

Identification and estimation of causal effects using non-concurrent controls in platform trials

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Abstract

Platform trials are multi-arm designs that simultaneously evaluate multiple treatments for a single disease within the same overall trial structure. Unlike traditional randomized controlled trials, they allow treatment arms to enter and exit the trial at distinct times while maintaining a control arm throughout. This control arm comprises both concurrent controls, where participants are randomized concurrently to either the treatment or control arm, and non-concurrent controls, who enter the trial when the treatment arm under study is unavailable. While flexible, platform trials introduce a unique challenge with the use of non-concurrent controls, raising questions about how to efficiently utilize their data to estimate treatment effects. Specifically, what estimands should be used to evaluate the causal effect of a treatment versus control? Under what assumptions can these estimands be identified and estimated? Do we achieve any efficiency gains? In this paper, we use structural causal models and counterfactuals to clarify estimands and formalize their identification in the presence of non-concurrent controls in platform trials. We also provide outcome regression, inverse probability weighting, and doubly robust estimators for their estimation. We discuss efficiency gains, demonstrate their performance in a simulation study, and apply them to the ACTT platform trial, resulting in a 20% improvement in precision.

Keywords: adaptive trials; causality; doubly robust; efficiency; estimand

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1 Introduction

Platform trials are multi-arm designs that simultaneously evaluate multiple treatments for a single disease within the same overall trial structure (Woodcock & LaVange 2017, Berry et al. 2015, Park et al. 2022). Unlike traditional randomized controlled trials, they allow treatment arms to enter and exit the trial at distinct times while maintaining a control arm throughout. These trials have been instrumental in assessing the efficacy of treatments across various therapeutic areas (Barker et al. 2009, Foltynie et al. 2023, Wells et al. 2012, among others) and gained traction during the COVID-19 pandemic (Hayward et al. 2021, Angus et al. 2020, Kalil et al. 2021, among others). For instance, the Adaptive COVID-19 Treatment Trial (ACTT) (Kalil et al. 2021) was a platform trial that investigated treatments for hospitalized adult patients with COVID-19 pneumonia. ACTT comprised of multiple stages, as depicted in Figure 1. In the initial stage (ACTT-1), the efficacy of remdesivir alone versus placebo was evaluated. Subsequently, in the second stage (ACTT-2), placebo was discontinued, and a new treatment, remdesivir plus baricitinib, was introduced while concurrently randomizing participants to remdesivir alone. Here, the remdesivir alone arm served as a shared arm between the ACTT-1 and ACTT-2 stages. The remdesivir alone arm is termed *non-concurrent* for remdesivir plus baricitinib during ACTT-1 and *concurrent* during ACTT-2. In this paper, we adhere to the terminology used in current literature (Bofill Roig et al. 2023, Lee & Wason 2020) and designate the shared arm as *control*, irrespective of whether it is a placebo arm or an active control or an experimental treatment. Thus, we consistently use the terms concurrent and non-concurrent controls regardless of the nature of the shared arm.

The central question revolves around the effective utilization of non-concurrent controls to estimate treatment effects in platform trials. Specifically, *what estimands should be used*

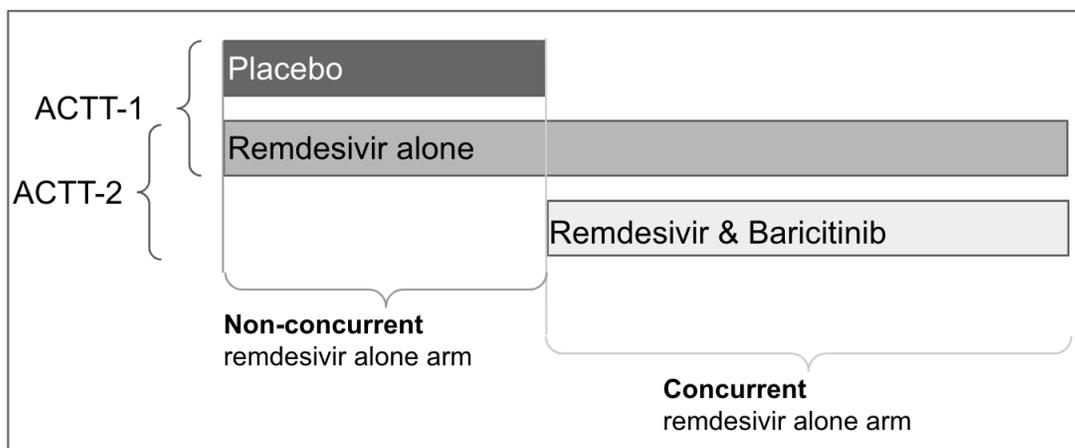


Figure 1: Adaptive COVID-19 Treatment Trial (ACTT) schema. Example of concurrent and non-concurrent arm

to evaluate the causal effect of a treatment versus a shared control? Under what assumptions these estimands can be identified and estimated? Do we achieve any efficiency gains?

Addressing these questions requires careful consideration of how the timing of entry into the platform trial may introduce bias into the study results, which is referred to as “time drift”, “temporal drift” or “time trend”. Various methods have been proposed to control for it, including test-then-pool approaches (Viele et al. 2014), frequentist and Bayesian regression models (Lee & Wason 2020, Sridhara et al. 2022, Bofill Roig et al. 2023, Saville et al. 2022), propensity-score-based methods (Yuan et al. 2019, Chen et al. 2020), and other approaches (Han et al. 2017, Collignon et al. 2020, Ibrahim & Chen 2000, Neuenschwander et al. 2009, Banbeta et al. 2019, Gravestock et al. 2017, Bennett et al. 2021, Hobbs et al. 2011, Normington et al. 2020, Schmidli et al. 2020, Hupf et al. 2021, Jiang et al. 2023).

While these methods provide a statistical way to incorporate non-concurrent controls and control for the “temporal drift” bias, they lack a formal framework for characterizing causal effects and their identifying conditions. Consequently, interpreting the effect estimates from these procedures and making recommendations regarding clinical choices become challenging. These concerns are underscored in recent reviews (Collignon et al.

2022) and are discussed in the FDA estimand framework (FDA 2021) and the International Council for Harmonisation (ICH) E9(R1) guidance (International Council for Harmonisation 2017).

In this paper, we propose the use of causal inference tools, such as structural causal models (Pearl 1995) and counterfactuals, to clarify estimands and to formalize their identification and estimation in the presence of non-concurrent controls in platform trials. To our knowledge this is the first attempt to formalize platform trials using causal inference tools. We therefore contribute to the literature of platform trials by: 1. postulating a general structural causal model that clearly describes the role of entry time and the use of non-concurrent controls in platform trials; 2. defining causal estimands and providing non-parametric identification results; 3. discussing efficiency considerations; and 4. developing estimators with desirable properties.

2 Notation and setup

For each of $i \in \{1, \dots, n\}$ study participants, let E_i denote the (random) entry time of a unit into the study, let W_i denote a set of baseline variables, let A_i denote the randomized treatment taking values in $\{0, \dots, K\}$, where 0 denotes the control arm and $k = 1, \dots, K$ denotes the treatments of interest. Let $V_{k,i}$ denote an indicator of whether treatment k was part of the assigned treatments at time E_i , and define $V_i = (V_{1,i}, \dots, V_{K,i})$. Let Y_i denote a binary or numerical outcome measured at a fixed time after entry E_i . The observed data is $D = (Z_1, \dots, Z_n)$, where Z_i represents the data for the experimental unit i , i.e., $Z_i = (E_i, W_i, V_i, A_i, Y_i) \sim P$. We define $V_0 = V_1 = \dots = V_j = 1$ with probability one so that at least j treatments plus control are available at the start of the trial. We also assume the data are ordered in time of study entry in the sense that $E_1 \leq E_2 \leq \dots \leq E_n$. Note

that $P(A_i = k \mid V_{i,k} = 0) = 0$ by design.

2.1 A structural causal model and associated DAG

To encapsulate the role of entry time and non-concurrent controls in platform trials, we pose the structural causal model and directed acyclic graph (DAG) (Pearl 1995) represented in Figure 2, and its interpretation in terms of a non-parametric structural equation model in eq. (1) respectively.

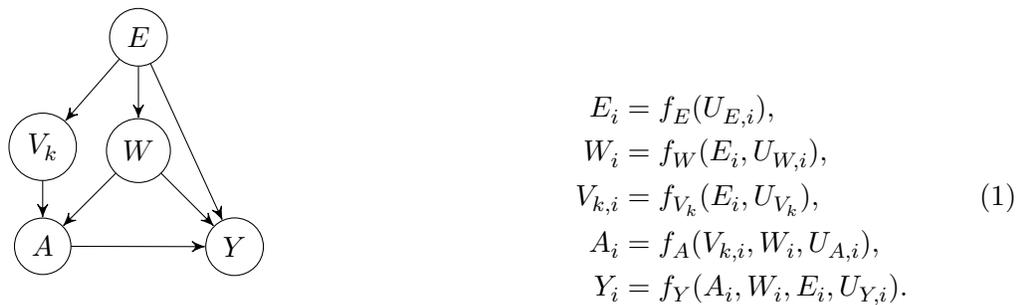


Figure 2: DAG associated to the structural equation model in equation (1).

We now discuss some important features of Model (1). Model (1) allows all variables to be dependent, directly or through other variables, on entry time E_i , and therefore appropriately models temporal drifts. It also allows the treatment assignment A_i to depend on the participant’s covariates W_i , thus allowing study designs such as stratified randomization (Broglia 2018). Model (1) also imposes some exclusion restrictions. First, the treatment assignment A_i is not allowed to depend on the entry time E_i other than through treatment availability $V_{k,i}$. In other words, a participant entering the study at time E_i can only be assigned to available treatments at that time, but the randomization probability of a treatment that is available for assignment does not vary in time. Second, the outcome for unit i , Y_i , is not allowed to depend on the availability of treatments $V_{k,i}$, other than through the treatment actually given to unit i , but it is allowed to directly depends on unit’s i entry time. Third, the availability of treatments $V_{k,i}$ does not depend on covariates W_i ,

which is a sensible assumption since the treatments under evaluation do not often depend on trial data. Finally, in this paper we assume that V_k is a deterministic function of E . In Model (1), the functions f_E , f_W , and f_Y are completely unknown, thus making the model non-parametric, while the treatment assignment function, f_A , and treatment availability function, f_{V_k} , are known by design. In addition, the random variables $U_{E,i}$, $U_{W,i}$, and $U_{Y,i}$ are unmeasured factors that impact the entry time, covariates, and outcomes, respectively. The random variables $U_{A,i}$ control the randomization probabilities and are known by design. The random variables U_{V_k} represent all factors that determine the availability of treatments for subjects in the trial.

Under this model and its associated DAG, in the following section, we define the causal estimands of interest and introduced their identification assumptions, aligning with the estimand framework advocated by the FDA (FDA 2021).

3 Causal estimands and identification

In this paper, we focus on continuous endpoints measured at fixed time-points post-randomization. Therefore, the causal estimands of interest are average treatment effects. Additionally, we consider an intention-to-treat (ITT) analysis. Our results can be easily extended to binary endpoints. We define the causal estimands of interest in terms of counterfactual variables (Pearl 2010), $Y_i(k) = f_Y(k, V_{k,i}, W_i, E_i, U_{Y,i})$ that would have been observed in a hypothetical world where treatment $A_i = k$ had been given, *i.e.*, $P(A_i = k) = 1$. We first define these estimands and then discuss their non-parametric identification.

Definition 1 (Conditional and marginal average treatment effect of treatment arm k)

compared to control).

$$\text{CATE}(k, w, e) = \text{E}[Y(k) - Y(0) \mid W = w, E = e]$$

$$\text{ATE}(k) = \text{E}[\text{CATE}(k, W, E)].$$

Definition 2 (Conditional and marginal average treatment effect of treatment arm k compared to control among concurrent population).

$$\text{cCATE}(k, w, e) = \text{E}[Y(k) - Y(0) \mid W = w, E = e, V_k = 1]$$

$$\text{cATE}(k) = \text{E}[\text{cCATE}(k, W, E) \mid V_k = 1].$$

$\text{ATE}(k)$ is the standard ITT-average treatment effect of treatment arm k considered in many clinical trials. This estimand considers the whole trial population comprised of all units enrolled throughout the duration of the trial. Conversely, $\text{cATE}(k)$ is the ITT-average treatment effect among *only* concurrent units, $V_k = 1$. $\text{CATE}(k, w, e)$ and $\text{cCATE}(k, w, e)$ are their conditional versions, conditioning on baseline variables W and entry time E . We now provide assumptions to identify these causal effects.

3.1 Non-parametric identification

Non-parametric identification allows us to express the causal target quantity of interest in terms of the distribution of the observed data without relying on assumptions on the functional form of the distributions ([Pearl 1995](#)). In order to discuss non-parametric identification of the above causal effects, we introduce the following assumptions:

A1 (weak A-ignorability).

$$\mathbf{E}[Y(k)|W = w, E = e, V_k = v] = \mathbf{E}[Y(k)|A = k, W = w, E = e, V_k = v].$$

A2 (weak V-ignorability).

$$\mathbf{E}[Y(k)|W = w, E = e] = \mathbf{E}[Y(k)|W = w, E = e, V_k = v].$$

A3 (Consistency).

$$\mathbf{P}(Y(k)|A = k, W = w, E = e, V_k = v) = \mathbf{P}(Y|A = k, W = w, E = e, V_k = v)$$

A4 (Positivity of treatment assignment mechanism among concurrent participants.). Assume

$$\mathbf{P}(A = k | W = w, V_k = 1) > 0 \text{ for all } w ,$$

A5 (Positivity of treatment assignment mechanism among all controls.). Assume

$$\mathbf{P}(A = 0 | W = w, E = e) > 0 \text{ for all } w \text{ and } e,$$

A6 (Conditional exchangeability of outcome mechanism among controls). Assume

$$\mathbf{E}(Y | A = 0, W = w, E = e, V_k = 1) = \mathbf{E}(Y | A = 0, W = w, E = e, V_k = 0) =$$

$$\mathbf{E}(Y | A = 0, W = w, E = e).$$

A7 (Conditional exchangeability of outcome mechanism among the treated). Assume

$$\mathbf{E}(Y | A = k, W = w, E = e, V_k = 1) = \mathbf{E}(Y | A = k, W = w, E = e, V_k = 0) =$$

$$\mathbf{E}(Y | A = k, W = w, E = e).$$

Assumptions **A6** and **A7** state that the outcome distribution among controls and treated are exchangeable between patients for whom treatment k is available and those for whom

it is not, respectively; given patients' baseline variables and entry time. Note that [A6](#) and [A7](#) are similar in nature in that they assume exchangeability of the outcome mechanism for treatment and control arms. However, there is a fundamental difference between these assumptions that makes identification based on [A6](#) more reliable than identification based on [A7](#). [A6](#) is a testable assumption that can be empirically checked. On the other hand, [A7](#) requires assuming that the conditional outcome expectation observed in patients who could hypothetically be randomized to treatment k can be used to *extrapolate* to those who could not. In other words, [A7](#) is an extrapolation assumption, since it assumes that the expected outcome under treatment $A = k$ in times $E = e$ and baseline variables $W = w$ of no treatment availability $V_k = 0$ can be extrapolated from a model fit on times $E = e$ and baseline variables $W = w$ where the treatment was available. Assumption [A4](#) states that once a treatment arm is available in the trial all covariate profiles w, e have a positive probability of receiving such treatment. Under these assumptions, we now provide an identification theorem.

Theorem 1 (Identification of average treatment effects in platform adaptive trials under Model (1)). *Assume Model (1) and assumptions [A1-A4](#). Then we have:*

1. *The parameter $\text{cCATE}(k, w, e)$ is non-parametrically identified as*

$$\mathbb{E}(Y \mid A = k, W = w, E = e, V_k = 1) - \mathbb{E}(Y \mid A = 0, W = w, E = e, V_k = 1), \quad (2)$$

2. *Under [A1-A6](#), $\text{cCATE}(k, w, e)$ is identified as*

$$\mathbb{E}(Y \mid A = k, W = w, E = e, V_k = 1) - \mathbb{E}(Y \mid A = 0, W = w, E = e). \quad (3)$$

3. *Under [A1-A7](#), $\text{CATE}(k, w, e)$ is identified as (3).*

Furthermore, $cATE(k)$ and $ATE(k)$ are identified by taking the average of the above expressions for $cCATE(k)$ and $CATE(k)$ over the distribution of (W, E) conditional on $V_k = 1$, and over the marginal distribution of (W, E) , respectively.

Equivalent expressions based on weighting are provided in the appendix. A comparison between expressions (2) and (3) reveals the motivation to use non-concurrent controls: they can be useful in estimating the outcome expectation for the controls, therefore reducing the variance of the estimator.

4 Relation to analytical approaches common in the literature

The current body of research concerning non-concurrent controls (Bofill Roig et al. 2023) focuses on estimating various estimands.

Regression models are often used to obtain $ATE(k)$. This usually involves estimating $E(Y | A = k, E = e)$ using a regression model, regressing the outcome on the treatment and entry time. Inferences are then made using the regression coefficient related to the treatment, whether within the frequentist (Lee & Wason 2020, Bofill Roig, Krotka, Burman, Glimm, Gold & Hees 2022) or Bayesian framework (Saville et al. 2022, Bofill Roig, König, Meyer & Posch 2022, Ibrahim & Chen 2000). Many approaches have been developed to construct priors (Neuenschwander et al. 2009, Bennett et al. 2021, among others). As showed above, $ATE(k)$ can be identified under Model (1), and assumptions A1-A7. We caution that this analysis can be risky as it relies on an extrapolation assumption, an assumption that is untestable and therefore undesirable in a randomized study.

Matching techniques have been proposed to estimate the average treatment effect among

the treated, $E[Y(k) - Y(0)|A = k]$. The idea is to balance covariates W between concurrent and non-concurrent controls by using for instance a matching algorithm based on the propensity score (Yuan et al. 2019).

Bayesian methods have been proposed to include non-concurrent controls to estimate $cATE(k)$. The idea is to learn a prior of the parameter of interest using non-concurrent controls only. Then, this prior is combined with the concurrent control data via Bayes' theorem. Meta-analytic priors (Schmidli et al. 2014) or elastic priors (Jiang et al. 2023) have been proposed. In addition, these methods assume an exchangeability assumption for the control parameters, which is related to A6. These methods, however, do not allow for the use of baseline covariates W .

In this paper, we propose estimators based on outcome regression (OR) and inverse-probability-weighting (IPW), and doubly robust estimators.

5 Estimation of $cATE(k)$ and $ATE(k)$

To build intuition, we start by introducing outcome regression (OR) and inverse probability weighting (IPW) estimators for $cATE$ and ATE . Since OR and IPW estimators are not robust to model misspecification, we then propose doubly robust (DR) estimators. To simplify notation, the following sections assume there are only two treatment arms $k = 1$ and $k = 0$. Furthermore, we assume that $V_k = \mathbb{1}\{E > t\}$ for some time t such that treatment $A = 1$ is only available for patients who entered the trial after time t .

5.1 Estimators based on parametric outcome regression

Based on the identification results presented in Theorem 1, eq. (2), we firstly propose to model the conditional mean $E(Y | A = a, W = w, E = e, V_k = 1)$, where $a = \{0, 1\}$ as

$$E(Y | A = a, W = w, E = e, V_k = 1) = \mu_{\text{oc}}(a, w, e, 1; \beta_a),$$

where (oc) stands for only-concurrent. Based on the identification results presented in Theorem 1, eq. (3), we also propose to model the conditional mean $E(Y | A = 0, W = w, E = e)$, as

$$E(Y | A = 0, W = w, E = e) = \mu_{\text{all}}(0, w, e; \alpha_a).$$

We then obtain an estimate of β_a and α_a by using maximum likelihood estimation, i.e., ordinary least squares, only among the concurrent controls $V_k = 1$ for $\mu_{\text{oc}}(a, w, e, 1; \beta_a)$ and among all concurrent and non-concurrent controls when using $\mu_{\text{all}}(0, w, e; \alpha_a)$, i.e., among $A = 0$ only. Let $\hat{\beta}_a$ and $\hat{\alpha}_a$ denote consistent estimators of β_a and α_a . We then propose

$$\begin{aligned} \widehat{\text{cATE}}_{\text{OR}}^{\text{oc}} &= \frac{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\} \mu_{\text{oc}}(1, w_i, e_i, 1; \hat{\beta}_1)}{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\}} \\ &\quad - \frac{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\} \mu_{\text{oc}}(0, w_i, e_i, 1; \hat{\beta}_0)}{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\}}, \end{aligned}$$

as an outcome regression estimator for $\text{cATE}(k)$. Under Theorem 1, eq. (3), we propose the alternative outcome regression estimator for $\text{cATE}(k)$,

$$\begin{aligned} \widehat{\text{cATE}}_{\text{OR}}^{\text{all}} &= \frac{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\} \mu_{\text{oc}}(1, w_i, e_i, 1; \hat{\beta}_1)}{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\}} \\ &\quad - \frac{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\} \mu_{\text{all}}(0, w_i, e_i; \hat{\alpha}_0)}{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\}}. \end{aligned}$$

Finally, under Theorem 1 eq. (3), we propose the following outcome regression estimator for $\text{ATE}(k)$,

$$\hat{\text{ATE}}_{\text{OR}} = \frac{\sum_{i=1}^n \mu_{\text{oc}}(1, w_i, e_i, 1; \hat{\beta}_1)}{n} - \frac{\sum_{i=1}^n \mu_{\text{all}}(0, w_i, e_i; \hat{\alpha}_0)}{n},$$

where $\mu_{\text{oc}}(1, w_i, e_i, 1; \hat{\beta}_1)$ is learned among only concurrent and marginalized over the whole trial population by extrapolation.

Large sample properties. We derived the asymptotic properties of $\hat{\text{cATE}}_{\text{OR}}^{\text{oc}}$, $\hat{\text{cATE}}_{\text{OR}}^{\text{all}}$, and $\hat{\text{ATE}}_{\text{OR}}$ using the approach of M-estimation (Boos & Stefanski 2013, Chapter 7). Under regularity conditions (Boos & Stefanski 2013, Section 7.2), $\hat{\text{cATE}}_{\text{OR}}^{\text{oc}}$, $\hat{\text{cATE}}_{\text{OR}}^{\text{all}}$, and $\hat{\text{ATE}}_{\text{OR}}$ are consistent and asymptotically Normal, with asymptotic variance derived in the appendix.

5.2 Estimators based on parametric inverse probability weighting

Identification results for $\text{ATE}(k)$ presented in the appendix show that to estimate $\text{ATE}(k)$, we should extrapolate $\text{P}(A = 0 \mid W, E)$ which equals 1 when $V_k = 0$. This is a problem as it creates a condition known as separation, where the data points from the control class ($A = 0$) are perfectly separated from a non-existent treatment class ($A = 1$) (Mansournia et al. 2018). This would lead the estimated coefficients approaching positive or negative infinity, making them unreliable and uninterpretable, in addition to numerical errors and difficulties in fitting the model. As a consequence, we propose an estimator based on inverse probability weighting solely for $\text{cATE}(k)$. Specifically, we propose to model the conditional probability of treatment assignment given W and E among only $V_k = 1$ by using a logistic

regression model,

$$\mathbb{E}(\mathbb{1}\{A = 1\} \mid W = w, E = e, V_k = 1) = \pi_{\text{oc}}(w, e, 1; \eta) = \frac{\exp(\eta^T x)}{1 + \exp(\eta^T x)},$$

where $x = (w, e, 1)$. We obtain an estimate of η by using maximum likelihood estimation, only among the concurrent controls $V_k = 1$. We then propose,

$$\widehat{\text{cATE}}_{\text{IPW}}^{\text{oc}} = \frac{\sum_{i=1}^n \gamma_i^1 \mathbb{1}\{V_{k,i} = 1\} Y_i}{\sum_{i=1}^n \gamma_i^1} - \frac{\sum_{i=1}^n \gamma_i^0 \mathbb{1}\{V_{k,i} = 1\} Y_i}{\sum_{i=1}^n \gamma_i^0},$$

where $\gamma_i^0 = \mathbb{1}\{A_i = 0\}/(1 - \hat{\pi}_{\text{oc}})$, $\gamma_i^1 = \mathbb{1}\{A_i = 1\}/\hat{\pi}_{\text{oc}}$, and $\hat{\pi}_{\text{oc}} = \pi_{\text{oc}}(w, e, 1; \hat{\eta})$ for clarity.

Large sample properties. We derived the asymptotic properties of $\widehat{\text{cATE}}_{\text{IPW}}^{\text{oc}}$ using the approach of M-estimation (Boos & Stefanski 2013, Chapter 7). Under regularity conditions (Boos & Stefanski 2013, Section 7.2), $\widehat{\text{cATE}}_{\text{IPW}}^{\text{oc}}$ is consistent and asymptotically Normal, with asymptotic variance derived in the appendix.

5.3 Doubly robust estimators

Doubly robust (DR) estimators for average treatment effects provide consistent estimates by combining outcome regression and IPW. Consequently, they suffer of the same separation problem described above for IPW. We then provide DR estimators for $\text{cATE}(k)$ only. To do so, we follow standard practice of constructing DR estimators based on efficient influence functions (EIF)s (Bickel et al. 1993, Fisher & Kennedy 2021, Hines et al. 2022, Kennedy 2022). Influence functions are a core component of classical statistical theory. They aid in constructing estimators with desirable properties such as double robustness, asymptotic normality, and fast rates of convergence. Additionally, they enable the incor-

poration of machine learning algorithms while preserving valid statistical inferences and providing insights into statistical efficiency, i.e., the best performance for estimating an estimand. We provide efficiency considerations of the proposed estimators in section 6.

The next theorem provide these EIFs,

Theorem 2. *The efficient influence function, $\varphi(Z, \text{cATE}(k))$, for $\text{cATE}(k)$ in the non-parametric model is equal to*

$$\frac{\mathbb{1}\{V_k = 1\}}{\mathbb{P}(V_k = 1)} \left[\frac{2A - 1}{\mathbb{P}(A | W, E, V_k = 1)} \{Y - \mathbb{E}(Y | A, W, E, V_k = 1)\} + \mathbb{E}(Y | A = 1, W, E, V_k = 1) - \mathbb{E}(Y | A = 0, W, E, V_k = 1) - \text{cATE}(k). \right] \quad (4)$$

The efficient influence function, $\varphi(Z, \text{cATE}(k))$, for $\text{cATE}(k)$ in the non-parametric model that assumes (A6) is equal to

$$\frac{\mathbb{1}\{V_k = 1\}}{\mathbb{P}(V_k = 1)} \left[\frac{A}{\mathbb{P}(A | V_k = 1, W, E)} \{Y - \mathbb{E}(Y | A, W, E, V_k = 1)\} - \frac{1 - A}{\mathbb{P}(A | W, E)} \frac{\mathbb{P}(V_k = 1 | E, W)}{\mathbb{P}(V_k = 1)} \{Y - \mathbb{E}(Y | A, E, W)\} + \frac{\mathbb{1}\{V_k = 1\}}{\mathbb{P}(V_k = 1)} \left[\mathbb{E}(Y | A = 1, W, E, V_k = 1) - \mathbb{E}(Y | A = 0, W, E) - \text{cATE}(k) \right] \right] \quad (5)$$

These influence functions suggest the following estimators,

$$\begin{aligned} \widehat{\text{cATE}}_{\text{DR}}^{\text{oc}} &= \frac{1}{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\}} \sum_{i=1}^n \left[\frac{\mathbb{1}\{V_{k,i} = 1\} (2a_i - 1)}{\pi_{\text{oc}}(w_i, e_i, 1)} \{Y_i - \mu_{\text{oc}}(a_i, w_i, e_i, 1)\} \right. \\ &\quad \left. + \mu_{\text{oc}}(1, w_i, e_i, 1) - \mu_{\text{oc}}(0, w_i, e_i, 1) \right] \\ \widehat{\text{cATE}}_{\text{DR}}^{\text{all}} &= \frac{1}{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\}} \sum_{i=1}^n \left[\frac{\mathbb{1}\{V_{k,i} = 1\} \mathbb{1}\{A_i = 1\}}{\pi_{\text{oc}}(w_i, e_i, 1)} \{Y_i - \mu_{\text{oc}}(1, w_i, e_i, 1)\} \right] \end{aligned}$$

$$\begin{aligned}
& + \frac{\mathbb{1}\{A_i = 0\}}{1 - \pi_{\text{all}}(w_i, e_i)} \frac{\nu(w_i, e_i)}{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\}} \{Y_i - \mu_{\text{all}}(0, w_i, e_i)\} \\
& + \frac{1}{\sum_{i=1}^n \mathbb{1}\{V_{k,i} = 1\}} \sum_{i=1}^n [\mu_{\text{oc}}(1, w_i, e_i, 1) - \mu_{\text{all}}(0, w_i, e_i)].
\end{aligned}$$

where, $\pi_{\text{oc}}(w_i, e_i, 1)$, $\mu_{\text{oc}}(1, w_i, e_i, 1)$, $\mu_{\text{all}}(0, w_i, e_i)$, and $\pi_{\text{all}}(w_i, e_i)$, can be estimated by using parametric and machine learning methods. In this paper, we propose to use the linear regression models $\mu_{\text{oc}}(0, w_i, e_i, 1; \beta_0)$, and $\mu_{\text{all}}(0, w_i, e_i; \alpha_0)$ introduced in the previous section as outcome models, and the logistic regression models $\pi_{\text{all}}(w, e; \eta)$ and $\nu(w, e; \xi)$ introduced before for $\text{P}[A = 1 \mid W = w, E = e]$ and $\text{P}[V_k = 1 \mid W = w, E = e]$, respectively. Note that by design, $\text{P}[V_k = 1 \mid W = w, E = e] = 1$ when $V_k = 0$. We then set $\pi_{\text{all}}(w, e; \eta) = 1$ for all $V_k = 0$.

Large sample properties. In this paper we assumed that V_k is a deterministic function of E , and therefore $\text{P}(V_k = 1 \mid E, W) = \mathbb{1}\{E > t\}$. As discussed in the next session, under this assumption, the two EIFs (4) and (5) are the same. In addition, the first influence function in Theorem 2 boils down to the standard influence function for the average treatment effect in the the $V_k = 1$ population. Therefore, it inherits the standard analysis of the one-step estimator for average treatment effects as discussed in (Kennedy et al. 2021, Section 4.1). In summary, it can be shown that estimators of the form of $\text{c}\hat{\text{ATE}}_{\text{DR}}^{\text{oc}}$ are root-n consistent, asymptotically normal with asymptotically valid 95% confidence intervals given by the closed-form expression $\text{c}\hat{\text{ATE}}_{\text{DR}}^{\text{oc}} \pm 1.96\sqrt{\text{var}\{\varphi(Z, \text{cATE}(k))\}/n}$, and efficient in the local asymptotic minimax sense.

Double robustness. Similarly, since the two estimators boils down to the standard DR estimator for the average treatment effect in the $V_k = 1$ population, they also inherit the same double robust property. This means that if either the outcome regression model

$(\mu_{\text{oc}}(0, w_i, e_i, 1; \beta_0), \mu_{\text{all}}(0, w_i, e_i; \alpha_0))$ or the treatment assignment model $(\pi_{\text{oc}}(w_i, e_i, 1; \eta), \pi_{\text{all}}(w, e; \eta))$ is correctly specified (in a parametric sense), then the DR estimator is consistent, see section 4.2 of [Kennedy \(2022\)](#) for details. We provide some empirical result of this property in our simulations in section [7](#).

6 Efficiency considerations

Estimators based on outcome regression. As shown in the appendix, the influence function of the conditional expectation under control, $\varphi(Z_i, \hat{\mu}_0)$, depends on two components: the influence function of μ_0 itself and that of the regression coefficients. Here, $\mu_0 = \text{E}[Y(0)]$ or $\mu_0 = \text{E}[Y(0)|V_k = 1]$ depending on the estimand under study. Therefore, a more precise estimation of the regression coefficients (the variance of the estimated regression coefficient is inversely proportional to the sample size), translate to a more precise estimation of μ_0 and consequently of $\text{c}\hat{\text{ATE}}_{\text{OR}}^{\text{all}}$ compared to $\text{c}\hat{\text{ATE}}_{\text{OR}}^{\text{oc}}$.

Estimators based on inverse probability weighting. As previously discussed in section [5.2](#), the separation problem ([Mansournia et al. 2018](#)) limits the construction of IPW estimators for $\text{cATE}(k)$ among only concurrent. Consequently, there is no efficiency gains when using such estimators when V_k is deterministic.

Doubly robust estimators. As previously discussed, V_k is a deterministic function of E leading to $\text{P}(V_k = 1 | E, W) = \mathbf{1}\{E > t\}$, and therefore the two EIFs presented in section [5.3](#) are the same. In this case, efficiency gains come solely from better fitting of the regression $E(Y | A = 0, W, E, V_k = 1)$, which under assumption [\(A6\)](#) is equal to $E(Y | A = 0, W, E, V_k = 1) = E(Y | A = 0, W, E)$ (because $V_k = \mathbf{1}\{E > t\}$). In this case it becomes purely about getting this regression right, and these efficiency gains do not

show up in the first order analysis of the estimator. We show some empirical results in our simulations in section 7.

7 Simulations

In this section we evaluate the performance of the proposed estimators with respect to, bias squared, variance, mean square error, and coverage of the 95% confidence interval, across levels of the percentage of concurrent controls, and model misspecification when estimating $\text{cATE}(k)$. Note that, since $\text{ATE}(k)$ requires stringent assumptions that only hold under the correct outcome model, in this section we focus only on $\text{cATE}(k)$. In addition, current methods described in section 4 for $\text{cATE}(k)$ estimation do not allow controlling for baseline covariates. We therefore do not compare our proposed estimators with those methods.

7.1 Setup

Aims To evaluate the performance and gains in efficiency of our proposed estimators across levels of (1) percentage of concurrent controls (90% to 10%) and (2) model misspecification (correct outcome and treatment; correct outcome; correct treatment; both misspecified). In addition, we also evaluated any gains in efficiency comparing the estimated variance of the outcome regression (Section 5.1) and doubly robust (Section 5.3) estimators that only use concurrent data compared with those that use all data.

Data-generating mechanisms We considered generating data from Model (1). Specifically, we considered a sample size of $n = 1,000$ and for each subject $i = 1, \dots, n$, we simulated the following data:

Step 1. the entry time $E \sim \text{Norm}(0, 1)$ and a baseline covariate $W = -\kappa_1 + 0.8E +$

Norm(0, 1), where $\kappa_1 = n^{-1} \sum_{i=1}^n 0.8E$;

Step 2. an indicator whether treatment k was available at time E , V_k as a deterministic function of E being less than a threshold describing the level of the percentage of concurrent controls;

Step 3. a binary treatment $A \sim \text{Bernoulli}(\pi(W))$, where $\pi(W) = (1 + \exp(-(\kappa_2 - 0.8W)))^{-1}$ and $\kappa_2 = n^{-1} \sum_{i=1}^n 0.8W$ when $V_k = 1$ and $A = 0$, otherwise (participants for which treatment only placebo is available);

Step 4. two counterfactual outcomes, $Y(0) = 0.8W + 0.5E + \text{Norm}(0, 1)$, and $Y(k) = Y(0) + \Delta$, with $\Delta = 0.8$, and the observed outcome $Y = AY(1) + (1 - A)Y(0)$. Since we consider a homogeneous treatment effect, $\Delta = \text{cATE}(k) = \text{ATE}(k) = 0.8$.

Estimands The estimand of interest is $\text{cATE}(k)$.

Methods For each dataset across levels of percentage of concurrent controls, and misspecification we used the methods summarized in Table 1.

Performance metrics Bias squared, variance, mean square error (MSE), and coverage of the 95% confidence interval. In addition, we also considered the ratio of the estimated variances.

Scenarios We considered levels of percentage of concurrent controls between 10% and 90% by 10%. Misspecified models were set to only include an intercept—not controlling for any covariate or entry time.

Table 1: Methods used in the estimation of cATE and ATE.

Method	Acronym	
	cATE(k)	ATE(k)
Outcome regression using only concurrent data, ($\widehat{\text{cATE}}_{\text{OR}}^{\text{oc}}$, Section 5.1)	OR-oc	-
Outcome regression using all data, ($\widehat{\text{cATE}}_{\text{OR}}^{\text{all}}$, $\widehat{\text{ATE}}_{\text{OR}}$, Section 5.1)	OR-ac	OR-ad
Weighting using only concurrent data ($\widehat{\text{cATE}}_{\text{IPW}}^{\text{oc}}$, Section 5.2)	IPW	-
Doubly robust using only concurrent data ($\widehat{\text{cATE}}_{\text{DR}}^{\text{oc}}$, Section 5.3)	DR-oc	-
Doubly robust using all data ($\widehat{\text{cATE}}_{\text{DR}}^{\text{all}}$, Section 5.3)	DR-ac	-

7.2 Results

7.2.1 Bias, variance, MSE, and coverage

Figure 3 and Figures 5-7 in the appendix, show bias squared, variance, MSE and coverage of the 95% confidence intervals in estimating cATE across percentage of concurrent controls and across misspecification scenarios. When both the outcome and the treatment models are correct (Figure 3), bias squared is negligible across levels of concurrent controls for all methods. Variance is shown to increase with decreasing levels of concurrent controls across all methods, with OR-ac being smaller than OR-oc, suggesting a gain in efficiency (more on this in the next section). Similar behavior can be seen for the MSE. Finally, all methods achieved desirable coverage levels. When the outcome model is misspecified (Figure 5 in the appendix), both outcome models show a large bias while maintaining a relatively small variance. MSE is consequently dominated by bias. DR estimators and the IPW estimator maintained negligible levels of bias and relatively small variance. Similarly, when only the outcome model is correctly specified, DR methods and OR estimators show desirable results while IPW show high bias (Figure 6 in the appendix). Finally, when all models are misspecified, bias becomes large for all methods with low coverage (Figure 7 in the appendix).

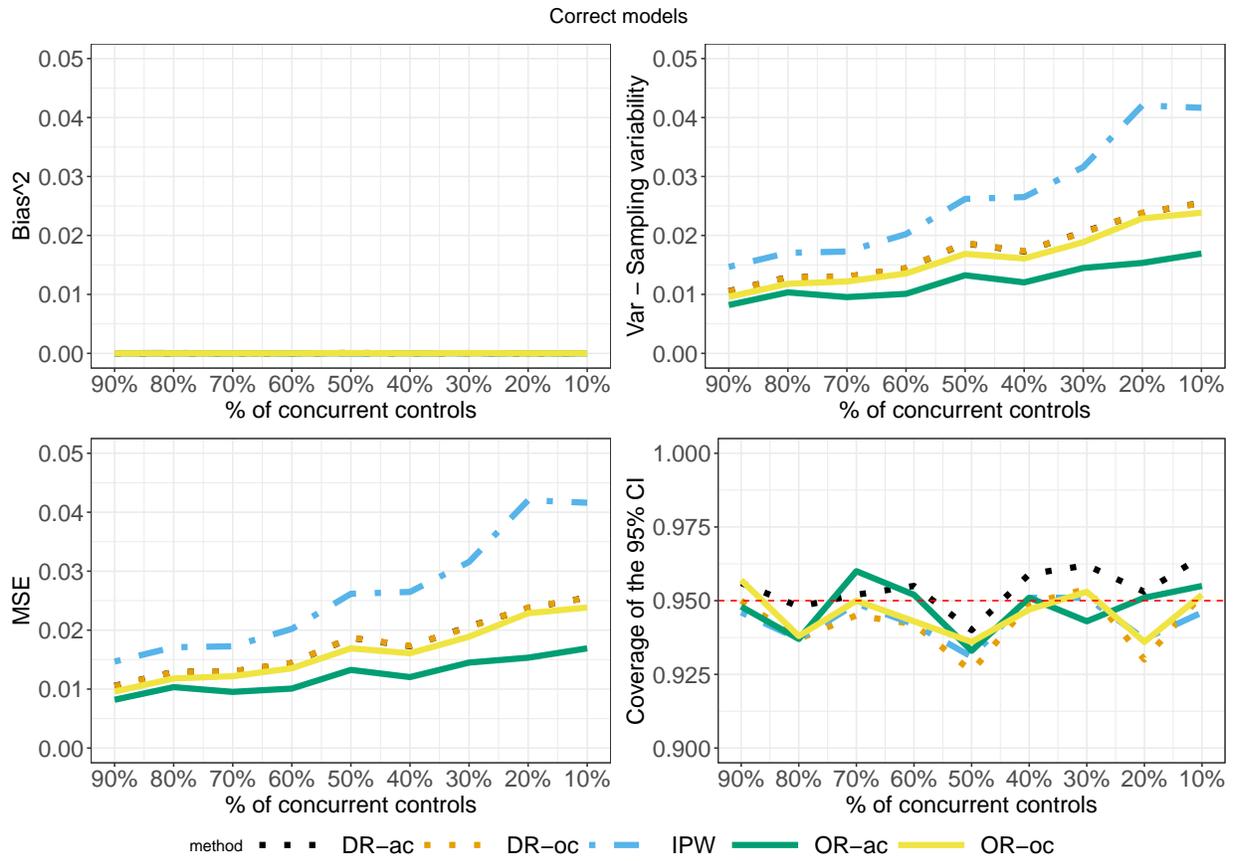


Figure 3: Bias squared, variance, MSE and coverage of the 95% confidence interval of DR-ac, DR-oc, IPW, OR-ac and OR-oc under correct models. Note that, DR-ac and DR-oc overlap in terms of bias squared, sampling variability and MSE.

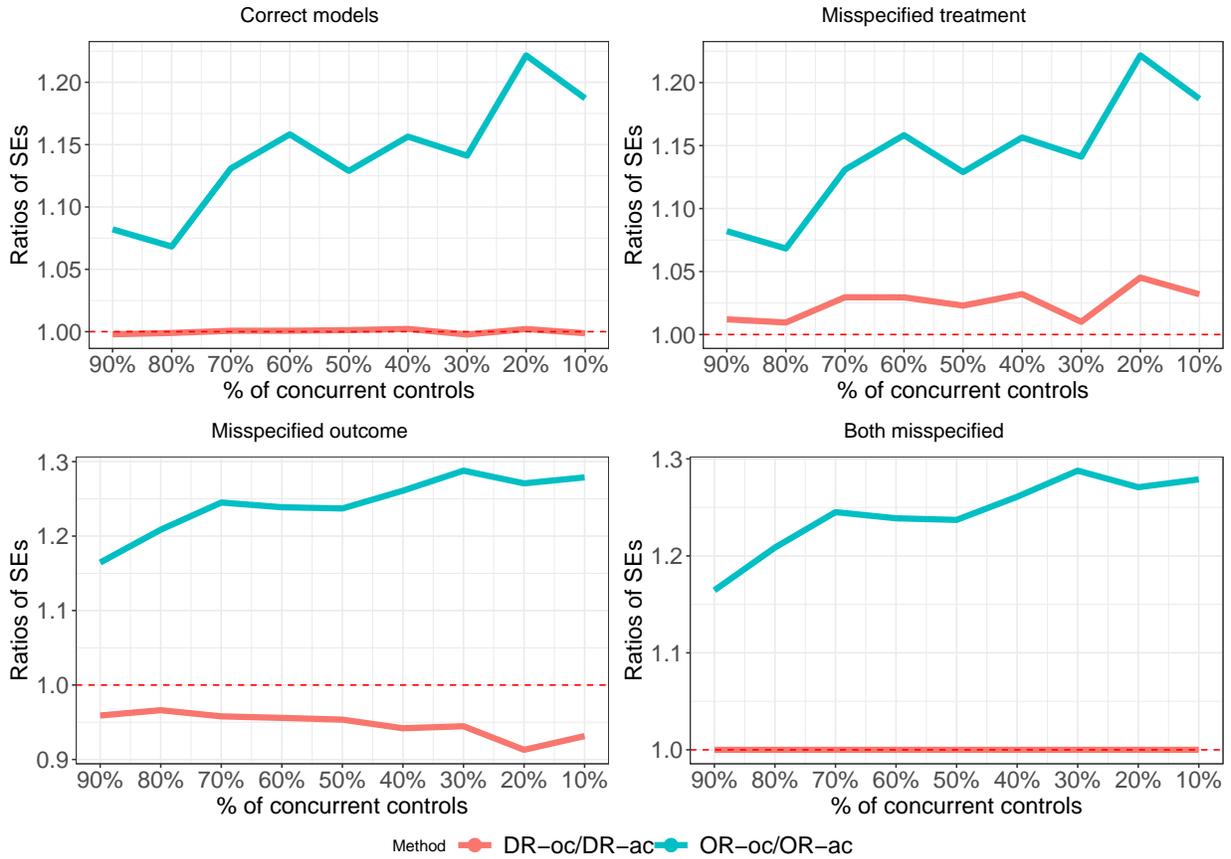


Figure 4: Ratio of standard errors DR-oc/DR-ac and OR-oc/OR-ac across model misspecifications. A ratio greater than 1 means efficiency gains.

7.2.2 Efficiency gains

Figure 4 shows the ratio of the estimated standard errors of DR-oc over DC-ac and OR-oc over OR-ac across levels of concurrent controls and misspecification. As discussed in Section 6, estimators based on outcome regression that use all controls seem to have a gain in efficiency, while DR estimators did not. These results are similar across all scenarios.

Summary of results. Methods based on outcome regression improve efficiency when using non-concurrent controls. However, they introduce bias when misspecified. In contrast, doubly robust estimators provide consistent estimates with relatively small variance when either the treatment or outcome model is correctly specified.

8 Practical considerations

What estimand should we target? Given the more stringent and untestable assumptions needed to identify $ATE(k)$, we suggest targeting $cATE(k)$. Note that $ATE(k)$ and $cATE(k)$ will coincide under the assumption of homogeneous treatment effect. While this is true in theory, we would expect it not to hold in practical settings, leading to different results as showed in our case study in the next section.

Are we actually increasing precision while retaining unbiasedness? In this paper, we argue that targeting $cATE(k)$ requires fewer stringent untestable assumptions compare to estimating $ATE(k)$. Additionally, the simple difference in means between treatment arms within the concurrent ($V_k = 1$) population (or controlling for stratified randomization if needed) can be used as a benchmark for the “true” sample $cATE(k)$ – we refer to this estimator as naive. In other words, point estimates from multiple methods can be benchmarked against those obtained by using the naive estimator. Ideally, our estimators should be close to the naive estimate while increasing precision. To do so during data analysis, we suggest computing two quantities: 1) the difference between the estimated $cATE(k)$ with the proposed estimators against that obtained by using the naive estimator; and 2) the ratio between the estimated standard errors of the proposed estimators against that obtained by using the naive estimator. Since the two estimators use the same data, they might be correlated. We, therefore, suggest computing the covariance between the two estimators using computational methods such as bootstrap. Wald hypothesis tests and 95% confidence intervals can then be computed. We show this in our case study in section 9 (Table 3).

Should we leverage prognostic baseline variables for additional precision? Recent literature suggests that incorporating baseline prognostic variables can improve the precision of estimates (Colantuoni & Rosenblum 2015). We propose following this approach by appropriately controlling for these variables in the analysis. This may explain the increased precision observed with DR-oc and OR-oc estimators compared to the naive estimator in our case study (presented in the next section), despite being computed within the concurrent population only.

Sample size calculation for a prospective trial with non-concurrent controls.

Our theoretical and methodological results suggest an efficiency gain when including non-concurrent control with estimators based on regression models. While these results are promising, we suggest to conduct standard sample size calculation as if the non-concurrent control data will not be available. At the analysis stage, precision can then be improved by using non-concurrent control data as previously described with the caveat that the outcome model must be correctly specified.

Multiple comparisons. Our proposed methods enable the use of standard type I error control procedures, such as Bonferroni or Benjamini-Hochberg corrections, due to the validity of 95% confidence intervals, test statistics, and p-values (demonstrated in previous sections). This allows for straightforward application of these corrections in platform trials with, for instance, pre-planned interim analyses, and multiple primary endpoints.

9 The Adaptive COVID-19 Treatment Platform Trial

In this section, we apply our proposed estimators using data from the Adaptive COVID-19 Treatment Trial (ACTT) (Kalil et al. 2021). This was a platform trial that investigated

treatments for hospitalized adult patients with COVID-19 pneumonia. The trial comprised multiple stages, as illustrated in Figure 1. The initial phase, ACTT-1, involved the assessment of the effectiveness of remdesivir alone compared to placebo. Subsequently, in the second stage (ACTT-2), the placebo was phased out, and a novel treatment, combining remdesivir with baricitinib, was introduced. Simultaneously, participants were randomized to receive either remdesivir alone or the combination therapy of remdesivir and baricitinib. Data were accessed using the NIAID Clinical Trials Data Repository (<https://data.niaid.nih.gov/>). We have a Data User Agreement in place for its use.

Study population. We considered the combined participants of ACCT-1 and ACTT-2 as our study population. The final study population was comprised of 1,379 participants, 541 from ACTT-1 and 1,033 from ACTT-2. We considered the time to recovery in days as our endpoint of interest. We considered two arms: remdesivir alone (which also acts as a shared control) and remdesivir plus baricitinib. We consider the following baseline covariates: age, sex assigned at birth (female, male), race (White, Black, Asian, Other: American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple), ethnicity (Hispanic or Latino, Not Hispanic or Latino), BMI, geographic region of study site (Asia, Europe, North America), disease severity stratum (mild, severe), and having any of these comorbidities: duration of symptoms, hypertension, coronary artery disease, congestive heart disease, chronic oxygen requirement, chronic respiratory disease, chronic liver disease, chronic kidney disease, diabetes type I, diabetes type II, obesity, cancer, immune deficiency, and asthma, in addition to the entry time which we normalized to be between 0 and 1.

Models setup. We computed OR-oc, OR-ac, OR-ad, IPW, DR-oc and DR-ac (Table 1) by using linear and logistic regression models. We computed the naive estimator by taking the average difference in the endpoint between the two arms among only concurrent participants. Variances were obtained by using the sandwich estimator (for naive, OR-oc, OR-ac, OR-ad, IPW) and by taking the variance of the efficient influence function (for DR-oc and DR-ac). Wald 95% confidence intervals and Wald tests were constructed.

Results. Table 2 shows the point estimate for cATE and ATE, standard errors, 95% confidence intervals and p-values. The naive estimate of cATE, resulted in a value of -1.33 with a standard error of 0.58. This suggest that baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time as in the original trial (Kalil et al. 2021). OR-oc, IPW, DR-oc and DR-ac improved precision while maintaining a similar point estimate. OR-ac improved precision the most (around 28% improvement compared with the naive estimator), however, it resulted in a different point estimate, -0.75 which led to a non significant result. This suggest that the outcome model used to obtain OR-ac might be misspecified. In contrast, doubly robust estimators improved precision while maintaining a similar point estimate as the naive estimator. We believe the improved precision observed in OR-oc, IPW, and DR-oc compared to the naive estimator stems from appropriately adjusting for baseline variables, as discussed in Colantuoni & Rosenblum (2015), and in our previous section.

Using OR-ad, a non significant point estimate of 0.45 was obtained for ATE, suggesting that either the outcome model is misspecified or that the effect is heterogeneous across concurrent and non-concurrent participants. Note that a conditional analysis using a standard linear regression model regressing the outcome in the full population on treatment arms, entry time and baseline covariates as suggested, for instance by Lee & Wason (2020), led

Table 2: Estimated $\widehat{\text{cATE}}(k)$ and $\widehat{\text{ATE}}(k)$ using the ACTT data.

Method	$\widehat{\text{cATE}}$	$\widehat{\text{ATE}}$	se	95% ci	p-value	Ratio
OR-oc	-1.29	-	0.47	(-2.21;-0.37)	<0.01	1.22
OR-ac	-0.75	-	0.45	(-1.63;0.13)	0.10	1.28
IPW	-1.28	-	0.47	(-2.20;-0.36)	<0.01	1.22
DR-oc	-1.30	-	0.47	(-2.22;-0.38)	<0.01	1.22
DR-ac	-1.30	-	0.47	(-2.22;-0.38)	<0.01	1.21
naive	-1.33	-	0.58	(-2.47;-0.19)	0.02	1.00
OR-ad	-	0.45	0.35	(1.15;-0.24)	0.19	-

Table 3: Estimated difference and ratio of standard errors between estimated $\widehat{\text{cATE}}(k)$ using OR-oc, OR-ac, IPW, DR-oc and DR-ac and naive, standard errors (se), 95% confidence intervals (CI), and p-values in the ACTT data.

Method	Difference	se	CI	p-value	Ratio	se	CI	p-value
OR-oc	0.03	0.36	(-0.67;0.74)	0.92	1.22	0.03	(1.16;1.28)	<0.01
OR-ac	0.58	0.37	(-0.15;1.31)	0.12	1.28	0.03	(1.22;1.33)	<0.01
IPW	0.05	0.36	(-0.65;0.75)	0.89	1.22	0.03	(1.17;1.27)	<0.01
DR-oc	0.03	0.35	(-0.66;0.72)	0.94	1.22	0.03	(1.16;1.28)	<0.01
DR-ac	0.03	0.32	(-0.59;0.65)	0.93	1.21	0.02	(1.16;1.26)	<0.01

a non significant point estimate of -0.46 (standard error equal to 0.52). We consequently caution the use of $\widehat{\text{ATE}}(k)$ as the estimand of interest in platform trials.

Table 3 shows the difference in $\widehat{\text{cATE}}(k)$ estimates and ratio of estimated standard errors between OR-oc, OR-ac, IPW, DR-oc, DR-ac and the naive estimator. Standard errors, confidence intervals and p-values were constructed as discussed in our practical guidelines. In summary, the difference between estimates was not significant across methods and all methods showed an improved efficiency (last column - confidence intervals not containing 1). While the p-value for the difference between OR-ac and naive was not statistically significant, we still cautiously suggest to not use results based on OR-ac.

10 Conclusion

In this paper, we introduced identification results and estimation techniques to identify and estimate causal effects in the presence of non-concurrent control in platform trials. We argue that identifying and estimating $ATE(k)$ relies on an extrapolation assumption that is both untestable and often too stringent, particularly in the context of platform trials, where multiple, potentially novel treatments or interventions are being evaluated and the outcome mechanism is poorly understood. Therefore, we advocate focusing primarily on $cATE(k)$, where assumptions can be tested and results can be benchmarked against standard procedures, such as the naive estimator in the concurrent population – known to be unbiased in well-conducted randomized trials. By focusing on $cATE(k)$ rather than $ATE(k)$, we also open the door to leveraging non-parametric models based on machine and deep learning techniques for learning outcome and treatment assignment mechanisms under the proposed doubly robust estimators (Kennedy 2022, Díaz 2020, Hirshberg & Wager 2021). In fact, while these methods can capture complex data relationships, potentially mitigating model misspecification, they may not be suitable for extrapolation. Furthermore, our proposed doubly robust estimator accommodates Bayesian techniques while retaining valid frequentist properties, as demonstrated in (Shin & Antonelli 2023, Antonelli et al. 2022). In this paper, we assumed V_k be a deterministic function of E . However, our results hold even when considering a non-deterministic function. In this scenario, we would expect the two EIFs in equations (4) and (5) to differ. Consequently, efficiency gains could be observed by using a doubly robust estimator using all controls (DR-ac) compared to only concurrent controls (DR-oc). Assumption A6 is a testable assumption, allowing for the construction of tests to verify its validity. This aligns with the test-then-pool literature (Viele et al. 2014, among others). In this paper, we focused on continuous endpoints.

Estimators can be constructed for binary, count and time-to-event endpoints under the non-parametric causal model introduced in eq. (1). Finally, in this paper, we demonstrate results assuming a structural equation model where treatment assignment may depend on baseline covariates; however, similar identification and estimation results can be obtained without baseline covariates.

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SUPPLEMENTARY MATERIAL

Identification and estimation of causal effects using non-concurrent controls in platform trials

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Additional simulation results: Bias squared, variance, MSE and coverage of the 95% confidence interval of DR-ac, DR-oc, IPW, OR-ac and OR-ac, across multiple scenarios.

Proofs and M-estimation details: Theorem [1](#), [2](#) and M-estimation details for estimators based on outcome regression and parametric weighting.

Additional simulation results

In this section, we provide additional results based on our simulations.

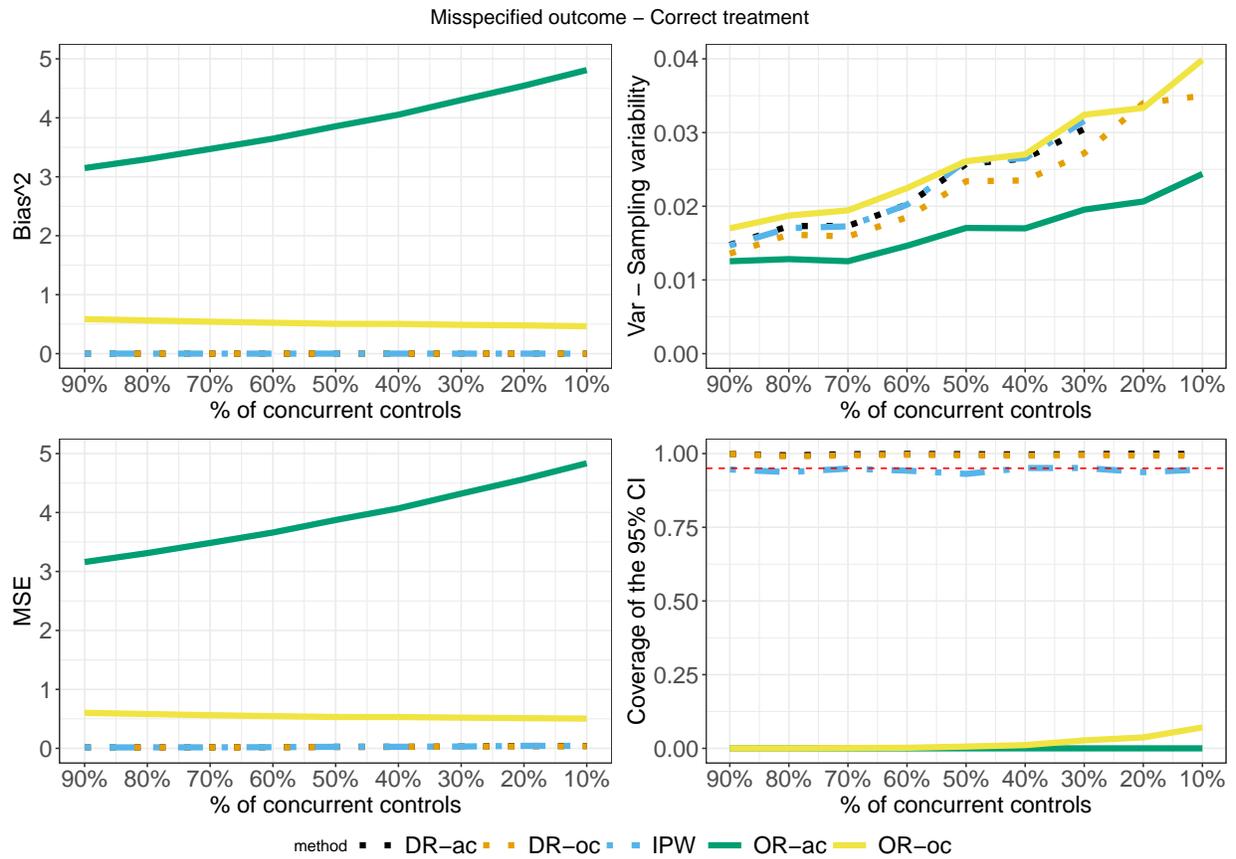


Figure 5: Bias squared, variance, MSE and coverage of the 95% confidence interval of DR-ac, DR-oc, IPW, OR-ac and OR-oc under misspecified outcome model and correct treatment assignment model. Note that, DR-ac and DR-oc overlap in terms of bias squared and MSE.

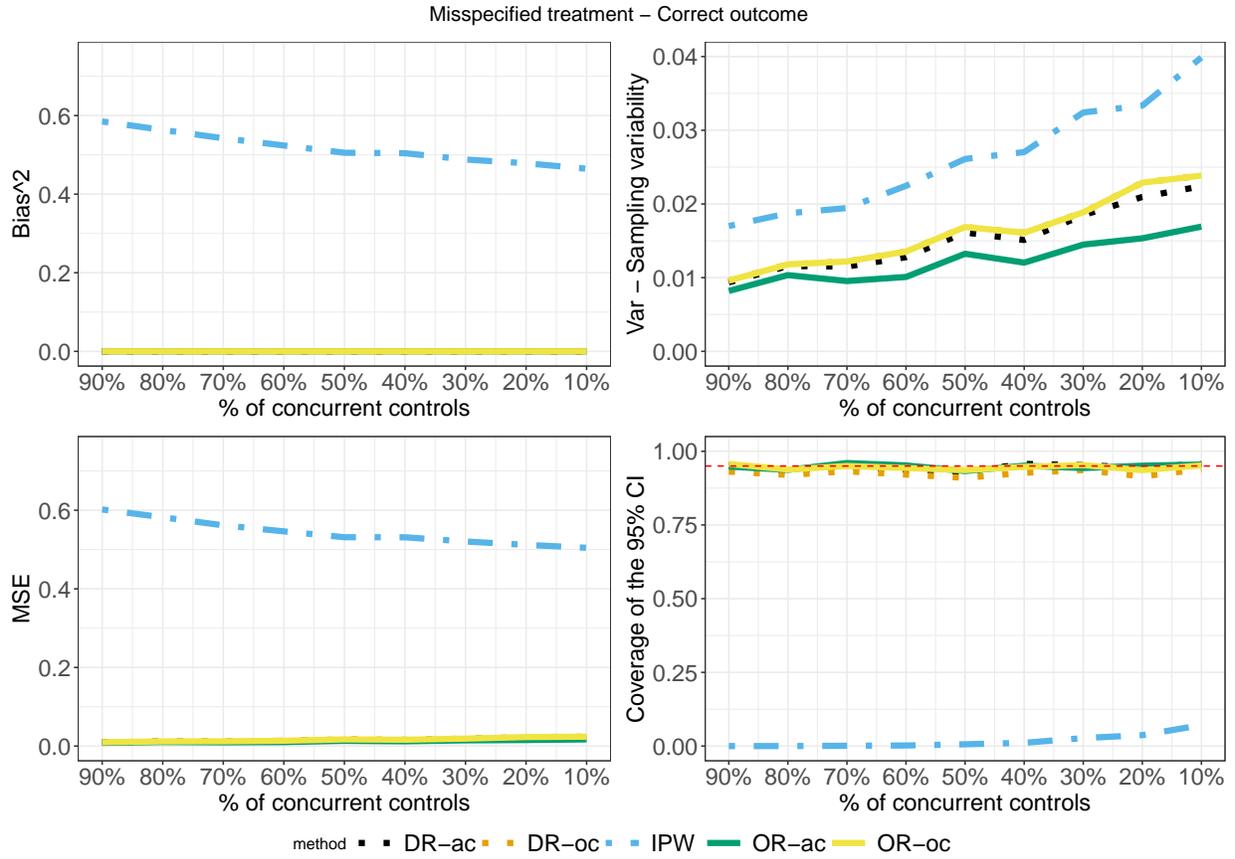


Figure 6: Bias squared, variance, MSE and coverage of the 95% confidence interval of DR-ac, DR-oc, IPW, OR-ac and OR-ac under correct outcome model and misspecified treatment assignment model.

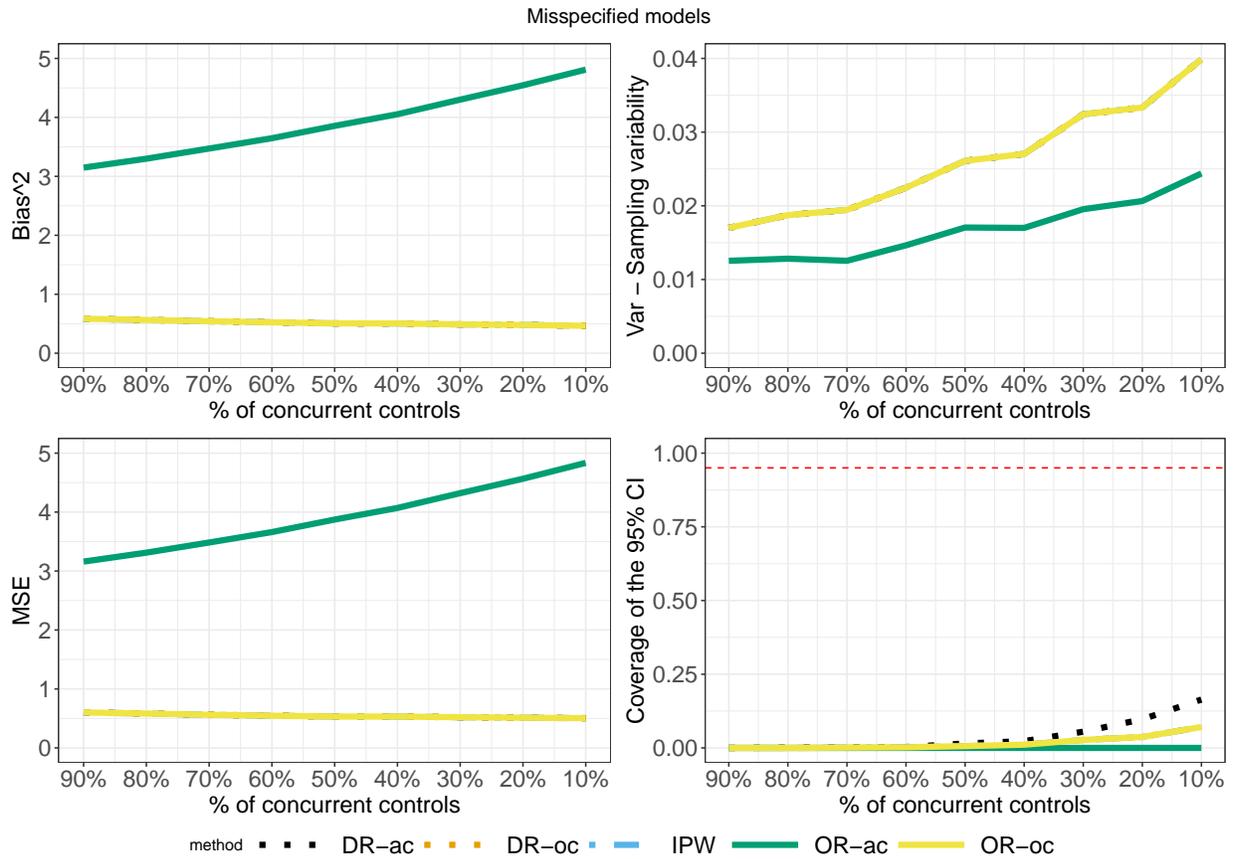
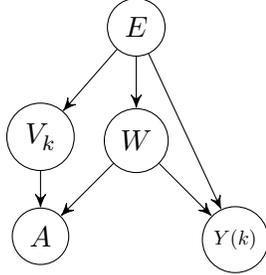


Figure 7: Bias squared, variance, MSE and coverage of the 95% confidence interval of DR-ac, DR-oc, IPW, OR-ac and OR-oc under misspecified models. Note that, since we are using simple means as misspecified models, DR-ac, DR-oc, and IPW overlap in terms of Bias squared and MSE.

Proofs and M-estimation details

Proof of Theorem 1



$$\begin{aligned}
 E_i &= f_E(U_{E,i}), \\
 W_i &= f_W(E_i, U_{W,i}), \\
 V_{k,i} &= f_{V_k}(E_i, U_V), \\
 A_i &= f_A(V_i, W_i, U_{A,i}), \\
 Y_i(k) &= f_{Y(k)}(k, W_i, E_i, U_{Y,i}).
 \end{aligned} \tag{6}$$

Figure 8: DAG associated to the structural equation model in equation (6).

Since we are interested in the effect of A on Y , and in using non-concurrent controls, $V_k = 0$, we study paths from A to $Y(k)$ and from V to $Y(k)$ and then apply d-separation. We start by studying paths from A to $Y(k)$.

$$\begin{aligned}
 A \leftarrow V_k \leftarrow E \rightarrow Y(k) & \quad \{V_k\}; \{E\}; \{V_k, E\} \\
 A \leftarrow V_k \leftarrow E \rightarrow W \rightarrow Y(k) & \quad \{V_k\}; \{E\}; \{W\}; \{V_k, E\}; \{V_k, W\}; \{E, W\}; \{V_k, W, E\} \\
 A \leftarrow W \rightarrow Y(k) & \quad \{W\} \\
 A \leftarrow W \leftarrow E \rightarrow Y(k) & \quad \{W\}; \{E\}; \{W, E\}
 \end{aligned}$$

By applying d-separation, the set $\{V_k, W, E\}$ conditionally block the path from A to $Y(k)$.

This leads to the following assumptions:

A1 (weak A-ignorability).

$$\mathbb{E}[Y(k)|V_k = v, W = w, E = e] = \mathbb{E}[Y(k)|A = k, V_k = v, W = w, E = e].$$

We now study paths between V_k to $Y(k)$.

$$\begin{array}{ll}
 V_k \leftarrow E \rightarrow Y(k) & \{E\}; \\
 V_k \rightarrow A \leftarrow W \rightarrow Y(k) & \{\}; \{W\} \\
 V_k \rightarrow A \leftarrow W \rightarrow E \leftarrow Y(k) & \{\}; \{W\}; \{E\}; \{W, E\}
 \end{array}$$

By applying d-separation, the set $\{W, E\}$ conditionally block the path from V_k to $Y(k)$.

This leads to the following assumptions:

A2 (weak V-ignorability).

$$\mathbb{E}[Y(k)|W = w, E = e] = \mathbb{E}[Y(k)|V_k = v, W = w, E = e].$$

We also assume consistency and positivity,

A3 (Consistency.).

$$\mathbb{P}(Y(k)|A = k, V_k = v, W = w, E = e) = \mathbb{P}(Y|A = k, V_k = v, W = w, E = e)$$

A4 (Positivity of treatment assignment mechanism among concurrent participants.). Assume

$$\mathbb{P}(A = k | V_k = 1, W = w) > 0 \text{ for all } w,$$

A5 (Positivity of treatment assignment mechanism among all controls.). Assume

$$\mathbb{P}(A = 0 | W = w, E = e) > 0 \text{ for all } w \text{ and } e,$$

A6 (Conditional exchangeability of outcome mechanism among controls). Assume
 $E(Y | A = 0, V_k = 1, W = w, E = e) = E(Y | A = 0, V_k = 0, W = w, E = e) =$
 $E(Y | A = 0, W = w, E = e)$.

A7 (Conditional exchangeability of outcome mechanism among the treated). Assume
 $E(Y | A = k, V_k = 1, W = w, E = e) = E(Y | A = k, V_k = 0, W = w, E = e) =$
 $E(Y | A = k, W = w, E = e)$,

Identification of concurrent ATE

Recall that

Definition 3 (Conditional and marginal average treatment effect of treatment arm k compared to control among concurrent population).

$$\begin{aligned} \text{cCATE}(k, w, e) &= E[Y(k) - Y(0) | V_k = 1, W = w, E = e] \\ \text{cATE}(k) &= E[\text{cCATE}(k, W, E) | V_k = 1]. \end{aligned}$$

Identification based on the G-formula.

Proof We start by showing it for treatment k . We refer to $W = w, E = e$ as W, E for clarity and (IE) as iterated expectation (we keep the conditioning on E even if it is not needed for assumption [A4](#)).

$$\begin{aligned} &E(Y(k) | V_k = 1) \\ &= E(E(Y(k)|V_k = 1, W, E) | V_k = 1) && \text{by (IE)} \\ &= E(E(Y(k)|A = k, V_k = 1, W, E) | V_k = 1) && \text{by (A1)} \\ &= E(E(Y|A = k, V_k = 1, W, E) | V_k = 1) && \text{by (A3,A4)} \end{aligned}$$

$$= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E}(\mathbb{1}[V_k = 1] \mathbb{E}(Y | A = k, V_k = 1, W, E))$$

We now show the proof under treatment 0.

$$\begin{aligned} & \mathbb{E}(Y(0) | V_k = 1) \\ &= \mathbb{E}(\mathbb{E}(Y(0) | V_k = 1, W, E) | V_k = 1) && \text{by (IE)} \\ &= \mathbb{E}(\mathbb{E}(Y(0) | A = 0, V_k = 1, W, E) | V_k = 1) && \text{by (A1)} \\ &= \mathbb{E}(\mathbb{E}(Y | A = 0, V_k = 1, W, E) | V_k = 1) && \text{by (A3)} \\ &= \mathbb{E}(\mathbb{E}(Y | A = 0, W, E) | V_k = 1) && \text{by (A5, A6)} \\ &= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E}(\mathbb{1}[V_k = 1] \mathbb{E}(Y | A = 0, W, E)) \end{aligned}$$

Consequently, under (A1), (A3), and (A4), $\text{cCATE}(k, w, e)$ is non-parametrically identified as

$$\mathbb{E}(Y | A = k, V_k = 1, W, E) - \mathbb{E}(Y | A = 0, V_k = 1, W, E). \quad (7)$$

In addition, under (A1), (A3), (A5) and (A6) $\text{cCATE}(k, w, e)$ is identified as

$$\mathbb{E}(Y | A = k, V_k = 1, W, E) - \mathbb{E}(Y | A = 0, W, E). \quad (8)$$

□

Identification based on weighting.

Proof We start by showing it for treatment k . We refer to $W = w, E = e$ as W, E for clarity, and (\mathbb{E}) as iterated expectation (we keep the conditioning on E even if it is not needed for assumption [A4](#)).

$$\begin{aligned}
& \mathbb{E}(Y(k) \mid V_k = 1) \\
&= \mathbb{E}(\mathbb{E}(Y(k) \mid V_k = 1, W, E) \mid V_k = 1) && \text{by (IE)} \\
&= \mathbb{E}(\mathbb{E}(Y(k) \mid A = k, V_k = 1, W, E) \mid V_k = 1) && \text{by (A1)} \\
&= \mathbb{E}(\mathbb{E}(Y \mid A = k, V_k = 1, W, E) \mid V_k = 1) && \text{by (A3)} \\
&= \mathbb{E} \left(\mathbb{E} \left(\frac{\mathbb{1}[A = k, V_k = 1]Y}{\mathbb{P}(A = k \mid V_k = 1, W, E)} \mid W, E \right) \mid V_k = 1 \right) && \text{by (A4)} \\
&= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\mathbb{1}[V_k = 1] \mathbb{E} \left(\frac{\mathbb{1}[A = k, V_k = 1]Y}{\mathbb{P}(A = k \mid V_k = 1, W, E)} \mid W, E \right) \right) \\
&= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\mathbb{E} \left(\frac{\mathbb{1}[A = k, V_k = 1]Y}{\mathbb{P}(A = k \mid V_k = 1, W, E)} \mid W, E \right) \right) \\
&= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\mathbb{E} \left(\frac{\mathbb{1}[A = k]Y \mathbb{P}(V_k = 1 \mid W, E)}{\mathbb{P}(A = k \mid V_k = 1, W, E)} \mid W, E \right) \right) \\
&= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\frac{\mathbb{1}[A = k]Y \mathbb{P}(V_k = 1 \mid W, E)}{\mathbb{P}(A = k \mid V_k = 1, W, E)} \right)
\end{aligned}$$

Note that if V_k is deterministic, then $\mathbb{P}(V_k = 1 \mid W, E) = \mathbb{1}[E > t] = \mathbb{1}[V_k = 1]$ and therefore

$$\frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\frac{\mathbb{1}[A = k]Y \mathbb{P}(V_k = 1 \mid W, E)}{\mathbb{P}(A = k \mid V_k = 1, W, E)} \right) = \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\frac{\mathbb{1}[A = k]Y \mathbb{1}[V_k = 1]}{\mathbb{P}(A = k \mid V_k = 1, W, E)} \right).$$

We now show the proof under treatment 0.

$$\begin{aligned}
& \mathbb{E}(Y(0) \mid V_k = 1) \\
&= \mathbb{E}(\mathbb{E}(Y(0) \mid V_k = 1, W, E) \mid V_k = 1) && \text{by (IE)} \\
&= \mathbb{E}(\mathbb{E}(Y(0) \mid A = 0, V_k = 1, W, E) \mid V_k = 1) && \text{by (A1)} \\
&= \mathbb{E}(\mathbb{E}(Y \mid A = 0, V_k = 1, W, E) \mid V_k = 1) && \text{by (A3)} \\
&= \mathbb{E}(\mathbb{E}(Y \mid A = 0, W, E) \mid V_k = 1) && \text{by (A6)} \\
&= \mathbb{E} \left(\mathbb{E} \left(\frac{\mathbb{1}[A = 0]Y}{\mathbb{P}(A = 0 \mid W, E)} \mid W, E \right) \mid V_k = 1 \right) && \text{by (A5)} \\
&= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\mathbb{1}[V_k = 1] \mathbb{E} \left(\frac{\mathbb{1}[A = 0]Y}{\mathbb{P}(A = 0 \mid W, E)} \mid W, E \right) \right) \\
&= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\mathbb{E}(\mathbb{1}[V_k = 1] \mid W, E) \mathbb{E} \left(\frac{\mathbb{1}[A = 0]Y}{\mathbb{P}(A = 0 \mid W, E)} \mid W, E \right) \right) && \text{by (IE)} \\
&= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\mathbb{E} \left(\frac{\mathbb{1}[A = 0]Y \mathbb{1}[V_k = 1]}{\mathbb{P}(A = 0 \mid W, E)} \mid W, E \right) \right) && \text{by (A2, A3)} \\
&= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\mathbb{E} \left(\frac{\mathbb{1}[A = 0]Y \mathbb{E}(\mathbb{1}[V_k = 1] \mid W, E)}{\mathbb{P}(A = 0 \mid W, E)} \mid W, E \right) \right) && \text{by (IE)} \\
&= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\mathbb{E} \left(\frac{\mathbb{1}[A = 0]Y \mathbb{P}(V_k = 1 \mid W, E)}{\mathbb{P}(A = 0 \mid W, E)} \mid W, E \right) \right) \\
&= \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\frac{\mathbb{1}[A = 0]Y \mathbb{P}(V_k = 1 \mid W, E)}{\mathbb{P}(A = 0 \mid W, E)} \right)
\end{aligned}$$

Note that if V_k is deterministic, then $\mathbb{P}(V_k = 1 \mid W, E) = \mathbb{1}[E > t] = \mathbb{1}[V_k = 1]$ and therefore

$$\frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\frac{\mathbb{1}[A = 0]Y \mathbb{P}(V_k = 1 \mid W, E)}{\mathbb{P}(A = 0 \mid W, E)} \right) = \frac{1}{\mathbb{P}(V_k = 1)} \mathbb{E} \left(\frac{\mathbb{1}[A = 0]Y \mathbb{1}[V_k = 1]}{\mathbb{P}(A = 0 \mid W, E)} \right).$$

□

Identification of ATE

Recall that

Definition 4 (Conditional and marginal average treatment effect of treatment arm k compared to control).

$$\text{CATE}(k, e, w) = \mathbb{E}[Y(k) - Y(0) \mid W = w, E = e]$$

$$\text{ATE}(k) = \mathbb{E}[\text{CATE}(k, W, E)].$$

10.0.1 Identification based on the G-formula.

Proof We show the proof for treatment 0. We refer to $W = w, E = e$ as W, E for clarity.

$$\begin{aligned} \mathbb{E}(Y(0)) &= \mathbb{E}(\mathbb{E}(Y(0) \mid W, E)) && \text{by (IE)} \\ &= \mathbb{E}(\mathbb{E}(Y(0) \mid A = k, W, E)) && \text{by (A1)} \\ &= \mathbb{E}(\mathbb{E}(Y \mid A = 0, W, E)) && \text{by (A3, A6)} \end{aligned}$$

The proof for treatment k can be shown by following the steps for identifying $\mathbb{E}(Y(k) \mid V_k = 1)$ in section 10 and then assuming (A7) to be able to marginalize to concurrent and non-concurrent controls combined. Consequently, under (A1), (A2), (A3), (A6), and (A7), $\text{CATE}(k, w, e)$ is identified as

$$\mathbb{E}(Y \mid A = k, W, E, V_k = 1) - \mathbb{E}(Y \mid A = 0, W, E). \tag{9}$$

□

M-estimation details

We here provide detail on the M-estimation approach for obtaining asymptotic variances for outcome regression and weighted estimators. Recall that Z_i represent the data for the experimental unit i , i.e., $Z_i = (E_i, W_i, V_{k,i}, A_i, Y_i) \sim P$ and consider $X_i = (E_i, W_i)$.

Outcome regression

$\widehat{\text{cATE}}_{\text{OR}}^{\text{oc}}$. This estimator consider only concurrent controls. Let's define $\widehat{\text{cATE}}_{\text{OR}}^{\text{oc}} = \mu_k - \mu_0$ where μ_k and μ_0 are the mean outcomes under treatment k and control in the only concurrent control population. We started by considering controls, $\theta_0 = (\beta_0, \mu_0)$ and the following estimating equations

$$\sum_{i=1}^n h(Z_i, \theta_0) = \sum_{i=1}^n \begin{pmatrix} h_1(Z_i, \beta_0) \\ h_2(Z_i, \mu_0) \end{pmatrix} = 0$$

where $h_1(Z_i, \beta_0) = X_i^\top V_i(1 - A_i)(Y_i - X_i\beta_0)$ and $h_2(X_i, \mu_0) = V_i(Z_i\beta_0 - \mu_0)$ are the score functions for the model of the conditional mean and the the marginal mean under control, respectively. We consider the following Jacobian matrix of the estimating equations,

$$\begin{aligned} \overline{\mathbf{G}}(\hat{\theta}_0) &= -\frac{1}{n} \sum_{i=1}^n \frac{\partial h(Z_i, \theta_0)}{\partial \theta_0^\top} \Big|_{\theta_0 = \hat{\theta}_0} \\ &= \frac{1}{n} \sum_{i=1}^n \begin{pmatrix} \overline{\mathbf{G}}_{11} & \mathbf{0} \\ \overline{\mathbf{G}}_{21} & \overline{\mathbf{G}}_{22} \end{pmatrix} \\ &= \frac{1}{n} \sum_{i=1}^n \begin{pmatrix} X_i^\top V_i(1 - A_i)X_i & 0 \\ -V_iX_i & V_i \end{pmatrix} \end{aligned}$$

We then constructed the following influence functions

$$\begin{aligned}\varphi(Z_i, \hat{\beta}_0) &= \overline{\mathbf{G}}_{11}^{-1} h_1(Z_i, \hat{\beta}_0) \\ \varphi(Z_i, \hat{\mu}_0) &= \overline{\mathbf{G}}_{22}^{-1} \left(h_2(Z_i, \mu_0) + (-\overline{\mathbf{G}}_{21}) \varphi(Z_i, \hat{\beta}_0) \right),\end{aligned}$$

where $\hat{\beta}_0$ where obtained by ordinary least squares. We conducted a similar analysis for $\theta_k = (\beta_k, \mu_k)$. Finally, we obtained the variance of $\widehat{\text{cATE}}_{\text{OR}}^{\text{oc}}$ as,

$$\widehat{V}(\widehat{\text{cATE}}_{\text{OR}}^{\text{oc}}) = \frac{1}{n} \left(\frac{1}{n} \sum_{i=1}^n \varphi(Z_i, \widehat{\text{cATE}}_{\text{OR}}^{\text{oc}}) \varphi(Z_i, \widehat{\text{cATE}}_{\text{OR}}^{\text{oc}})^\top \right),$$

where $\varphi(Z_i, \widehat{\text{cATE}}_{\text{OR}}^{\text{oc}}) = \varphi(Z_i, \hat{\mu}_k) - \varphi(Z_i, \hat{\mu}_0)$.

$\widehat{\text{cATE}}_{\text{OR}}^{\text{all}}$. This estimator consider both concurrent and non concurrent controls when estimating $\mathbf{E}(Y \mid A = 0, W = w, E = e)$. Hence, the analysis for $\widehat{\text{cATE}}_{\text{OR}}^{\text{all}}$ looks the same as that for $\widehat{\text{cATE}}_{\text{OR}}^{\text{oc}}$ only changing the estimating equation for $\mathbf{E}(Y \mid A = 0, W = w, E = e)$, i.e., $h_1(Z_i, \beta_0) = Z_i^\top (1 - A_i)(Y_i - Z_i \beta_0)$, while the conditional mean of the outcome among the treated remains computed within only concurrent, i.e., $\mathbf{E}(Y \mid A = k, V_k = 1, W = w, E = e)$. Specifically, we started by considering controls, $\theta_0 = (\alpha_0, \mu_0)$ and the following estimating equations

$$\sum_{i=1}^n h(Z_i, \theta_0) = \sum_{i=1}^n \begin{pmatrix} h_1(Z_i, \alpha_0) \\ h_2(Z_i, \mu_0) \end{pmatrix} = 0$$

where $h_1(Z_i, \alpha_0) = X_i^\top (1 - A_i)(Y_i - X_i \alpha_0)$ and $h_2(Z_i, \mu_0) = V_i(X_i \alpha_0 - \mu_0)$ are the score functions for the model of the conditional mean and the the marginal mean under control,

respectively. While for the treated units we considered, $\theta_k = (\beta_k, \mu_k)$ and the following estimating equations

$$\sum_{i=1}^n h(Z_i, \theta_k) = \sum_{i=1}^n \begin{pmatrix} h_1(Z_i, \beta_k) \\ h_2(Z_i, \mu_k) \end{pmatrix} = 0$$

where $h_1(Z_i, \beta_k) = X_i^\top V_i A_i (Y_i - X_i \beta_k)$ and $h_2(Z_i, \mu_k) = V_i (X_i \beta_k - \mu_k)$. Derivation of the Jacobian matrix of the estimating equations is similar to the above.

$\hat{\text{ATE}}_{\text{OR}}$. We considered for controls, $\theta_0 = (\alpha_0, \mu_0)$ and the following estimating equations

$$\sum_{i=1}^n h(Z_i, \theta_0) = \sum_{i=1}^n \begin{pmatrix} h_1(Z_i, \alpha_0) \\ h_2(Z_i, \mu_0) \end{pmatrix} = 0$$

where $h_1(Z_i, \alpha_0) = X_i^\top (1 - A_i) (Y_i - X_i \alpha_0)$ and $h_2(Z_i, \mu_0) = (X_i \alpha_0 - \mu_0)$ are the score functions for the model of the conditional mean and the the marginal mean under control, respectively. While for the treated units we considered, $\theta_k = (\alpha_k, \mu_k)$ and the following estimating equations

$$\sum_{i=1}^n h(Z_i, \theta_k) = \sum_{i=1}^n \begin{pmatrix} h_1(Z_i, \alpha_k) \\ h_2(Z_i, \mu_k) \end{pmatrix} = 0$$

where $h_1(Z_i, \alpha_k) = Z_i^\top V_i A_i (Y_i - X_i \alpha_k)$ and $h_2(Z_i, \mu_k) = (X_i \alpha_k - \mu_k)$. Derivation of the Jacobian matrix of the estimating equations is similar to the above.

Parametric inverse probability weighting

$\widehat{\text{cATE}}_{\text{IPW}}^{\text{oc}}$. This estimator consider only concurrent controls. Let's define $\widehat{\text{cATE}}_{\text{IPW}}^{\text{oc}} = \mu_k - \mu_0$. We started by considering controls, $\theta = (\eta, \mu_0, \mu_1)$ and the following estimating equations

$$\sum_{i=1}^n h(Z_i, \theta) = \sum_{i=1}^n \begin{pmatrix} h_1(Z_i, \eta) \\ h_2(Z_i, \mu_0) \\ h_3(Z_i, \mu_1) \end{pmatrix} = 0$$

where $h_1(Z_i, \eta) = X_i^\top V_i(A_i - \pi)$ and $h_2(Z_i, \mu_0) = V_i(\gamma_i^0 Y_i - \mu_0)$, $h_3(Z_i, \mu_1) = V_i(\gamma_i^1 Y_i - \mu_1)$ are the score functions for the model of the conditional probability and the marginal mean under control and treatment, respectively, and where $\gamma_i^0 = \mathbb{1}\{A_i = 0\}/(1 - \pi_i)$, $\gamma_i^k = \mathbb{1}\{A_i = k\}/(\pi_i)$, and $\pi_i = \frac{\exp(X_i^\top \eta)}{1 + \exp(X_i^\top \eta)}$. We consider the following Jacobian matrix of the estimating equations,

$$\begin{aligned} \overline{\mathbf{G}}(\hat{\theta}_0) &= -\frac{1}{n} \sum_{i=1}^n \left. \frac{\partial h(Z_i, \theta_0)}{\partial \theta_0^\top} \right|_{\theta = \hat{\theta}} \\ &= \frac{1}{n} \sum_{i=1}^n \begin{pmatrix} \overline{\mathbf{G}}_{11} & \mathbf{0} & \mathbf{0} \\ \overline{\mathbf{G}}_{21} & \overline{\mathbf{G}}_{22} & \mathbf{0} \\ \overline{\mathbf{G}}_{31} & \mathbf{0} & \overline{\mathbf{G}}_{33} \end{pmatrix} \\ &= \frac{1}{n} \sum_{i=1}^n \begin{pmatrix} X_i^\top V_i \frac{\exp(X_i^\top \eta)}{1 + \exp(X_i^\top \eta)^2} X_i & 0 & 0 \\ (1 - A_i) V_i X_i Y_i \exp(X_i^\top \eta) & V_i & 0 \\ A_i V_i X_i Y_i \exp(-X_i^\top \eta) & 0 & V_i \end{pmatrix} \end{aligned}$$

We then constructed the following influence functions

$$\begin{aligned}\varphi(Z_i, \hat{\eta}) &= \overline{\mathbf{G}}_{11}^{-1} h_1(Z_i, \hat{\eta}), \\ \varphi(Z_i, \hat{\mu}_0) &= \overline{\mathbf{G}}_{22}^{-1} (h_2(Z_i, \mu_0) + (-\overline{\mathbf{G}}_{21})\varphi(Z_i, \hat{\eta})), \\ \varphi(Z_i, \hat{\mu}_k) &= \overline{\mathbf{G}}_{33}^{-1} (h_3(Z_i, \mu_k) + (-\overline{\mathbf{G}}_{31})\varphi(Z_i, \hat{\eta}))\end{aligned}$$

where $\hat{\eta}$ where obtained by ordinary least squares. Finally, we obtained the variance of $\text{c}\hat{\text{ATE}}_{\text{IPW}}^{\text{oc}}$ as,

$$\hat{V}(\text{c}\hat{\text{ATE}}_{\text{IPW}}^{\text{oc}}) = \frac{1}{n} \left(\frac{1}{n} \sum_{i=1}^n \varphi(Z_i, \text{c}\hat{\text{ATE}}_{\text{IPW}}^{\text{oc}}) \varphi(Z_i, \text{c}\hat{\text{ATE}}_{\text{IPW}}^{\text{oc}})^\top \right),$$

where $\varphi(Z_i, \text{c}\hat{\text{ATE}}_{\text{IPW}}^{\text{oc}}) = \varphi(Z_i, \hat{\mu}_k) - \varphi(Z_i, \hat{\mu}_0)$.

Proof of Theorem 2

We start by introducing some notation. We introduce an operator $\text{IF} : \psi \rightarrow L_2(\mathbb{P})$, where \mathbb{P} is a probability distribution assumed to lie in some nonparametric model \mathcal{P} , that maps functionals $\psi : \mathcal{P} \rightarrow \mathbb{R}$ to their influence function $\varphi(z) \in L_2(\mathbb{P})$ and where z is our observed data. Recall the following building blocks:

(bb1) the influence function of $\mu(x) = \mathbb{E}[Y|X = x]$ is $\text{IF}(\mu(x)) = \frac{\mathbf{1}[X=x]}{\mathbb{P}(X=x)}(Y - \mathbb{E}[Y|X = x])$

(bb2) the influence function of $p(x) = \mathbb{P}(X = x)$ is $\text{IF}(p(x)) = (\mathbf{1}[X = x] - p(x))$

(bb3) $\text{IF}(\psi_1\psi_2) = \text{IF}(\psi_1)\psi_2 + \psi_1\text{IF}(\psi_2)$ (product rule)

(bb4) $\text{IF}(f(\psi)) = \psi'\text{IF}(\psi)$ (chain rule)

(bb5) $\mathbb{P}(A, B, C) = \mathbb{P}(A|B, C)\mathbb{P}(B, C) = \mathbb{P}(A|B, C)\mathbb{P}(B|C)\mathbb{P}(C)$

$$(bb6) \sum_x \mathbf{1}[A = k, X = x] = \mathbf{1}[A = k].$$

Finally, recall that the parameter of interest (under the aforementioned identification assumption) is

$$cATE(k) = E[E[Y|A = k, W = w, E = e, V_k = 1] - E[Y|A = 0, W = w, E = e, V_k = 1] | V_k = 1].$$

while in the nonparametric model that assumes (A6) is

$$cATE(k) = E[E[Y|A = k, W = w, E = e, V_k = 1] - E[Y|A = 0, W = w, E = e] | V_k = 1].$$

Theorem 2, eq. (5). We define $(X = x) = (W = w, E = e)$ and pretend that the data is discrete. Recall that under discrete data

$$\begin{aligned} E[E[Y|A = 1, X = x, V_k = 1] | V_k = 1] &= \frac{E[\mathbf{1}[V_k = 1]E[Y|A = 1, X = x, V_k = 1]]}{P(V_k = 1)} \\ &= \frac{\sum_x \mathbf{1}[V_k = 1]E[Y|A = 1, X = x, V_k = 1]P(X = x)}{P(V_k = 1)} \\ &= \frac{\sum_x \mathbf{1}[V_k = 1]\mu_{oc}(1, x, 1)p(x)}{P(V_k = 1)} \\ &= \frac{\psi_{num}^1}{\psi_{den}} = \psi^1. \end{aligned}$$

We now analyze the influence function of ψ_{num}^1 ,

$$\begin{aligned} \varphi(Z, \psi_{num}^1) &\equiv \text{IF}\{\psi_{num}^1\} \\ &= \text{IF}\left\{\sum_x \mathbf{1}[V_k = 1]\mu_{oc}(1, x, 1)p(x)\right\} \\ &= \mathbf{1}[V_k = 1] \sum_x [\text{IF}\{\mu_{oc}(1, x, 1)\}p(x) + \mu(1, x, 1)\text{IF}\{p(x)\}] \quad \text{by (bb3)} \end{aligned}$$

$$\begin{aligned}
&= \mathbb{1}[V_k = 1] \sum_x \left[\left(\frac{\mathbb{1}[A = 1, X = x, V_k = 1]}{p(1, x, 1)} \{Y - \mu_{oc}(1, x, 1)\} \right) p(x) \right. \\
&\quad \left. + \mu_{oc}(1, x, 1) (\mathbb{1}[X = x] - p(x)) \right] \quad \text{by (bb1,bb2)} \\
&= \mathbb{1}[V_k = 1] \sum_x \left[\left(\frac{\mathbb{1}[A = 1, X = x, V_k = 1]}{\mathbb{P}(A = 1 | X = x, V_k = 1)\mathbb{P}(V_k = 1|X = x)} \{Y - \mu_{oc}(1, x, 1)\} \right) \right. \\
&\quad \left. + \mu_{oc}(1, x, 1)\mathbb{1}[X = x] - \mu_{oc}(1, x, 1)p(x) \right] \quad \text{by (bb5)} \\
&= \mathbb{1}[V_k = 1] \left[\left(\frac{\mathbb{1}[A = 1]}{\mathbb{P}(A = 1 | X = x, V_k = 1)} \{Y - \mu_{oc}(1, x, 1)\} \right) + \mu_{oc}(1, x, 1) \right] - \psi_{num}^1 \quad \text{by (bb6)}
\end{aligned}$$

where in the last equality we also used the fact that $\mathbb{P}(V_k = 1|X = x) = 1$ under $\mathbb{1}[V_k = 1]$, and $\psi_{num}^1 = \sum_x \mathbb{1}[V_k = 1]\mu_{oc}(1, x, 1)p(x)$. Analogously we can compute the influence function of ψ_{num}^0 ,

$$\begin{aligned}
\varphi(Z, \psi_{num}^0) &\equiv \mathbf{IF}\{\psi_{num}^0\} \\
&= \mathbf{IF}\left\{ \sum_x \mathbb{1}[V_k = 1]\mu_{oc}(0, x, 1)p(x) \right\} \\
&= \mathbb{1}[V_k = 1] \left[\left(\frac{\mathbb{1}[A = 0]}{\mathbb{P}(A = 0 | X = x, V_k = 1)} \{Y - \mu_{oc}(0, x, 1)\} \right) + \mu_{oc}(0, x, 1) \right] - \psi_{num}^0
\end{aligned}$$

We now compute the influence function of ψ_{den} ,

$$\varphi(Z, \psi_{den}) \equiv \mathbf{IF}\{\psi_{den}\} = \mathbb{1}[V_k = 1] - \psi_{den}$$

We now consider the influence function of $\frac{\psi_{num}^1}{\psi_{den}} = \psi^1$,

$$\begin{aligned}
\varphi(Z, \psi^1) &\equiv \text{IF}\{\psi^1\} = \frac{\text{IF}\{\psi_{num}^1\}}{\psi_{den}} - \frac{\psi_{num}^1}{\psi_{den}} \frac{\text{IF}\{\psi_{den}\}}{\psi_{den}} \\
&= \frac{1}{\psi_{den}} \left[\text{IF}\{\psi_{num}^1\} - \frac{\psi_{num}^1}{\psi_{den}} \text{IF}\{\psi_{den}\} \right] \\
&= \frac{1}{\text{P}(V_k = 1)} \left[\left(\mathbb{1}[V_k = 1] \left[\left(\frac{\mathbb{1}[A = 1]}{\text{P}(A = 1 | X = x, V_k = 1)} \{Y - \mu_{oc}(1, x, 1)\} \right) + \mu_{oc}(1, x, 1) \right] - \psi_{num}^1 \right) \right. \\
&\quad \left. - \frac{\psi_{num}^1}{\psi_{den}} (\mathbb{1}[V_k = 1] - \psi_{den}) \right] \\
&= \frac{1}{\text{P}(V_k = 1)} \left[\left(\mathbb{1}[V_k = 1] \left[\left(\frac{\mathbb{1}[A = 1]}{\text{P}(A = 1 | X = x, V_k = 1)} \{Y - \mu_{oc}(1, x, 1)\} \right) + \mu_{oc}(1, x, 1) \right] - \psi_{num}^1 \right) \right. \\
&\quad \left. - \frac{\psi_{num}^1}{\psi_{den}} \mathbb{1}[V_k = 1] + \frac{\psi_{num}^1}{\psi_{den}} \psi_{den} \right] \\
&= \frac{\mathbb{1}[V_k = 1]}{\text{P}(V_k = 1)} \left[\frac{\mathbb{1}[A = 1]}{\text{P}(A = 1 | X = x, V_k = 1)} \{Y - \mu_{oc}(1, x, 1)\} + \mu_{oc}(1, x, 1) - \psi^1 \right]
\end{aligned}$$

We can now combine $\frac{\psi_{num}^1 - \psi_{num}^0}{\psi_{den}} = \text{cATE}(k)$ to obtain

$$\begin{aligned}
\varphi(Z, \text{cATE}(k)) &\equiv \text{IF}\{\text{cATE}(k)\} = \frac{\mathbb{1}\{V_k = 1\}}{\text{P}(V_k = 1)} \left[\frac{2A - 1}{\text{P}(A | W, E, V_k = 1)} \{Y - \text{E}(Y | A, W, E, V_k = 1)\} \right. \\
&\quad \left. + \text{E}(Y | A = 1, W, E, V_k = 1) - \text{E}(Y | A = 0, W, E, V_k = 1) - \text{cATE}(k) \right].
\end{aligned}$$

Theorem 2, eq. (6). Under assumption (A6), we now target (among controls),

$$\begin{aligned}
\text{E}[\text{E}[Y|A = 0, X = x] | V_k = 1] &= \frac{\text{E}[\mathbb{1}[V_k = 1]\text{E}[Y|A = 0, X = x]]}{\text{P}(V_k = 1)} \\
&= \frac{\text{E}[\text{E}[\mathbb{1}[V_k = 1] | X = x]\text{E}[Y|A = 0, X = x]]}{\text{P}(V_k = 1)} \\
&= \frac{\sum_x \text{P}(V_k = 1 | X = x)\text{E}[Y|A = 0, X = x]\text{P}(X = x)}{\text{P}(V_k = 1)} \\
&= \frac{\sum_x \nu(w_i, e_i)\mu_{\text{all}}(1, x)p(x)}{\text{P}(V_k = 1)}
\end{aligned}$$

$$= \frac{\psi_{num}^0}{\psi_{den}} = \psi^0.$$

The influence function of ψ_{num}^0 is

$$\begin{aligned} \varphi(Z, \psi_{num}^0) &\equiv \text{IF}\{\psi_{num}^0\} \\ &= \sum_x \left[\frac{\mathbf{1}[X = x]}{\mathbf{P}(X = x)} (\mathbf{1}[V_k = 1] - \nu(x)) \mu_{\text{all}}(0, x) p(x) \right. \\ &\quad \left. + \nu(x) \left(\frac{\mathbf{1}[A = 0, X = x]}{\mathbf{P}(A = 0 | X = x) \mathbf{P}(X = x)} \{Y - \mu_{\text{all}}(0, x)\} \right) p(x) \right. \\ &\quad \left. + \nu(x) \mu_{\text{all}}(0, x) (\mathbf{1}[X = x] - p(x)) \right] \\ &= \sum_x \left[\frac{\mathbf{1}[X = x] \mathbf{1}[V_k = 1]}{\mathbf{P}(X = x)} \mu_{\text{all}}(0, x) p(x) - \frac{\mathbf{1}[X = x]}{\mathbf{P}(X = x)} \nu(x) \mu_{\text{all}}(0, x) p(x) \right. \\ &\quad \left. + \nu(x) \left(\frac{\mathbf{1}[A = 0, X = x]}{\mathbf{P}(A = 0 | X = x) \mathbf{P}(X = x)} \{Y - \mu_{\text{all}}(0, x)\} \right) p(x) \right. \\ &\quad \left. + \mathbf{1}[X = x] \nu(x) \mu_{\text{all}}(0, x) - \nu(x) \mu_{\text{all}}(0, x) p(x) \right] \\ &= \mathbf{1}[V_k = 1] \mu_{\text{all}}(0, x) + \nu(x) \left(\frac{\mathbf{1}[A = 0]}{\mathbf{P}(A = 0 | X = x)} \{Y - \mu_{\text{all}}(0, x)\} \right) - \psi_{num}^0 \end{aligned}$$

As shown before, we can then compute the influence function of $\frac{\psi_{num}^0}{\psi_{den}}$, and finally of $\text{cATE}(k)$

under assumption (A6), leading to,

$$\begin{aligned} \varphi(Z, \text{cATE}(k)) &\equiv \text{IF}\{\text{cATE}(k)\} = \frac{\mathbf{1}\{V_k = 1\}}{\mathbf{P}(V_k = 1)} \left[\frac{A}{\mathbf{P}(A | V_k = 1, W, E)} \{Y - \mathbf{E}(Y | A, W, E, V_k = 1)\} \right] \\ &\quad - \frac{1 - A}{\mathbf{P}(A | W, E)} \frac{\mathbf{P}(V_k = 1 | E, W)}{\mathbf{P}(V_k = 1)} \{Y - \mathbf{E}(Y | A, E, W)\} \\ &\quad + \frac{\mathbf{1}\{V_k = 1\}}{\mathbf{P}(V_k = 1)} \left[\mathbf{E}(Y | A = 1, W, E, V_k = 1) - \mathbf{E}(Y | A = 0, W, E) - \text{cATE}(k) \right] \end{aligned}$$