non-participants are realizations of $(X_i, S_i=0)$, $i=1,\ldots,\widetilde{n}_{\text{obs}}$. The total number of sampled individuals contributing data to the analysis is $\widetilde{n} = n_{\text{RCT}} + \widetilde{n}_{\text{obs}}$. Note that the number of trial participants, n_{RCT}, is the same as in nested trial designs, because in non-nested trial designs all trial participants are sampled; but $\widetilde{n}_{\text{obs}} \neq n_{\text{obs}}$ and $\widetilde{n} \neq n$, because only a subset of the non-participants are sampled. We assume that the trial sample and the sample of non-participants are obtained separately (the latter via Bernoulli sampling [14,15] with unknown sampling probability $\Pr[D=1|S=0]$).

As we show now, the estimation results for nested-trial designs can be used for non-nested trial designs with only minor modifications. The key differences are that (1) the summations are over the $\widetilde{n}$ individuals contributing data to the analysis and (2) all working models

are estimated among the sampled individuals (e.g., the probability of trial participation is estimated conditional on having been sampled).

For completeness, we give expressions for the outcome model-based and IO weighting estimators. The next subsection discusses doubly robust estimation.

B.4.1 Estimation by g-formula

The outcome model-based estimator is

$$\widetilde{\mu}_{\text{OM}}(a) = \left\{ \sum_{i=1}^{\widetilde{n}} (1 - S_i) \right\}^{-1} \sum_{i=1}^{\widetilde{n}} (1 - S_i) g_a(X_i; \widehat{\theta}), \tag{B.9}$$

where $g_a(X; \widehat{\theta})$ is an estimator for $\mathrm{E}[Y|X, A = a, S = 1]$ (same as for nested trial designs).

B.4.2 Estimation by IO weighting

The first IO weighting estimator is

$$\widetilde{\mu}_{\text{IOW1}}(a) = \left\{ \sum_{i=1}^{\widetilde{n}} (1 - S_i) \right\}^{-1} \sum_{i=1}^{\widetilde{n}} \widetilde{w}_a(X_i, S_i, A_i) Y_i, \tag{B.10}$$

where $\widetilde{w}_a(X_i, S_i, A_i)$ is defined as

$$\widetilde{w}_a(X_i, S_i, A_i) = \frac{1 - h(X_i; \widetilde{\beta})}{h(X_i; \widetilde{\beta}) e_a(X_i; \widehat{\gamma})} \times I(S_i = 1, A_i = a).$$

Importantly, here $h(X; \widetilde{\beta})$ is an estimator for $\Pr[S = 1|X, D = 1]$ (not $\Pr[S = 1|X]$, which is unidentifiable in the non-nested trial design) and $e_a(X; \widehat{\gamma})$, as before, is an estimator for $\Pr[A = a|X, S = 1]$ (same as for nested trial designs). The weighting estimator with

normalized weights is

$$\widehat{\mu}_{\text{IOW2}}(a) = \left\{ \sum_{i=1}^{\widetilde{n}} \widetilde{w}_a(X_i, S_i, A_i) \right\}^{-1} \sum_{i=1}^{\widetilde{n}} \widetilde{w}_a(X_i, S_i, A_i) Y_i. \tag{B.11}$$

B.4.3 Doubly robust estimation

Influence function for non-nested trial designs. Using the arguments in [16], identification under the biased sampling model implies that influence functions for $\mu(a)$ under sampling from $q(x, s, a, y)$ are equivalent to those under sampling from $p(x, s, a, y)$, but with densities from $q(x, s, a, y)$ replacing those under $p(x, s, a, y)$ (see [17] for a similar argument in the context of matched cohort studies). Specifically, under the biased sampling model, the influence function of $\mu(a)$ is

$$\begin{aligned} M^1_{q_0}(a) = \frac{1}{\Pr_{q_0}[S=0]} \Bigg\{ & \frac{I(S=1, A=a) \Pr_{q_0}[S=0|X]}{\Pr_{q_0}[S=1|X] \Pr_{q_0}[A=a|X, S=1]} \\ & \times \Big\{ Y - \mathrm{E}_{q_0}[Y|X, S=1, A=a] \Big\} \\ & + (1-S) \Big\{ \mathrm{E}_{q_0}[Y|X, S=1, A=a] - \mu_{q_0}(a) \Big\} \Bigg\}. \end{aligned}$$

Note that, by design $\Pr_{q_0}[S=0] \neq \Pr_{p_0}[S=0]$ and $\dfrac{\Pr_{q_0}[S=0|X]}{\Pr_{q_0}[S=1|X]} \neq \dfrac{\Pr_{p_0}[S=0|X]}{\Pr_{p_0}[S=1|X]}$, but $\Pr_{q_0}[A=a|X, S=1] = \Pr_{p_0}[A=a|X, S=1]$, $\mathrm{E}_{q_0}[Y|X, S=1, A=a] = \mathrm{E}_{p_0}[Y|X, S=1, A=a]$, and, as shown in B.2.1, $\mu_{q_0}(a) = \mu_{p_0}(a)$.

The influence function above suggests an augmented IO weighting estimator of $\mu(a)$

appropriate for non-nested trial designs,

$$\widetilde{\mu}_{\text{DR1}}(a) = \left\{ \sum_{i=1}^{\widetilde{n}} (1-S_i) \right\}^{-1} \sum_{i=1}^{\widetilde{n}} \left\{ \widetilde{w}_a(X_i, S_i, A_i) \Big\{ Y_i - g_a(X_i; \widehat{\theta}) \Big\} + (1-S_i) g_a(X_i; \widehat{\theta}) \right\}, \quad \text{(B.12)}$$

where $g_a(X; \widehat{\theta})$ and $\widetilde{w}_a(X_i, S_i, A_i)$ are as defined above.

As for nested designs, we can normalize the weights to obtain

$$\begin{aligned} \widetilde{\mu}_{\text{DR2}}(a) = &\left\{ \sum_{i=1}^{\widetilde{n}} \widetilde{w}_a(X_i, S_i, A_i) \right\}^{-1} \sum_{i=1}^{\widetilde{n}} \widetilde{w}_a(X_i, S_i, A_i) \Big\{ Y_i - g_a(X_i; \widehat{\theta}) \Big\} \\ &+ \left\{ \sum_{i=1}^{\widetilde{n}} (1-S_i) \right\}^{-1} \sum_{i=1}^{\widetilde{n}} (1-S_i) g_a(X_i; \widehat{\theta}). \end{aligned} \quad \text{(B.13)}$$

Last, we can fit a model for the outcome conditional on covariates among trial participants, using a weighted regression with the weights $\widetilde{w}_a(X_i, S_i, A_i)$, and then marginalize the predictions $g_a(X_i; \widetilde{\theta}_{\text{w}})$ over the covariate distribution of non-participants,

$$\widetilde{\mu}_{\text{DR3}}(a) = \left\{ \sum_{i=1}^{\widetilde{n}} (1-S_i) \right\}^{-1} \sum_{i=1}^{\widetilde{n}} (1-S_i) g_a(X_i; \widetilde{\theta}_{\text{w}}), \quad \text{(B.14)}$$

where $\widetilde{\theta}_{\text{w}}$ is the vector of estimated parameters from the weighted outcome regression.

The double robustness of $\widetilde{\mu}_{\text{DR1}}(a)$ and $\widetilde{\mu}_{\text{DR2}}(a)$ follows from arguments entirely analogous to those for the nested trial design estimators $\widehat{\mu}_{\text{DR1}}(a)$ and $\widehat{\mu}_{\text{DR2}}(a)$. Similarly, $\widetilde{\mu}_{\text{DR3}}(a)$ is doubly robust when the outcome is modeled with a linear exponential family quasi-likelihood [2] and the canonical link function [3, 18].

C Simulation studies for nested trial designs

C.1 Complete results for continuous outcomes

In this sub-section we report the complete results of simulation studies for continuous outcomes. The relevant methods are described in the main text of the paper.

Table C1: Bias of estimators for $\mu(1)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for continuous outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	1.6545	0.0057	0.0745	-0.0023	0.0003	-0.0006	-0.0006
200	2000	0	1	2.2946	0.0169	0.1791	0.0043	0.0009	0.0007	0.0015
200	2000	1	0	1.6527	-0.0007	0.0691	-0.0041	-0.0057	-0.0055	-0.0059
200	2000	1	1	3.0592	0.0151	0.2424	-0.0030	0.0007	-0.0004	-0.0016
200	5000	0	0	1.7866	0.0020	0.0838	-0.0015	-0.0005	0.0004	0.0009
200	5000	0	1	2.5186	0.0155	0.2077	-0.0017	0.0054	0.0019	-0.0021
200	5000	1	0	1.7871	0.0090	0.0870	-0.0021	-0.0016	-0.0015	-0.0010
200	5000	1	1	3.3595	0.0033	0.2749	0.0052	0.0054	0.0050	0.0035
200	10000	0	0	1.8637	0.0092	0.0972	0.0027	0.0029	0.0030	0.0036
200	10000	0	1	2.6610	-0.0018	0.2281	-0.0021	-0.0073	-0.0055	-0.0044
200	10000	1	0	1.8603	0.0085	0.0965	-0.0007	-0.0004	-0.0001	0.0009
200	10000	1	1	3.5502	0.0278	0.3173	0.0002	0.0070	0.0047	0.0042
500	2000	0	0	1.5163	-0.0010	0.0225	-0.0006	0.0010	0.0010	0.0010
500	2000	0	1	2.0672	0.0019	0.0682	-0.0005	0.0010	0.0004	-0.0008
500	2000	1	0	1.5165	0.0042	0.0281	0.0014	0.0008	0.0009	0.0013
500	2000	1	1	2.7555	-0.0080	0.0843	-0.0005	0.0032	0.0004	-0.0005
500	5000	0	0	1.6553	0.0063	0.0386	-0.0015	-0.0016	-0.0019	-0.0017
500	5000	0	1	2.2941	-0.0038	0.0857	-0.0007	-0.0002	0.0002	-0.0011
500	5000	1	0	1.6593	0.0009	0.0327	-0.0012	-0.0014	-0.0012	-0.0005
500	5000	1	1	3.0598	0.0040	0.1184	-0.0005	-0.0015	-0.0017	-0.0017
500	10000	0	0	1.7558	-0.0061	0.0314	-0.0009	-0.0020	-0.0019	-0.0019
500	10000	0	1	2.4690	0.0025	0.1030	0.0019	0.0031	0.0010	-0.0011
500	10000	1	0	1.7575	0.0010	0.0373	-0.0011	-0.0011	-0.0008	-0.0008
500	10000	1	1	3.2910	0.0171	0.1486	-0.0007	0.0000	-0.0000	-0.0015
1000	2000	0	0	1.4527	0.0011	0.0107	-0.0009	-0.0010	-0.0009	-0.0008
1000	2000	0	1	1.9736	0.0008	0.0269	0.0001	0.0007	0.0007	0.0008
1000	2000	1	0	1.4525	-0.0005	0.0088	-0.0001	-0.0004	-0.0003	-0.0001
1000	2000	1	1	2.6309	0.0038	0.0374	-0.0005	-0.0006	-0.0007	-0.0008
1000	5000	0	0	1.5477	0.0005	0.0146	-0.0011	-0.0003	-0.0005	-0.0004
1000	5000	0	1	2.1182	-0.0016	0.0372	-0.0012	-0.0006	-0.0007	-0.0005
1000	5000	1	0	1.5484	0.0043	0.0176	0.0009	0.0011	0.0010	0.0010
1000	5000	1	1	2.8248	-0.0087	0.0470	0.0001	-0.0027	-0.0022	-0.0018
1000	10000	0	0	1.6587	0.0016	0.0185	0.0006	-0.0002	-0.0000	0.0006
1000	10000	0	1	2.2947	0.0091	0.0569	-0.0001	0.0009	-0.0000	-0.0011
1000	10000	1	0	1.6585	0.0062	0.0217	-0.0006	0.0003	0.0000	-0.0005
1000	10000	1	1	3.0620	0.0134	0.0787	-0.0006	0.0008	0.0005	0.0001

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C2: Bias of estimators for $\mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for continuous outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	1.6577	0.0019	0.0734	-0.0021	-0.0040	-0.0034	-0.0029
200	2000	0	1	2.2933	-0.0280	0.1705	-0.0013	-0.0074	-0.0033	-0.0039
200	2000	1	0	1.6583	0.0190	0.0832	0.0024	0.0047	0.0035	0.0026
200	2000	1	1	2.2938	-0.0106	0.1726	-0.0019	0.0025	-0.0007	-0.0016
200	5000	0	0	1.7875	0.0081	0.0864	0.0007	0.0000	0.0011	0.0030
200	5000	0	1	2.5163	0.0183	0.2153	-0.0009	-0.0032	-0.0029	-0.0045
200	5000	1	0	1.7869	-0.0005	0.0839	-0.0020	-0.0010	-0.0019	-0.0021
200	5000	1	1	2.5188	0.0105	0.2125	0.0011	-0.0017	-0.0003	0.0006
200	10000	0	0	1.8625	0.0022	0.0896	0.0007	-0.0011	-0.0005	-0.0002
200	10000	0	1	2.6630	0.0327	0.2307	-0.0008	0.0031	0.0006	-0.0011
200	10000	1	0	1.8628	0.0075	0.0927	0.0006	0.0020	0.0013	0.0007
200	10000	1	1	2.6597	0.0204	0.2308	0.0018	0.0028	0.0026	0.0007
500	2000	0	0	1.5153	0.0006	0.0256	0.0006	0.0018	0.0016	0.0013
500	2000	0	1	2.0690	-0.0140	0.0639	0.0007	0.0006	0.0017	0.0017
500	2000	1	0	1.5170	0.0054	0.0286	0.0005	0.0016	0.0016	0.0021
500	2000	1	1	2.0686	0.0095	0.0689	-0.0012	-0.0014	-0.0009	-0.0009
500	5000	0	0	1.6580	-0.0036	0.0288	-0.0003	-0.0016	-0.0015	-0.0009
500	5000	0	1	2.2931	0.0146	0.0974	-0.0002	0.0036	0.0025	0.0016
500	5000	1	0	1.6586	-0.0054	0.0288	0.0008	-0.0006	-0.0007	-0.0005
500	5000	1	1	2.2957	0.0084	0.0924	0.0012	-0.0009	-0.0002	0.0006
500	10000	0	0	1.7614	0.0034	0.0385	0.0035	0.0046	0.0047	0.0050
500	10000	0	1	2.4653	0.0240	0.1103	-0.0003	-0.0000	-0.0007	-0.0021
500	10000	1	0	1.7584	-0.0060	0.0307	0.0003	-0.0004	-0.0004	-0.0001
500	10000	1	1	2.4677	-0.0008	0.1057	0.0011	0.0030	0.0035	0.0038
1000	2000	0	0	1.4521	0.0023	0.0117	-0.0000	0.0008	0.0007	0.0004
1000	2000	0	1	1.9721	0.0075	0.0293	-0.0003	-0.0012	-0.0010	-0.0005
1000	2000	1	0	1.4536	0.0050	0.0131	0.0014	0.0016	0.0015	0.0012
1000	2000	1	1	1.9707	0.0046	0.0286	0.0000	-0.0002	-0.0002	-0.0000
1000	5000	0	0	1.5481	0.0033	0.0166	-0.0004	-0.0007	-0.0006	-0.0006
1000	5000	0	1	2.1202	-0.0001	0.0380	-0.0003	0.0005	0.0003	0.0007
1000	5000	1	0	1.5478	-0.0013	0.0129	-0.0001	-0.0001	-0.0000	-0.0001
1000	5000	1	1	2.1192	0.0046	0.0416	0.0015	0.0006	0.0011	0.0017
1000	10000	0	0	1.6573	-0.0037	0.0133	-0.0006	-0.0005	-0.0007	-0.0010
1000	10000	0	1	2.2951	0.0143	0.0576	0.0001	-0.0002	0.0001	0.0005
1000	10000	1	0	1.6583	-0.0001	0.0158	0.0001	-0.0001	-0.0000	0.0001
1000	10000	1	1	2.2938	0.0094	0.0531	0.0004	0.0008	0.0007	0.0005

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C3: Bias of estimators for $\mu(1)-\mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for continuous outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	-0.0032	0.0038	0.0010	-0.0003	0.0043	0.0028	0.0023
200	2000	0	1	0.0013	0.0449	0.0086	0.0055	0.0083	0.0040	0.0054
200	2000	1	0	-0.0057	-0.0197	-0.0141	-0.0066	-0.0104	-0.0090	-0.0085
200	2000	1	1	0.7654	0.0257	0.0698	-0.0011	-0.0018	0.0003	0.0000
200	5000	0	0	-0.0009	-0.0061	-0.0026	-0.0022	-0.0005	-0.0007	-0.0021
200	5000	0	1	0.0023	-0.0028	-0.0076	-0.0008	0.0087	0.0048	0.0024
200	5000	1	0	0.0001	0.0094	0.0031	-0.0001	-0.0007	0.0005	0.0011
200	5000	1	1	0.8407	-0.0073	0.0624	0.0041	0.0071	0.0053	0.0029
200	10000	0	0	0.0011	0.0070	0.0076	0.0019	0.0040	0.0036	0.0037
200	10000	0	1	-0.0020	-0.0345	-0.0026	-0.0013	-0.0104	-0.0061	-0.0032
200	10000	1	0	-0.0025	0.0010	0.0038	-0.0013	-0.0024	-0.0014	0.0003
200	10000	1	1	0.8905	0.0074	0.0864	-0.0016	0.0042	0.0021	0.0035
500	2000	0	0	0.0010	-0.0016	-0.0031	-0.0011	-0.0009	-0.0007	-0.0003
500	2000	0	1	-0.0018	0.0159	0.0042	-0.0012	0.0004	-0.0013	-0.0025
500	2000	1	0	-0.0005	-0.0012	-0.0005	0.0008	-0.0008	-0.0007	-0.0008
500	2000	1	1	0.6869	-0.0175	0.0154	0.0007	0.0046	0.0013	0.0005
500	5000	0	0	-0.0027	0.0099	0.0098	-0.0012	-0.0001	-0.0004	-0.0008
500	5000	0	1	0.0011	-0.0185	-0.0117	-0.0005	-0.0038	-0.0024	-0.0027
500	5000	1	0	0.0007	0.0063	0.0039	-0.0020	-0.0008	-0.0004	0.0000
500	5000	1	1	0.7641	-0.0044	0.0260	-0.0017	-0.0007	-0.0015	-0.0023
500	10000	0	0	-0.0055	-0.0095	-0.0071	-0.0043	-0.0066	-0.0066	-0.0069
500	10000	0	1	0.0036	-0.0214	-0.0073	0.0021	0.0031	0.0016	0.0010
500	10000	1	0	-0.0009	0.0071	0.0066	-0.0014	-0.0007	-0.0004	-0.0007
500	10000	1	1	0.8233	0.0179	0.0429	-0.0018	-0.0030	-0.0035	-0.0052
1000	2000	0	0	0.0006	-0.0012	-0.0010	-0.0009	-0.0018	-0.0016	-0.0012
1000	2000	0	1	0.0015	-0.0066	-0.0024	0.0003	0.0018	0.0017	0.0013
1000	2000	1	0	-0.0011	-0.0055	-0.0043	-0.0014	-0.0021	-0.0018	-0.0013
1000	2000	1	1	0.6602	-0.0008	0.0089	-0.0005	-0.0004	-0.0005	-0.0008
1000	5000	0	0	-0.0004	-0.0028	-0.0020	-0.0007	0.0004	0.0002	0.0001
1000	5000	0	1	-0.0020	-0.0015	-0.0009	-0.0009	-0.0010	-0.0010	-0.0012
1000	5000	1	0	0.0005	0.0057	0.0048	0.0010	0.0012	0.0011	0.0011
1000	5000	1	1	0.7055	-0.0133	0.0054	-0.0014	-0.0033	-0.0033	-0.0035
1000	10000	0	0	0.0013	0.0053	0.0051	0.0012	0.0003	0.0006	0.0017
1000	10000	0	1	-0.0004	-0.0052	-0.0007	-0.0002	0.0012	-0.0001	-0.0015
1000	10000	1	0	0.0002	0.0063	0.0060	-0.0006	0.0004	0.0001	-0.0005
1000	10000	1	1	0.7682	0.0041	0.0256	-0.0011	0.0000	-0.0002	-0.0003

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C4: Variance of estimators for $\mu(1)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for continuous outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.0360	0.3115	0.2249	0.0313	0.0635	0.0500	0.0499
200	2000	0	1	0.0310	0.7458	0.3944	0.0385	0.1159	0.0747	0.0788
200	2000	1	0	0.0677	0.4383	0.3545	0.0328	0.0704	0.0534	0.0525
200	2000	1	1	0.0530	2.2201	0.6813	0.0397	0.1224	0.0763	0.0808
200	5000	0	0	0.0373	0.3339	0.2722	0.0317	0.0692	0.0536	0.0526
200	5000	0	1	0.0326	1.2226	0.4442	0.0420	0.1370	0.0856	0.0923
200	5000	1	0	0.0679	0.4422	0.3782	0.0321	0.0636	0.0532	0.0547
200	5000	1	1	0.0548	2.2564	0.8006	0.0421	0.1559	0.0851	0.0922
200	10000	0	0	0.0379	0.3337	0.2764	0.0319	0.0686	0.0549	0.0555
200	10000	0	1	0.0349	1.3494	0.5084	0.0430	0.1572	0.0877	0.0966
200	10000	1	0	0.0674	0.4849	0.4019	0.0324	0.0691	0.0553	0.0569
200	10000	1	1	0.0600	2.1547	0.8376	0.0412	0.1628	0.0858	0.0950
500	2000	0	0	0.0138	0.1001	0.0993	0.0125	0.0218	0.0202	0.0192
500	2000	0	1	0.0118	0.4201	0.1868	0.0148	0.0397	0.0311	0.0292
500	2000	1	0	0.0264	0.1417	0.1350	0.0144	0.0236	0.0222	0.0212
500	2000	1	1	0.0206	2.0710	0.3231	0.0159	0.0979	0.0329	0.0301
500	5000	0	0	0.0143	0.0988	0.1131	0.0120	0.0244	0.0216	0.0207
500	5000	0	1	0.0122	0.4999	0.2499	0.0155	0.0589	0.0379	0.0348
500	5000	1	0	0.0265	0.1715	0.1677	0.0129	0.0248	0.0222	0.0210
500	5000	1	1	0.0214	0.7502	0.4265	0.0157	0.0566	0.0384	0.0349
500	10000	0	0	0.0145	0.1438	0.1382	0.0124	0.0270	0.0230	0.0214
500	10000	0	1	0.0128	0.3855	0.2757	0.0159	0.0560	0.0391	0.0365
500	10000	1	0	0.0267	0.2065	0.1893	0.0122	0.0274	0.0232	0.0215
500	10000	1	1	0.0223	0.7828	0.4737	0.0162	0.0556	0.0395	0.0366
1000	2000	0	0	0.0069	0.0437	0.0435	0.0074	0.0115	0.0111	0.0106
1000	2000	0	1	0.0063	0.1507	0.0891	0.0079	0.0178	0.0159	0.0145
1000	2000	1	0	0.0129	0.0658	0.0637	0.0103	0.0143	0.0138	0.0133
1000	2000	1	1	0.0106	0.2666	0.1526	0.0099	0.0197	0.0177	0.0164
1000	5000	0	0	0.0069	0.0520	0.0575	0.0060	0.0116	0.0106	0.0098
1000	5000	0	1	0.0060	0.1719	0.1292	0.0073	0.0245	0.0184	0.0158
1000	5000	1	0	0.0129	0.0732	0.0776	0.0066	0.0116	0.0112	0.0105
1000	5000	1	1	0.0103	0.3948	0.2420	0.0080	0.0238	0.0186	0.0161
1000	10000	0	0	0.0073	0.0547	0.0671	0.0058	0.0121	0.0113	0.0104
1000	10000	0	1	0.0061	0.1622	0.1458	0.0074	0.0259	0.0197	0.0174
1000	10000	1	0	0.0135	0.0781	0.0872	0.0063	0.0130	0.0120	0.0110
1000	10000	1	1	0.0106	0.3597	0.2654	0.0079	0.0279	0.0210	0.0181

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C5: Variance of estimators for $\mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for continuous outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.0355	0.4908	0.2441	0.0316	0.0642	0.0517	0.0509
200	2000	0	1	0.0304	14.9410	0.4102	0.0391	0.1801	0.0759	0.0777
200	2000	1	0	0.0365	0.4015	0.2326	0.0312	0.0647	0.0528	0.0516
200	2000	1	1	0.0301	3.3258	0.4068	0.0390	0.3236	0.0773	0.0791
200	5000	0	0	0.0370	0.5231	0.2635	0.0316	0.0639	0.0542	0.0549
200	5000	0	1	0.0324	1.8324	0.4520	0.0414	0.1361	0.0826	0.0894
200	5000	1	0	0.0377	0.5560	0.2664	0.0316	0.0701	0.0540	0.0536
200	5000	1	1	0.0324	2.4373	0.4587	0.0419	0.1379	0.0817	0.0900
200	10000	0	0	0.0378	0.5606	0.2876	0.0317	0.0729	0.0548	0.0548
200	10000	0	1	0.0338	1.4746	0.4684	0.0430	0.1459	0.0895	0.0979
200	10000	1	0	0.0369	0.6156	0.2681	0.0321	0.0700	0.0545	0.0548
200	10000	1	1	0.0344	1.9267	0.4847	0.0420	0.1996	0.0879	0.0927
500	2000	0	0	0.0134	0.1591	0.0981	0.0125	0.0221	0.0204	0.0194
500	2000	0	1	0.0120	1.6801	0.2047	0.0149	0.0567	0.0323	0.0293
500	2000	1	0	0.0140	0.1473	0.0957	0.0122	0.0224	0.0205	0.0193
500	2000	1	1	0.0115	0.4980	0.1834	0.0144	0.0403	0.0313	0.0291
500	5000	0	0	0.0143	0.2101	0.1232	0.0119	0.0253	0.0215	0.0199
500	5000	0	1	0.0122	0.5983	0.2358	0.0153	0.0531	0.0367	0.0331
500	5000	1	0	0.0145	0.2376	0.1272	0.0123	0.0264	0.0226	0.0207
500	5000	1	1	0.0120	0.8217	0.2397	0.0149	0.0493	0.0363	0.0333
500	10000	0	0	0.0145	0.2165	0.1322	0.0121	0.0271	0.0232	0.0212
500	10000	0	1	0.0128	0.5652	0.2499	0.0160	0.0534	0.0391	0.0374
500	10000	1	0	0.0142	0.2728	0.1330	0.0120	0.0260	0.0228	0.0214
500	10000	1	1	0.0129	1.7376	0.2806	0.0161	0.0571	0.0400	0.0376
1000	2000	0	0	0.0070	0.0685	0.0439	0.0075	0.0115	0.0112	0.0107
1000	2000	0	1	0.0062	0.1751	0.0840	0.0079	0.0177	0.0159	0.0145
1000	2000	1	0	0.0070	0.0617	0.0411	0.0074	0.0116	0.0112	0.0108
1000	2000	1	1	0.0061	0.2072	0.0859	0.0081	0.0181	0.0159	0.0144
1000	5000	0	0	0.0070	0.0807	0.0558	0.0058	0.0109	0.0103	0.0097
1000	5000	0	1	0.0059	0.2518	0.1266	0.0069	0.0215	0.0175	0.0154
1000	5000	1	0	0.0071	0.0838	0.0584	0.0060	0.0113	0.0106	0.0099
1000	5000	1	1	0.0060	0.2427	0.1238	0.0072	0.0199	0.0173	0.0157
1000	10000	0	0	0.0071	0.0947	0.0689	0.0059	0.0129	0.0118	0.0106
1000	10000	0	1	0.0061	0.2522	0.1461	0.0077	0.0237	0.0197	0.0178
1000	10000	1	0	0.0071	0.0852	0.0662	0.0060	0.0119	0.0113	0.0106
1000	10000	1	1	0.0060	0.2508	0.1454	0.0075	0.0246	0.0204	0.0180

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C6: Variance of estimators for $\mu(1) - \mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for continuous outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.0718	0.8185	0.4899	0.0596	0.1256	0.0993	0.0975
200	2000	0	1	0.0611	15.7046	0.8073	0.0744	0.2959	0.1477	0.1530
200	2000	1	0	0.1037	0.8450	0.6004	0.0601	0.1312	0.1025	0.1002
200	2000	1	1	0.0831	5.5995	1.1089	0.0741	0.4344	0.1471	0.1535
200	5000	0	0	0.0746	0.8426	0.5375	0.0617	0.1310	0.1062	0.1067
200	5000	0	1	0.0653	3.0626	0.9023	0.0832	0.2747	0.1685	0.1834
200	5000	1	0	0.1065	1.0057	0.6532	0.0614	0.1332	0.1060	0.1065
200	5000	1	1	0.0868	4.6314	1.2669	0.0834	0.2846	0.1661	0.1811
200	10000	0	0	0.0756	0.9000	0.5688	0.0639	0.1435	0.1114	0.1117
200	10000	0	1	0.0688	2.8288	0.9807	0.0840	0.3005	0.1753	0.1912
200	10000	1	0	0.1046	1.1129	0.6741	0.0642	0.1374	0.1084	0.1108
200	10000	1	1	0.0947	4.0693	1.3245	0.0837	0.3631	0.1738	0.1877
500	2000	0	0	0.0271	0.2606	0.2001	0.0214	0.0405	0.0372	0.0352
500	2000	0	1	0.0243	2.1127	0.4041	0.0271	0.0935	0.0605	0.0558
500	2000	1	0	0.0411	0.2919	0.2350	0.0217	0.0411	0.0378	0.0355
500	2000	1	1	0.0319	2.5983	0.5227	0.0264	0.1347	0.0609	0.0554
500	5000	0	0	0.0287	0.3119	0.2399	0.0229	0.0482	0.0417	0.0392
500	5000	0	1	0.0242	1.0987	0.4958	0.0300	0.1111	0.0737	0.0671
500	5000	1	0	0.0415	0.4124	0.2982	0.0235	0.0495	0.0431	0.0399
500	5000	1	1	0.0334	1.5853	0.6758	0.0292	0.1048	0.0735	0.0666
500	10000	0	0	0.0292	0.3580	0.2701	0.0238	0.0542	0.0461	0.0425
500	10000	0	1	0.0258	0.9583	0.5363	0.0315	0.1095	0.0779	0.0732
500	10000	1	0	0.0411	0.4853	0.3257	0.0232	0.0519	0.0444	0.0413
500	10000	1	1	0.0358	2.5301	0.7583	0.0318	0.1116	0.0784	0.0734
1000	2000	0	0	0.0140	0.1153	0.0896	0.0100	0.0182	0.0176	0.0165
1000	2000	0	1	0.0126	0.3374	0.1790	0.0122	0.0313	0.0278	0.0251
1000	2000	1	0	0.0201	0.1273	0.1042	0.0109	0.0186	0.0178	0.0168
1000	2000	1	1	0.0166	0.4873	0.2452	0.0125	0.0323	0.0280	0.0253
1000	5000	0	0	0.0135	0.1343	0.1157	0.0106	0.0210	0.0194	0.0181
1000	5000	0	1	0.0120	0.4280	0.2605	0.0130	0.0445	0.0344	0.0298
1000	5000	1	0	0.0199	0.1562	0.1365	0.0108	0.0209	0.0198	0.0185
1000	5000	1	1	0.0162	0.6536	0.3778	0.0135	0.0426	0.0347	0.0304
1000	10000	0	0	0.0141	0.1494	0.1371	0.0112	0.0246	0.0226	0.0204
1000	10000	0	1	0.0124	0.4246	0.3009	0.0146	0.0490	0.0387	0.0345
1000	10000	1	0	0.0207	0.1647	0.1551	0.0113	0.0238	0.0222	0.0204
1000	10000	1	1	0.0166	0.6139	0.4160	0.0147	0.0514	0.0404	0.0353

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C7: Mean squared error of estimators for $\mu(1)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for continuous outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	2.7732	0.3116	0.2304	0.0313	0.0635	0.0500	0.0499
200	2000	0	1	5.2960	0.7461	0.4265	0.0385	0.1159	0.0747	0.0789
200	2000	1	0	2.7991	0.4383	0.3592	0.0329	0.0704	0.0535	0.0526
200	2000	1	1	9.4117	2.2203	0.7400	0.0397	0.1224	0.0763	0.0808
200	5000	0	0	3.2294	0.3339	0.2792	0.0317	0.0692	0.0536	0.0526
200	5000	0	1	6.3759	1.2229	0.4873	0.0420	0.1370	0.0857	0.0923
200	5000	1	0	3.2615	0.4423	0.3857	0.0321	0.0636	0.0532	0.0547
200	5000	1	1	11.3410	2.2564	0.8762	0.0422	0.1559	0.0852	0.0922
200	10000	0	0	3.5111	0.3338	0.2859	0.0319	0.0686	0.0549	0.0555
200	10000	0	1	7.1158	1.3494	0.5604	0.0430	0.1572	0.0877	0.0967
200	10000	1	0	3.5280	0.4850	0.4112	0.0324	0.0691	0.0553	0.0569
200	10000	1	1	12.6642	2.1554	0.9383	0.0412	0.1629	0.0858	0.0950
500	2000	0	0	2.3131	0.1001	0.0998	0.0125	0.0218	0.0202	0.0192
500	2000	0	1	4.2853	0.4201	0.1915	0.0148	0.0397	0.0311	0.0292
500	2000	1	0	2.3262	0.1417	0.1358	0.0144	0.0236	0.0222	0.0212
500	2000	1	1	7.6132	2.0711	0.3302	0.0159	0.0980	0.0329	0.0301
500	5000	0	0	2.7543	0.0989	0.1146	0.0120	0.0244	0.0216	0.0207
500	5000	0	1	5.2753	0.4999	0.2572	0.0155	0.0589	0.0379	0.0348
500	5000	1	0	2.7797	0.1715	0.1688	0.0129	0.0248	0.0222	0.0210
500	5000	1	1	9.3840	0.7502	0.4405	0.0157	0.0566	0.0384	0.0349
500	10000	0	0	3.0975	0.1438	0.1392	0.0124	0.0270	0.0230	0.0214
500	10000	0	1	6.1085	0.3855	0.2863	0.0159	0.0561	0.0391	0.0365
500	10000	1	0	3.1156	0.2065	0.1907	0.0122	0.0274	0.0232	0.0215
500	10000	1	1	10.8531	0.7831	0.4958	0.0162	0.0556	0.0395	0.0366
1000	2000	0	0	2.1172	0.0437	0.0436	0.0074	0.0115	0.0111	0.0106
1000	2000	0	1	3.9013	0.1507	0.0898	0.0079	0.0178	0.0159	0.0145
1000	2000	1	0	2.1226	0.0658	0.0638	0.0103	0.0143	0.0138	0.0133
1000	2000	1	1	6.9321	0.2666	0.1540	0.0099	0.0197	0.0177	0.0164
1000	5000	0	0	2.4023	0.0520	0.0577	0.0060	0.0116	0.0106	0.0098
1000	5000	0	1	4.4927	0.1719	0.1306	0.0073	0.0245	0.0184	0.0158
1000	5000	1	0	2.4103	0.0732	0.0779	0.0066	0.0116	0.0112	0.0105
1000	5000	1	1	7.9897	0.3949	0.2442	0.0080	0.0238	0.0186	0.0161
1000	10000	0	0	2.7584	0.0547	0.0674	0.0058	0.0121	0.0113	0.0104
1000	10000	0	1	5.2720	0.1623	0.1490	0.0074	0.0259	0.0197	0.0174
1000	10000	1	0	2.7642	0.0782	0.0877	0.0063	0.0130	0.0120	0.0110
1000	10000	1	1	9.3863	0.3598	0.2716	0.0079	0.0279	0.0210	0.0181

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C8: Mean squared error of estimators for $\mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for continuous outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	2.7833	0.4908	0.2495	0.0316	0.0642	0.0517	0.0509
200	2000	0	1	5.2896	14.9418	0.4392	0.0391	0.1801	0.0760	0.0777
200	2000	1	0	2.7865	0.4019	0.2395	0.0312	0.0647	0.0528	0.0517
200	2000	1	1	5.2915	3.3259	0.4366	0.0390	0.3236	0.0773	0.0791
200	5000	0	0	3.2322	0.5232	0.2710	0.0316	0.0639	0.0542	0.0549
200	5000	0	1	6.3641	1.8328	0.4984	0.0414	0.1361	0.0826	0.0895
200	5000	1	0	3.2308	0.5560	0.2735	0.0316	0.0701	0.0540	0.0536
200	5000	1	1	6.3769	2.4374	0.5038	0.0419	0.1379	0.0817	0.0900
200	10000	0	0	3.5069	0.5606	0.2956	0.0317	0.0729	0.0548	0.0548
200	10000	0	1	7.1255	1.4756	0.5216	0.0430	0.1459	0.0895	0.0979
200	10000	1	0	3.5069	0.6156	0.2767	0.0321	0.0700	0.0545	0.0548
200	10000	1	1	7.1086	1.9272	0.5380	0.0420	0.1996	0.0879	0.0927
500	2000	0	0	2.3096	0.1591	0.0988	0.0125	0.0221	0.0204	0.0194
500	2000	0	1	4.2929	1.6803	0.2088	0.0149	0.0567	0.0323	0.0293
500	2000	1	0	2.3153	0.1474	0.0965	0.0122	0.0224	0.0205	0.0193
500	2000	1	1	4.2905	0.4981	0.1881	0.0144	0.0403	0.0313	0.0291
500	5000	0	0	2.7634	0.2102	0.1241	0.0119	0.0253	0.0215	0.0199
500	5000	0	1	5.2704	0.5986	0.2453	0.0153	0.0531	0.0367	0.0331
500	5000	1	0	2.7654	0.2376	0.1281	0.0123	0.0264	0.0226	0.0207
500	5000	1	1	5.2823	0.8217	0.2482	0.0149	0.0493	0.0363	0.0333
500	10000	0	0	3.1169	0.2165	0.1337	0.0121	0.0271	0.0232	0.0212
500	10000	0	1	6.0906	0.5658	0.2621	0.0160	0.0534	0.0391	0.0374
500	10000	1	0	3.1061	0.2728	0.1340	0.0120	0.0260	0.0228	0.0214
500	10000	1	1	6.1026	1.7376	0.2917	0.0161	0.0572	0.0401	0.0376
1000	2000	0	0	2.1157	0.0685	0.0440	0.0075	0.0115	0.0112	0.0107
1000	2000	0	1	3.8955	0.1752	0.0848	0.0079	0.0177	0.0159	0.0145
1000	2000	1	0	2.1199	0.0618	0.0413	0.0074	0.0116	0.0113	0.0108
1000	2000	1	1	3.8896	0.2073	0.0867	0.0081	0.0181	0.0159	0.0144
1000	5000	0	0	2.4036	0.0807	0.0561	0.0058	0.0109	0.0103	0.0097
1000	5000	0	1	4.5011	0.2518	0.1280	0.0069	0.0215	0.0175	0.0154
1000	5000	1	0	2.4029	0.0838	0.0586	0.0060	0.0113	0.0106	0.0099
1000	5000	1	1	4.4971	0.2427	0.1255	0.0072	0.0199	0.0173	0.0157
1000	10000	0	0	2.7539	0.0947	0.0690	0.0059	0.0129	0.0118	0.0106
1000	10000	0	1	5.2737	0.2524	0.1494	0.0077	0.0237	0.0197	0.0178
1000	10000	1	0	2.7572	0.0852	0.0664	0.0060	0.0119	0.0113	0.0106
1000	10000	1	1	5.2676	0.2509	0.1482	0.0075	0.0246	0.0204	0.0180

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C9: Mean squared error of estimators for $\mu(1) - \mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for continuous outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.0718	0.8185	0.4899	0.0596	0.1256	0.0993	0.0975
200	2000	0	1	0.0611	15.7067	0.8074	0.0745	0.2960	0.1478	0.1530
200	2000	1	0	0.1038	0.8454	0.6006	0.0601	0.1313	0.1026	0.1003
200	2000	1	1	0.6689	5.6001	1.1138	0.0741	0.4344	0.1471	0.1535
200	5000	0	0	0.0746	0.8426	0.5375	0.0617	0.1310	0.1062	0.1067
200	5000	0	1	0.0653	3.0626	0.9024	0.0832	0.2748	0.1685	0.1834
200	5000	1	0	0.1065	1.0057	0.6532	0.0614	0.1332	0.1060	0.1065
200	5000	1	1	0.7935	4.6315	1.2708	0.0834	0.2847	0.1661	0.1811
200	10000	0	0	0.0756	0.9001	0.5688	0.0639	0.1435	0.1114	0.1117
200	10000	0	1	0.0689	2.8300	0.9807	0.0840	0.3006	0.1753	0.1912
200	10000	1	0	0.1046	1.1129	0.6741	0.0642	0.1374	0.1084	0.1108
200	10000	1	1	0.8877	4.0694	1.3320	0.0837	0.3631	0.1738	0.1877
500	2000	0	0	0.0271	0.2606	0.2001	0.0214	0.0405	0.0372	0.0352
500	2000	0	1	0.0243	2.1130	0.4041	0.0271	0.0935	0.0605	0.0558
500	2000	1	0	0.0411	0.2919	0.2350	0.0217	0.0411	0.0378	0.0355
500	2000	1	1	0.5037	2.5986	0.5229	0.0264	0.1347	0.0609	0.0554
500	5000	0	0	0.0287	0.3120	0.2400	0.0229	0.0482	0.0417	0.0392
500	5000	0	1	0.0242	1.0990	0.4959	0.0300	0.1111	0.0737	0.0672
500	5000	1	0	0.0415	0.4125	0.2982	0.0235	0.0495	0.0431	0.0399
500	5000	1	1	0.6173	1.5853	0.6765	0.0292	0.1048	0.0735	0.0666
500	10000	0	0	0.0292	0.3581	0.2702	0.0239	0.0542	0.0462	0.0426
500	10000	0	1	0.0258	0.9588	0.5363	0.0316	0.1095	0.0779	0.0732
500	10000	1	0	0.0411	0.4854	0.3257	0.0232	0.0519	0.0444	0.0413
500	10000	1	1	0.7136	2.5305	0.7602	0.0318	0.1116	0.0784	0.0734
1000	2000	0	0	0.0140	0.1153	0.0896	0.0100	0.0182	0.0176	0.0165
1000	2000	0	1	0.0126	0.3374	0.1790	0.0122	0.0313	0.0278	0.0251
1000	2000	1	0	0.0201	0.1273	0.1042	0.0109	0.0186	0.0178	0.0168
1000	2000	1	1	0.4525	0.4873	0.2452	0.0125	0.0323	0.0280	0.0253
1000	5000	0	0	0.0135	0.1343	0.1157	0.0106	0.0210	0.0194	0.0181
1000	5000	0	1	0.0120	0.4280	0.2605	0.0130	0.0445	0.0344	0.0298
1000	5000	1	0	0.0199	0.1562	0.1365	0.0108	0.0209	0.0198	0.0185
1000	5000	1	1	0.5140	0.6538	0.3779	0.0135	0.0426	0.0347	0.0304
1000	10000	0	0	0.0141	0.1494	0.1371	0.0112	0.0246	0.0226	0.0204
1000	10000	0	1	0.0124	0.4247	0.3009	0.0146	0.0490	0.0387	0.0345
1000	10000	1	0	0.0207	0.1648	0.1552	0.0113	0.0238	0.0222	0.0204
1000	10000	1	1	0.6067	0.6139	0.4167	0.0147	0.0514	0.0404	0.0353

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

C.2 Methods for simulation studies with binary outcomes

We considered cohorts of $n = 2000$, 5000 or 10,000 individuals with the number of randomized individuals n_{RCT} approximately equal to 200, 500, or 1000. Specifically, we generated baseline covariates for cohorts of 2000, 5000 or 10,000 individuals as $X = (1, X_1, X_2, X_3)$, each X_j had an independent standard normal normal distribution. We then simulated selection into the trial using a binary indicator S with $\text{logit}\Pr[S = 1|X] = \beta X^\intercal$, with $\beta = (\beta_0, \ldots, \beta_3)$. We chose β_0 using numerical methods [19], such that for a given cohort sample size n the trial sample size n_{RCT} was 200, 500, or 1000. We examined scenarios with $\beta_1 = 0$, indicating no selection on X_1, and $\beta_1 = 1$, indicating strong selection; in all scenarios we used $\beta_2 = \beta_3 = 1$, indicating strong selection on X_2 and X_3.

We generated potential outcomes as $Y^a \sim \text{Bernoulli}(\Pr[Y^a = 1|X])$ with $\text{logit}\Pr[Y^a = 1|X] = \theta^a X^\intercal$. We used $\theta^1 = (-1, \theta_1^1, 1, 1)$ with $\theta_1^1 = 1$ or 2. We used $\theta^0 = (-2, 1, 1, 1)$ in all scenarios. Note that $\theta_1^1 \neq 1$ indicates the presence of effect modification on the log-odds ratio scale. For observations "selected" into the trial ($S = 1$) we generated treatment assignment A as a binomial random variable with parameter 0.5 (i.e., we simulated marginally randomized trials). Last, we generated observed outcomes as $Y = AY^1 + (1 - A)Y^0$.

For each simulated dataset, we applied the estimators in equations (A.7) through (A.12), and also obtained a trial-only estimator of the treatment effect. All working models required for the different estimators were correctly specified, in the sense that the true models were nested within the parametric working models on which the estimators relied. Specifically, outcome models included main effects for all covariates and were fit separately in each arm; logistic regression models for trial participation and treatment included the main effects of

all covariates; all models had intercept terms. We estimated the bias and variance for each estimator over 100,000 runs for each scenario.

C.3 Results for binary outcomes

Table C10: Bias of estimators for $\mu(1)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for binary outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.2714	0.0002	0.0083	0.0017	0.0003	0.0004	0.0006
200	2000	0	1	0.3848	0.0008	0.0194	0.0023	0.0010	0.0010	0.0021
200	2000	1	0	0.2194	-0.0019	0.0055	0.0011	-0.0008	-0.0005	-0.0003
200	2000	1	1	0.4171	0.0001	0.0208	0.0031	0.0008	0.0010	0.0016
200	5000	0	0	0.2927	0.0005	0.0103	0.0026	0.0009	0.0012	0.0016
200	5000	0	1	0.4126	0.0002	0.0241	0.0028	0.0012	0.0013	0.0033
200	5000	1	0	0.2371	0.0002	0.0101	0.0014	0.0005	0.0006	0.0008
200	5000	1	1	0.4379	-0.0010	0.0256	0.0016	-0.0003	-0.0000	0.0009
200	10000	0	0	0.3031	0.0000	0.0117	0.0020	0.0003	0.0006	0.0011
200	10000	0	1	0.4274	0.0002	0.0287	0.0044	0.0014	0.0019	0.0041
200	10000	1	0	0.2450	-0.0035	0.0076	0.0000	-0.0011	-0.0009	-0.0008
200	10000	1	1	0.4498	-0.0003	0.0314	0.0026	0.0004	0.0006	0.0023
500	2000	0	0	0.2453	0.0004	0.0031	0.0005	0.0003	0.0003	0.0001
500	2000	0	1	0.3466	0.0006	0.0061	0.0011	0.0006	0.0006	0.0004
500	2000	1	0	0.1991	0.0003	0.0028	0.0003	0.0001	0.0002	0.0001
500	2000	1	1	0.3833	-0.0004	0.0055	0.0004	-0.0002	-0.0002	-0.0003
500	5000	0	0	0.2717	-0.0000	0.0038	0.0008	0.0001	0.0001	-0.0001
500	5000	0	1	0.3849	-0.0003	0.0089	0.0004	-0.0003	-0.0003	-0.0002
500	5000	1	0	0.2195	-0.0006	0.0033	0.0004	-0.0001	-0.0000	-0.0002
500	5000	1	1	0.4155	-0.0000	0.0096	0.0003	-0.0000	0.0000	-0.0001
500	10000	0	0	0.2877	-0.0000	0.0044	0.0007	0.0002	0.0002	-0.0000
500	10000	0	1	0.4067	-0.0006	0.0101	0.0008	-0.0006	-0.0004	-0.0004
500	10000	1	0	0.2329	-0.0001	0.0048	0.0010	0.0004	0.0004	0.0002
500	10000	1	1	0.4340	-0.0000	0.0124	0.0011	-0.0000	0.0001	-0.0001
1000	2000	0	0	0.2231	-0.0001	0.0006	0.0000	-0.0001	-0.0001	-0.0002
1000	2000	0	1	0.3093	-0.0002	0.0012	0.0001	-0.0002	-0.0002	-0.0003
1000	2000	1	0	0.1852	-0.0001	0.0007	0.0002	0.0001	0.0001	-0.0001
1000	2000	1	1	0.3485	-0.0002	0.0017	0.0002	-0.0001	-0.0001	-0.0001
1000	5000	0	0	0.2518	0.0001	0.0018	0.0003	0.0002	0.0002	0.0001
1000	5000	0	1	0.3569	0.0002	0.0029	0.0004	0.0001	0.0002	0.0001
1000	5000	1	0	0.2042	-0.0001	0.0012	0.0001	0.0002	0.0002	0.0000
1000	5000	1	1	0.3926	0.0004	0.0040	0.0006	0.0004	0.0004	0.0003
1000	10000	0	0	0.2718	0.0003	0.0021	0.0006	0.0004	0.0004	0.0003
1000	10000	0	1	0.3851	0.0001	0.0054	0.0006	0.0000	0.0001	-0.0000
1000	10000	1	0	0.2196	0.0001	0.0016	0.0004	0.0002	0.0002	-0.0000
1000	10000	1	1	0.4159	-0.0000	0.0053	0.0002	0.0000	0.0000	-0.0001

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C11: Bias of estimators for $\mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for binary outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.2303	-0.0003	0.0045	0.0012	0.0001	0.0001	0.0001
200	2000	0	1	0.3426	-0.0001	0.0113	0.0014	0.0001	0.0003	0.0012
200	2000	1	0	0.2313	-0.0006	0.0045	0.0017	-0.0002	0.0000	0.0003
200	2000	1	1	0.3417	-0.0004	0.0111	0.0017	-0.0003	-0.0002	0.0008
200	5000	0	0	0.2581	0.0012	0.0076	0.0023	0.0012	0.0012	0.0013
200	5000	0	1	0.3858	0.0001	0.0148	0.0019	0.0004	0.0003	0.0014
200	5000	1	0	0.2573	0.0011	0.0069	0.0024	0.0011	0.0011	0.0013
200	5000	1	1	0.3858	0.0006	0.0155	0.0018	0.0008	0.0007	0.0016
200	10000	0	0	0.2706	0.0007	0.0079	0.0018	0.0009	0.0009	0.0013
200	10000	0	1	0.4109	0.0010	0.0182	0.0027	0.0012	0.0012	0.0024
200	10000	1	0	0.2706	0.0002	0.0075	0.0018	0.0005	0.0005	0.0009
200	10000	1	1	0.4092	-0.0010	0.0164	0.0010	-0.0007	-0.0006	0.0003
500	2000	0	0	0.1972	-0.0001	0.0015	0.0006	0.0000	0.0000	-0.0000
500	2000	0	1	0.2827	0.0001	0.0030	0.0004	0.0001	0.0002	0.0001
500	2000	1	0	0.1974	-0.0000	0.0014	0.0006	0.0000	0.0000	-0.0001
500	2000	1	1	0.2830	0.0000	0.0030	0.0006	0.0000	0.0001	0.0001
500	5000	0	0	0.2311	-0.0004	0.0016	0.0003	-0.0003	-0.0003	-0.0004
500	5000	0	1	0.3417	-0.0007	0.0042	0.0003	-0.0007	-0.0007	-0.0007
500	5000	1	0	0.2307	-0.0004	0.0020	0.0005	-0.0003	-0.0003	-0.0004
500	5000	1	1	0.3421	-0.0004	0.0046	0.0004	-0.0004	-0.0004	-0.0004
500	10000	0	0	0.2519	0.0005	0.0028	0.0010	0.0006	0.0006	0.0004
500	10000	0	1	0.3764	0.0001	0.0064	0.0004	0.0001	0.0001	0.0000
500	10000	1	0	0.2519	-0.0002	0.0023	0.0003	-0.0002	-0.0002	-0.0003
500	10000	1	1	0.3766	0.0003	0.0068	0.0008	0.0003	0.0003	0.0003
1000	2000	0	0	0.1685	0.0000	0.0005	0.0002	0.0001	0.0001	0.0000
1000	2000	0	1	0.2293	0.0000	0.0007	0.0002	0.0000	0.0000	-0.0000
1000	2000	1	0	0.1682	-0.0000	0.0006	0.0002	-0.0000	-0.0000	-0.0001
1000	2000	1	1	0.2294	-0.0000	0.0008	0.0003	-0.0000	-0.0000	-0.0001
1000	5000	0	0	0.2058	-0.0003	0.0002	0.0001	-0.0002	-0.0002	-0.0003
1000	5000	0	1	0.2984	-0.0001	0.0017	0.0003	-0.0001	-0.0001	-0.0002
1000	5000	1	0	0.2059	-0.0001	0.0008	0.0004	0.0000	0.0000	-0.0000
1000	5000	1	1	0.2984	-0.0004	0.0016	0.0001	-0.0004	-0.0004	-0.0004
1000	10000	0	0	0.2311	0.0003	0.0014	0.0004	0.0003	0.0003	0.0002
1000	10000	0	1	0.3420	0.0002	0.0032	0.0002	0.0002	0.0002	0.0002
1000	10000	1	0	0.2311	0.0001	0.0014	0.0004	0.0002	0.0002	0.0001
1000	10000	1	1	0.3419	-0.0002	0.0029	0.0002	-0.0002	-0.0002	-0.0003

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C12: Bias of estimators for $\mu(1)-\mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for binary outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.0411	0.0005	0.0038	0.0004	0.0002	0.0002	0.0005
200	2000	0	1	0.0422	0.0009	0.0081	0.0009	0.0009	0.0007	0.0009
200	2000	1	0	-0.0119	-0.0014	0.0010	-0.0005	-0.0006	-0.0006	-0.0006
200	2000	1	1	0.0754	0.0005	0.0097	0.0014	0.0011	0.0012	0.0008
200	5000	0	0	0.0346	-0.0007	0.0027	0.0002	-0.0002	-0.0000	0.0002
200	5000	0	1	0.0268	0.0001	0.0094	0.0009	0.0009	0.0010	0.0019
200	5000	1	0	-0.0202	-0.0009	0.0031	-0.0011	-0.0007	-0.0005	-0.0006
200	5000	1	1	0.0520	-0.0016	0.0101	-0.0003	-0.0011	-0.0007	-0.0008
200	10000	0	0	0.0325	-0.0007	0.0037	0.0001	-0.0006	-0.0003	-0.0002
200	10000	0	1	0.0165	-0.0008	0.0105	0.0017	0.0003	0.0006	0.0018
200	10000	1	0	-0.0256	-0.0036	0.0001	-0.0017	-0.0016	-0.0014	-0.0016
200	10000	1	1	0.0406	0.0007	0.0151	0.0016	0.0011	0.0013	0.0020
500	2000	0	0	0.0481	0.0005	0.0017	-0.0001	0.0003	0.0003	0.0001
500	2000	0	1	0.0639	0.0005	0.0031	0.0007	0.0004	0.0004	0.0004
500	2000	1	0	0.0018	0.0004	0.0013	-0.0003	0.0001	0.0001	0.0002
500	2000	1	1	0.1003	-0.0004	0.0025	-0.0002	-0.0003	-0.0003	-0.0004
500	5000	0	0	0.0406	0.0004	0.0022	0.0005	0.0004	0.0004	0.0003
500	5000	0	1	0.0432	0.0003	0.0046	0.0002	0.0004	0.0004	0.0005
500	5000	1	0	-0.0113	-0.0002	0.0013	-0.0000	0.0003	0.0002	0.0002
500	5000	1	1	0.0734	0.0004	0.0050	-0.0001	0.0004	0.0004	0.0003
500	10000	0	0	0.0357	-0.0006	0.0017	-0.0002	-0.0005	-0.0004	-0.0005
500	10000	0	1	0.0302	-0.0008	0.0037	0.0005	-0.0007	-0.0006	-0.0004
500	10000	1	0	-0.0190	0.0001	0.0025	0.0007	0.0006	0.0006	0.0005
500	10000	1	1	0.0574	-0.0003	0.0057	0.0003	-0.0003	-0.0002	-0.0004
1000	2000	0	0	0.0547	-0.0002	0.0001	-0.0002	-0.0002	-0.0002	-0.0002
1000	2000	0	1	0.0800	-0.0003	0.0005	-0.0001	-0.0002	-0.0002	-0.0003
1000	2000	1	0	0.0169	-0.0001	0.0002	-0.0001	0.0002	0.0002	0.0000
1000	2000	1	1	0.1191	-0.0001	0.0009	-0.0001	-0.0001	-0.0000	-0.0000
1000	5000	0	0	0.0460	0.0005	0.0016	0.0001	0.0004	0.0004	0.0004
1000	5000	0	1	0.0585	0.0003	0.0012	0.0000	0.0002	0.0003	0.0003
1000	5000	1	0	-0.0017	-0.0000	0.0004	-0.0003	0.0002	0.0002	0.0001
1000	5000	1	1	0.0942	0.0007	0.0024	0.0005	0.0008	0.0008	0.0007
1000	10000	0	0	0.0408	-0.0000	0.0007	0.0002	0.0001	0.0001	0.0001
1000	10000	0	1	0.0431	-0.0001	0.0023	0.0004	-0.0001	-0.0001	-0.0002
1000	10000	1	0	-0.0115	-0.0000	0.0002	-0.0000	0.0001	0.0001	-0.0001
1000	10000	1	1	0.0740	0.0001	0.0023	-0.0000	0.0002	0.0002	0.0002

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C13: Variance $\times 100$ of estimators for $\mu(1)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for binary outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.2482	0.5484	0.7011	0.3096	0.4921	0.4583	0.4485
200	2000	0	1	0.2115	0.6188	0.9787	0.3440	0.6163	0.5510	0.5672
200	2000	1	0	0.2489	0.6669	0.7903	0.3006	0.4751	0.4473	0.4425
200	2000	1	1	0.1927	0.4835	1.0667	0.3192	0.4572	0.4364	0.4555
200	5000	0	0	0.2390	0.5910	0.8049	0.3456	0.5293	0.4952	0.4966
200	5000	0	1	0.1948	0.7393	1.2453	0.4046	0.7459	0.6420	0.6953
200	5000	1	0	0.2440	0.8230	0.8771	0.3090	0.5148	0.4668	0.4544
200	5000	1	1	0.1620	0.6194	1.3414	0.3760	0.5915	0.5303	0.5513
200	10000	0	0	0.2374	0.6108	0.8536	0.3496	0.5503	0.5238	0.5364
200	10000	0	1	0.1871	0.7508	1.3837	0.4650	0.7499	0.7133	0.7848
200	10000	1	0	0.2369	0.8144	0.9296	0.3186	0.5334	0.4929	0.4908
200	10000	1	1	0.1587	0.6092	1.4945	0.4209	0.5890	0.5733	0.6283
500	2000	0	0	0.1019	0.1611	0.2176	0.1019	0.1505	0.1471	0.1417
500	2000	0	1	0.0961	0.1677	0.2881	0.1045	0.1673	0.1639	0.1608
500	2000	1	0	0.0982	0.2188	0.2670	0.1052	0.1629	0.1590	0.1529
500	2000	1	1	0.0938	0.1344	0.2864	0.0944	0.1280	0.1272	0.1265
500	5000	0	0	0.0961	0.1935	0.2798	0.1174	0.1785	0.1739	0.1678
500	5000	0	1	0.0862	0.2142	0.4137	0.1311	0.2144	0.2088	0.2077
500	5000	1	0	0.0997	0.2747	0.3275	0.1140	0.1917	0.1824	0.1712
500	5000	1	1	0.0773	0.1887	0.4656	0.1205	0.1775	0.1759	0.1739
500	10000	0	0	0.0954	0.2122	0.3178	0.1270	0.1948	0.1893	0.1842
500	10000	0	1	0.0789	0.2475	0.5174	0.1511	0.2447	0.2394	0.2411
500	10000	1	0	0.1004	0.3115	0.3727	0.1242	0.2134	0.2017	0.1910
500	10000	1	1	0.0651	0.2079	0.5835	0.1346	0.1911	0.1912	0.1920
1000	2000	0	0	0.0481	0.0644	0.0793	0.0442	0.0617	0.0613	0.0599
1000	2000	0	1	0.0499	0.0553	0.0820	0.0360	0.0554	0.0549	0.0536
1000	2000	1	0	0.0493	0.0944	0.1084	0.0514	0.0763	0.0751	0.0716
1000	2000	1	1	0.0490	0.0453	0.0767	0.0332	0.0442	0.0443	0.0442
1000	5000	0	0	0.0497	0.0819	0.1170	0.0534	0.0772	0.0765	0.0751
1000	5000	0	1	0.0468	0.0885	0.1687	0.0556	0.0884	0.0875	0.0857
1000	5000	1	0	0.0496	0.1165	0.1439	0.0542	0.0869	0.0849	0.0805
1000	5000	1	1	0.0427	0.0741	0.1739	0.0493	0.0709	0.0703	0.0689
1000	10000	0	0	0.0495	0.0960	0.1452	0.0592	0.0877	0.0868	0.0846
1000	10000	0	1	0.0438	0.1056	0.2258	0.0656	0.1052	0.1046	0.1032
1000	10000	1	0	0.0492	0.1323	0.1708	0.0562	0.0943	0.0924	0.0874
1000	10000	1	1	0.0388	0.0911	0.2404	0.0578	0.0855	0.0851	0.0831

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C14: Variance $\times 100$ of estimators for $\mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for binary outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.2441	0.2851	0.3484	0.1682	0.2669	0.2531	0.2450
200	2000	0	1	0.2525	0.2784	0.4393	0.1651	0.2769	0.2668	0.2797
200	2000	1	0	0.2515	0.2605	0.3421	0.1696	0.2541	0.2450	0.2458
200	2000	1	1	0.2508	0.2575	0.4215	0.1631	0.2571	0.2548	0.2746
200	5000	0	0	0.2545	0.3198	0.4088	0.1842	0.2978	0.2830	0.2782
200	5000	0	1	0.2490	0.3638	0.5784	0.1990	0.3646	0.3316	0.3438
200	5000	1	0	0.2573	0.3257	0.4074	0.1892	0.3079	0.2911	0.2862
200	5000	1	1	0.2420	0.4091	0.5685	0.1871	0.4051	0.3288	0.3436
200	10000	0	0	0.2546	0.3305	0.4400	0.1924	0.3141	0.3027	0.3022
200	10000	0	1	0.2365	0.3982	0.6552	0.2103	0.3981	0.3665	0.3890
200	10000	1	0	0.2511	0.3352	0.4366	0.1943	0.3161	0.2998	0.2997
200	10000	1	1	0.2367	0.3755	0.6431	0.2046	0.3772	0.3477	0.3651
500	2000	0	0	0.0911	0.0809	0.1013	0.0558	0.0787	0.0781	0.0772
500	2000	0	1	0.0995	0.0770	0.1116	0.0464	0.0769	0.0763	0.0734
500	2000	1	0	0.0912	0.0807	0.1019	0.0552	0.0777	0.0770	0.0763
500	2000	1	1	0.0983	0.0764	0.1138	0.0468	0.0767	0.0757	0.0748
500	5000	0	0	0.0964	0.1026	0.1366	0.0636	0.0974	0.0961	0.0929
500	5000	0	1	0.1014	0.0993	0.1746	0.0597	0.0994	0.0972	0.0954
500	5000	1	0	0.0991	0.1027	0.1372	0.0667	0.0988	0.0978	0.0965
500	5000	1	1	0.1010	0.1050	0.1809	0.0619	0.1050	0.1015	0.0989
500	10000	0	0	0.0982	0.1220	0.1614	0.0721	0.1159	0.1109	0.1059
500	10000	0	1	0.0978	0.1342	0.2304	0.0686	0.1342	0.1255	0.1199
500	10000	1	0	0.0988	0.1143	0.1549	0.0694	0.1088	0.1067	0.1038
500	10000	1	1	0.0984	0.1211	0.2243	0.0707	0.1204	0.1188	0.1169
1000	2000	0	0	0.0416	0.0317	0.0372	0.0223	0.0313	0.0312	0.0311
1000	2000	0	1	0.0436	0.0245	0.0311	0.0154	0.0246	0.0245	0.0243
1000	2000	1	0	0.0405	0.0320	0.0368	0.0223	0.0315	0.0313	0.0307
1000	2000	1	1	0.0441	0.0255	0.0313	0.0153	0.0256	0.0248	0.0236
1000	5000	0	0	0.0474	0.0436	0.0562	0.0287	0.0422	0.0419	0.0411
1000	5000	0	1	0.0491	0.0416	0.0659	0.0253	0.0416	0.0410	0.0401
1000	5000	1	0	0.0471	0.0433	0.0556	0.0291	0.0418	0.0416	0.0412
1000	5000	1	1	0.0502	0.0397	0.0639	0.0254	0.0397	0.0397	0.0390
1000	10000	0	0	0.0485	0.0523	0.0716	0.0331	0.0501	0.0499	0.0489
1000	10000	0	1	0.0492	0.0526	0.0951	0.0303	0.0526	0.0521	0.0512
1000	10000	1	0	0.0485	0.0513	0.0695	0.0316	0.0492	0.0484	0.0466
1000	10000	1	1	0.0499	0.0523	0.0937	0.0302	0.0522	0.0515	0.0494

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C15: Variance $\times 100$ of estimators for $\mu(1) - \mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for binary outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.4923	0.8198	1.0523	0.4704	0.7407	0.6944	0.6833
200	2000	0	1	0.4623	0.9027	1.4540	0.5083	0.8984	0.8208	0.8497
200	2000	1	0	0.5076	0.9313	1.1331	0.4586	0.7239	0.6871	0.6821
200	2000	1	1	0.4385	0.7381	1.5213	0.4792	0.7171	0.6930	0.7275
200	5000	0	0	0.4894	0.9046	1.2129	0.5297	0.8237	0.7762	0.7718
200	5000	0	1	0.4413	1.0765	1.8560	0.5930	1.0801	0.9537	1.0212
200	5000	1	0	0.4983	1.1616	1.3019	0.5020	0.8309	0.7673	0.7531
200	5000	1	1	0.3999	1.0339	1.9320	0.5574	0.9989	0.8590	0.8964
200	10000	0	0	0.4933	0.9540	1.3129	0.5444	0.8700	0.8321	0.8479
200	10000	0	1	0.4205	1.1483	2.0524	0.6738	1.1448	1.0804	1.1742
200	10000	1	0	0.4939	1.1296	1.3499	0.5050	0.8327	0.7780	0.7797
200	10000	1	1	0.3979	0.9989	2.1432	0.6339	0.9844	0.9369	1.0182
500	2000	0	0	0.1940	0.2383	0.3259	0.1526	0.2236	0.2196	0.2129
500	2000	0	1	0.1952	0.2403	0.4100	0.1463	0.2394	0.2350	0.2295
500	2000	1	0	0.1924	0.2954	0.3696	0.1531	0.2326	0.2279	0.2204
500	2000	1	1	0.1956	0.2059	0.4100	0.1367	0.2002	0.1989	0.1980
500	5000	0	0	0.1907	0.2915	0.4194	0.1765	0.2714	0.2660	0.2574
500	5000	0	1	0.1888	0.3140	0.6028	0.1870	0.3139	0.3058	0.3022
500	5000	1	0	0.2028	0.3859	0.4803	0.1813	0.2933	0.2827	0.2699
500	5000	1	1	0.1782	0.2927	0.6585	0.1785	0.2807	0.2748	0.2701
500	10000	0	0	0.1907	0.3341	0.4859	0.1969	0.3089	0.2975	0.2855
500	10000	0	1	0.1779	0.3844	0.7528	0.2208	0.3811	0.3678	0.3641
500	10000	1	0	0.1976	0.4286	0.5377	0.1915	0.3249	0.3102	0.2946
500	10000	1	1	0.1663	0.3254	0.8049	0.2044	0.3079	0.3060	0.3044
1000	2000	0	0	0.0891	0.0898	0.1136	0.0591	0.0855	0.0850	0.0837
1000	2000	0	1	0.0943	0.0761	0.1145	0.0481	0.0761	0.0755	0.0739
1000	2000	1	0	0.0897	0.1205	0.1420	0.0664	0.1005	0.0992	0.0954
1000	2000	1	1	0.0921	0.0655	0.1082	0.0436	0.0643	0.0636	0.0622
1000	5000	0	0	0.0973	0.1236	0.1753	0.0789	0.1162	0.1152	0.1130
1000	5000	0	1	0.0948	0.1267	0.2378	0.0775	0.1265	0.1249	0.1225
1000	5000	1	0	0.0955	0.1582	0.2008	0.0796	0.1254	0.1232	0.1186
1000	5000	1	1	0.0927	0.1126	0.2434	0.0727	0.1093	0.1087	0.1067
1000	10000	0	0	0.0960	0.1467	0.2161	0.0909	0.1359	0.1348	0.1313
1000	10000	0	1	0.0923	0.1571	0.3334	0.0941	0.1564	0.1553	0.1531
1000	10000	1	0	0.0977	0.1840	0.2437	0.0876	0.1429	0.1401	0.1337
1000	10000	1	1	0.0882	0.1418	0.3389	0.0862	0.1358	0.1348	0.1307

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C16: Mean squared error of estimators for $\mu(1)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for binary outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.0762	0.0055	0.0071	0.0031	0.0049	0.0046	0.0045
200	2000	0	1	0.1502	0.0062	0.0102	0.0034	0.0062	0.0055	0.0057
200	2000	1	0	0.0506	0.0067	0.0079	0.0030	0.0048	0.0045	0.0044
200	2000	1	1	0.1759	0.0048	0.0111	0.0032	0.0046	0.0044	0.0046
200	5000	0	0	0.0881	0.0059	0.0082	0.0035	0.0053	0.0050	0.0050
200	5000	0	1	0.1722	0.0074	0.0130	0.0041	0.0075	0.0064	0.0070
200	5000	1	0	0.0586	0.0082	0.0089	0.0031	0.0051	0.0047	0.0045
200	5000	1	1	0.1933	0.0062	0.0141	0.0038	0.0059	0.0053	0.0055
200	10000	0	0	0.0943	0.0061	0.0087	0.0035	0.0055	0.0052	0.0054
200	10000	0	1	0.1845	0.0075	0.0147	0.0047	0.0075	0.0071	0.0079
200	10000	1	0	0.0624	0.0082	0.0094	0.0032	0.0053	0.0049	0.0049
200	10000	1	1	0.2039	0.0061	0.0159	0.0042	0.0059	0.0057	0.0063
500	2000	0	0	0.0612	0.0016	0.0022	0.0010	0.0015	0.0015	0.0014
500	2000	0	1	0.1211	0.0017	0.0029	0.0010	0.0017	0.0016	0.0016
500	2000	1	0	0.0406	0.0022	0.0027	0.0011	0.0016	0.0016	0.0015
500	2000	1	1	0.1479	0.0013	0.0029	0.0009	0.0013	0.0013	0.0013
500	5000	0	0	0.0748	0.0019	0.0028	0.0012	0.0018	0.0017	0.0017
500	5000	0	1	0.1490	0.0021	0.0042	0.0013	0.0021	0.0021	0.0021
500	5000	1	0	0.0492	0.0027	0.0033	0.0011	0.0019	0.0018	0.0017
500	5000	1	1	0.1734	0.0019	0.0047	0.0012	0.0018	0.0018	0.0017
500	10000	0	0	0.0837	0.0021	0.0032	0.0013	0.0019	0.0019	0.0018
500	10000	0	1	0.1662	0.0025	0.0053	0.0015	0.0024	0.0024	0.0024
500	10000	1	0	0.0553	0.0031	0.0037	0.0012	0.0021	0.0020	0.0019
500	10000	1	1	0.1890	0.0021	0.0060	0.0013	0.0019	0.0019	0.0019
1000	2000	0	0	0.0503	0.0006	0.0008	0.0004	0.0006	0.0006	0.0006
1000	2000	0	1	0.0962	0.0006	0.0008	0.0004	0.0006	0.0005	0.0005
1000	2000	1	0	0.0348	0.0009	0.0011	0.0005	0.0008	0.0008	0.0007
1000	2000	1	1	0.1219	0.0005	0.0008	0.0003	0.0004	0.0004	0.0004
1000	5000	0	0	0.0639	0.0008	0.0012	0.0005	0.0008	0.0008	0.0008
1000	5000	0	1	0.1279	0.0009	0.0017	0.0006	0.0009	0.0009	0.0009
1000	5000	1	0	0.0422	0.0012	0.0014	0.0005	0.0009	0.0008	0.0008
1000	5000	1	1	0.1546	0.0007	0.0018	0.0005	0.0007	0.0007	0.0007
1000	10000	0	0	0.0744	0.0010	0.0015	0.0006	0.0009	0.0009	0.0008
1000	10000	0	1	0.1487	0.0011	0.0023	0.0007	0.0011	0.0010	0.0010
1000	10000	1	0	0.0487	0.0013	0.0017	0.0006	0.0009	0.0009	0.0009
1000	10000	1	1	0.1734	0.0009	0.0024	0.0006	0.0009	0.0009	0.0008

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C17: Mean squared error of estimators for $\mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for binary outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.0555	0.0029	0.0035	0.0017	0.0027	0.0025	0.0024
200	2000	0	1	0.1199	0.0028	0.0045	0.0017	0.0028	0.0027	0.0028
200	2000	1	0	0.0560	0.0026	0.0034	0.0017	0.0025	0.0025	0.0025
200	2000	1	1	0.1193	0.0026	0.0043	0.0016	0.0026	0.0025	0.0027
200	5000	0	0	0.0691	0.0032	0.0041	0.0018	0.0030	0.0028	0.0028
200	5000	0	1	0.1513	0.0036	0.0060	0.0020	0.0036	0.0033	0.0034
200	5000	1	0	0.0688	0.0033	0.0041	0.0019	0.0031	0.0029	0.0029
200	5000	1	1	0.1513	0.0041	0.0059	0.0019	0.0041	0.0033	0.0034
200	10000	0	0	0.0758	0.0033	0.0045	0.0019	0.0031	0.0030	0.0030
200	10000	0	1	0.1712	0.0040	0.0069	0.0021	0.0040	0.0037	0.0039
200	10000	1	0	0.0757	0.0034	0.0044	0.0019	0.0032	0.0030	0.0030
200	10000	1	1	0.1698	0.0038	0.0067	0.0020	0.0038	0.0035	0.0037
500	2000	0	0	0.0398	0.0008	0.0010	0.0006	0.0008	0.0008	0.0008
500	2000	0	1	0.0809	0.0008	0.0011	0.0005	0.0008	0.0008	0.0007
500	2000	1	0	0.0399	0.0008	0.0010	0.0006	0.0008	0.0008	0.0008
500	2000	1	1	0.0811	0.0008	0.0011	0.0005	0.0008	0.0008	0.0007
500	5000	0	0	0.0544	0.0010	0.0014	0.0006	0.0010	0.0010	0.0009
500	5000	0	1	0.1178	0.0010	0.0018	0.0006	0.0010	0.0010	0.0010
500	5000	1	0	0.0542	0.0010	0.0014	0.0007	0.0010	0.0010	0.0010
500	5000	1	1	0.1180	0.0010	0.0018	0.0006	0.0011	0.0010	0.0010
500	10000	0	0	0.0645	0.0012	0.0016	0.0007	0.0012	0.0011	0.0011
500	10000	0	1	0.1427	0.0013	0.0023	0.0007	0.0013	0.0013	0.0012
500	10000	1	0	0.0644	0.0011	0.0016	0.0007	0.0011	0.0011	0.0010
500	10000	1	1	0.1428	0.0012	0.0023	0.0007	0.0012	0.0012	0.0012
1000	2000	0	0	0.0288	0.0003	0.0004	0.0002	0.0003	0.0003	0.0003
1000	2000	0	1	0.0530	0.0002	0.0003	0.0002	0.0002	0.0002	0.0002
1000	2000	1	0	0.0287	0.0003	0.0004	0.0002	0.0003	0.0003	0.0003
1000	2000	1	1	0.0530	0.0003	0.0003	0.0002	0.0003	0.0002	0.0002
1000	5000	0	0	0.0428	0.0004	0.0006	0.0003	0.0004	0.0004	0.0004
1000	5000	0	1	0.0896	0.0004	0.0007	0.0003	0.0004	0.0004	0.0004
1000	5000	1	0	0.0429	0.0004	0.0006	0.0003	0.0004	0.0004	0.0004
1000	5000	1	1	0.0896	0.0004	0.0006	0.0003	0.0004	0.0004	0.0004
1000	10000	0	0	0.0539	0.0005	0.0007	0.0003	0.0005	0.0005	0.0005
1000	10000	0	1	0.1175	0.0005	0.0010	0.0003	0.0005	0.0005	0.0005
1000	10000	1	0	0.0539	0.0005	0.0007	0.0003	0.0005	0.0005	0.0005
1000	10000	1	1	0.1174	0.0005	0.0009	0.0003	0.0005	0.0005	0.0005

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table C18: Mean squared error of estimators for $\mu(1) - \mu(0)$ across different magnitudes of effect modification ($\theta_1^1 - \theta_1^0$), selection effects (β_1), and sample sizes in simulations for binary outcomes.

n_{RCT}	n	$\theta_1^1 - \theta_1^0$	β_1	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	2000	0	0	0.0066	0.0082	0.0105	0.0047	0.0074	0.0069	0.0068
200	2000	0	1	0.0064	0.0090	0.0146	0.0051	0.0090	0.0082	0.0085
200	2000	1	0	0.0052	0.0093	0.0113	0.0046	0.0072	0.0069	0.0068
200	2000	1	1	0.0101	0.0074	0.0153	0.0048	0.0072	0.0069	0.0073
200	5000	0	0	0.0061	0.0090	0.0121	0.0053	0.0082	0.0078	0.0077
200	5000	0	1	0.0051	0.0108	0.0186	0.0059	0.0108	0.0095	0.0102
200	5000	1	0	0.0054	0.0116	0.0130	0.0050	0.0083	0.0077	0.0075
200	5000	1	1	0.0067	0.0103	0.0194	0.0056	0.0100	0.0086	0.0090
200	10000	0	0	0.0060	0.0095	0.0131	0.0054	0.0087	0.0083	0.0085
200	10000	0	1	0.0045	0.0115	0.0206	0.0067	0.0114	0.0108	0.0117
200	10000	1	0	0.0056	0.0113	0.0135	0.0051	0.0083	0.0078	0.0078
200	10000	1	1	0.0056	0.0100	0.0217	0.0063	0.0098	0.0094	0.0102
500	2000	0	0	0.0043	0.0024	0.0033	0.0015	0.0022	0.0022	0.0021
500	2000	0	1	0.0060	0.0024	0.0041	0.0015	0.0024	0.0023	0.0023
500	2000	1	0	0.0019	0.0030	0.0037	0.0015	0.0023	0.0023	0.0022
500	2000	1	1	0.0120	0.0021	0.0041	0.0014	0.0020	0.0020	0.0020
500	5000	0	0	0.0036	0.0029	0.0042	0.0018	0.0027	0.0027	0.0026
500	5000	0	1	0.0038	0.0031	0.0060	0.0019	0.0031	0.0031	0.0030
500	5000	1	0	0.0022	0.0039	0.0048	0.0018	0.0029	0.0028	0.0027
500	5000	1	1	0.0072	0.0029	0.0066	0.0018	0.0028	0.0027	0.0027
500	10000	0	0	0.0032	0.0033	0.0049	0.0020	0.0031	0.0030	0.0029
500	10000	0	1	0.0027	0.0038	0.0075	0.0022	0.0038	0.0037	0.0036
500	10000	1	0	0.0023	0.0043	0.0054	0.0019	0.0032	0.0031	0.0029
500	10000	1	1	0.0050	0.0033	0.0081	0.0020	0.0031	0.0031	0.0030
1000	2000	0	0	0.0039	0.0009	0.0011	0.0006	0.0009	0.0009	0.0008
1000	2000	0	1	0.0074	0.0008	0.0011	0.0005	0.0008	0.0008	0.0007
1000	2000	1	0	0.0012	0.0012	0.0014	0.0007	0.0010	0.0010	0.0010
1000	2000	1	1	0.0151	0.0007	0.0011	0.0004	0.0006	0.0006	0.0006
1000	5000	0	0	0.0031	0.0012	0.0018	0.0008	0.0012	0.0012	0.0011
1000	5000	0	1	0.0044	0.0013	0.0024	0.0008	0.0013	0.0012	0.0012
1000	5000	1	0	0.0010	0.0016	0.0020	0.0008	0.0013	0.0012	0.0012
1000	5000	1	1	0.0098	0.0011	0.0024	0.0007	0.0011	0.0011	0.0011
1000	10000	0	0	0.0026	0.0015	0.0022	0.0009	0.0014	0.0013	0.0013
1000	10000	0	1	0.0028	0.0016	0.0033	0.0009	0.0016	0.0016	0.0015
1000	10000	1	0	0.0011	0.0018	0.0024	0.0009	0.0014	0.0014	0.0013
1000	10000	1	1	0.0064	0.0014	0.0034	0.0009	0.0014	0.0013	0.0013

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

D Simulation studies for non-nested trial designs

To confirm the theoretical results about non-nested trial designs we conducted an additional simulation study, focusing on continuous outcomes with a strong treatment effect and effect modification (our simulations for nested trial designs suggested that these scenarios showed the most prominent differences in the performance of different methods).

D.1 Methods for simulation studies for non-nested trial designs

We began by simulating cohorts of n = 20,000, 50,000, or 100,000 individuals with the number of randomized individuals n_{RCT} approximately equal to 200, 500, or 1000 (note that the cohort sizes are ten times larger than those used for nested trial designs). Specifically, we generated baseline covariates for cohorts of 20,000, 50,000, or 100,000 individuals as $X = (1, X_1, X_2, X_3)$, where X_j, $j = 1, 2, 3$, had independent standard normal distributions. We then simulated selection into the trial using a binary indicator S with $\operatorname{logit} \Pr[S = 1|X] = \beta X^\intercal$, $\beta = (\beta_0, 1, 1, 1)$. We chose β_0 using numerical methods [19], such that for a given cohort sample size n the trial sample size n_{RCT} was 200, 500, or 1000. The coefficients of the covariates X_1, X_2, and X_3 were all equal to 1, representing strong selection. We then took a simple random sample of 10% of the non-participants ($S = 0$) in the simulated cohort of sample size n, resulting in average samples sizes for the sample of the target population of $\widetilde{n}_{\text{obs}} = 0.1 \times (n - n_{\text{RCT}})$. This sampling step in the simulation is meant to reflect the sampling properties described in Subsection B.1. The resulting composite dataset had average sample size $\widetilde{n} = n_{\text{RCT}} + \widetilde{n}_{\text{obs}}$, and was analysed without using any information about the sampling probability for non-participants (that probability would be unknown in actual studies using

a non-nested design).

We generated potential outcomes as $Y^a = \theta^a X^\intercal + \epsilon^a$. We used $\theta^1 = (1, 2, 1, 1)$ and $\theta^0 = (0, 1, 1, 1)$ in all scenarios and independent standard normal distributions for ϵ^a. For observations "selected" into the trial ($S = 1$) we generated treatment assignment A as a binomial random variable with parameter 0.5 (i.e., we simulated marginally randomized trials). Last, we generated observed outcomes as $Y = AY^1 + (1 - A)Y^0$.

For each simulated dataset, we applied the estimators in equations (B.9) through (B.13), and also obtained a trial-only estimator of the treatment effect. All working models required for the different estimators were correctly specified, in the sense that the true models were nested within the parametric working models on which the estimators relied. Specifically, outcome models included main effects for all covariates and were fit separately in each arm; logistic regression models for trial participation and treatment included the main effects of all covariates; all models had intercept terms. We estimated the bias and variance for each estimator over 10,000 runs for each scenario.

D.2 Results for simulation studies for non-nested trial designs

Table D1: Bias of estimators for $\mu(1)$ for $\theta_1^1 - \theta_1^0 = 1$, $\beta_1 = 1$, and different sample sizes in simulations for continuous outcomes in non-nested trial designs (sampling a random 10% of non-participants in the cohort, i.e., 10% of $n - n_{\text{RCT}}$).

n_{RCT}	n	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	20000	3.6954	0.0145	0.3172	-0.0007	-0.0007	-0.0007	0.0001
200	50000	3.8331	0.0148	0.3292	-0.0006	-0.0024	-0.0018	-0.0018
200	100000	3.8979	0.0138	0.3350	0.0005	-0.0005	0.0002	0.0008
500	20000	3.4917	0.0042	0.1511	0.0003	0.0005	0.0007	0.0006
500	50000	3.6958	0.0022	0.1611	0.0001	0.0003	0.0003	0.0001
500	100000	3.8046	0.0058	0.1689	-0.0000	-0.0002	-0.0000	0.0000
1000	20000	3.2905	0.0059	0.0806	-0.0004	-0.0012	-0.0010	-0.0007
1000	50000	3.5493	0.0056	0.0919	-0.0002	-0.0005	-0.0002	-0.0002
1000	100000	3.6955	0.0014	0.0940	-0.0001	0.0001	0.0001	0.0000

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table D2: Bias of estimators for $\mu(0)$ for $\theta_1^1 - \theta_1^0 = 1$, $\beta_1 = 1$, and different sample sizes in simulations for continuous outcomes in non-nested trial designs (sampling a random 10% of non-participants in the cohort, i.e., 10% of $n - n_{\text{RCT}}$).

n_{RCT}	n	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	20000	2.7723	0.0141	0.2391	-0.0001	0.0020	0.0013	0.0008
200	50000	2.8749	0.0168	0.2486	0.0009	0.0007	0.0006	0.0007
200	100000	2.9229	0.0107	0.2500	-0.0003	-0.0002	-0.0000	-0.0005
500	20000	2.6187	0.0054	0.1131	-0.0008	-0.0018	-0.0013	-0.0009
500	50000	2.7717	0.0020	0.1218	-0.0003	-0.0002	-0.0005	-0.0008
500	100000	2.8532	0.0033	0.1258	-0.0007	-0.0011	-0.0010	-0.0008
1000	20000	2.4678	0.0026	0.0568	0.0000	0.0004	0.0005	0.0005
1000	50000	2.6615	-0.0000	0.0644	-0.0001	0.0006	0.0004	0.0001
1000	100000	2.7718	0.0003	0.0689	0.0003	0.0002	0.0001	0.0001

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table D3: Bias of estimators for $\mu(1) - \mu(0)$ for $\theta_1^1 - \theta_1^0 = 1$, $\beta_1 = 1$, and different sample sizes in simulations for continuous outcomes in non-nested trial designs (sampling a random 10% of non-participants in the cohort, i.e., 10% of $n - n_{\text{RCT}}$).

n_{RCT}	n	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	20000	0.9231	0.0004	0.0781	-0.0006	-0.0028	-0.0020	-0.0007
200	50000	0.9582	-0.0020	0.0806	-0.0015	-0.0031	-0.0024	-0.0025
200	100000	0.9751	0.0031	0.0850	0.0008	-0.0003	0.0002	0.0013
500	20000	0.8730	-0.0012	0.0380	0.0011	0.0023	0.0020	0.0014
500	50000	0.9241	0.0002	0.0394	0.0004	0.0005	0.0008	0.0008
500	100000	0.9513	0.0025	0.0431	0.0007	0.0009	0.0010	0.0008
1000	20000	0.8227	0.0033	0.0238	-0.0005	-0.0016	-0.0015	-0.0011
1000	50000	0.8877	0.0056	0.0275	-0.0001	-0.0011	-0.0006	-0.0003
1000	100000	0.9237	0.0011	0.0252	-0.0004	-0.0002	-0.0000	-0.0000

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table D4: Variance of estimators for $\mu(1)$ for $\theta_1^1 - \theta_1^0 = 1$, $\beta_1 = 1$, and different sample sizes in simulations for continuous outcomes in non-nested trial designs (sampling a random 10% of non-participants in the cohort, i.e., 10% of $n - n_{\text{RCT}}$).

n_{RCT}	n	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	20000	0.0621	3.0022	0.8740	0.0452	0.1752	0.0932	0.1019
200	50000	0.0657	2.6788	0.9063	0.0438	0.1760	0.0935	0.1041
200	100000	0.0657	2.7220	0.9214	0.0423	0.1757	0.0935	0.1043
500	20000	0.0234	1.3030	0.5183	0.0190	0.0697	0.0457	0.0431
500	50000	0.0248	1.1689	0.5579	0.0175	0.0769	0.0465	0.0437
500	100000	0.0254	1.2036	0.5701	0.0170	0.0718	0.0465	0.0440
1000	20000	0.0112	0.4883	0.3075	0.0107	0.0335	0.0255	0.0226
1000	50000	0.0120	0.5524	0.3468	0.0093	0.0366	0.0259	0.0229
1000	100000	0.0122	0.5864	0.3701	0.0087	0.0360	0.0265	0.0233

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table D5: Variance of estimators for $\mu(0)$ for $\theta_1^1 - \theta_1^0 = 1$, $\beta_1 = 1$, and different sample sizes in simulations for continuous outcomes in non-nested trial designs (sampling a random 10% of non-participants in the cohort, i.e., 10% of $n - n_{\text{RCT}}$).

n_{RCT}	n	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	20000	0.0355	2.4693	0.5017	0.0441	0.1712	0.0924	0.1016
200	50000	0.0371	2.3038	0.5200	0.0430	0.1834	0.0928	0.1037
200	100000	0.0374	2.6822	0.5258	0.0421	0.1780	0.0934	0.1038
500	20000	0.0133	0.9520	0.2955	0.0175	0.0709	0.0437	0.0412
500	50000	0.0141	1.8336	0.3148	0.0170	0.0701	0.0456	0.0430
500	100000	0.0147	0.9944	0.3271	0.0168	0.0755	0.0468	0.0441
1000	20000	0.0064	0.3454	0.1748	0.0091	0.0304	0.0238	0.0210
1000	50000	0.0068	0.4255	0.2000	0.0087	0.0360	0.0258	0.0226
1000	100000	0.0071	0.4697	0.2090	0.0083	0.0364	0.0262	0.0230

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table D6: Variance of estimators for $\mu(1) - \mu(0)$ for $\theta_1^1 - \theta_1^0 = 1$, $\beta_1 = 1$, and different sample sizes in simulations for continuous outcomes in non-nested trial designs (sampling a random 10% of non-participants in the cohort, i.e., 10% of $n - n_{\text{RCT}}$).

n_{RCT}	n	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	20000	0.0975	5.4945	1.4083	0.0858	0.3418	0.1822	0.2000
200	50000	0.1026	4.9770	1.4481	0.0853	0.3555	0.1838	0.2054
200	100000	0.1034	5.4066	1.4528	0.0835	0.3526	0.1862	0.2074
500	20000	0.0368	2.2682	0.8342	0.0325	0.1367	0.0856	0.0804
500	50000	0.0389	3.0153	0.8853	0.0330	0.1456	0.0909	0.0855
500	100000	0.0399	2.2073	0.9106	0.0331	0.1467	0.0926	0.0873
1000	20000	0.0175	0.8411	0.4920	0.0159	0.0599	0.0454	0.0397
1000	50000	0.0187	0.9861	0.5568	0.0163	0.0709	0.0500	0.0439
1000	100000	0.0193	1.0603	0.5861	0.0162	0.0714	0.0518	0.0454

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table D7: Mean squared error of estimators for $\mu(1)$ for $\theta_1^1 - \theta_1^0 = 1$, $\beta_1 = 1$, and different sample sizes in simulations for continuous outcomes in non-nested trial designs (sampling a random 10% of non-participants in the cohort, i.e., 10% of $n - n_{\text{RCT}}$).

n_{RCT}	n	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	20000	13.7178	3.0025	0.9746	0.0452	0.1752	0.0932	0.1019
200	50000	14.7581	2.6791	1.0147	0.0438	0.1760	0.0935	0.1041
200	100000	15.2596	2.7222	1.0336	0.0423	0.1757	0.0935	0.1043
500	20000	12.2155	1.3031	0.5411	0.0190	0.0697	0.0457	0.0431
500	50000	13.6834	1.1689	0.5839	0.0175	0.0769	0.0465	0.0437
500	100000	14.5003	1.2037	0.5987	0.0170	0.0718	0.0465	0.0440
1000	20000	10.8387	0.4884	0.3140	0.0107	0.0335	0.0255	0.0226
1000	50000	12.6094	0.5524	0.3553	0.0093	0.0366	0.0259	0.0229
1000	100000	13.6690	0.5864	0.3789	0.0087	0.0360	0.0265	0.0233

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table D8: Mean squared error of estimators for $\mu(0)$ for $\theta_1^1 - \theta_1^0 = 1$, $\beta_1 = 1$, and different sample sizes in simulations for continuous outcomes in non-nested trial designs (sampling a random 10% of non-participants in the cohort, i.e., 10% of $n - n_{\text{RCT}}$).

n_{RCT}	n	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	20000	7.7209	2.4695	0.5589	0.0441	0.1712	0.0924	0.1016
200	50000	8.3022	2.3041	0.5818	0.0430	0.1834	0.0928	0.1037
200	100000	8.5804	2.6823	0.5883	0.0421	0.1780	0.0934	0.1038
500	20000	6.8708	0.9520	0.3083	0.0175	0.0709	0.0437	0.0412
500	50000	7.6963	1.8336	0.3297	0.0170	0.0701	0.0456	0.0430
500	100000	8.1557	0.9944	0.3429	0.0168	0.0755	0.0468	0.0441
1000	20000	6.0966	0.3454	0.1781	0.0091	0.0304	0.0238	0.0210
1000	50000	7.0906	0.4255	0.2042	0.0087	0.0360	0.0258	0.0226
1000	100000	7.6897	0.4697	0.2137	0.0083	0.0364	0.0262	0.0230

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

Table D9: Mean squared error of estimators for $\mu(1) - \mu(0)$ for $\theta_1^1 - \theta_1^0 = 1$, $\beta_1 = 1$, and different sample sizes in simulations for continuous outcomes in non-nested trial designs (sampling a random 10% of non-participants in the cohort, i.e., 10% of $n - n_{\text{RCT}}$).

n_{RCT}	n	**Trial**	**IOW1**	**IOW2**	**OM**	**DR1**	**DR2**	**DR3**
200	20000	0.9497	5.4945	1.4144	0.0858	0.3418	0.1822	0.2000
200	50000	1.0207	4.9771	1.4546	0.0853	0.3555	0.1838	0.2054
200	100000	1.0542	5.4066	1.4601	0.0835	0.3526	0.1862	0.2074
500	20000	0.7990	2.2682	0.8356	0.0325	0.1367	0.0856	0.0804
500	50000	0.8928	3.0153	0.8868	0.0330	0.1456	0.0909	0.0855
500	100000	0.9450	2.2073	0.9125	0.0331	0.1467	0.0926	0.0873
1000	20000	0.6944	0.8411	0.4925	0.0159	0.0599	0.0454	0.0397
1000	50000	0.8068	0.9861	0.5576	0.0163	0.0709	0.0500	0.0439
1000	100000	0.8726	1.0603	0.5868	0.0162	0.0714	0.0518	0.0454

Trial = trial-only, unadjusted estimator; OM = outcome model-based estimator; IOW1 = inverse odds weighting estimator without normalized weights; IOW2 = inverse odds estimator with normalized weights; DR1 = doubly robust estimator without normalized weights; DR2 = doubly robust estimator with normalized weights; DR3 = doubly robust estimator based on weighted multi-variable regression.

E Balance in the CASS analyses

Table E1: Balance post-weighting in the CASS study.

Variable	$S = 1$ (weighted)		$S = 0$		**Balance**	
	Mean	**Variance**	**Mean**	**Variance**	**SMD**	**Var. ratio**
Age	50.93	59.65	50.89	59.70	0.00	1.00
Angina	0.79	0.17	0.80	0.16	0.01	1.02
History of MI	0.58	0.24	0.57	0.24	0.00	1.00
LAD % obstruction	38.56	1420.55	39.14	1500.29	0.02	0.95
Left ventricular score	7.08	6.81	7.07	7.21	0.00	0.94
Diseased vessels	0.63	0.23	0.64	0.23	0.01	1.01
Ejection fraction, %	60.03	147.44	60.16	150.14	0.01	0.98

LAD = left anterior descending coronary artery; MI = myocardial infarction; SMD = standardized mean difference; Var. ratio = variance ratio.

F Functions to implement the methods in R

This section provides R functions to implement the methods using separate regressions to estimate the parameters of each working model. We suggest using these functions for bootstrap-based inference. The current version of the code can be downloaded from https://github.com/serobertson/ExtendingInferences.

Outcome model-based estimator

```
OM_est<-function(data){
  S1data_A1<-subset(data, S==1 & A==1)
  OM1mod<-glm(formula=Y~X1+X2+X3, data=S1data_A1)
  p1<- predict(OM1mod,newdata=data, type="response")
  data$p1<-p1
  S1data_A0<-subset(data, S==1 & A==0)
  OM0mod<-glm(formula=Y~X1+X2+X3, data=S1data_A0)
  p0<- predict(OM0mod,newdata=data, type="response")
  data$p0<-p0
   S0sub<-subset(data, S==0)
   OM_1<-mean(S0sub$p1)
   OM_0<-mean(S0sub$p0)
   OM<-mean(S0sub$p1)-mean(S0sub$p0)
   list<-list(OM_1=OM_1, OM_0=OM_0, OM=OM, p1=p1, p0=p0, OM1mod=OM1mod, OM0mod=OM0mod)
   return(list)
 }
```

Generate weights

```
generate_weights<-function(Smod,Amod, data){
  S1data<-subset(data, S==1)
  w_reg<-glm(Smod, family="binomial", data=data)
  ps<- predict(w_reg,newdata=data, type="response")
  w_reg2<-glm(Amod, family="binomial", data=S1data)
  pa<- predict(w_reg2,newdata=data, type="response")
  w= (data$A*data$S*(1-ps) )/(ps*pa) + ((1 -data$A) *data$S*(1-ps) ) /(ps*(1-pa))
  data$w<-w
  list<-list(dat=data, Smod=w_reg, Amod=w_reg2)
   return(list)
 }
```

IOW1

```
IOW1_est<-function(data){
  A<-data$A
  S<-data$S
  w<-data$w
  Y<-data$Y
  IOW1_1 <-(sum((1-S))^-1)* sum(A*S*w*Y)
  IOW1_0 <-(sum((1-S))^-1)* sum((1-A)*S*w*Y)
  IOW1 = IOW1_1 - IOW1_0
  return(list(IOW1_1=IOW1_1,IOW1_0=IOW1_0, IOW1=IOW1))
 }
```

IOW2

```
IOW2_est<-function(data){
  S0data<-subset(data, S==0)
  S1data_A1<-subset(data, S==1 & A==1)
  IOW1mod<-glm(formula=Y~1, data=S1data_A1, weights=w)
  p1<- predict(IOW1mod,newdata=S0data, type="response")
  S1data_A0<-subset(data, S==1 & A==0)
  IOW0mod<-glm(formula=Y~1, data=S1data_A0, weights=w)
  p0<- predict(IOW0mod,newdata=S0data, type="response")
  IOW2_1<-mean(p1)
   IOW2_0<-mean(p0)
   IOW2<-mean(p1)-mean(p0)
   list<-list(IOW2_1=IOW2_1,IOW2_0=IOW2_0, IOW2=IOW2,IOW1mod=IOW1mod,IOW0mod=IOW0mod)
   return(list)
 }
```

DR1

```
DR1_est<-function(data){
  A<-data$A
  S<-data$S
  Y<-data$Y
  p1<-data$p1
  p0<-data$p0
  w<-data$w
  DR1_1<-(sum((1-S))^-1)* sum(S*A*w*(Y-p1) + (1-S)*p1)
  DR1_0<-(sum((1-S))^-1)* sum(S*(1-A)*w*(Y-p0) + (1-S)*p0)
   DR1<-DR1_1-DR1_0
   list<-list(DR1_1=DR1_1,DR1_0=DR1_0, DR1=DR1)
   return(list)
 }
```

DR2

```
DR2_est<-function(data){
  A<-data$A
  S<-data$S
  Y<-data$Y
  p1<-data$p1
  p0<-data$p0
  w<-data$w
  sum1_DR2<-sum(S*A*w*(Y-p1))
  sum0_DR2<-sum(S*(1-A)*w*(Y-p0))
   norm1<-(sum(S*A*w))^-1
   norm0<-(sum(S*(1-A)*w))^-1
   DR2_1<-norm1*sum1_DR2 + (sum(1-S)^-1)*sum((1-S)*p1)
   DR2_0<-norm0*sum0_DR2 + (sum(1-S)^-1)*sum((1-S)*p0)
   DR2<-DR2_1-DR2_0
   list<-list(DR2_1=DR2_1,DR2_0=DR2_0, DR2=DR2)
   return(list)
 }
```

DR3

```
DR3_est<-function(data){
  S0data<-subset(data, S==0)
  S1data_A1<-subset(data, S==1 & A==1)
  DR1mod<-glm(formula=Y~X1+X2+X3, data=S1data_A1, weights=w)
  p1<- predict(DR1mod,newdata=S0data, type="response")
  S1data_A0<-subset(data, S==1 & A==0)
  DR0mod<-glm(formula=Y~X1+X2+X3, data=S1data_A0, weights=w)
  p0<- predict(DR0mod,newdata=S0data, type="response")
  DR3_1<- mean(p1)
   DR3_0<- mean(p0)
   DR3<-mean(p1)-mean(p0)
   list<-list(DR3_1=DR3_1,DR3_0=DR3_0, DR3=DR3,DR1mod=DR1mod, DR0mod=DR0mod)
   return(list)
 }
```

G Functions for M-estimation in R

These are R functions to implement the methods using an M-estimation approach. All functions require the package geex. The current version of the code can be downloaded from

https://github.com/serobertson/ExtendingInferences.

Outcome regression-based estimator

```
OM_EE <- function(data){
  A<-data$A
  S<- data$S
  Y <- data$Y
  X <- cbind(1, data$X1, data$X2, data$X3)
  matA <- cbind(1, data$A)
  A[is.na(A)] <- 0
  Y[is.na(Y)] <- 0
  function(theta){
    #outcome model
    beta<-theta[1:4]
    alpha<-theta[5:8]
    mu1<-theta[9]
    mu0<-theta[10]
    muate<-theta[11]
    m_A1 <-X %*% beta
    m_A0<-X %*% alpha
    ols_A1 <-crossprod(X, (S*A)*(Y - m_A1))
    ols_A0 <-crossprod(X, (S*(1-A))*(Y - m_A0))
    #estimates
    mean1<-(1-S)*(m_A1-mu1)
    mean0 <- (1-S)*(m_A0-mu0)
    ate<-(1-S)*(m_A1-m_A0-muate)
    c(ols_A1,ols_A0,mean1, mean0,ate)
  }
}
```

IOW1

```
IOW1_EE <- function(data){
  A<-data$A
  S<- data$S
  Y <- data$Y
  X <- cbind(1, data$X1, data$X2, data$X3)
  matA <- cbind(1, data$A)
  A[is.na(A)] <- 0
  Y[is.na(Y)] <- 0
  function(theta){
    mu1<-theta[9]
    mu0<-theta[10]
    mu_ate<-theta[11]
    #participation model
    lp  <- X %*% theta[1:4]
    ps <- plogis(lp)
    score_eqns<-crossprod(X, S-ps)
    #treatment model
    lp2  <- X %*% theta[5:8]
    pa<- plogis(lp2)
    score_eqns2<-crossprod(X,S*(A - pa) )
    w = (A * S*(1-ps))/(ps*pa) + ((1 - A)*S*(1-ps))/(ps*(1-pa))
    #estimates
    summand1<-(w*A*S*Y)
    summand0<-(w*(1-A)*S*Y)
    mean1<-(summand1)- (1-S)*mu1
    mean0<-(summand0)- (1-S)*mu0
    ate<-(summand1)-(summand0)- (1-S)*mu_ate
    c(score_eqns,score_eqns2,mean1,mean0, ate)
   }
 }
```

IOW2

```
IOW2_EE <- function(data){
  A<-data$A
  S<- data$S
  Y <- data$Y
  X <- cbind(1, data$X1, data$X2, data$X3)
  matA <- cbind(1, data$A)
  A[is.na(A)] <- 0
  Y[is.na(Y)] <- 0
  function(theta){
    #participation model
    lp  <- X %*% theta[1:4]
    ps <- plogis(lp)
    score_eqns<-crossprod(X, S-ps)
    #treatment model
    lp2  <- X %*% theta[5:8]
    pa<- plogis(lp2)
    score_eqns2<-crossprod(X,S*(A - pa) )
    w = (A * S*(1-ps))/(ps*pa) + ((1 - A)*S*(1-ps))/(ps*(1-pa))
    #outcome model
    m_A1<-1 %*% theta[9]
    m_A0<-1 %*% theta[10]
    linear_eqns1<-crossprod(1, (S*A*w)*(Y -  m_A1) )
    linear_eqns0<-crossprod(1, (S*(1-A)*w)*(Y - 1 %*% theta[10]) )
    mu1<-theta[11]
    mu0<-theta[12]
    muate<-theta[13]
    #estimates
    mean1 <- (1-S)*( m_A1 -mu1)
    mean0 <- (1-S)*( m_A0 -mu0)
    ate <- (1-S)*(m_A1- m_A0 - muate)
    c(score_eqns,score_eqns2, linear_eqns1,linear_eqns0,  mean1,  mean0,ate)
   }
 }
```

DR1

```
DR1_EE <- function(data){
  A<-data$A
  S<- data$S
  Y <- data$Y
  X <- cbind(1, data$X1, data$X2, data$X3)
  matA <- cbind(1, data$A)
  A[is.na(A)] <- 0
  Y[is.na(Y)] <- 0
  function(theta){
    #participation model
    lp  <- X %*% theta[1:4]
    ps <- plogis(lp)
    score_eqns<-crossprod(X, S-ps)
    #treatment model
    lp2  <- X %*% theta[5:8]
    pa<- plogis(lp2)
    score_eqns2<-crossprod(X,S*(A - pa) )
    w = (A * S*(1-ps))/(ps*pa) + ((1 - A)*S*(1-ps))/(ps*(1-pa))
    #outcome model
    beta<-theta[9:12]
    alpha<-theta[13:16]
    mu1<-theta[17]
    mu0<-theta[18]
    mu<-theta[19]
    m_A1 <-X %*% beta
    m_A0<-X %*% alpha
    ols_A1 <-crossprod(X, (S*A)*(Y - m_A1))
    ols_A0 <-crossprod(X, (S*(1-A))*(Y - m_A0))
    ey1<-w*S*A*(Y-m_A1) + (1-S)*m_A1
    ey0<-w*S*(1-A)*(Y-m_A0) + (1-S)*m_A0
    #estimates
    mean1<-ey1-(1-S)*mu1
    mean0<-ey0-(1-S)*mu0
    ate<-ey1-ey0- (1-S)*mu
    c(score_eqns,score_eqns2,ols_A1,ols_A0,mean1,mean0, ate)
   }
 }
```

DR2

```
DR2_EE <- function(data){
  A<-data$A
  S<- data$S
  Y <- data$Y
  X <- cbind(1, data$X1, data$X2, data$X3)
  matA <- cbind(1, data$A)
  A[is.na(A)] <- 0
  Y[is.na(Y)] <- 0
  function(theta){
    #participation model
    lp  <- X %*% theta[1:4]
    ps <- plogis(lp)
    score_eqns<-crossprod(X, S-ps)
    #treatment model
    lp2  <- X %*% theta[5:8]
    pa<- plogis(lp2)
    score_eqns2<-crossprod(X,S*(A - pa) )
    w = (A * S*(1-ps))/(ps*pa) + ((1 - A)*S*(1-ps))/(ps*(1-pa))
    #outcome model
    beta<-theta[9:12]
    alpha<-theta[13:16]
    mu1<-theta[20]
    mu0<-theta[21]
    mu<-theta[22]
    m_A1 <-X %*% beta
    m_A0<-X %*% alpha
    ols_A1 <-crossprod(X, (S*A)*(Y - m_A1))
    ols_A0 <-crossprod(X, (S*(1-A))*(Y - m_A0))
    mu_S<-theta[17]
    propS1<-S-mu_S
    one_over<-(1/(1-mu_S))
    mu_norm1<-theta[18]
    norm1eq<-(A*S*w)-mu_norm1
    norm1<-1/mu_norm1
    mu_norm0<-theta[19]
    norm0eq<-((1-A)*S*w)-mu_norm0
    norm0<-1/mu_norm0
    ey1<-norm1*((w*S*A*(Y-m_A1))) + one_over*((1-S)*m_A1)
    ey0<-norm0*((w*S*(1-A)*(Y-m_A0))) + one_over*((1-S)*m_A0)
    #estimates
    mean1<-ey1-mu1
    mean0<-ey0-mu0
    ate<-ey1-ey0-mu
    c(score_eqns,score_eqns2,ols_A1,ols_A0,propS1, norm1eq, norm0eq,mean1,mean0,ate)
   }
 }
```

DR3

```
DR3_EE <- function(data){
  A<-data$A
  S<- data$S
  Y <- data$Y
  X <- cbind(1, data$X1, data$X2, data$X3)
  matA <- cbind(1, data$A)
  A[is.na(A)] <- 0
  Y[is.na(Y)] <- 0
  function(theta){
    #participation model
    lp  <- X %*% theta[1:4]
    ps <- plogis(lp)
    score_eqns<-crossprod(X, S-ps)
    #treatment model
    lp2  <- X %*% theta[5:8]
    pa<- plogis(lp2)
    score_eqns2<-crossprod(X,S*(A - pa) )
    w = (A * S*(1-ps))/(ps*pa) + ((1 - A)*S*(1-ps))/(ps*(1-pa))
    #outcome model
    beta<-theta[9:12]
    alpha<-theta[13:16]
    mu1<-theta[17]
    mu0<-theta[18]
    mu<-theta[19]
    m_A1 <-X %*% beta
    m_A0<-X %*% alpha
    ols_A1 <-crossprod(X, (S*A*w)*(Y - m_A1))
    ols_A0 <-crossprod(X, (S*(1-A)*w)*(Y - m_A0))
    #estimates
    mean1 <- (1-S)*(m_A1-mu1)
    mean0 <- (1-S)*(m_A0-mu0)
    mean <- (1-S)*(m_A1-m_A0-mu)
    c(score_eqns,score_eqns2,ols_A1,ols_A0,mean1,mean0, mean)
   }
 }
```

H Simulation code

`Stata` code to replciate the results of the simulations reported in the main text is available at https://github.com/serobertson/ExtendingInferences/blob/master/simulationStata.do.

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