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On the evaluation of individualized treatment rules using real-world data

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ABSTRACT

Individualized treatment rules tailor treatment decisions to individual patients' characteristics. These rules can be estimated without bias using data from randomized clinical trials. However, the benefits derived from trials, which often have restrictive inclusion-exclusion criteria, may not reflect the true benefits when applied to a broader target population. To address this challenge, we utilize large real-world data from the target population to propose a consistent estimator to evaluate the benefits of the individualized treatment rules and obtain their inferential properties. Furthermore, we derive two novel composite features. These two features, replacing the potentially high-dimensional original features, preserve the consistency of the evaluation for the estimated treatment rule and yield the smallest variability for inference. Finally, we conduct extensive simulation studies to demonstrate the small-sample performance of the proposed estimators and further illustrate the method via application to tailor treatment of type 2 diabetic patients.

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1. Introduction

Individualized treatment rules (ITRs) deviate from the traditional 'one-size-fits-all' paradigm by tailoring treatments to maximize patient benefit based on individual characteristics. Randomized clinical trials are considered the gold standard for unbiased treatment comparisons between any subgroup because randomization eliminates the effects of hidden confounders. A crucial challenge in applying individualized treatment rules is evaluating their real-world benefit in a target population (e.g., a specific hospital or community). This evaluation typically relies on comparing the clinical benefit of the average favourable disease outcome achieved by applying the estimated treatment rule to all patients in the target population against the standard of care. However, because randomized clinical trials often have restrictive inclusion-exclusion criteria, the benefits observed in trials may not accurately reflect true benefits in the target population due to distributional differences between the trial and target populations. In contrast, real-world data, such as biobanks and electronic health records, provide a comprehensive representation of the target population. These data sources offer valuable auxiliary information to examine the distributional differences from randomized

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clinical trials, so they can be used to evaluate the individualized treatment rule's real-world benefit.

Many statistical and machine learning methods have been proposed to learn individualized treatment rules using both trial and real-world data, a problem that belongs to the broader literature on data integration in causal inference (Colnet et al., 2024; Degtiar & Rose, 2023; Hünermund & Bareinboim, 2025). For example, to improve the efficiency using real-world data, Kallus et al. (2018), S. Yang, Zeng et al. (2020), Wu and Yang (2022), and S. Yang, Gao et al. (2023) modelled the confounding bias function in real-world data. Zhou and Ji (2021) used external control to augment the control arm in trials. Additionally, Wu, Zeng et al. (2020) incorporated pre-trained features from real-world data into estimating individualized treatment rules using trial data. Another line of research addresses the generalizability of the individualized treatment rule by handling differential covariate distributions between the trial and real-world populations (Chu et al., 2023; Johansson et al., 2018; Uehara et al., 2020; Wu & Yang, 2023; Y. Q. Zhao et al., 2019), or by learning a rule that is robust to the worst case shift within an ambiguity set when the target population is not observed (Mo et al., 2021). However, these methods focus on improving efficiency, reducing bias, or guarding against distributional shift in estimating individualized treatment rules, rather than evaluating their benefits. On the other hand, there has been a growing body of literature for evaluating treatment rules based on a variety of evaluating metrics, including the Qini curve (Radcliffe, 2007), the effect for a selected subpopulation (L. Zhao et al., 2013), the population average prescriptive effect, and its area under curve with budget constraints (Imai & Li, 2023; Sun et al., 2021), and rank-weighted treatment effects (Yadlowsky et al., 2025), but they focus on metrics where the evaluation is performed on the training population instead of the real-world population to be considered in this paper.

In this paper, we propose a method to estimate the benefits of individualized treatment rules using real-world data. We assume that the conditional average treatment effect is the same between the two populations and derive the individualized treatment rule through doubly robust estimation of this effect using trial data. Subsequently, we estimate the benefit of the individualized treatment rule compared to the standard of care using real-world data. We show that the proposed estimator is asymptotically unbiased and normally distributed. Furthermore, we derive two composite features: one representing the prediction score of the treatment effect and the other capturing residual heterogeneity. These features are used to obtain an improved estimator of the individualized treatment rule. We show that the new individualized treatment rule estimator improves the efficiency of benefit estimation compared to the original one. This improvement is particularly useful in designing future trials since the two composite features can be determined pre-treatment. These features effectively reduce a large number of covariates into two composite covariates along the dimensions that best capture the interaction between treatments and covariates. While ITR estimation has been extensively studied, our work introduces a formal inference framework for evaluating ITR performance in real-world settings. Another contribution of our work is to derive two novel composite features that can result in more efficient ITR than using the full covariates. This is particularly useful for designing a future trial, as will be demonstrated in our application.

The paper is organized as follows: Section 2 introduces the estimand of interest, which is the benefit of the estimated optimal individualized treatment rule in the target population. This section also describes the inference procedure for the individualized treatment rule and

its benefit estimator and provides their theoretical properties. Additionally, this section outlines the algorithm for deriving the two composite features that minimize the variance of the benefit estimator and improve the individualized treatment rule based on these composite features. Section 3 demonstrates the small-sample performance of the proposed method, including bias and efficiency through extensive simulation studies. Section 4 illustrates the utility of our method via an application to estimate the optimal individualized treatment rule and evaluate its benefit for treating type 2 diabetic patients. The paper concludes with a discussion in Section 5.

2. Method

2.1. Estimand and assumptions

Let $\mathbf{X} \in \mathbb{R}^p$ denote the p-dimensional covariates, and let A denote a binary treatment variable taking values in $\mathcal{A} = \{-1, 1\}$. Let Y denote the observed outcome, where a larger value indicates a favourable outcome. Given the potential differences between the randomized clinical trials and real-world data populations, we let $\mathbb{P}$ denote the probability measure generated by $(\mathbf{X}, A, Y)$ in randomized clinical trials, and $\widetilde{\mathbb{P}}$ for real-world data. Correspondingly, the expectations under $\mathbb{P}$ and $\widetilde{\mathbb{P}}$ are denoted as $\mathbb{E}$ and $\widetilde{\mathbb{E}}$, respectively.

Following the potential outcome framework in Rubin (1974), let $Y(a)$ be the potential outcome under treatment a, where $a = 1, -1$. An individualized treatment rule is a mapping $d : \mathbb{R}^p \to \mathcal{A}$ that prescribes treatment $d(\mathbf{x})$ to a patient with covariate value $\mathbf{x}$. The benefit attained in the target population by adhering to an individualized treatment rule d compared to the standard care d_0 is defined as

$$G(d) \equiv \widetilde{\mathbb{E}}\left[Y\{d(\mathbf{X})\} - Y\{d_0(\mathbf{X})\}\right],$$

which is the expected difference in outcome between d and d_0 in the target population. A simple calculation shows that the benefit of d in the target population can be expressed as

$$\widetilde{\mathbb{E}}\left[\{\mathbb{I}(d(\mathbf{X}) = 1) - \mathbb{I}(d_0(\mathbf{X}) = 1)\}\widetilde{\mathbb{E}}\{Y(1) - Y(-1) \mid \mathbf{X}\}\right],$$

indicating the expected increase in the average treatment effect by following the individualized treatment rule d instead of the standard care d_0 in the target population. We note that $G(d)$ quantifies the average gain in outcome, and differs from the benefit and harm rates in Kallus (2022), Wu, Ding et al. (2026) and Wu, Jiang et al. (2025), namely $\widetilde{\mathbb{E}}[\mathbb{I}(d(\mathbf{X}) = 1)\widetilde{\mathbb{P}}\{Y(1) - Y(-1) > 0 \mid \mathbf{X}\}]$ and $\widetilde{\mathbb{E}}[\mathbb{I}(d(\mathbf{X}) = 1)\widetilde{\mathbb{P}}\{Y(1) - Y(-1) < 0 \mid \mathbf{X}\}]$, which measure how often treatment helps or harms instead of by how much. We assume the following.

Assumption 2.1 (Exchangeability in effect measure): *We assume*

$$\mathbb{E}[Y(1) - Y(-1) \mid \mathbf{X} = \mathbf{x}] = \widetilde{\mathbb{E}}[Y(1) - Y(-1) \mid \mathbf{X} = \mathbf{x}].$$

This assumption, necessary for extending the conditional treatment effect from randomized clinical trials to the target population, is commonly adopted in various data integration methods in causal inference (e.g., Lee et al., 2023; Wu & Yang, 2022). The assumption is weaker than the mean exchangeability assumption (Dahabreh et al., 2019), which states that $\mathbb{E}[Y(a) \mid \mathbf{X} = \mathbf{x}] = \widetilde{\mathbb{E}}[Y(a) \mid \widetilde{\mathbf{X}} = \mathbf{x}]$ for any $a \in \mathcal{A}$, and the ignorability of trial participation

assumption (Stuart et al., 2011), where $Y(a)$ is independent of data sources conditional on $\mathbf{X}$. In addition, we give the following assumptions.

Assumption 2.2 (Stable unit treatment value assumption (SUTVA)): *The observed outcome is the potential outcome under the treatment received, i.e.,* $Y(A) = Y$.

Assumption 2.3 (Positivity): *All treatments a are possible for all* $\mathbf{x}$*, i.e.,* $\mathbb{P}(A = a \mid \mathbf{X} = \mathbf{x}) > 0$ *for* $a = -1, 1$ *and for all* $\mathbf{x} \in \mathbb{R}^p$.

Assumption 2.4 (Ignorability): *In the randomized trial population,* $A \perp \{Y(a)\} \mid \mathbf{X}$ for $a = -1, 1$.

Note that the SUTVA is a standard assumption in most causal inference literature. Both positivity and ignorability assumptions hold in well-designed randomized studies, where each participant has a nonzero probability of receiving any given treatment.

Under the above assumptions, the value function of an individualized treatment rule d, defined as $\mathcal{V}_{\mathbb{P}}(d) = \widetilde{\mathbb{E}}[Y(d)]$, is equivalent to $\mathcal{V}_{\mathbb{P}}(d) = \widetilde{\mathbb{E}}[Q_{\mathbb{P}}(\mathbf{X}, d(\mathbf{X}))]$, where $Q_{\mathbb{P}}(\mathbf{X}, a) = \mathbb{E}(Y(a)|\mathbf{X}) = \mathbb{E}(Y|\mathbf{X}, A = a)$, also known as the Q-function (Qian & Murphy, 2011). The optimal individualized treatment rule that maximizes the value function is

$$d^*(\mathbf{x}) = \text{argmax}_{a \in \mathcal{A}} Q_{\mathbb{P}}(\mathbf{x}, a) = \text{sign}[Q_{\mathbb{P}}(\mathbf{x}, 1) - Q_{\mathbb{P}}(\mathbf{x}, -1)].$$

Here, the function $C_{\mathbb{P}}(\mathbf{x}) = Q_{\mathbb{P}}(\mathbf{x}, 1) - Q_{\mathbb{P}}(\mathbf{x}, -1)$ is known as the conditional average treatment effect function. Finally, the estimand of interest for the optimal individualized treatment rule is given as

$$G(d^*) = \widetilde{\mathbb{E}}[(\mathbb{I}(d^*(\mathbf{X}) = 1) - \mathbb{I}(d_0(\mathbf{X}) = 1))C_{\mathbb{P}}(\mathbf{X})].$$

In the next sections, we will introduce our method as follows. First, we describe a procedure to estimate the optimal ITR using the trial data. Next, we propose an inference procedure to evaluate this ITR using real-world data. Finally, based on the variance derived in the inference procedure, we develop an algorithm to further improve the efficiency of ITR estimation. In particular, the improved ITR will be based on some composite features instead of all the covariates.

2.2. Estimating the conditional average treatment effect using randomized clinical trials

In randomized clinical trials, we observe $\{(\mathbf{X}_i, A_i, Y_i)\}_{i=1}^n$ from n patients. Due to randomization, the treatment assignment A is independent of the potential outcomes $\{Y(a) : a = -1, 1\}$ given $\mathbf{X}$, and the probability of the treatment assignment, denoted by $\pi(\mathbf{x}) = \mathbb{P}(A = 1|\mathbf{X} = \mathbf{x})$, is known and assumed to be bounded away from zero. Furthermore, we assume that real-world data consists of covariates from a sample of N subjects, $\{\widetilde{\mathbf{X}}_j\}_{j=1}^N$, drawn independently of the trial patients, where N is usually much larger than n. Note that for this work, we do not require treatment or outcome measurements in the real-world data.

We estimate the conditional average treatment effect directly with a two-step pseudo-outcome regression. We assume

$$Y(a) = \eta(\mathbf{X}) + a\mathbf{X}^\top \boldsymbol{\psi}/2 + \epsilon(a),$$

where $\epsilon(a)$ satisfies $\mathbb{E}(\epsilon(a) \mid \mathbf{X}) = 0$ and $\sigma^2(\mathbf{X}, a) = \mathbb{E}(\epsilon(a)^2 \mid \mathbf{X})$. In this model, the conditional average treatment effect is $C_{\mathbb{P}}(\mathbf{X}) = \mathbf{X}^\top \boldsymbol{\psi}$. Although this model implies a linear treatment rule, which is commonly used in practice due to its interpretability, $\mathbf{X}$ can be replaced by more complex functions of $\mathbf{X}$ to yield a non-linear rule. Additionally, we note that in this model, the main effect $\eta(\mathbf{X})$ is fully nonparametric, and the residual variance function can depend on both covariates $\mathbf{X}$ and treatment option a to accommodate potential heteroskedasticity.

We adopt the doubly robust method to estimate $\boldsymbol{\psi}$ using data from a randomized clinical trial. Specifically, following Bang and Robins (2005) and similarly given in Semenova and Chernozhukov (2021) and Kennedy (2023), we consider an oracle pseudo-outcome:

$$\varphi(\mathbf{X}, A, Y; Q) = \frac{A\,(Y - Q(\mathbf{X}, A))}{\pi(\mathbf{X}) + I(A = -1)(1 - 2\pi(\mathbf{X}))} + Q(\mathbf{X}, 1) - Q(\mathbf{X}, -1).$$

It can be verified that $\mathbb{E}[\varphi(\mathbf{X}, A, Y; Q, \pi) \mid \mathbf{X}] = C(\mathbf{X})$. We estimate the oracle pseudo-outcome by

$$\varphi(\mathbf{X}, A, Y; \widehat{Q}_n) = \frac{A\left\{Y - \widehat{Q}_n(\mathbf{X}, A)\right\}}{\pi(\mathbf{X}) + I(A = -1)(1 - 2\pi(\mathbf{X}))} + \widehat{Q}_n(\mathbf{X}, 1) - \widehat{Q}_n(\mathbf{X}, -1),$$

where $\widehat{Q}_n(\mathbf{X}, a)$ is an estimate of $Q(\mathbf{X}, a)$ based on the clinical trial data. As shown in Robins and Rotnitzky (1995), this estimate is doubly robust in the sense that $\mathbb{E}(\varphi(\mathbf{X}, A, Y; \widehat{Q}) \mid \mathbf{X}) = C(\mathbf{X})$ almost surely, even if $\widehat{Q}_n(\mathbf{X}, a)$ is not a consistent estimator for $Q(\mathbf{X}, a)$. Finally, $\boldsymbol{\psi}$ can be estimated by minimizing

$$\widehat{\boldsymbol{\psi}}(\widehat{Q}_n) = \operatorname{argmin}_{\boldsymbol{\psi}} \mathbb{P}_n\left[\varphi(\mathbf{X}, A, Y; \widehat{Q}_n) - \mathbf{X}^\top \boldsymbol{\psi}\right]^2 = \mathbb{P}_n(\mathbf{X}\mathbf{X}^\top)^{-1}\mathbb{P}_n(\mathbf{X}\varphi(\mathbf{X}, A, Y; \widehat{Q}_n)),$$

where $\mathbb{P}_n$ denotes the empirical measure of n observations from randomized clinical trials. Let $\boldsymbol{\psi}_0$ denote the true value for $\boldsymbol{\psi}$. The following theorem shows that $\widehat{\boldsymbol{\psi}}$ is consistent and asymptotically normal.

Theorem 2.1: *Assume that $\widehat{Q}_n$ belongs to a P-Donsker class and converges to the true outcome model Q in $L_2(P)$. Then $\widehat{\boldsymbol{\psi}}$ converges to $\boldsymbol{\psi}_0$ in probability and $\sqrt{n}[\widehat{\boldsymbol{\psi}} - \boldsymbol{\psi}_0] \to N(0, \boldsymbol{\Sigma})$, where*

$$\boldsymbol{\Sigma} = \mathbb{E}(\mathbf{X}\mathbf{X}^\top)^{-1}\mathbb{E}\left[\mathbf{X}\mathbf{X}^\top\left\{\frac{\sigma^2(\mathbf{X}, 1)}{\pi(\mathbf{X})} + \frac{\sigma^2(\mathbf{X}, -1)}{1 - \pi(\mathbf{X})}\right\}\right]\mathbb{E}(\mathbf{X}\mathbf{X}^\top)^{-1}.$$

Theorem 2.1 suggests that the asymptotic variance of treatment effect $\widehat{\boldsymbol{\psi}}$ depends on the design matrix, the treatment assignment probability, and the residual heterogeneity in randomized clinical trials. Clearly, an estimator for the conditional average treatment effect function $C_{\mathbb{P}}(\mathbf{x})$ is $\mathbf{x}^\top\widehat{\boldsymbol{\psi}}$ and the optimal linear individualized treatment rule is estimated by $\widehat{d}(\mathbf{x}) = \operatorname{sign}(\mathbf{x}^\top\widehat{\boldsymbol{\psi}})$.

2.3. Evaluation of $\widehat{d}(\mathbf{x})$ using real-world data

Given $C_{\mathbb{P}}(\mathbf{x}) = \mathbf{x}^\top \boldsymbol{\psi}_0$ and the exchangeability assumption, the benefit of the individualized treatment rule $\widehat{d}$ in the target population is given by

$$G(\widehat{d}) = \widetilde{\mathbb{E}}[(I(\widetilde{\mathbf{X}}^\top \widehat{\boldsymbol{\psi}} > 0) - I(d_0(\widetilde{\mathbf{X}}) > 0))\widetilde{\mathbf{X}}^\top \boldsymbol{\psi}_0].$$

To estimate this benefit, we substitute $\boldsymbol{\psi}_0$ by $\widehat{\boldsymbol{\psi}}$ and replace the expectation by the empirical average over the real-world data samples to obtain an estimator for $G(\widehat{d})$ as

$$\widehat{G}(\widehat{d}) = \widetilde{\mathbb{P}}_N[(I(\widetilde{\mathbf{X}}^\top \widehat{\boldsymbol{\psi}} > 0) - I(d_0(\widetilde{\mathbf{X}}) > 0))\widetilde{\mathbf{X}}^\top \widehat{\boldsymbol{\psi}}],$$

where, for any function $g(\widetilde{\mathbf{X}})$, $\widetilde{\mathbb{P}}_N(g(\widetilde{\mathbf{X}})) = N^{-1}\sum_{i=1}^{N} g(\widetilde{X}_i)$.

The following theorem gives the asymptotic property of $\widehat{G}(\widehat{d})$ as an estimator of $G(d^*)$, the benefit of the optimal rule in the target population.

Theorem 2.2: *Assume* $\widetilde{\mathbb{P}}(\widetilde{\mathbf{X}}^\top \boldsymbol{\psi}_0 = 0) = 0$ *and* $n/N = o(1)$. *Then* $\sqrt{n}[\widehat{G}(\widehat{d}) - G(d^*)] \to N(0, \sigma_G^2)$, *where*

$$\sigma_G^2 = \widetilde{\mathbb{E}}\left[\left\{\text{sign}(\widetilde{\mathbf{X}}^\top \boldsymbol{\psi}_0) - \text{sign}(d_0(\widetilde{\mathbf{X}}))\right\}\widetilde{\mathbf{X}}^\top\right]\boldsymbol{\Sigma}\widetilde{\mathbb{E}}\left[\left\{\text{sign}(\widetilde{\mathbf{X}}^\top \boldsymbol{\psi}_0) - \text{sign}(d_0(\widetilde{\mathbf{X}}))\right\}\widetilde{\mathbf{X}}\right]/4.$$

Theorem 2.2 shows that $\widehat{G}(\widehat{d})$ is consistent for $G(d^*)$ and asymptotically normal, and that its asymptotic variance depends on the marginal distribution of covariates in target population patients who will benefit from the non-standard care treatment. This implies that the variability in the estimated benefits of the individualized treatment rule $\widehat{d}$ is influenced by the characteristics of the target patient subgroup for whom the non-standard treatment would be advantageous.

Remark 2.1: The first condition, $\widetilde{\mathbb{P}}(\widetilde{\mathbf{X}}^\top \boldsymbol{\psi}_0 = 0) = 0$, requires the target population to carry no mass at the boundary where the two treatments are equally beneficial. It holds whenever $\widetilde{\mathbf{X}}^\top \boldsymbol{\psi}_0$ follows a continuous distribution. The second condition, $n/N = o(1)$, requires the real-world sample to be much larger than the trial sample, which is reasonable since electronic health records and biobanks usually provide far more subjects than a randomized study. If instead $n/N \to \rho > 0$, it can be shown that $\widehat{G}(\widehat{d})$ remains consistent for $G(d^*)$, and its asymptotic variance becomes $\sigma_G^2 + \rho\tau^2$, where

$$\tau^2 = \widetilde{\text{Var}}\left[\left\{I(\widetilde{\mathbf{X}}^\top \boldsymbol{\psi}_0 > 0) - I(d_0(\widetilde{\mathbf{X}}) > 0)\right\}\widetilde{\mathbf{X}}^\top \boldsymbol{\psi}_0\right].$$

The additional term is proportional to ρ and disappears as ρ tends to zero. Here $\widetilde{\text{Var}}$ denotes the variance taken under the target population.

2.4. Efficiency improvement based on composite features

Based on the variance in Theorem 2.2, we construct low-dimensional composite features to create an individualized treatment rule that remains optimal but more efficient in terms of reducing variability in the resulting benefit for the target population. Specifically, we focus on composite features that are linear transformations of X, denoted by $Z = \Theta^\top X$, where

$\Theta \in \mathbb{R}^{p\times q}$ with $q \le p$. For identifiability, we restrict the transformation matrix Θ to be a column orthogonal matrix, i.e., $\Theta^\top\Theta = I_{q\times q}$. Furthermore, to ensure that the conditional average treatment effect based on Z, $C(Z) = Z^\top\gamma$, is the same as that based on the original covariates X, we restrict Θ to be the matrix space that satisfies $[I - \Theta(\Theta^\top\Theta)^{-1}\Theta^\top]\psi_0 = 0$.

This treatment-effect-preserving constraint ensures that the space spanned by the columns of Θ should be large enough to include ψ_0. It guarantees that the treatment rule derived from Z is equivalent to the true rule based on X, thereby maintaining the same benefit in the target population.

Using the composite features Z, we can estimate the individualized treatment rule and its benefit as described in Section 2.3 by replacing X with Z. Specifically, we estimate γ by solving $\mathbb{P}_n\{Z[\varphi(Z, A, Y; \widehat{Q}_n) - Z^\top\gamma\,]\} = 0$, and evaluate its benefit by

$$\widehat{G}(d(Z;\Theta)) = \widetilde{\mathbb{P}}_N\{[I(Z^\top\widehat{\gamma} > 0) - I(d_0(\widetilde{Z}) > 0))]Z^\top\widehat{\gamma}\}.$$

Furthermore, we obtain that

$$\sqrt{n}\left[\widehat{G}(d(Z;\Theta)) - G(d^*)\right] \to N(0, \sigma^2_{G_Z}(\Theta)),$$

where

$$\begin{aligned}\sigma^2_{G_Z}(\Theta) =& \widetilde{\mathbb{E}}\left\{[\mathrm{sign}(\widetilde{X}^\top\psi_0) - \mathrm{sign}(d_0(\widetilde{X}))]X^\top\right\}\Theta \\ &\times \Sigma_Z\Theta^\top\widetilde{\mathbb{E}}\left\{[\mathrm{sign}(\widetilde{X}^\top\psi_0) - \mathrm{sign}(d_0(\widetilde{X}))]X\right\}/4, \\ \Sigma_Z =& \mathbb{E}(\Theta^\top XX^\top\Theta)^{-1}\mathbb{E}\left(\Theta^\top XX^\top\Theta\left[\frac{\sigma^2(X,1)}{\pi(X)} + \frac{\sigma^2(X,-1)}{1-\pi(X)}\right]\right)\mathbb{E}(\Theta^\top XX^\top\Theta)^{-1}.\end{aligned}$$

Based on the above variance expression, it is natural to find the optimal transformation Θ that minimizes $\sigma^2_{G_Z}(\Theta)$.

Without loss of generality, we assume that $\mathbb{E}(XX^\top) = I_{p\times p}$ so $\Theta^\top\Theta = I_{q\times q}$. The asymptotic variance of $\widehat{G}(d(Z;\Theta))$ is then simplified as

$$\begin{aligned}\sigma^2_{G_Z}(\Theta) =& \left\|\widetilde{\mathbb{E}}\left\{[\mathrm{sign}(\widetilde{X}^\top\psi_0) - \mathrm{sign}(d_0(\widetilde{X}))]\widetilde{X}^\top\right\}\Theta\right. \\ &\left.\times\,\Theta^\top\mathbb{E}\left(XX^\top\left[\frac{\sigma^2(X,1)}{\pi(X)} + \frac{\sigma^2(X,-1)}{1-\pi(X)}\right]\right)^{1/2}\right\|^2/4.\end{aligned}$$

Thus, obtaining the optimal transformation matrix Θ becomes a problem of minimizing $\sigma^2_{G_Z}(\Theta)$ over $\Theta \in \mathbb{R}^{p\times q}$ under constraints. We denote $\widetilde{\mathbb{E}}\{[\mathrm{sign}(\widetilde{X}^\top\psi_0) - \mathrm{sign}(d_0(\widetilde{X}))]\widetilde{X}\}/2$ by u and the expression

$$\mathbb{E}\left(XX^\top\left[\frac{\sigma^2(X,1)}{\pi(X)} + \frac{\sigma^2(X,-1)}{1-\pi(X)}\right]\right)$$

as Σ, which is the same as Σ defined in Theorem 2.1 assuming $\mathbb{E}(XX^\top) = I_{p\times p}$. Thus, obtaining the optimal transformation matrix Θ becomes a problem of minimizing $\sigma^2_{G_Z} = \|u^\top\Theta\Theta^\top\Sigma^{1/2}\|^2$ over $\Theta \in \mathbb{R}^{p\times q}$ under constraints that $\Theta^\top\Theta = I_{q\times q}$ and $[I - \Theta(\Theta^\top\Theta)^{-1}\Theta^\top]\psi_0 = 0$.

To solve this minimization problem, we first perform eigenvalue decomposition of the matrix Σ as $\Sigma = U\Lambda U^\top$, where Λ is a diagonal matrix consisting of eigenvalues of Σ and U

is an orthonormal matrix composed of the eigenvectors of Σ. We reparameterize the problem in the eigenbasis of Σ by defining $\Theta^* = U^\top \Theta$, $u^* = U^\top u$ and $\psi^* = U^\top \psi_0$. The objective function to be minimized then becomes

$$\begin{aligned} \min \quad & \|\Lambda^{\frac{1}{2}} \Theta^* \Theta^{*\top} u^*\|^2 \\ \text{subject to} \quad & \Theta^{*\top} \Theta^* = I, \quad (I - \Theta^* \Theta^{*\top}) \psi^* = 0. \end{aligned} \tag{1}$$

Note that $\Theta^* \Theta^{*\top} u^*$ is the projection of u^* onto the space spanned by columns of Θ^*, or $C(\Theta^*)$. The two constraints imply $\psi^* \in C(\Theta^*)$. Therefore, solving the minimization problem is equivalent to identifying the projection vector v^* that minimizes $v^{*\top} \Lambda v^*$ under the condition that v^* is an orthogonal projection of u^* onto a space that contains ψ^*. Mathematically, the optimization problem can be formulated as a quadratically constrained quadratic program,

$$\begin{aligned} \min \quad & v^{*\top} \Lambda v^* \\ \text{subject to} \quad & (u^* - v^*)^\top \psi^* = 0; \quad (u^* - v^*)^\top v^* = 0. \end{aligned}$$

For the solution, we apply the Lagrange multiplier method to minimize the function

$$f(v^*, \lambda_1, \lambda_2) = v^{*\top} \Lambda v^* - \lambda_1 (u^* - v^*)^\top \psi^* - \lambda_2 (u^* - v^*)^\top v^*.$$

Differentiating with respect to v^*, λ_1 and λ_2 yields the equations

$$\begin{aligned} & 2\Lambda v^* + \lambda_1 \psi^* + 2\lambda_2 v^* - \lambda_2 u^* = 0, \\ & (u^* - v^*)^\top \psi^* = 0, \quad (u^* - v^*)^\top v^* = 0. \end{aligned} \tag{2}$$

Solving the first equation in (2) yields $v^*(\lambda_1, \lambda_2) = (2\Lambda + 2\lambda_2 I)^{-1} (\lambda_2 u^* - \lambda_1 \psi^*)$. Substituting $v^*(\lambda_1, \lambda_2)$ into the second equation gives

$$\lambda_1(\lambda_2) = \frac{\lambda_2 \psi^{*\top} (\Lambda + \lambda_2 I)^{-1} u^* - 2 u^{*\top} \psi^*}{\psi^{*\top} (\Lambda + \lambda_2 I)^{-1} \psi^*}.$$

The solution can be found numerically by searching for a λ_2 that satisfies the last equation constraint in (2), and plugging it in the expressions for v^* and λ_1.

Proposition 2.3: *Assume the conditions of Theorem* 2.2 *and* $\mathbb{E}(XX^\top) = I_{p\times p}$. *Let* v^* *be the global minimizer of the quadratically constrained quadratic program above, and let* $v = Uv^*$. *Then* $\sigma^2_{G_Z}(\Theta) \le \sigma^2_G$ *for every* Θ *satisfying* $\Theta^\top \Theta = I_{q\times q}$ *and* $\psi_0 \in C(\Theta)$. *The lower bound* $v^{*\top} \Lambda v^*$ *is attained when the columns of* Θ *span* $\{\psi_0, v\}$. *If* Σ *is proportional to* $I_{p\times p}$, *the bound is attained at* $\Theta = \psi_0 / \|\psi_0\|$.

Proposition 2.3 shows that the optimal Θ consists of two vectors, (ψ_0, v), resulting in two composite features: $\psi_0^\top x$ and $v^\top x$. We refer to these as the prediction and residual scores, respectively. The first feature, the prediction score, ensures that the rule based on the composite features remains optimal, so that the benefit estimator stays consistent for $G(d^*)$. The second feature, the residual score, controls the residual variance and yields the largest efficiency gain in the individualized treatment rule benefits among all linear transformations. Thus, our approach balances the need for consistency and efficiency in the evaluation of

individualized treatment rules, providing two composite features for maximal benefit gain. Furthermore, when the residual variance is homogeneous, that is, $\Sigma = \Lambda$ is proportional to the identity matrix, the last statement of Proposition 2.3 shows that the prediction score alone is sufficient to achieve full efficiency in estimating the benefit. Algorithm 1 summarizes the above calculation.

Algorithm 1 Estimation Procedure for Transformation Matrix $\boldsymbol{\Theta}$

Input: Data $\mathbf{X}$; parameter $\boldsymbol{\psi}_0$

Compute the vector and matrix:

$$\mathbf{u} = \widetilde{\mathbb{E}}\left[\left\{\text{sign}(\widetilde{\mathbf{X}}^\top \boldsymbol{\psi}_0) - \text{sign}(d_0(\widetilde{\mathbf{X}}))\right\}\widetilde{\mathbf{X}}\right]/2$$

$$\boldsymbol{\Sigma} = \mathbb{E}\left[\mathbf{X}\mathbf{X}^\top\left(\frac{\sigma^2(\mathbf{X},1)}{\pi(\mathbf{X})} + \frac{\sigma^2(\mathbf{X},-1)}{1-\pi(\mathbf{X})}\right)\right]$$

Perform eigendecomposition: $\boldsymbol{\Sigma} = \mathbf{U}\boldsymbol{\Lambda}\mathbf{U}^\top$

Linear transformation:

$$\boldsymbol{\Theta} = \mathbf{U}\boldsymbol{\Theta}^*, \quad \mathbf{u}^* = \mathbf{U}^\top\mathbf{u}, \quad \boldsymbol{\psi}^* = \mathbf{U}^\top\boldsymbol{\psi}_0$$

Solve the following optimization problem:

$$\min_{\boldsymbol{\nu}^*} \quad \boldsymbol{\nu}^{*\top}\boldsymbol{\Lambda}\boldsymbol{\nu}^*$$

$$\text{subject to} \quad \left(\mathbf{u}^* - \boldsymbol{\nu}^*\right)^\top\boldsymbol{\psi}^* = 0; \quad \left(\mathbf{u}^* - \boldsymbol{\nu}^*\right)^\top\boldsymbol{\nu}^* = 0$$

Let $\boldsymbol{\nu} = \mathbf{U}\boldsymbol{\nu}^*$

Output: Transformation matrix $\boldsymbol{\Theta} = (\boldsymbol{\psi}_0, \boldsymbol{\nu})$

3. Simulation studies

3.1. Simulation settings

We conducted three sets of simulation studies to evaluate the proposed ITR's performance under different levels of outcome residual heterogeneity. In each simulation setting, the standard care treatment was $d_0(\mathbf{X}) = -1$. We generated the RCT data for each simulation scenario with sample sizes of 100, 200, 400, and 1000. In the first simulation setting, we examined the scenario with homogeneous residual variance in the clinical outcome over the covariate and treatment space. The covariates in the RCT, $\mathbf{X} = (X_1, \ldots, X_{10})$, were generated independently from a standard normal distribution. Patients in the RCT received a binary treatment A that took value in {1, -1} with equal randomization probability of 1/2. The potential outcome under treatment a was generated based on an additive model $Y(a) = \eta(\mathbf{X}) + a\Delta(\mathbf{X}) + \epsilon$, where $\eta(\mathbf{X}) = X_6^2 + |X_8 + X_9| - I(X_7 > 0) + (X_7 - X_{10})^2$ was the main effect of covariates and the conditional treatment effect was given as $\Delta(\mathbf{X}) = 0.2 + 0.5X_1 - 0.4X_2 + 0.3X_3 - 0.2X_4 + 0.1X_5$. The random error ϵ was generated from a normal distribution with zero mean and a variance of 4. In the second simulation setting, we explored the situation with heterogeneous variance in the clinical outcome that depends on

the covariates. The simulation settings were the same as those in the first scenario, except that the residual term in the outcome model now followed a normal distribution with zero mean and a standard deviation expressed as $\exp(-0.5X_6 - 0.5X_7 - 0.5X_8 + 0.5X_9 + 0.5X_{10})$. In the third setting, we introduced treatment-dependent residual variance, setting the standard deviation to $\exp(-0.1X_6 - 0.1X_7 - 0.1X_8 + 0.8X_9)$ for $a = 1$ and $\exp(-0.7X_6 - 0.7X_7 - 0.7X_8 + 0.8X_{10})$ for $a = -1$.

Finally, we considered two situations for the target population. In the first scenario, the covariate distribution matched that of the trial population. In the second scenario, the covariate distribution differed by assuming a multivariate normal distribution with the components of the mean vector being equally spaced values ranging from -2 to 2. We generated 20,000 subjects from the target population. The optimal treatment rule was estimated in each simulation setting based on the RCT data from the doubly robust method as described in Section 2.2. We used the Bayesian additive regression trees (Chipman et al., 2010) with a bounded number of terminal nodes and bounded terminal node values to estimate $Q(\mathbf{X}, a)$. In the simulations, we compared ITRs using the following: (a) one composite feature (1 CF), the predictive score alone; (b) both composite features (2 CFs), predictive score and residual score; and (c) all covariates. Here, the composite features were obtained using the true covariate distribution and treatment effects. The performance metric was based on a validation data set consisting of 200,000 subjects in the target population.

3.2. Simulation results

The simulation results based on 500 replicates are summarized in Table 1, showing the bias and the standard error of the benefit gain compared to treating all patients with the standard care $A = -1$. This table also presents the mean squared error (MSE) reduction percentage using the treatment rule derived using all covariates as the reference. Figure 1 further shows the MSEs of target benefits. The coverage rate in Table 1 is the proportion of the estimated 95% confidence intervals containing the true target benefit. From the table and figure, all three treatment rules exhibit a small bias. The treatment rule using all covariates yields a slight numerical bias that decreases as the sample size increases. Of all scenarios, the treatment rule based on the composite features outperforms the ITR using all covariates in terms of a lower variability. Adopting a second feature to reduce the variability is not necessary under a homogeneous residual variance, also implied in Section 2. In this case, the empirical standard error is almost the same when using only the predictive score or both composite features. However, the second feature is more useful with heterogeneous residual variance, especially when the variance depends on the treatment. For example, with a sample size of 100, the empirical SEs for the treatment rule based on all covariates, one composite feature, and both composite features are 0.56, 0.23, and 0.21, respectively. The ITRs derived from one or two composite scores can reduce the variability by more than half, with MSE reduction reaching 90.5% and 92.2%, respectively, compared to the ITR with all covariates.

Table 2 compares the estimated target benefits evaluated using the RCT and data from the target population when there are distributional differences. RCT generally tends to yield overly optimistic estimates of the optimal ITR's benefits. Even using a large RCT sample of 1000, the estimated benefit is, on average, 0.83 under the homogeneous residual setting, significantly higher than the true benefit value in the target population, which is only 0.55. This difference highlights that when covariate distributional differences exist, evaluating the benefit solely with RCT may lead to incorrect clinical decisions.

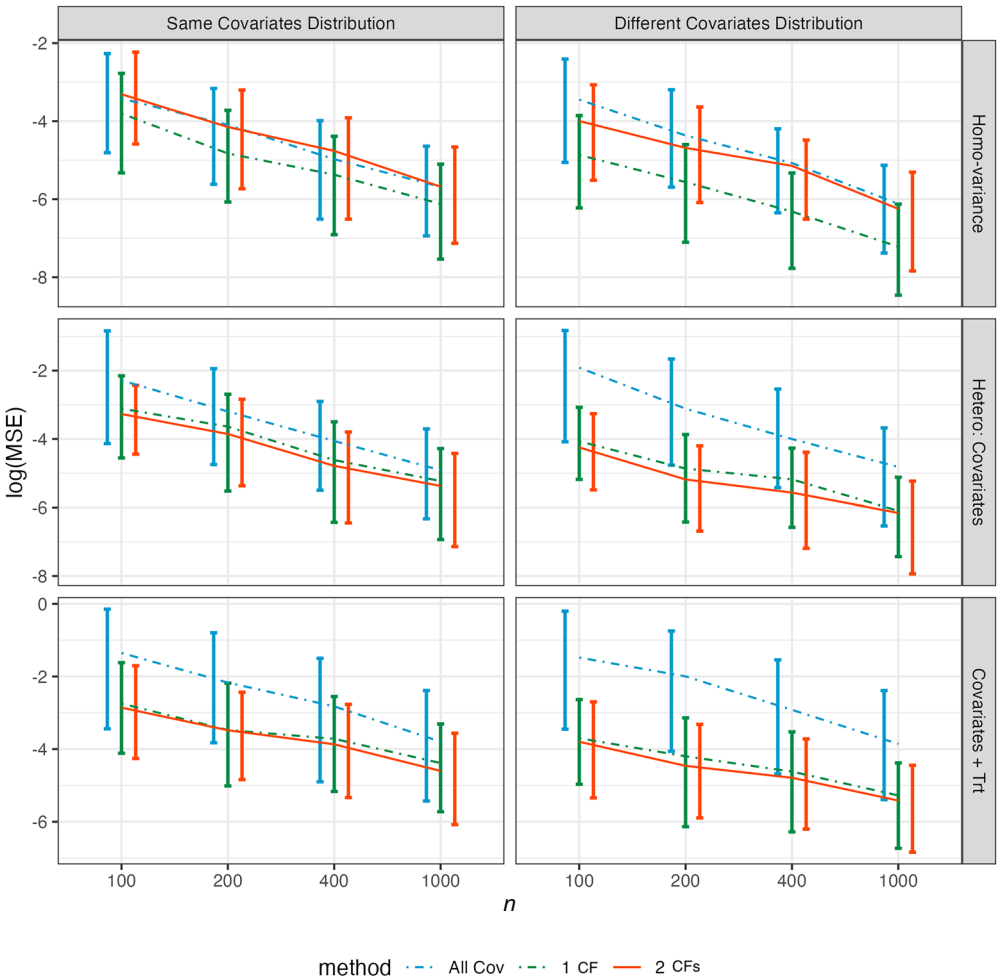


Figure 1. Plots of MSE on model-based value gain. From top to bottom are the three scenarios characterized by the residual variance. Top: Homogeneous variance; Middle: Heterogeneous variance depending on covariates; Bottom: Heterogeneous variance depending on covariates and treatment. The left column corresponds to the clinical trial data sharing the same covariate distribution as the target population; the right column corresponds to a different covariate distribution. Blue dashed line: the treatment rule using all covariates; red solid line: the treatment rule based on predictive score; green dashed line: the treatment rule using both predictive and residual score.

3.3. Sensitivity analysis

Sensitivity analyses were conducted to evaluate the performance of composite features under incorrect assumptions. Sensitivity analysis I assesses the performance of the ITR using composite features derived from a misspecified treatment effect function. The treatment effect used for computing the second composite feature is set to be $\widetilde{\Delta}(\mathbf{X}) = \Delta(\mathbf{X}) = 0.2 + 0.5X_1 - 0.4X_2 + 0.3X_3 - 0.2X_4 + 0.05X_5$. We explored this setting under different sample sizes, covariate distributions, and residual variances. The results are presented in the Appendix. Sensitivity analysis II studied the robustness against the exchangeability assumption under four scenarios where the treatment effect differed between

Table 1. Summary of benefit gain when applying derived treatment rule to target population.

		Same covariate distribution (True value 0.90)					Different covariate distribution (True value 0.55)				
n	Method[a]	Bias	EstSE	EmpSE	MSE Reduct %	Cov	Bias	EstSE	EmpSE	MSE Reduct %	Cov
Homogeneous residual variance											
100	All Cov	0.203	0.29	0.25	–	95	0.164	0.24	0.20	–	97
	1 CF	0.036	0.23	0.22	51.4	97	−0.002	0.14	0.14	72.6	98
	2 CFs	0.061	0.30	0.28	23.9	96	0.005	0.23	0.21	36.5	98
200	All Cov	0.055	0.21	0.20	–	97	0.081	0.17	0.16	–	93
	1 CF	−0.036	0.17	0.17	30.9	95	−0.004	0.10	0.10	68.6	95
	2 CFs	−0.027	0.22	0.21	−3.7	96	−0.002	0.16	0.16	21.3	94
400	All Cov	0.044	0.15	0.15	–	93	0.051	0.12	0.11	–	95
	1 CF	−0.006	0.12	0.12	43.5	96	0.009	0.07	0.07	67.7	95
	2 CFs	0.009	0.15	0.16	−0.4	93	0.005	0.11	0.11	18.2	95
1000	All Cov	0.001	0.10	0.09	–	97	0.016	0.07	0.07	–	97
	1 CF	−0.008	0.07	0.07	34.5	97	−0.001	0.05	0.04	62.3	98
	2 CFs	−0.009	0.10	0.09	−3.9	98	−0.004	0.07	0.07	6.3	97
Heterogeneous residual variance depending on covariates											
100	All Cov	0.436	0.53	0.47	–	96	0.485	0.56	0.51	–	95
	1 CF	−0.011	0.36	0.34	72.9	96	−0.027	0.23	0.22	90.5	96
	2 CFs	0.001	0.33	0.30	77.9	97	0.009	0.21	0.20	92.2	96
200	All Cov	0.248	0.38	0.31	–	98	0.290	0.38	0.37	–	97
	1 CF	−0.007	0.27	0.25	59.4	97	−0.021	0.16	0.15	89.2	96
	2 CFs	−0.002	0.24	0.23	66.4	95	−0.002	0.14	0.14	91.7	94
400	All Cov	0.157	0.27	0.26	–	97	0.177	0.26	0.25	–	97
	1 CF	0.002	0.19	0.18	65.5	98	0.008	0.12	0.11	87.3	98
	2 CFs	0.001	0.17	0.15	74.8	97	0.013	0.11	0.10	90.3	97
1000	All Cov	0.068	0.17	0.16	–	95	0.080	0.16	0.13	–	98
	1 CF	−0.002	0.12	0.12	55.7	97	0.001	0.08	0.07	81.9	97
	2 CFs	0.000	0.11	0.10	66.0	96	0.004	0.07	0.06	84.0	97
Heterogeneous residual variance depending on covariates and treatment											
100	All Cov	0.799	0.91	1.08	–	92	0.707	0.85	0.85	–	96
	1 CF	0.035	0.56	0.46	88.3	93	−0.002	0.33	0.28	93.4	98
	2 CFs	0.067	0.52	0.45	88.6	95	0.027	0.31	0.29	92.9	97
200	All Cov	0.522	0.63	0.66	–	94	0.537	0.64	0.64	–	94
	1 CF	−0.001	0.40	0.38	79.9	94	0.006	0.27	0.21	93.5	98
	2 CFs	0.020	0.36	0.35	83.1	93	0.032	0.24	0.19	94.6	97
400	All Cov	0.334	0.43	0.38	–	96	0.371	0.49	0.43	–	95
	1 CF	−0.004	0.30	0.27	70.8	95	0.011	0.19	0.17	91.1	96
	2 CFs	0.019	0.27	0.23	78.6	96	0.028	0.17	0.15	92.4	95
1000	All Cov	0.168	0.30	0.27	–	97	0.213	0.32	0.30	–	96
	1 CF	−0.002	0.21	0.17	70.6	97	−0.000	0.13	0.12	89.5	95
	2 CFs	−0.004	0.18	0.15	77.6	96	0.015	0.12	0.12	89.8	96

Note: EstSE denotes the estimated standard error derived from Theorem 2.2; EmpSE represents the empirical standard error calculated from 500 Monte Carlo replications; Cov indicates the empirical coverage proportion of the estimated 95% confidence intervals.

[a] All covariates are included in All Cov; 1 CF includes only the predictive score in the model; 2 CFs include both the predictive and residual score.

the RCT and target population, and they were $\Delta(\mathbf{X}) = 0.2 + 0.5X_1 - 0.4X_2 + 0.3X_3 - 0.2X_4 + 0.1X_5$ and $\widetilde{\Delta}(\mathbf{X}) = 0.2 + 0.5X_1 - 0.4X_2 + 0.3X_3 - 0.2X_4 + kX_5$, respectively, where $k = 0,\ 0.05,\ 0.15,\ 0.2$. In Sensitivity analysis III, we evaluated the ITR estimation when the true treatment effect was non-linear as $\widetilde{\Delta}(\mathbf{X}) = \Delta(\mathbf{X}) = 0.2 + 0.5X_1 - 0.4X_2 + 0.3X_3 - 0.2X_4 + \text{sign}(0.1X_5)\log(|0.1X_5| + 1)|X_5|^k$, where the violation magnitude k is chosen from $0,\ 0.5,\ 1$ and 2.

The simulation results for sensitivity analysis based on 500 replicates can be found in the Appendix. Similarly to the main analysis, the MSEs of target benefits are also included in

Table 2. Comparison of target benefits evaluated using RCT or data from target population (true value: 0.55).

	$n = 100$		$n = 200$		$n = 400$		$n = 1000$	
Method[a]	Target	RCT	Target	RCT	Target	RCT	Target	RCT
Homogeneous residual variance								
All Cov	0.72	1.01	0.66	0.92	0.60	0.86	0.58	0.84
1 CF	0.54	0.80	0.55	0.81	0.55	0.81	0.56	0.82
2 CFs	0.55	0.81	0.57	0.83	0.56	0.82	0.56	0.83
Heterogeneous residual variance depending on covariates								
All Cov	1.01	1.26	0.83	1.10	0.72	0.98	0.64	0.89
1 CF	0.53	0.78	0.54	0.80	0.54	0.80	0.55	0.81
2 CFs	0.56	0.82	0.55	0.81	0.55	0.81	0.55	0.81
Heterogeneous residual variance depending on covariates and treatment								
All Cov	1.26	1.51	1.07	1.35	0.87	1.14	0.73	1.01
1 CF	0.60	0.87	0.56	0.82	0.55	0.81	0.56	0.82
2 CFs	0.63	0.91	0.59	0.85	0.57	0.83	0.57	0.83

Note: [a]All covariates are included in All Cov; 1 CF includes only the predictive score in the model; 2 CFs include both the predictive and residual score.

plots. The results demonstrate that the proposed method based on the two composite features can still give smaller bias than using all the features, and this is more evident when the trial size is small. At the same time, as the degree of violation increases to some extent, our method consistently exhibits smaller bias and MSE, along with stable coverage probability. This suggests that the inference with the proposed method is reasonable even if the treatment effect is incorrectly specified or the exchangeability or linear assumption is violated.

Finally, our composite features assume that $\boldsymbol{\psi}_0$ is known or has been estimated from a pilot study. This is important because estimating $\boldsymbol{\psi}_0$ from the same trial data would result in incorrect inference due to double use of the data, an instance of the generated-regressor problem studied by Hahn and Ridder (2013). To examine the impact of using a pilot study or trial data to estimate $\boldsymbol{\psi}_0$, we conducted a simulation study as reported in the Appendix. The results indicate that estimating $\boldsymbol{\psi}_0$ from the same trial can lead to inferior inference compared with using the true $\boldsymbol{\psi}_0$. A pilot study mitigates the error caused by the double use of data and improves the performance of the benefit estimator. Interestingly, in either case, the composite features still outperform the full covariates in terms of the mean squared error for the value function.

4. RWD-guided design with an application to type 2 diabetes

In this section, we demonstrate how utilizing two derived composite features can enhance the efficiency of estimating ITR benefits for type 2 diabetes treatment. Since the composite features need to be estimated, we consider a hypothetical trial design as follows: a pilot trial is conducted first with all potential covariates. Using the pilot data, we apply our method to estimate the coefficients in the composite features. Then, we design a future trial in the real-world population, which is assumed to have the same treatment effects but with potentially different covariate distribution from the first trial. In both the design and analysis stages, we will rely only on the two composite features derived in the pilot study. We expect that the latter will yield a smaller sample size than a trial using all the covariates. For our illustration, DURABLE (Fahrbach et al., 2008) was considered as the pilot trial, which was a type 2 diabetes RCT that aimed to lower patients' blood glucose as measured by hemoglobin A1c (HbA1c). The trial enrolled insulin-naive adults aged 30 to 80 years whose HbA1c exceeded

Table 3. Sample size calculation for designing type 2 diabetes trial.

Standardized effect size	Method[a]	Power (80%)	Power (85%)	Power (90%)
0.8	All Cov	163	186	218
	1 CF	67	77	90
	2 CFs	70	80	94
0.5	All Cov	416	475	556
	1 CF	172	197	230
	2 CFs	179	205	240
0.3	All Cov	1153	1319	1544
	1 CF	477	545	638
	2 CFs	497	568	665

Note: [a]1 CF and 2 CFs correspond to the ITR based on the predictive score only and ITR based on both the predictive and residual scores, respectively. All Cov refers to the ITR derived using all available covariates.

7.0% after treatment with at least two oral antihyperglycemic agents. Covariate data from the electronic health records obtained in The Ohio State University Wexner Medical Center (Lou et al., 2021) were used as real-world data.

We used the reduction of HbA1c at 24 weeks from baseline as the outcome, so that a larger value indicates a more favourable response, and considered five baseline covariates: BMI (X_1), diastolic blood pressure (X_2), systolic blood pressure (X_3), HbA1c (X_4), and fasting glucose (X_5). We calculated the conditional treatment effect for randomized patients who received either lispro mix ($n = 917$) or insulin glargine ($n = 927$) with no missing covariates or outcomes. The standard care was taken as a uniform prescription of insulin glargine to all patients. The conditional treatment effect was derived following the procedure described in Section 2, for which the baseline systolic blood pressure has a significant positive effect (coefficient: 0.16 with p-value 0.001). A contour plot in Appendix 4 indicates a wide range of the covariate distribution shift between the trial and target population. We also report additional results in Appendix 4, including the estimated rule and the estimated benefit in the target population.

We denote the difference in the value gain as $\Delta\mu$ and set the type I error rate of a two-sided test as 0.05, with a power denoted by δ to detect the difference. The total sample size is given by $\frac{\sigma^2_{G_Z}}{\Delta\mu^2}(z_{0.05/2} + z_{1-\delta})^2$. Table 3 presents the required sample sizes for conducting clinical trials to achieve powers of 80%, 85%, and 90% with $\Delta\mu = 0.3, 0.5, 0.8$ based on the predictive score alone, the combination of the predictive score and residual score composite features, and all covariates, where in computing the scores, $\boldsymbol{\psi}_0$ is set to be the same as the trial estimate. In the Appendix, we plot the residuals against each baseline predictor and they show a slight but not severe heteroscedasticity. Therefore, as noted in Section 2, including the residual score does not necessarily improve estimation power beyond what is achieved using the predictive score alone. This is evidenced by the near-identical sample sizes required to achieve the same statistical power when using one or two composite features across all scenarios. In contrast, the sample size required when using all features is more than twice that of the model with composite features.

5. Conclusion

We proposed a method to estimate the benefit of ITR in a target population using RWD observations and to accommodate the covariate shift from the RCT data. We further obtained two composite features: one corresponded to the predictive score for the treatment effect, while the other controlled for the residual heterogeneity. The predictive score was specifically tailored to mitigate the bias in the estimated ITR, while the residual score was useful in reducing the ITR variability due to the heterogeneous residual variance of the outcome. The derived composite features ensure that the benefits a target population gains from the ITR are maximized while the variability of the estimated benefit gain is minimized. Since collecting specific clinical data, especially some biomarkers, can be costly and time-consuming, clinicians can focus on collecting only the most pertinent biomarkers, for example, those with coefficients in the composite feature that are significantly larger than the others. These important biomarkers can be identified by a formal testing or variable selection procedure. As a note, the derivation of the second feature is related to the covariate distribution in the target population and different from previous work by Mo and Liu (2022), where the focus was on maximizing the efficiency of the estimated coefficients in ITR through weighted regression instead of studying the efficiency gain on the value function.

One key assumption in our work is the exchangeability between the trial and real-world populations (Assumption 2.1). Under this assumption and the linearity of ITR, the overlapping assumption between the trial and real-world population is not necessary since our goal is to evaluate the ITR-induced value in the real-world population. However, the violation of exchangeability will inevitably result in bias in estimating the optimal treatment decisions for the target populations. When the exchangeability assumption is violated, our estimand, $G(d)$, may overestimate or underestimate the true value for the real-world population under the treatment decision d. A possible relaxation is to assume $\widetilde{\mathbb{E}}[Y(1) - Y(-1) \mid \mathbf{X}] = h\{\mathbb{E}[Y(1) - Y(-1) \mid \mathbf{X}]\}$ for a known function h (Wu, Luo et al., 2025), which permits posterior drift in addition to covariate shift (Cai & Wei, 2021). Our procedure carries over once the estimated effect from the trial is transformed by h before evaluation in the target population. When h is unknown, it can be treated as a sensitivity analysis function, and a detailed development of this extension is left to future work. Other recent developments avoid the exchangeability assumption (Gao et al., 2025; Q. Yang et al., 2026), and comparing these approaches with the present framework would be worthwhile. Our method also assumes the linearity of ITR in the covariates, but this assumption is not essential: when the linearity does not hold, our estimated treatment rule based on the trial data can be considered the best linear rule that approximates individual treatment effects, $C(\mathbf{X}) = \mathbb{E}[Y(1) - Y(-1) \mid \mathbf{X}]$, and the corresponding value for the target population is obtained by applying this rule to the real-world subjects and evaluating the gain at $C(\mathbf{X})$ itself. Note that the variance of the obtained value estimator as given in Theorem 2.1 is a robust variance taking a sandwich form, so it remains valid whether the treatment decision is optimal or linear. Therefore, the composite features based on minimizing the variance of the value estimator are not affected by the violation of these assumptions. This has also been confirmed when comparing the composite features with the full covariate vector in the simulation studies. Another assumption is that the target population has no mass at the boundary $\widetilde{\mathbf{X}}^\top \boldsymbol{\psi}_0 = 0$ in Theorem 2.2. It can fail with discrete covariates, or when a subgroup of positive probability has zero treatment effect. Although the estimated benefit remains consistent, the limiting distribution is no longer normal. How to construct efficient composite features in this situation deserves further study.

On the other hand, linear treatment rules are favoured in clinical settings because of ease of implementation and interpretability. We can remove the linear restriction on the treatment effect and derive the predictive score based on the nonparametrically estimated treatment effect. The latter is expected to reduce the estimated benefit's bias when the true treatment effect is non-linear. In fact, the results of Chen et al. (2025) suggest that inference on the benefit would remain at the $\sqrt{n}$ rate in this case under some mild conditions. Another foundational linear assumption concerns the form of our derived composite features. The primary feature we derived corrects bias and thus relates to the true linear treatment rule. The second feature, aimed at reducing target variance, is derived as a linear form of clinical covariates. This feature stands out as the best composite feature among linear options. While crafting a non-linear residual score could further diminish target benefit gain variance, it will come at the expense of interpretability. Finally, although the value function we studied in this paper is natural and practical, there are other alternatives to evaluate ITRs in the real-world population. For example, Shi et al. (2021) used the concordance index to evaluate the decision rule, but they require both treatment and outcome information for calculating the index in the target population. It would be interesting to extend our Theorem 2.2 to obtain efficient composite features under the alternative performance metrics.

Author contributions

CRediT: **Zhenyu Wang:** Formal analysis, Investigation, Software, Validation, Writing – review & editing; **Wenyi Xie:** Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft; **Yuanjia Wang:** Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing; **Donglin Zeng:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing

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Data availability statement

The data for DURABLE and the EHR data are obtained under data use agreement with data providers.

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Appendices

Appendix 1. Proof for Theorem 2.1

In this subsection, we give the proof for Theorem 2.1. Recall that the treatment effect is estimated by solving the estimating equation:

$$\mathbb{P}_n\left[\mathbf{X}\left\{\varphi(\mathbf{X}, A, Y; \widehat{Q}_n) - \mathbf{X}_i\boldsymbol{\psi}\right\}\right] = 0,$$

where

$$\varphi(\mathbf{X}, A, Y; Q) = \frac{A\{Y - Q(\mathbf{X}, A)\}}{\pi(\mathbf{X}) + I(A = -1)(1 - 2\pi(\mathbf{X}))} + Q(\mathbf{X}, 1) - Q(\mathbf{X}, -1).$$

The solution can be given explicitly by

$$\widehat{\boldsymbol{\psi}}(\widehat{Q}_n) = [\mathbb{P}_n(\mathbf{X}\mathbf{X}^\top)]^{-1}\mathbb{P}_n(\mathbf{X}\varphi(\mathbf{X}, A, Y; \widehat{Q}_n)).$$

To make inference for $\widehat{\boldsymbol{\psi}}$, we can write

$$\sqrt{n}(\widehat{\boldsymbol{\psi}} - \boldsymbol{\psi}) = \sqrt{n}[\mathbb{P}_n(\mathbf{X}\mathbf{X}^\top)]^{-1}\mathbb{P}_n(\mathbf{X}\varphi(\mathbf{X}, A, Y; \widehat{Q}_n) - \mathbf{X}\mathbf{X}^\top\boldsymbol{\psi}).$$

Our goal is to prove that

$$\sqrt{n}(\widehat{\boldsymbol{\psi}} - \boldsymbol{\psi}) = \sqrt{n}[\mathbb{P}(\mathbf{X}\mathbf{X}^\top)]^{-1}(\mathbb{P}_n - \mathbb{P})(\mathbf{X}\varphi(\mathbf{X}, A, Y; \overline{Q}) - \mathbf{X}\mathbf{X}^\top\boldsymbol{\psi}) + o_p(1).$$

To start with, observe that the above expression can be decomposed as

$$\sqrt{n}(\widehat{\boldsymbol{\psi}} - \boldsymbol{\psi}) = B_n^{-1}(A_1 + A_2 + A_3 + A_4),$$

where

$$\begin{aligned}
A_1 &= \sqrt{n}(\mathbb{P}_n - \mathbb{P})(\mathbf{X}\varphi(\mathbf{X}, A, Y; \overline{Q}) - \mathbf{X}\mathbf{X}^\top \boldsymbol{\psi}),\\
A_2 &= \sqrt{n}(\mathbb{P}_n - \mathbb{P})(\mathbf{X}\varphi(\mathbf{X}, A, Y; \widehat{Q}_n) - \mathbf{X}\varphi(\mathbf{X}, A, Y; \overline{Q})),\\
A_3 &= \sqrt{n}\mathbb{P}(\mathbf{X}\varphi(\mathbf{X}, A, Y; \widehat{Q}_n) - \mathbf{X}\varphi(\mathbf{X}, A, Y; \overline{Q})),\\
A_4 &= \sqrt{n}\mathbb{P}(\mathbf{X}\varphi(\mathbf{X}, A, Y; \overline{Q}) - \mathbf{X}\mathbf{X}^\top \boldsymbol{\psi}),\\
B_n &= \mathbb{P}_n(\mathbf{X}\mathbf{X}^\top).
\end{aligned}$$

Next, we evaluate each term and show that A_2, A_3, A_4 are all negligible, and $\|B_n^{-1} - B^{-1}\|_2 = o_p(1)$, where $B = \mathbb{P}(\mathbf{X}\mathbf{X}^\top)$.

We start with B_n. Observe that $B_n^{-1} - B^{-1} = B_n^{-1}(B - B_n)B^{-1}$. Given that $\|B_n - B\| = o_p(1)$, $\|B_n^{-1} - B^{-1}\| \le \|B_n^{-1}\|\|B - B_n\|\|B^{-1}\| = O_p(1)o_p(1)O_p(1) = o_p(1)$. Moreover, since $A_1 = O_p(1)$ and A_2, A_3, A_4 are all $o_p(1)$, $\|(B_n^{-1} - B^{-1})(A_1 + A_2 + A_3 + A_4)\| \le \|B_n^{-1} - B^{-1}\| \times \|A_1 + A_2 + A_3 + A_4\| = o_p(1)$. Plugging this bound back into the expression for $\sqrt{n}(\widehat{\boldsymbol{\psi}} - \boldsymbol{\psi})$ yields $\sqrt{n}(\widehat{\boldsymbol{\psi}} - \boldsymbol{\psi}) = B^{-1}(A_1 + A_2 + A_3 + A_4) + o_p(1)$.

Next, we prove that $A_2 = o_p(1)$. First, we note that the transformation $Q_1, Q_{-1} \to \frac{A\{Y - Q(\mathbf{X}, A)\}}{\pi(\mathbf{X}) + I(A=-1)(1-2\pi(\mathbf{X}))} + \widehat{Q}(\mathbf{X}, 1) - \widehat{Q}(\mathbf{X}, -1)$ is a Lipschitz function. Therefore, $\mathbf{X}\varphi(\mathbf{X}, A, Y; Q)$ is also a Donsker class. Given that $\|\widehat{Q}(X, a) - \overline{Q}(\mathbf{X}, a)\|_2 = o_p(1)$, the term A_2 is $o_p(1)$ according to Lemma 19.24 in Vaart (2000).

To prove that $A_3 = o_p(1)$, we first define a function

$$f(r) = \mathbb{P}(\mathbf{X}\varphi(\mathbf{X}, A, Y; \overline{Q} + r(\widehat{Q}_n - \overline{Q})) - \mathbf{X}\varphi(\mathbf{X}, A, Y; \overline{Q})), \quad r \in [0, 1].$$

A_3 can be considered as $A_3 = f(1)$. Then by Taylor expansion, $f(1) = f(0) + f'(0) + f''(\widetilde{r})$ for some $\widetilde{r} \in (0, 1)$, where $f'(0)$ is the Gateaux derivative in the direction of $\widehat{Q}_n - Q$. Note that $f(0) = 0$. In addition, the function f satisfies Neyman orthogonality such that

$$\begin{aligned}
f'(0) = {} & \mathbb{P}(\widehat{Q}_n(\mathbf{X}, 1) - \overline{Q}(\mathbf{X}, 1)) - \mathbb{P}(\widehat{Q}_n(\mathbf{X}, -1) - \overline{Q}(\mathbf{X}, -1))\\
& - \mathbb{P}\left[\frac{I(A = 1)(\widehat{Q}_n(\mathbf{X}, 1) - \overline{Q}(\mathbf{X}, 1))}{\pi(\mathbf{X})}\right]\\
& + \mathbb{P}\left[\frac{I(A = -1)(\widehat{Q}_n(\mathbf{X}, -1) - \overline{Q}(\mathbf{X}, -1))}{\pi(\mathbf{X})}\right] = 0.
\end{aligned}$$

The last equality holds due to iterated expectation. The second derivative $f''(\widetilde{r}) = 0$ by the assumption that the treatment probability $\pi(\mathbf{X})$ is known. Therefore, $A_3 = 0$.

Next we show that $A_4 = 0$. Recall that

$$\begin{aligned}
A_4 &= \sqrt{n}\mathbb{P}(\mathbf{X}\varphi(\mathbf{X}, A, Y; \overline{Q}) - \mathbf{X}\mathbf{X}^\top \boldsymbol{\psi})\\
&= \sqrt{n}\mathbb{E}\left(\mathbf{X}\left(\frac{A\left(Y - \overline{Q}(\mathbf{X}, A)\right)}{\pi(\mathbf{X}) + I(A = -1)(1 - 2\pi(\mathbf{X}))} + \overline{Q}(\mathbf{X}, 1) - \overline{Q}(\mathbf{X}, -1)\right) - \mathbf{X}\mathbf{X}^\top \boldsymbol{\psi}\right).
\end{aligned}$$

By iterative expectation,

$$\begin{aligned}
A_4 &= \sqrt{n}\mathbb{E}\left(\mathbf{X}\left(\frac{A\left(Q^*(\mathbf{X},A)-\overline{Q}(\mathbf{X},A)\right)}{\pi(\mathbf{X})+I(A=-1)(1-2\pi(\mathbf{X}))}+\overline{Q}(\mathbf{X},1)-\overline{Q}(\mathbf{X},-1)\right)-\mathbf{X}\mathbf{X}^\top\boldsymbol{\psi}\right)\\
&= \sqrt{n}\mathbb{E}\left(\mathbf{X}\left(\frac{\pi(\mathbf{X})\left(Q^*(\mathbf{X},1)-\overline{Q}(\mathbf{X},1)\right)}{\pi(\mathbf{X})}-\frac{(1-\pi(\mathbf{X}))\left(Q^*(\mathbf{X},-1)-\overline{Q}(\mathbf{X},A)\right)}{1-\pi(\mathbf{X})}\right.\right.\\
&\quad \left.\left.+\overline{Q}(\mathbf{X},1)-\overline{Q}(\mathbf{X},-1)\right)-\mathbf{X}\mathbf{X}^\top\boldsymbol{\psi}\right).\\
&= \sqrt{n}\mathbb{E}\left(\mathbf{X}\left(Q^*(\mathbf{X},1)-Q^*(\mathbf{X},-1))-\mathbf{X}\mathbf{X}^\top\boldsymbol{\psi}\right)\right)=0.
\end{aligned}$$

Then we can write

$$\sqrt{n}(\widehat{\boldsymbol{\psi}}-\boldsymbol{\psi})=\sqrt{n}[\mathbb{P}(\mathbf{X}\mathbf{X}^\top)]^{-1}(\mathbb{P}_n-\mathbb{P})(\mathbf{X}\varphi(\mathbf{X},A,Y;\overline{Q})-\mathbf{X}\mathbf{X}^\top\boldsymbol{\psi})+o_p(1).$$

$\widehat{\boldsymbol{\psi}}$ is $\sqrt{n}$ consistent, and has an asymptotic normal distribution given by

$$\mathrm{Var}\left\{\mathbb{P}(\mathbf{X}\mathbf{X}^\top)^{-1}(\mathbf{X}\varphi(\mathbf{X},A,Y;\overline{Q})-\mathbf{X}\mathbf{X}^\top\boldsymbol{\psi})\right\}.$$

If $\widehat{Q}$ converges to the true Q^*, further calculation gives

$$\begin{aligned}
&\mathrm{Var}\left\{(\mathbf{X}\varphi(\mathbf{X},A,Y;Q^*)-\mathbf{X}\mathbf{X}^\top\boldsymbol{\psi})\right\}\\
&\quad=\mathrm{Var}\left\{\mathbb{E}\left\{(\mathbf{X}\varphi(\mathbf{X},A,Y;Q^*)-\mathbf{X}\mathbf{X}^\top\boldsymbol{\psi})\,|\,\mathbf{X},A\right\}\right\}\\
&\qquad+\mathbb{E}\left\{\mathrm{Var}\left\{(\mathbf{X}\varphi(\mathbf{X},A,Y;Q^*)-\mathbf{X}\mathbf{X}^\top\boldsymbol{\psi})\,|\,\mathbf{X},A\right\}\right\}.
\end{aligned}$$

The first term equals zero since $\mathbb{E}\{\mathbf{X}\varphi(\mathbf{X},A,Y;Q^*)-\mathbf{X}\mathbf{X}^\top\boldsymbol{\psi}\,|\,\mathbf{X},A\}=0$. The second term is given as

$$\begin{aligned}
&\mathbb{E}\left\{\mathrm{Var}\left\{\mathbf{X}\varphi(\mathbf{X},A,Y;Q^*)-\mathbf{X}\mathbf{X}^\top\boldsymbol{\psi}\,|\,\mathbf{X},A\right\}\right\}\\
&=\mathbb{E}\left\{\mathbf{X}\mathbf{X}^\top\frac{\sigma^2(\mathbf{X},A)}{I(A=1)\pi(\mathbf{X})^2+I(A=-1)(1-\pi(\mathbf{X}))^2}\right\}\\
&=\mathbb{E}\left[\mathbf{X}\mathbf{X}^\top\left\{\frac{\sigma^2(\mathbf{X},1)}{\pi(\mathbf{X})}+\frac{\sigma^2(\mathbf{X},-1)}{1-\pi(\mathbf{X})}\right\}\right].
\end{aligned}$$

This completes the proof.

Appendix 2. Proof for Theorem 2.2

The asymptotic distribution of the benefits in the target population can depend only on the asymptotic behaviour of the treatment effect $\widehat{\boldsymbol{\psi}}$. In particular,

$$\begin{aligned}
&\sqrt{n}\left[\widehat{\widetilde{G}}(\widehat{d})-\widetilde{G}(d^*)\right]\\
&\quad=\sqrt{n}\left[\widetilde{\mathbb{P}}_N[(\mathbf{I}(\widetilde{\mathbf{X}}^\top\widehat{\boldsymbol{\psi}}>0)-\mathbf{I}(d_0(\widetilde{\mathbf{X}})>0))\widetilde{\mathbf{X}}^\top\widehat{\boldsymbol{\psi}}]-\widetilde{\mathbb{P}}[(\mathbf{I}(\widetilde{\mathbf{X}}^\top\boldsymbol{\psi}_0>0)-\mathbf{I}(d_0(\widetilde{\mathbf{X}})>0))\widetilde{\mathbf{X}}^\top\boldsymbol{\psi}_0]\right].
\end{aligned}$$

It can be further expressed as an empirical process term plus a term only related to $\widehat{\boldsymbol{\psi}}-\boldsymbol{\psi}$.

$$\begin{aligned}
&\sqrt{n}\left[\widehat{\widetilde{G}}(\widehat{d})-\widetilde{G}(d^*)\right]\\
&\quad=\sqrt{n}(\widetilde{\mathbb{P}}_N-\widetilde{\mathbb{P}})\left[(\mathbf{I}(\widetilde{\mathbf{X}}^\top\widehat{\boldsymbol{\psi}}>0)-\mathbf{I}(d_0(\widetilde{\mathbf{X}})>0))\widetilde{\mathbf{X}}^\top\widehat{\boldsymbol{\psi}}\right]\\
&\qquad+\sqrt{n}\widetilde{\mathbb{P}}\left[(\mathbf{I}(\widetilde{\mathbf{X}}^\top\widehat{\boldsymbol{\psi}}>0)-\mathbf{I}(d_0(\widetilde{\mathbf{X}})>0))\widetilde{\mathbf{X}}^\top\widehat{\boldsymbol{\psi}}-(\mathbf{I}(\widetilde{\mathbf{X}}^\top\boldsymbol{\psi}_0>0)-\mathbf{I}(d_0(\widetilde{\mathbf{X}})>0))\widetilde{\mathbf{X}}^\top\boldsymbol{\psi}_0\right].
\end{aligned}$$

It suffices only to evaluate the last term since the convergence rate of the first term is faster than the last term due to the dominating large sample size in the target population.

Write $g(\boldsymbol{\psi}) = \widetilde{\mathbb{P}}[(\mathbf{I}(\widetilde{\mathbf{X}}^\top\boldsymbol{\psi} > 0) - \mathbf{I}(d_0(\widetilde{\mathbf{X}}) > 0))\widetilde{\mathbf{X}}^\top\boldsymbol{\psi}]$, so the last term equals $\sqrt{n}\{g(\widehat{\boldsymbol{\psi}}) - g(\boldsymbol{\psi}_0)\}$. Since $\mathbf{I}(\widetilde{\mathbf{X}}^\top\boldsymbol{\psi} > 0)\widetilde{\mathbf{X}}^\top\boldsymbol{\psi}$ is the positive part of $\widetilde{\mathbf{X}}^\top\boldsymbol{\psi}$, the elementary bound $|(a+h)_+ - a_+ - \mathbf{I}(a > 0)h| \le |h|\mathbf{I}(|a| \le |h|)$ with $a = \widetilde{\mathbf{X}}^\top\boldsymbol{\psi}_0$ and $h = \widetilde{\mathbf{X}}^\top(\boldsymbol{\psi} - \boldsymbol{\psi}_0)$ gives

$$\left|g(\boldsymbol{\psi}) - g(\boldsymbol{\psi}_0) - \nabla g(\boldsymbol{\psi}_0)^\top(\boldsymbol{\psi} - \boldsymbol{\psi}_0)\right| \le C\|\boldsymbol{\psi} - \boldsymbol{\psi}_0\|\,\widetilde{\mathbb{P}}\left(|\widetilde{\mathbf{X}}^\top\boldsymbol{\psi}_0| \le C\|\boldsymbol{\psi} - \boldsymbol{\psi}_0\|\right),$$

where C is a bound for $\|\widetilde{\mathbf{X}}\|$ and $\nabla g(\boldsymbol{\psi}_0) = \widetilde{\mathbb{P}}[(\text{sign}(\widetilde{\mathbf{X}}^\top\boldsymbol{\psi}_0) - \text{sign}(d_0(\widetilde{\mathbf{X}})))\widetilde{\mathbf{X}}]/2$. The probability on the right hand side tends to zero as $\boldsymbol{\psi}$ approaches $\boldsymbol{\psi}_0$, since $\widetilde{P}[\widetilde{\mathbf{X}}^\top\boldsymbol{\psi}_0 = 0] = 0$. Therefore, g is differentiable at $\boldsymbol{\psi}_0$. Combining this with $\widehat{\boldsymbol{\psi}} - \boldsymbol{\psi}_0 = O_p(n^{-1/2})$ from Theorem 2.1, we rewrite $\sqrt{n}[\widehat{\widetilde{G}}(\widehat{d}) - \widetilde{G}(d^*)]$ as

$$\sqrt{n}\left[\widehat{\widetilde{G}}(\widehat{d}) - \widetilde{G}(d^*)\right] = \sqrt{n}\widetilde{\mathbb{P}}\left[(\text{sign}(\widetilde{\mathbf{X}}^\top\boldsymbol{\psi}_0) - \text{sign}(d_0(\widetilde{\mathbf{X}})))\widetilde{\mathbf{X}}^\top(\widehat{\boldsymbol{\psi}} - \boldsymbol{\psi}_0)/2\right] + o_p(1),$$

which is a function of $\widehat{\boldsymbol{\psi}} - \boldsymbol{\psi}_0$. Therefore, from the asymptotic distribution of $\widehat{\boldsymbol{\psi}} - \boldsymbol{\psi}_0$, we can derive the asymptotic distribution of the benefit in the target population as given in this theorem.

Appendix 3. Results and analysis of the sensitivity analysis

A.1 Sensitivity analysis I

To evaluate the performance of the ITR using composite features constructed from a misspecified treatment effect function, the treatment effect used to compute the second composite feature is defined as

$$\widetilde{\Delta}(\mathbf{X}) = \Delta(\mathbf{X}) = 0.2 + 0.5X_1 - 0.4X_2 + 0.3X_3 - 0.2X_4 + 0.05X_5.$$

We examined this scenario across varying sample sizes, covariate distributions, and types of residual variance. The results are summarized in Table A1, and the MSEs are shown in Figure A1.

A.2 Sensitivity analysis II

Sensitivity analysis II studied the robustness against the exchangeability assumption under four scenarios where the treatment effect differed between the RCT and target population, and they were

$$\Delta(\mathbf{X}) = 0.2 + 0.5X_1 - 0.4X_2 + 0.3X_3 - 0.2X_4 + 0.1X_5$$

and

$$\widetilde{\Delta}(\mathbf{X}) = 0.2 + 0.5X_1 - 0.4X_2 + 0.3X_3 - 0.2X_4 + kX_5,$$

respectively, where $k = 0,\ 0.05,\ 0.15,\ 0.2$.

We conducted a detailed analysis of how violating the exchangeability assumption affects estimation and inference under different covariate distributions and types of residual variance, with a fixed sample size of 1000. The results are shown in Table A2 and Figure A2.

A.3 Sensitivity analysis III

In Sensitivity analysis III, we evaluated the ITR estimation when the true treatment effect was nonlinear as

$$\widetilde{\Delta}(\mathbf{X}) = \Delta(\mathbf{X}) = 0.2 + 0.5X_1 - 0.4X_2 + 0.3X_3 - 0.2X_4 + \text{sign}(0.1X_5)\log(|0.1X_5| + 1)|X_5|^k,$$

where the violation magnitude k is chosen from 0, 0.5, 1 and 2. The comparisons of bias and MSE under different settings are presented in Table A3 and Figure A3.

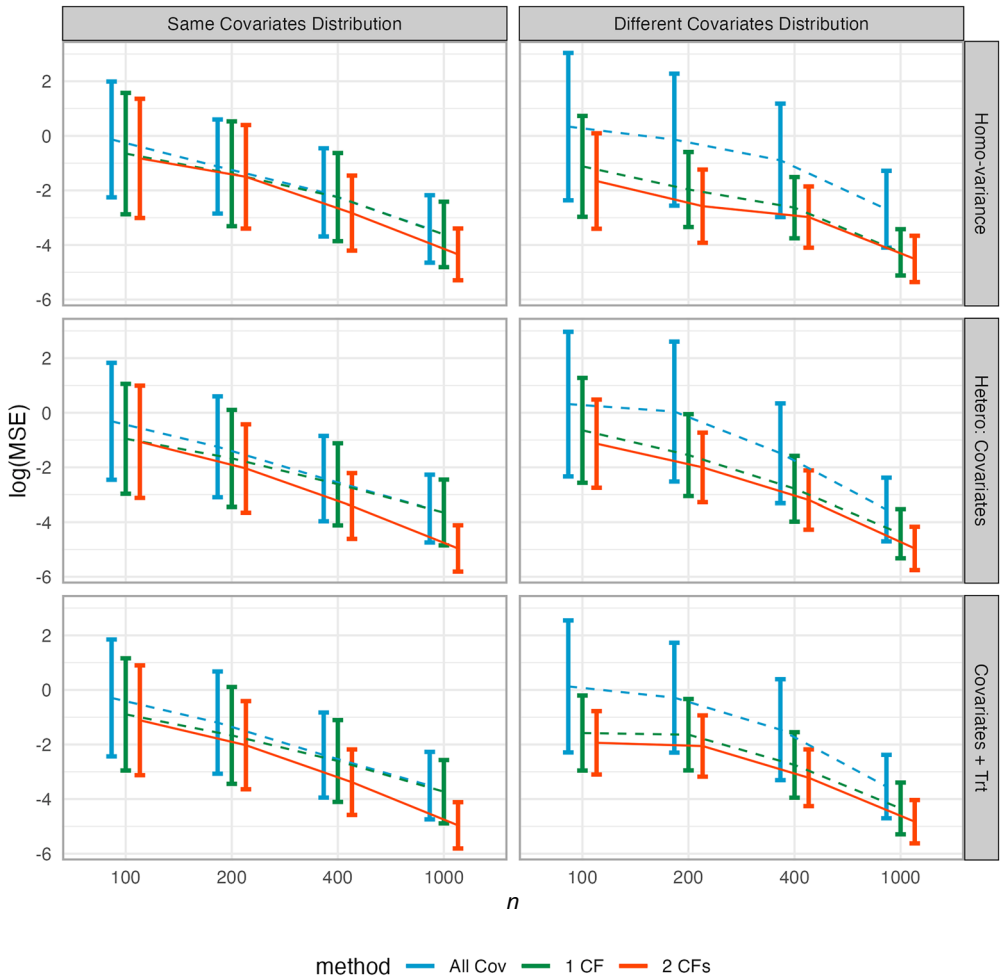


Figure A1. Plots of MSE with misspecified treatment effect function. From top to bottom are the three scenarios characterized by the residual variance. Top: Homogeneous variance; Middle: Heterogeneous variance depending on covariates; Bottom: Heterogeneous variance depending on covariates and treatment. The left column corresponds to the clinical trial data sharing the same covariate distribution as the target population; the right column corresponds to a different covariate distribution. Blue dashed line: the treatment rule using all covariates; red solid line: the treatment rule based on predictive score; green dashed line: the treatment rule using both predictive and residual score.

A.4 Results analysis

In Sensitivity analysis I, we examined the impact of using an incorrect ψ when calculating the second composite feature on the bias and MSE of the benefit estimator for the target population. Theoretically, when the covariate distribution of the RCT population matches that of the target population, the true value of the benefit is 0.90, while in cases where the covariate distribution differs, the true value is 0.55. Table A1 shows that using composite features to estimate the benefit outperforms using all variables across various settings. Specifically, with sample sizes of 100 and 200, the relative bias to the true value is substantial, at 88% and 52%, respectively, when all covariates are used, and remains over 30% even with composite features. However, as the sample size increases, both bias and MSE decline, and the benefit of composite features in reducing MSE becomes more obvious. Notably, across all settings, using two composite features reduces the estimator's MSE by more than 50% compared to using all covariates.

Table A1. Sensitivity analysis I: results based on 500 replicates.

		Same covariate distribution					Different covariate distribution				
n	Method	Bias	EstSE	EmpSE	MSE Reduct %	Cov	Bias	EstSE	EmpSE	MSE Reduct %	Cov
Homogeneous residual variance											
100	All Cov	−0.792	0.34	0.50	–	88	−0.864	0.62	0.81	–	90
	1 CF	−0.469	0.41	0.55	39.7	93	−0.427	0.51	0.38	76.7	91
	2 CFs	−0.396	0.44	0.53	49.5	92	−0.274	0.46	0.34	86.4	91
200	All Cov	−0.465	0.39	0.33	–	93	−0.669	0.70	0.65	–	92
	1 CF	−0.284	0.50	0.41	22.6	92	−0.310	0.39	0.21	83.9	93
	2 CFs	−0.250	0.48	0.40	30.7	91	−0.191	0.28	0.20	91.2	90
400	All Cov	−0.205	0.22	0.29	–	94	−0.422	0.33	0.48	–	95
	1 CF	−0.148	0.25	0.29	16.0	97	−0.229	0.20	0.14	82.4	93
	2 CFs	−0.120	0.24	0.21	53.6	95	−0.176	0.19	0.14	87.6	96
1000	All Cov	−0.060	0.21	0.17	–	91	−0.140	0.28	0.22	–	93
	1 CF	−0.042	0.18	0.16	15.8	94	−0.083	0.13	0.08	79.5	95
	2 CFs	−0.050	0.17	0.10	61.5	95	−0.075	0.13	0.08	83.3	96
Heterogeneous residual variance depending on covariates											
100	All Cov	−0.686	0.44	0.51	–	92	−0.874	0.68	0.78	–	91
	1 CF	−0.427	0.56	0.45	47.3	90	−0.597	0.52	0.41	61.8	94
	2 CFs	−0.352	0.40	0.47	52.8	97	−0.488	0.37	0.29	76.5	92
200	All Cov	−0.377	0.44	0.38	–	86	−0.715	0.66	0.73	–	93
	1 CF	−0.255	0.46	0.35	34.6	93	−0.387	0.36	0.25	79.7	95
	2 CFs	−0.214	0.35	0.29	54.7	94	−0.320	0.11	0.18	87.1	90
400	All Cov	−0.129	0.31	0.27	–	93	−0.300	0.42	0.37	–	96
	1 CF	−0.102	0.28	0.25	18.6	97	−0.190	0.23	0.16	72.8	92
	2 CFs	−0.085	0.21	0.16	63.3	94	−0.156	0.18	0.13	81.8	94
1000	All Cov	−0.032	0.22	0.17	–	93	−0.079	0.12	0.15	–	96
	1 CF	−0.027	0.13	0.16	12.0	94	−0.059	0.08	0.09	59.7	96
	2 CFs	−0.027	0.12	0.08	76.2	95	−0.045	0.10	0.07	75.9	97
Heterogeneous residual variance depending on covariates and treatment											
100	All Cov	−0.697	0.63	0.51	–	81	−0.845	0.53	0.65	–	91
	1 CF	−0.432	0.50	0.47	45.4	90	−0.402	0.28	0.21	81.9	88
	2 CFs	−0.355	0.44	0.45	56.0	87	−0.348	0.21	0.15	87.4	94
200	All Cov	−0.387	0.28	0.39	–	93	−0.742	0.39	0.45	–	91
	1 CF	−0.257	0.26	0.35	37.5	94	−0.397	0.16	0.19	74.3	96
	2 CFs	−0.219	0.19	0.29	56.3	94	−0.329	0.18	0.14	83.0	94
400	All Cov	−0.138	0.24	0.27	–	91	−0.301	0.45	0.38	–	95
	1 CF	−0.109	0.18	0.25	19.1	96	−0.194	0.18	0.16	72.4	96
	2 CFs	−0.092	0.13	0.16	63.0	95	−0.159	0.13	0.12	82.6	97
1000	All Cov	−0.039	0.20	0.17	–	92	−0.081	0.17	0.15	–	89
	1 CF	−0.035	0.19	0.15	22.0	95	−0.062	0.13	0.10	54.4	88
	2 CFs	−0.029	0.15	0.08	76.2	94	−0.047	0.06	0.07	73.3	89

In Sensitivity analysis II, we examined the impact of varying degrees of exchangeability violations on benefit estimation when the conditional treatment effects differ between the target population and the RCT data, assuming a sample size of 1000. As shown in Table A2, our proposed method consistently achieves low bias and MSE across all scenarios. In particular, using two composite features reduces the MSE by over 70% compared to estimators based on all covariates. Although both bias and MSE increase as the degree of violation intensifies (e.g., when $k = 0$ or 0.20 compared to $k = 0.05$ or 0.15), the bias remains below 3% relative to the true value, and the coverage probability consistently remains around 95%.

A detailed investigation of scenarios where the CATE is the same for both the RCT data and the target population but has non-linear patterns, with the sample size fixed at 1000, is discussed in Sensitivity analysis III. We explored four types of non-linearity – corresponding to powers of 0, 0.5, 1, and 2 – under varying covariate distributions and forms of heteroscedasticity. As shown in Table A3, across all settings, the bias of our proposed estimator remains below 5% relative to the true value, and the MSE is uniformly about 1/3 of that obtained using all covariates. At the same time, the coverage probability

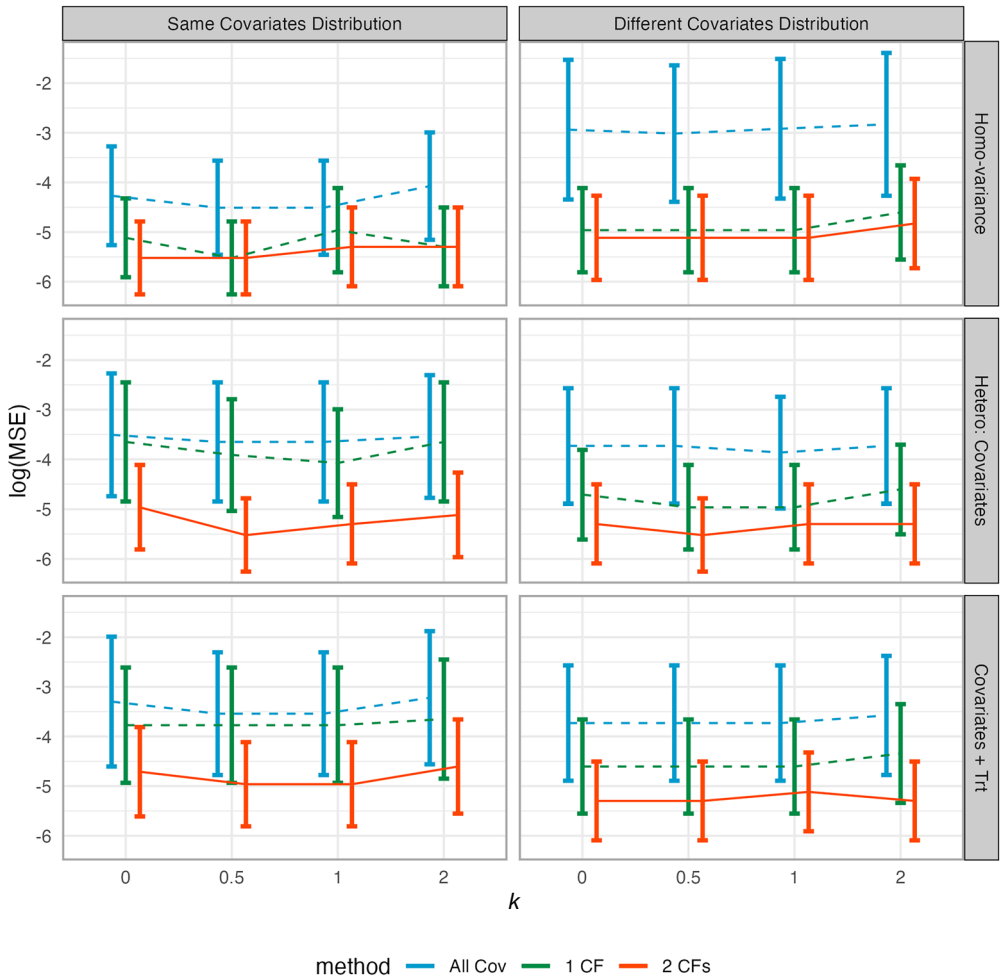


Figure A2. Plots of MSE under varying degrees of violation of the exchangeability assumption. From top to bottom are the three scenarios characterized by the residual variance. Top: Homogeneous variance; Middle: Heterogeneous variance depending on covariates; Bottom: Heterogeneous variance depending on covariates and treatment. The left column corresponds to the clinical trial data sharing the same covariate distribution as the target population; the right column corresponds to a different covariate distribution. Blue dashed line: the treatment rule using all covariates; red solid line: the treatment rule based on predictive score; green dashed line: the treatment rule using both predictive and residual score.

remains stable around 94% $\pm$ 1% in all cases. It suggests that our method performs well across a range of non-linear treatment effect scenarios.

Appendix 4. Additional results for real application

Figure A4 is a contour plot of pairwise baseline predictors for comparison between the trial and the target population in order to understand the covariate distributional difference. Figure A5 plots the residuals against each baseline predictor in DURABLE application.

Table A4 reports the estimated treatment rule. The coefficients are given on the standardized covariate scale, and the rule assigns lispro mix when the resulting linear combination is positive and insulin glargine when it is negative. Systolic blood pressure and diastolic blood pressure receive the largest

Table A2. Sensitivity analysis II: results based on 500 replicates.

		Same covariate distribution					Different covariate distribution				
k	Method	Bias	EstSE	EmpSE	MSE Reduct %	Cov	Bias	EstSE	EmpSE	MSE Reduct %	Cov
Homogeneous residual variance											
0	All Cov	−0.040	0.17	0.11	–	93	−0.070	0.28	0.22	–	93
	1 CF	−0.030	0.14	0.07	57.7	94	−0.013	0.13	0.08	86.8	94
	2 CFs	0.021	0.10	0.06	70.5	95	−0.004	0.14	0.08	89.1	94
0.05	All Cov	−0.034	0.13	0.10	–	93	−0.072	0.18	0.21	–	95
	1 CF	−0.025	0.11	0.06	62.1	94	−0.014	0.08	0.08	86.6	95
	2 CFs	0.016	0.09	0.06	65.4	95	−0.006	0.09	0.08	86.9	96
0.15	All Cov	−0.024	0.08	0.10	–	94	−0.075	0.20	0.22	–	93
	1 CF	−0.014	0.09	0.08	37.6	94	−0.018	0.12	0.08	86.7	95
	2 CFs	−0.005	0.11	0.07	53.4	94	−0.010	0.11	0.08	89.1	94
0.20	All Cov	−0.019	0.22	0.13	–	95	−0.077	0.08	0.23	–	93
	1 CF	−0.009	0.14	0.07	71.1	94	−0.020	0.12	0.10	82.3	94
	2 CFs	0.000	0.13	0.07	71.6	96	−0.012	0.13	0.09	86.0	93
Heterogeneous residual variance depending on covariates											
0	All Cov	−0.025	0.30	0.17	–	94	−0.037	0.25	0.15	–	94
	1 CF	−0.019	0.27	0.16	12.1	98	−0.017	0.14	0.09	60.7	94
	2 CFs	−0.020	0.21	0.08	77.0	95	−0.003	0.13	0.07	77.3	94
0.05	All Cov	−0.024	0.23	0.16	–	96	−0.039	0.14	0.15	–	96
	1 CF	−0.014	0.19	0.14	24.4	96	−0.019	0.11	0.08	71.9	95
	2 CFs	−0.020	0.14	0.06	84.7	94	−0.005	0.08	0.06	84.9	95
0.15	All Cov	−0.014	0.22	0.16	–	95	−0.043	0.16	0.14	–	95
	1 CF	−0.004	0.15	0.13	34.4	95	−0.023	0.10	0.08	67.7	96
	2 CFs	−0.010	0.15	0.07	80.6	95	−0.009	0.11	0.07	76.8	95
0.20	All Cov	−0.009	0.24	0.17	–	94	−0.045	0.23	0.15	–	92
	1 CF	−0.005	0.22	0.16	11.6	94	−0.025	0.12	0.09	60.4	93
	2 CFs	0.001	0.17	0.08	77.9	95	−0.011	0.14	0.07	77.4	93
Heterogeneous residual variance depending on covariates and treatment											
0	All Cov	−0.030	0.29	0.19	–	94	−0.037	0.20	0.15	–	94
	1 CF	−0.020	0.24	0.15	38.1	95	−0.018	0.19	0.10	59.0	95
	2 CFs	−0.026	0.15	0.09	76.3	95	−0.003	0.11	0.07	76.8	95
0.05	All Cov	−0.024	0.21	0.17	–	97	−0.039	0.16	0.15	–	94
	1 CF	−0.021	0.20	0.15	22.2	98	−0.020	0.08	0.10	58.9	95
	2 CFs	−0.015	0.07	0.08	77.5	96	−0.005	0.07	0.07	76.9	94
0.15	All Cov	−0.014	0.22	0.17	–	95	−0.043	0.18	0.15	–	94
	1 CF	−0.004	0.13	0.15	22.6	95	−0.024	0.12	0.10	58.8	95
	2 CFs	−0.011	0.14	0.08	77.6	95	−0.009	0.08	0.07	77.0	95
0.20	All Cov	−0.009	0.32	0.20	–	93	−0.045	0.21	0.16	–	93
	1 CF	−0.006	0.24	0.16	36.0	95	−0.026	0.20	0.11	53.8	96
	2 CFs	0.001	0.15	0.10	75.0	94	−0.011	0.17	0.07	81.8	95

weights and enter with opposite signs, so patients with a wider pulse pressure at baseline are more likely to be assigned to lispro mix.

Table A5 reports the estimated benefit relative to prescribing insulin glargine to all patients, together with the proportion of the target population assigned to lispro mix. The rule based on all covariates assigns almost every patient to lispro mix, while the rules based on the composite features assign a smaller and more balanced proportion. The benefit of the rule based on both composite features is estimated with a narrower interval than the benefit of the rule using all covariates.

Figure A6 shows the distribution of the prediction score in the trial and in the target population. The two distributions overlap over most of their range, and the target distribution is shifted toward smaller values, which is consistent with the milder glycemic profile of the electronic health record cohort. The median score is 0.108 in the target population and 0.129 in the trial, and the first and third quartiles are 0.058 and 0.169 in the target population against 0.078 and 0.181 in the trial. The score is continuous with little mass near zero, so the condition $\widetilde{\mathbb{P}}(\widetilde{X}^\top \psi_0 = 0) = 0$ in Theorem 2.2 is reasonable for these data.

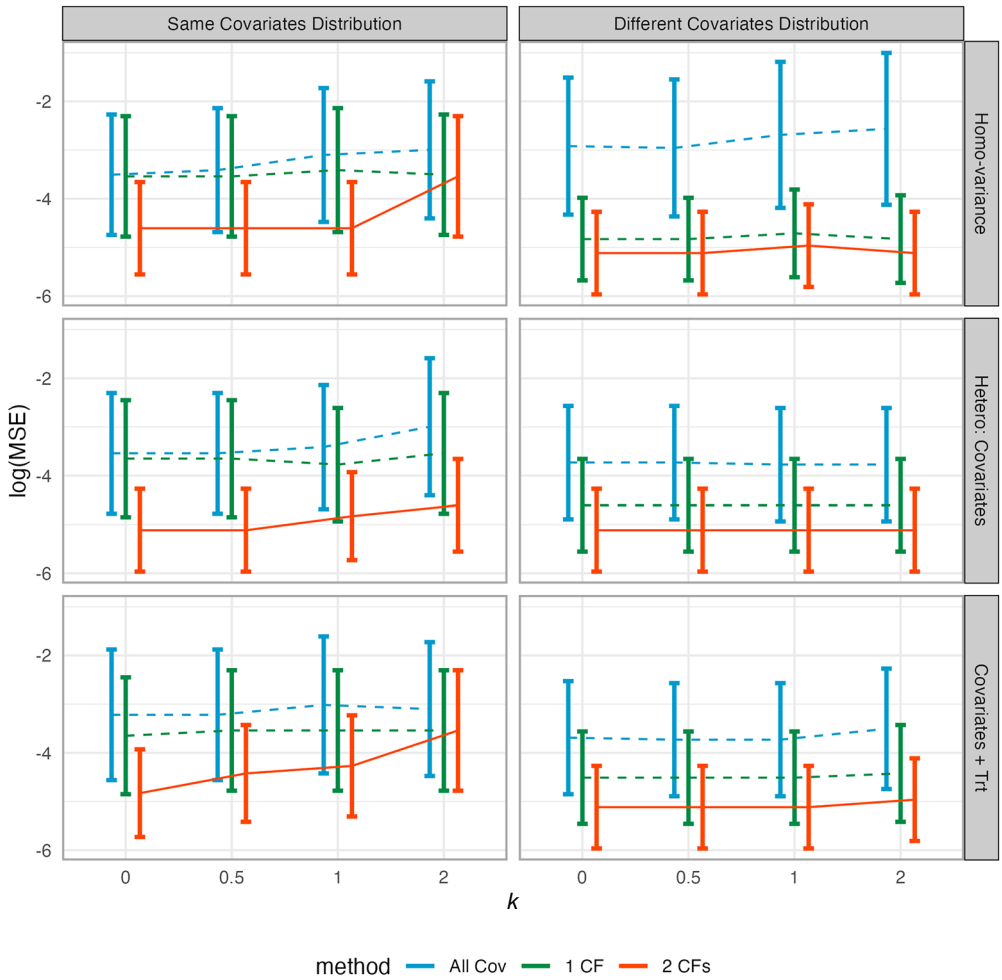


Figure A3. Plots of MSE under varying degrees of violation of the linearity assumption. From top to bottom are the three scenarios characterized by the residual variance. Top: Homogeneous variance; Middle: Heterogeneous variance depending on covariates; Bottom: Heterogeneous variance depending on covariates and treatment. The left column corresponds to the clinical trial data sharing the same covariate distribution as the target population; the right column corresponds to a different covariate distribution. Blue dashed line: the treatment rule using all covariates; red solid line: the treatment rule based on predictive score; green dashed line: the treatment rule using both predictive and residual score.

Appendix 5. Estimation of ψ_0 via a pilot study

In practical applications involving the design of a trial to evaluate the individualized treatment rule for a target population, if the value of ψ_0 is not pre-specified, we recommend conducting a pilot study to estimate ψ_0. To investigate the potential impact of this approach, we have included an additional simulation study. This simulation adopts the same setting as described in Section 3.1 of the main text, but varies the construction of the two composite features through the following four approaches to specifying ψ_0:

(1) The true ψ_0;
(2) An estimate $\widehat{\psi}$ based on all covariates;
(3) An estimate obtained from a pilot study using 1/4 of the RCT sample size;
(4) An estimate obtained from a pilot study using 1/2 of the RCT sample size.

Table A3. Sensitivity analysis III: results based on 500 replicates.

		Same covariate distribution					Different covariate distribution				
k	Method	Bias	EstSE	EmpSE	MSE Reduct %	Cov	Bias	EstSE	EmpSE	MSE Reduct %	Cov
Homogeneous residual variance											
0	All Cov	−0.030	0.19	0.17	–	93	−0.073	0.21	0.22	–	93
	1 CF	−0.016	0.18	0.17	2.2	95	−0.026	0.10	0.08	85.5	93
	2 CFs	−0.008	0.12	0.10	66.2	95	−0.017	0.09	0.08	88.0	92
0.5	All Cov	−0.030	0.15	0.18	–	93	−0.072	0.21	0.22	–	92
	1 CF	−0.016	0.15	0.17	12.4	95	−0.027	0.10	0.08	85.0	93
	2 CFs	−0.008	0.11	0.10	69.8	95	−0.018	0.10	0.08	87.7	93
1	All Cov	−0.029	0.26	0.21	–	94	−0.072	0.30	0.25	–	93
	1 CF	−0.010	0.17	0.18	27.7	95	−0.025	0.13	0.09	87.1	93
	2 CFs	0.000	0.13	0.10	77.7	95	−0.017	0.12	0.08	90.1	94
2	All Cov	−0.035	0.30	0.22	–	95	−0.061	0.19	0.27	–	93
	1 CF	0.033	0.21	0.17	39.6	94	−0.013	0.13	0.09	89.6	94
	2 CFs	0.019	0.22	0.17	41.0	95	−0.003	0.20	0.08	92.2	95
Heterogeneous residual variance depending on covariates											
0	All Cov	−0.013	0.18	0.17	–	96	−0.041	0.17	0.15	–	93
	1 CF	−0.015	0.16	0.16	11.2	98	−0.030	0.11	0.10	56.9	94
	2 CFs	−0.006	0.10	0.08	77.9	96	−0.016	0.10	0.08	75.1	94
0.5	All Cov	−0.014	0.21	0.17	–	95	−0.041	0.18	0.15	–	93
	1 CF	−0.014	0.19	0.16	11.3	95	−0.030	0.11	0.10	57.0	94
	2 CFs	−0.004	0.12	0.08	77.9	95	−0.017	0.10	0.08	74.8	93
1	All Cov	−0.013	0.24	0.18	–	94	−0.037	0.20	0.15	–	94
	1 CF	0.012	0.20	0.15	30.5	95	−0.030	0.12	0.10	55.9	94
	2 CFs	0.001	0.18	0.09	75.1	95	−0.016	0.11	0.08	74.6	94
2	All Cov	0.035	0.29	0.22	–	95	−0.032	0.24	0.15	–	94
	1 CF	−0.002	0.25	0.17	41.8	95	−0.016	0.15	0.10	55.8	94
	2 CFs	0.019	0.17	0.10	79.1	94	−0.002	0.14	0.08	74.7	95
Heterogeneous residual variance depending on covariates and treatment											
0	All Cov	−0.015	0.21	0.20	–	96	−0.039	0.18	0.15	–	94
	1 CF	−0.014	0.16	0.16	35.9	98	−0.031	0.12	0.10	56.2	95
	2 CFs	−0.007	0.10	0.09	79.7	97	−0.016	0.11	0.08	75.5	94
0.5	All Cov	−0.015	0.22	0.20	–	94	−0.004	0.20	0.15	–	94
	1 CF	−0.013	0.21	0.17	27.7	96	−0.032	0.18	0.10	55.7	95
	2 CFs	−0.005	0.15	0.11	69.9	95	−0.017	0.12	0.08	75.1	93
1	All Cov	−0.014	0.29	0.22	–	94	−0.039	0.14	0.15	–	94
	1 CF	−0.006	0.15	0.17	40.5	96	−0.030	0.12	0.10	55.5	95
	2 CFs	0.000	0.08	0.12	70.4	95	−0.016	0.13	0.08	75.0	93
2	All Cov	0.034	0.27	0.21	–	95	−0.031	0.25	0.17	–	94
	1 CF	0.024	0.23	0.17	34.9	95	−0.017	0.22	0.11	58.5	96
	2 CFs	−0.008	0.24	0.17	36.0	95	−0.002	0.17	0.08	76.6	95

Table A4. Estimated individualized treatment rule for the DURABLE application.

Term	Coefficient
Intercept	1.214
BMI	0.216
Diastolic blood pressure	−0.556
Systolic blood pressure	0.753
HbA1c	−0.127
Fasting glucose	0.248

We evaluate the bias and MSE of these four methods under different sample sizes: 100, 200, 400, and 1000. The results are summarized in Tables A6–A7 and illustrated in Figures A7–A8, grouped by sample sizes.

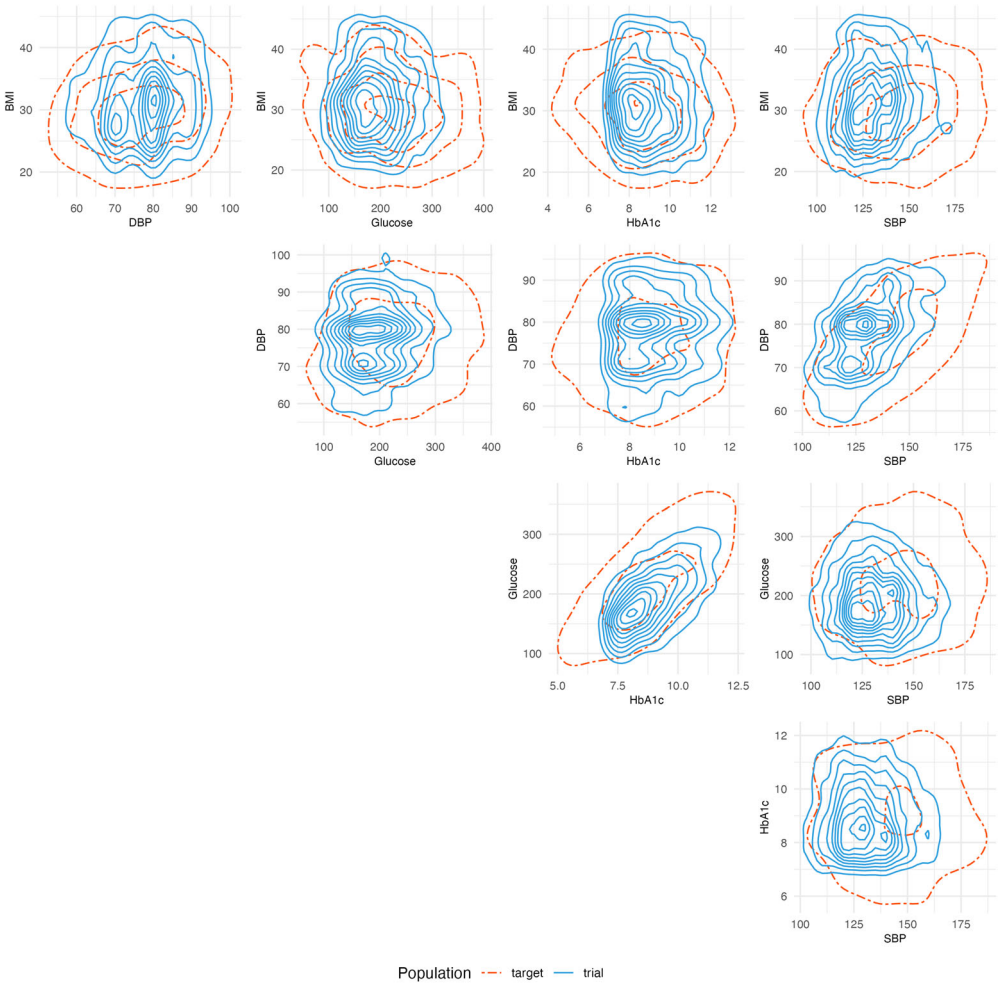


Figure A4. Contour plot of pairwise predictors for comparison between trial and target population.

Table A5. Estimated benefit in the target population and proportion assigned to lispro mix.

Rule	Benefit	95% CI	Proportion on lispro mix
All covariates	0.118	(−0.049, 0.284)	0.943
Prediction score	0.044	(−0.024, 0.111)	0.745
Prediction and residual scores	0.088	(0.010, 0.165)	0.691

The simulation results show that, across all sample sizes, estimating ψ_0 through a pilot study and subsequently using it to construct two composite features effectively reduces both bias and MSE compared to directly using all covariates, while maintaining a high coverage probability around 95%. Specifically, when the sample size is 100 or 200, the use of a pilot study leads to bias below 15% of the true value in most settings, and the MSE is reduced by more than 30% relative to the all-covariate approach. As the sample size increases to 400 and 1000, where the size of pilot studies also increases, these improvements become more obvious: the bias basically falls below 10% of the true value, and the

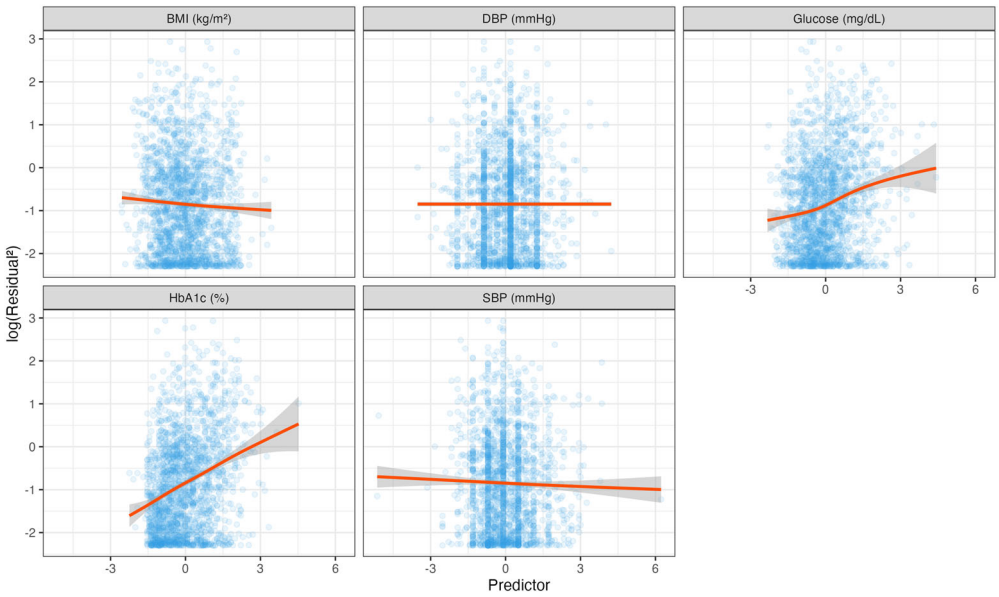


Figure A5. Residual heterogeneity plot for DURABLE study.

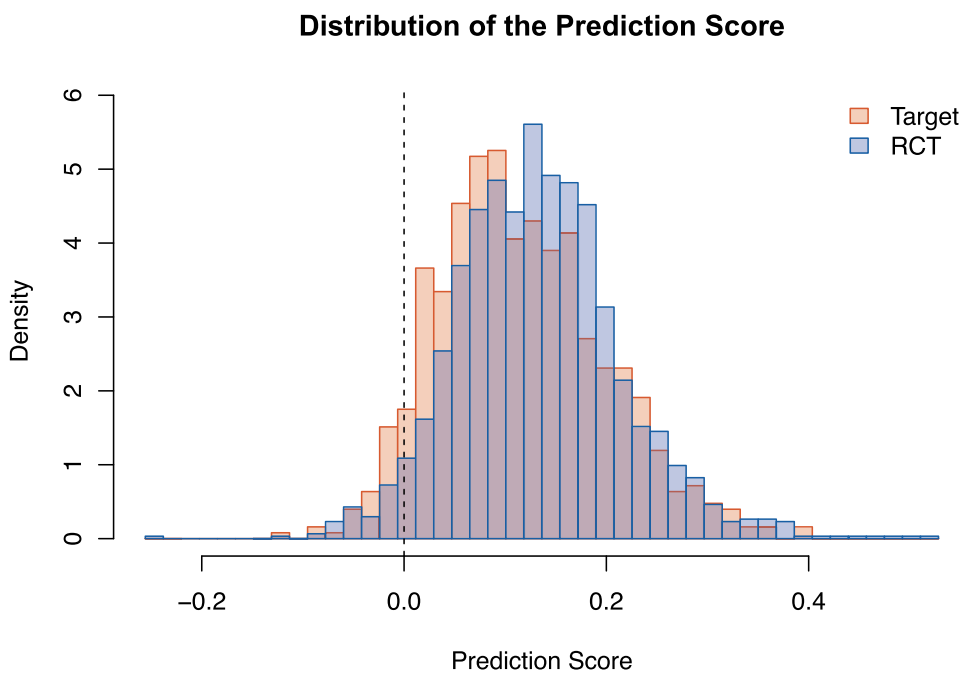


Figure A6. Distribution of the prediction score in the trial and in the target population.

MSE differs from that obtained using the true $\boldsymbol{\psi}_0$ by less than 1 on the logarithmic scale, as illustrated in Figures A10 and A8.

In contrast, directly estimating $\boldsymbol{\psi}_0$ using all covariates and applying it to construct the transformation matrix leads to inferior performance. In most cases, repeatedly using $\widehat{\boldsymbol{\psi}}$ results in greater bias

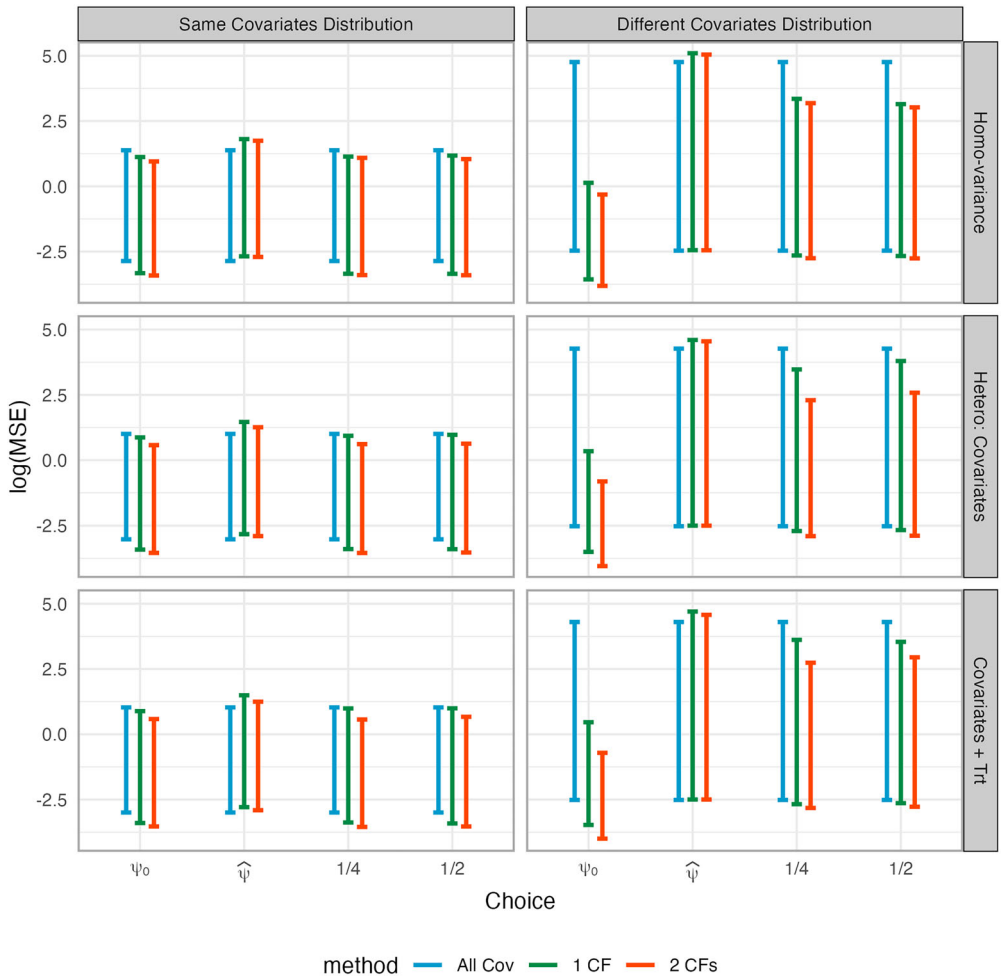


Figure A7. Plots of MSE under varying construction methods of the two composite features. From top to bottom are the three scenarios characterized by the residual variance. Top: Homogeneous variance; Middle: Heterogeneous variance depending on covariates; Bottom: Heterogeneous variance depending on covariates and treatment. The left column corresponds to the clinical trial data sharing the same covariate distribution as the target population; the right column corresponds to a different covariate distribution. Blue dashed line: the treatment rule using all covariates; red solid line: the treatment rule based on predictive score; green dashed line: the treatment rule using both predictive and residual score. The total sample size of RCT data is 100.

and higher MSE compared to directly using all covariates, and this drawback does not diminish with increasing sample size. In fact, when the sample size is 400, the use of composite features in some settings even leads to an MSE that is two to three times larger than that of the baseline method. This is primarily because this approach involves reusing the RCT data for both estimating $\boldsymbol{\psi}_0$ to evaluate the benefit and constructing the transformation matrix, leading to inflated variance.

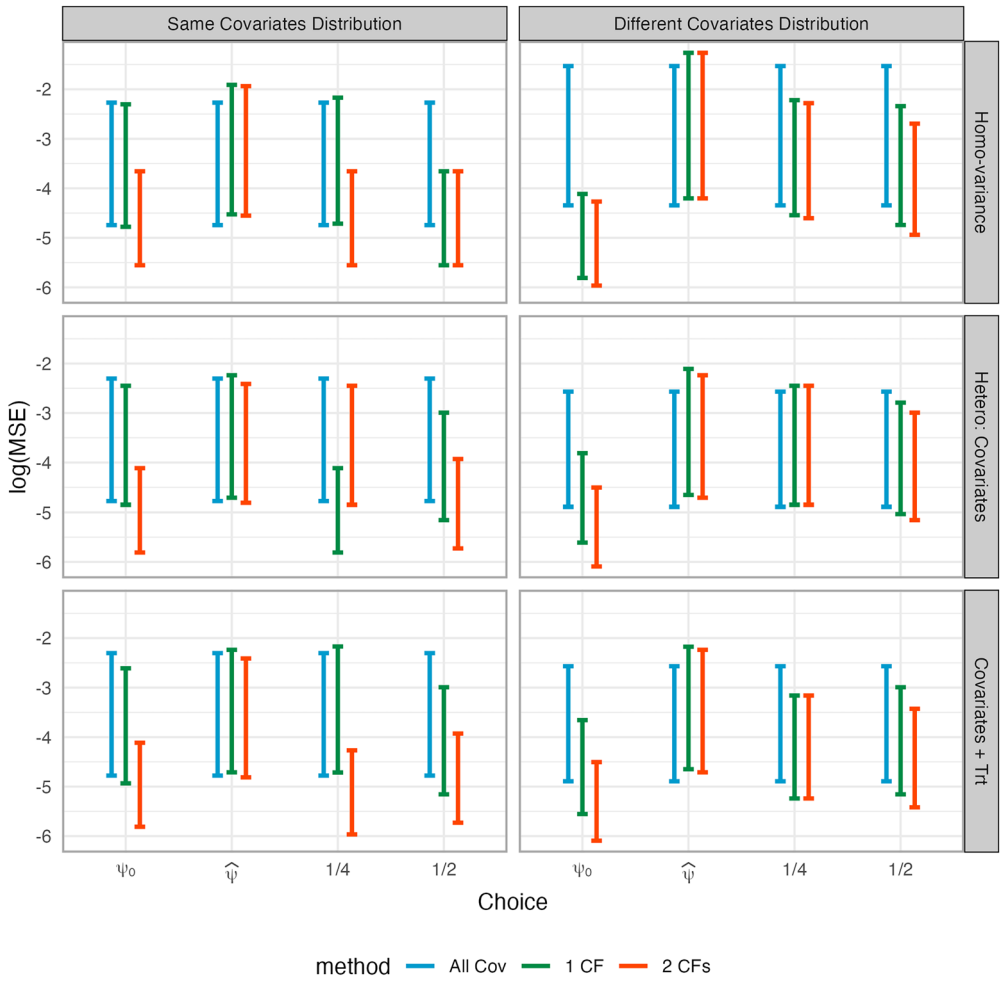


Figure A8. Plots of MSE under varying construction methods of the two composite features. From top to bottom are the three scenarios characterized by the residual variance. Top: Homogeneous variance; Middle: Heterogeneous variance depending on covariates; Bottom: Heterogeneous variance depending on covariates and treatment. The left column corresponds to the clinical trial data sharing the same covariate distribution as the target population; the right column corresponds to a different covariate distribution. Blue dashed line: the treatment rule using all covariates; red solid line: the treatment rule based on predictive score; green dashed line: the treatment rule using both predictive and residual score. The total sample size of RCT data is 1000.

Table A6. Performance comparison of various ψ_0 specifications with RCT sample size 100 (500 replications).

		Same covariate distribution					Different covariate distribution				
Choice	Method	Bias	EstSE	EmpSE	MSE Reduct %	Cov	Bias	EstSE	EmpSE	MSE Reduct %	Cov
Homogeneous residual variance											
ψ_0	All Cov	0.203	0.29	0.25	–	95	0.164	0.24	0.20	–	97
	1 CF	0.036	0.23	0.22	51.4	97	−0.002	0.14	0.14	72.6	98
	2 CFs	0.061	0.30	0.28	23.9	96	0.005	0.23	0.21	36.5	98
$\widehat{\psi}$	All Cov	0.203	0.29	0.25	–	95	0.164	0.24	0.20	–	97
	1 CF	−0.244	0.48	0.56	−259.8	83	−0.503	0.47	0.53	−698.1	89
	2 CFs	−0.239	0.63	0.55	−246.8	82	−0.560	0.57	0.52	−773.0	90
1/4	All Cov	0.203	0.29	0.25	–	95	0.164	0.24	0.20	–	97
	1 CF	0.051	0.21	0.28	21.9	96	−0.129	0.19	0.23	−4.0	92
	2 CFs	−0.061	0.18	0.28	20.8	95	−0.104	0.19	0.25	−9.7	91
2/4	All Cov	0.203	0.29	0.25	–	95	0.164	0.24	0.20	–	97
	1 CF	0.040	0.21	0.28	22.9	96	−0.123	0.16	0.18	28.9	92
	2 CFs	−0.036	0.30	0.27	28.5	95	−0.105	0.15	0.20	23.9	91
Heterogeneous residual variance depending on covariates											
ψ_0	All Cov	0.436	0.53	0.47	–	96	0.485	0.56	0.51	–	95
	1 CF	−0.011	0.36	0.34	72.9	96	−0.027	0.23	0.22	90.5	96
	2 CFs	0.001	0.33	0.30	77.9	97	0.009	0.21	0.20	92.2	96
$\widehat{\psi}$	All Cov	0.436	0.53	0.47	–	96	0.485	0.56	0.51	–	95
	1 CF	−0.493	0.63	0.51	−22.4	85	−0.950	1.29	1.40	−477.9	89
	2 CFs	−0.461	0.61	0.48	−7.8	84	−0.949	1.21	1.38	−466.3	89
1/4	All Cov	0.436	0.53	0.47	–	96	0.485	0.56	0.51	–	95
	1 CF	0.155	0.43	0.52	28.4	97	−0.296	0.49	0.53	25.6	91
	2 CFs	0.059	0.46	0.48	43.1	97	−0.210	0.43	0.50	40.7	90
2/4	All Cov	0.436	0.53	0.47	–	96	0.485	0.56	0.51	–	95
	1 CF	0.131	0.61	0.53	27.5	97	−0.107	0.30	0.28	81.9	91
	2 CFs	0.039	0.55	0.48	43.6	97	−0.118	0.27	0.28	81.4	93
Heterogeneous residual variance depending on covariates and treatment											
ψ_0	All Cov	0.799	0.91	1.08	–	92	0.707	0.85	0.85	–	96
	1 CF	0.035	0.56	0.46	88.3	93	−0.002	0.33	0.28	93.4	98
	2 CFs	0.067	0.52	0.45	88.6	95	0.027	0.31	0.29	92.9	97
$\widehat{\psi}$	All Cov	0.799	0.91	1.08	–	92	0.707	0.85	0.85	–	96
	1 CF	−0.509	0.39	0.51	71.2	84	−0.971	1.28	1.44	−146.8	90
	2 CFs	−0.453	0.41	0.48	75.9	86	−0.942	1.26	1.39	−130.7	89
1/4	All Cov	0.799	0.91	1.08	–	92	0.707	0.85	0.85	–	96
	1 CF	0.137	0.50	0.53	83.4	97	−0.419	0.43	0.55	60.9	89
	2 CFs	0.051	0.45	0.47	87.6	96	−0.459	0.32	0.43	67.6	85
2/4	All Cov	0.799	0.91	1.08	–	92	0.707	0.85	0.85	–	96
	1 CF	0.099	0.44	0.54	83.3	97	−0.193	0.39	0.30	89.6	91
	2 CFs	0.033	0.42	0.49	86.6	97	−0.207	0.27	0.36	85.9	89

Table A7. Performance comparison of various ψ_0 specifications with RCT sample size 1000 (500 replications).

		Same covariate distribution					Different covariate distribution				
Choice	Method	Bias	EstSE	EmpSE	MSE Reduct %	Cov	Bias	EstSE	EmpSE	MSE Reduct %	Cov
Homogeneous residual variance											
ψ_0	All Cov	−0.029	0.20	0.17	–	94	−0.074	0.19	0.22	–	93
	1 CF	−0.019	0.22	0.17	3.8	95	−0.016	0.10	0.08	86.8	94
	2 CFs	−0.011	0.15	0.10	66.4	94	−0.008	0.09	0.08	89.1	94
$\widehat{\psi}$	All Cov	−0.029	0.20	0.17	–	94	−0.074	0.19	0.22	–	93
	1 CF	−0.059	0.39	0.19	−32.1	93	−0.089	0.52	0.24	−22.6	92
	2 CFs	−0.057	0.31	0.19	−30.3	93	−0.087	0.48	0.24	−21.8	93
1/4	All Cov	−0.029	0.20	0.17	–	94	−0.074	0.19	0.22	–	93
	1 CF	0.009	0.17	0.18	−6.7	96	−0.105	0.23	0.15	35.8	91
	2 CFs	0.007	0.13	0.10	65.2	94	−0.099	0.14	0.15	39.6	90
1/2	All Cov	−0.029	0.20	0.17	–	94	−0.074	0.19	0.22	–	93
	1 CF	0.020	0.18	0.10	66.4	95	0.058	0.18	0.16	45.3	93
	2 CFs	0.013	0.14	0.10	68.5	95	0.050	0.16	0.14	58.5	93
Heterogeneous residual variance depending on covariates											
ψ_0	All Cov	−0.019	0.20	0.17	–	95	−0.041	0.14	0.15	–	94
	1 CF	−0.009	0.15	0.16	10.3	94	−0.021	0.12	0.09	60.5	94
	2 CFs	−0.015	0.11	0.08	75.9	96	−0.007	0.08	0.07	77.4	94
$\widehat{\psi}$	All Cov	−0.019	0.20	0.17	–	95	−0.041	0.14	0.15	–	94
	1 CF	−0.041	0.26	0.17	−6.9	94	−0.055	0.25	0.18	−44.1	93
	2 CFs	−0.040	0.32	0.16	7.1	95	−0.052	0.26	0.17	−30.8	93
1/4	All Cov	−0.019	0.20	0.17	–	95	−0.041	0.14	0.15	–	94
	1 CF	−0.015	0.12	0.08	75.9	96	0.018	0.19	0.16	−8.3	92
	2 CFs	0.011	0.13	0.16	10.3	98	0.010	0.20	0.16	−8.3	91
1/2	All Cov	−0.019	0.20	0.17	–	95	−0.041	0.14	0.15	–	94
	1 CF	0.013	0.17	0.13	41.4	95	−0.013	0.13	0.14	16.7	93
	2 CFs	0.008	0.15	0.09	72.5	96	−0.008	0.11	0.13	29.2	91
Heterogeneous residual variance depending on covariates and treatment											
ψ_0	All Cov	−0.019	0.15	0.17	–	94	−0.041	0.18	0.15	–	94
	1 CF	−0.009	0.12	0.15	20.7	95	−0.022	0.09	0.10	58.9	95
	2 CFs	−0.016	0.10	0.08	75.9	95	−0.007	0.09	0.07	73.8	94
$\widehat{\psi}$	All Cov	−0.019	0.15	0.17	–	94	−0.041	0.18	0.15	–	94
	1 CF	−0.042	0.43	0.17	−8.1	94	−0.053	0.27	0.17	−37.1	94
	2 CFs	−0.040	0.38	0.16	6.4	94	−0.053	0.25	0.17	−29.9	95
1/4	All Cov	−0.019	0.15	0.17	–	94	−0.041	0.18	0.15	–	94
	1 CF	0.006	0.24	0.18	−10.3	95	0.014	0.14	0.12	37.8	93
	2 CFs	0.004	0.16	0.08	79.5	95	0.011	0.14	0.12	37.5	92
1/2	All Cov	−0.019	0.15	0.17	–	94	−0.041	0.18	0.15	–	94
	1 CF	0.014	0.14	0.13	41.2	95	−0.009	0.15	0.13	29.2	94
	2 CFs	0.010	0.14	0.09	72.4	94	−0.006	0.16	0.11	50.4	93

Table A8. Performance comparison of various ψ_0 specifications with RCT sample size 200 (500 replications).

		Same covariate distribution					Different covariate distribution				
Choice	Method	Bias	EstSE	EmpSE	MSE Reduct %	Cov	Bias	EstSE	EmpSE	MSE Reduct %	Cov
Homogeneous residual variance											
ψ_0	All Cov	0.055	0.21	0.20	–	97	0.081	0.17	0.16	–	93
	1 CF	−0.036	0.17	0.17	30.9	95	−0.004	0.10	0.10	68.6	95
	2 CFs	−0.027	0.22	0.21	−3.7	96	−0.002	0.16	0.16	21.3	94
$\widehat{\psi}$	All Cov	0.055	0.21	0.20	–	97	0.081	0.17	0.16	–	93
	1 CF	−0.068	0.33	0.26	−67.4	86	−0.194	0.32	0.22	−168.8	89
	2 CFs	−0.066	0.31	0.25	−55.8	86	−0.190	0.29	0.22	−165.6	89
1/4	All Cov	0.055	0.21	0.20	–	97	0.081	0.17	0.16	–	93
	1 CF	0.038	0.18	0.19	11.6	98	−0.043	0.18	0.17	3.1	92
	2 CFs	0.031	0.23	0.17	30.2	97	−0.037	0.11	0.16	15.6	91
2/4	All Cov	0.055	0.21	0.20	–	97	0.081	0.17	0.16	–	93
	1 CF	0.028	0.16	0.15	46.5	97	−0.042	0.19	0.14	34.4	91
	2 CFs	0.013	0.19	0.15	46.5	96	−0.037	0.20	0.14	34.4	91
Heterogeneous residual variance depending on covariates											
ψ_0	All Cov	0.248	0.38	0.31	–	98	0.290	0.38	0.37	–	97
	1 CF	−0.007	0.27	0.25	59.4	97	−0.021	0.16	0.15	89.2	96
	2 CFs	−0.002	0.24	0.23	66.4	95	−0.002	0.14	0.14	91.7	94
$\widehat{\psi}$	All Cov	0.248	0.38	0.31	–	98	0.290	0.38	0.37	–	97
	1 CF	−0.281	0.27	0.36	−32.9	88	−0.495	0.61	0.42	−90.5	91
	2 CFs	−0.253	0.24	0.34	−13.9	88	−0.483	0.67	0.41	−81.4	91
1/4	All Cov	0.248	0.38	0.31	–	98	0.290	0.38	0.37	–	97
	1 CF	0.182	0.34	0.29	25.9	92	−0.212	0.28	0.33	30.3	92
	2 CFs	0.124	0.31	0.26	47.5	94	−0.167	0.25	0.34	35.3	91
2/4	All Cov	0.248	0.38	0.31	–	98	0.290	0.38	0.37	–	97
	1 CF	0.140	0.30	0.28	38.0	95	−0.044	0.36	0.40	26.7	93
	2 CFs	0.083	0.21	0.26	53.2	97	−0.032	0.35	0.33	50.2	90
Heterogeneous residual variance depending on covariates and treatment											
ψ_0	All Cov	0.522	0.63	0.66	–	94	0.537	0.64	0.64	–	94
	1 CF	−0.001	0.40	0.38	79.9	94	0.006	0.27	0.21	93.5	98
	2 CFs	0.020	0.36	0.35	83.1	93	0.032	0.24	0.19	94.6	97
$\widehat{\psi}$	All Cov	0.522	0.63	0.66	–	94	0.537	0.64	0.64	–	94
	1 CF	−0.287	0.61	0.36	69.6	88	−0.514	1.01	0.83	−37.2	91
	2 CFs	−0.257	0.58	0.34	74.2	88	−0.503	0.96	0.82	−33.8	91
1/4	All Cov	0.522	0.63	0.66	–	94	0.537	0.64	0.64	–	94
	1 CF	0.170	0.29	0.41	72.5	94	−0.407	0.55	0.66	13.9	94
	2 CFs	0.116	0.30	0.37	78.2	95	−0.283	0.49	0.58	40.4	90
2/4	All Cov	0.522	0.63	0.66	–	94	0.537	0.64	0.64	–	94
	1 CF	0.136	0.43	0.41	74.0	95	−0.426	0.29	0.39	52.1	96
	2 CFs	0.080	0.41	0.37	79.9	96	−0.306	0.28	0.31	72.8	94

Table A9. Performance comparison of various ψ_0 specifications with RCT sample size 400 (500 replications).

		Same covariate distribution					Different covariate distribution				
Choice	Method	Bias	EstSE	EmpSE	MSE Reduct %	Cov	Bias	EstSE	EmpSE	MSE Reduct %	Cov
Homogeneous residual variance											
ψ_0	All Cov	−0.106	0.23	0.21	–	93	−0.237	0.40	0.48	–	91
	1 CF	−0.049	0.24	0.19	29.1	95	−0.045	0.16	0.14	92.2	95
	2 CFs	−0.021	0.18	0.19	32.7	95	−0.021	0.14	0.14	93.4	94
$\widehat{\psi}$	All Cov	−0.106	0.23	0.21	–	93	−0.237	0.40	0.48	–	91
	1 CF	−0.166	0.41	0.28	−94.6	92	−0.274	0.31	0.52	−20.9	90
	2 CFs	−0.166	0.44	0.28	−92.2	92	−0.273	0.37	0.52	−20.1	90
1/4	All Cov	−0.106	0.23	0.21	–	93	−0.237	0.40	0.48	–	91
	1 CF	0.092	0.22	0.17	32.7	89	−0.166	0.35	0.39	37.7	91
	2 CFs	0.067	0.18	0.15	50.9	92	−0.142	0.36	0.38	42.9	89
2/4	All Cov	−0.106	0.23	0.21	–	93	−0.237	0.40	0.48	–	91
	1 CF	0.062	0.18	0.16	47.3	92	−0.227	0.42	0.45	11.4	92
	2 CFs	0.039	0.19	0.15	56.4	93	−0.189	0.43	0.45	17.0	92
Heterogeneous residual variance depending on covariates											
ψ_0	All Cov	−0.063	0.15	0.16	–	92	−0.163	0.42	0.37	–	91
	1 CF	−0.036	0.13	0.13	35.7	95	−0.054	0.13	0.16	82.9	95
	2 CFs	−0.019	0.13	0.12	46.4	95	−0.019	0.17	0.12	90.4	92
$\widehat{\psi}$	All Cov	−0.063	0.15	0.16	–	92	−0.163	0.42	0.37	–	91
	1 CF	−0.127	0.42	0.27	−204.2	92	−0.197	0.56	0.42	−30.5	90
	2 CFs	−0.110	0.39	0.25	−162.6	93	−0.192	0.57	0.42	−28.1	91
1/4	All Cov	−0.063	0.15	0.16	–	92	−0.163	0.42	0.37	–	91
	1 CF	0.047	0.18	0.15	10.7	93	−0.160	0.40	0.31	26.5	92
	2 CFs	0.030	0.11	0.14	25.0	93	−0.119	0.36	0.28	44.0	89
2/4	All Cov	−0.063	0.15	0.16	–	92	−0.163	0.42	0.37	–	91
	1 CF	0.067	0.12	0.14	14.3	92	−0.171	0.30	0.29	31.9	91
	2 CFs	0.052	0.19	0.13	28.6	93	−0.094	0.28	0.22	65.7	89
Heterogeneous residual variance depending on covariates and treatment											
ψ_0	All Cov	−0.069	0.19	0.16	–	93	−0.162	0.35	0.38	–	92
	1 CF	−0.039	0.15	0.14	30.4	95	−0.055	0.19	0.16	82.8	95
	2 CFs	−0.023	0.12	0.12	50.8	94	−0.020	0.18	0.12	90.7	93
$\widehat{\psi}$	All Cov	−0.069	0.19	0.16	–	93	−0.162	0.35	0.38	–	92
	1 CF	−0.136	0.50	0.27	−190.1	92	−0.201	0.71	0.43	−33.8	92
	2 CFs	−0.120	0.52	0.25	−149.1	92	−0.193	0.68	0.42	−28.4	91
1/4	All Cov	−0.069	0.19	0.16	–	93	−0.162	0.35	0.38	–	92
	1 CF	0.072	0.22	0.15	6.4	91	−0.147	0.35	0.31	29.8	91
	2 CFs	0.050	0.20	0.13	36.7	93	−0.112	0.30	0.27	49.4	92
2/4	All Cov	−0.069	0.19	0.16	–	93	−0.162	0.35	0.38	–	92
	1 CF	0.041	0.18	0.14	30.0	94	−0.113	0.28	0.25	55.4	93
	2 CFs	0.042	0.15	0.13	36.9	95	−0.068	0.24	0.21	70.8	91

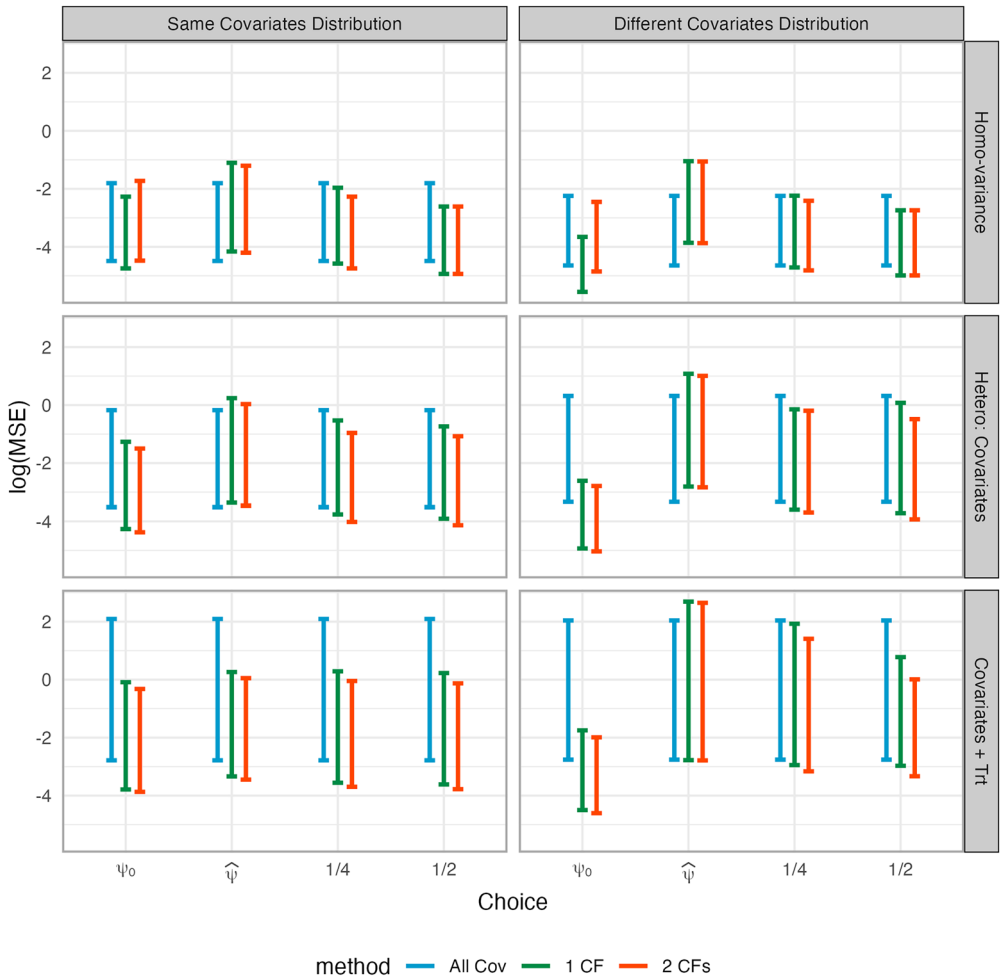


Figure A9. Plots of MSE under varying construction methods of the two composite features. From top to bottom are the three scenarios characterized by the residual variance. Top: Homogeneous variance; Middle: Heterogeneous variance depending on covariates; Bottom: Heterogeneous variance depending on covariates and treatment. The left column corresponds to the clinical trial data sharing the same covariate distribution as the target population; the right column corresponds to a different covariate distribution. Blue dashed line: the treatment rule using all covariates; red solid line: the treatment rule based on predictive score; green dashed line: the treatment rule using both predictive and residual score. The total sample size of RCT data is 200.

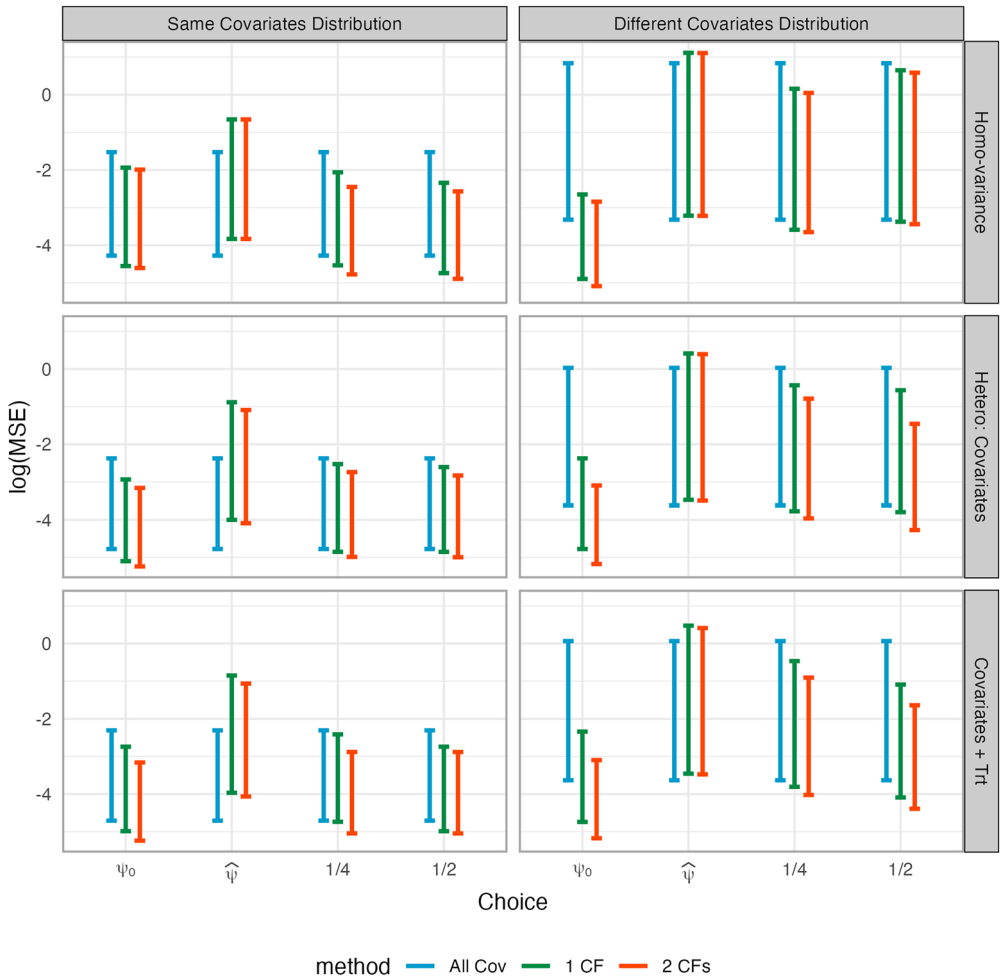


Figure A10. Plots of MSE under varying construction methods of the two composite features. From top to bottom are the three scenarios characterized by the residual variance. Top: Homogeneous variance; Middle: Heterogeneous variance depending on covariates; Bottom: Heterogeneous variance depending on covariates and treatment. The left column corresponds to the clinical trial data sharing the same covariate distribution as the target population; the right column corresponds to a different covariate distribution. Blue dashed line: the treatment rule using all covariates; red solid line: the treatment rule based on predictive score; green dashed line: the treatment rule using both predictive and residual score. The total sample size of RCT data is 400.