Incorporating external data into the analysis of clinical trials via Bayesian additive regression trees

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Most clinical trials involve the comparison of a new treatment to a control arm (eg, the standard of care) and the estimation of a treatment effect. External data, including historical clinical trial data and real-world observational data, are commonly available for the control arm. With proper statistical adjustments, borrowing information from external data can potentially reduce the mean squared errors of treatment effect estimates and increase the power of detecting a meaningful treatment effect. In this article, we propose to use Bayesian additive regression trees (BART) for incorporating external data into the analysis of clinical trials, with a specific goal of estimating the conditional or population average treatment effect. BART naturally adjusts for patient-level covariates and captures potentially heterogeneous treatment effects across different data sources, achieving flexible borrowing. Simulation studies demonstrate that BART maintains desirable and robust performance across a variety of scenarios and compares favorably to alternatives. We illustrate the proposed method with an acupuncture trial and a colorectal cancer trial.

KEYWORDS
Bayesian method, borrow information, historical control, real-world data, treatment effect

1 | INTRODUCTION

Most clinical trials involve the comparison of a new treatment to a control arm (eg, the standard of care) and the estimation of a treatment effect. While the investigational drug is new, external data are usually available for the control arm. Here, external data can be historical data from past clinical trials, or real-world data (RWD) routinely gathered from a variety of sources other than traditional clinical trials. Examples of RWD include data derived from electronic health records, and medical claims and billing data. Incorporation of external data into the analysis of clinical trials can potentially reduce the mean squared errors of treatment effect estimates and increase the power of detecting a meaningful treatment effect. With additional information about the control arm, more resources can be devoted to the new treatment, and the required total sample size may be reduced. In the ideal situation, external data can be used to synthesize an external control arm, and the clinical trial can be conducted in a single-arm fashion. Since clinical trials are designed to be context-specific and rarely is the same trial repeated, one would invariably expect bias when incorporating external evidence into the analysis of a clinical trial. Therefore, proper statistical adjustments that mitigate such bias are necessary for external evidence to be useful.

A variety of statistical methods have been developed for borrowing information from historical trial data, with the majority of these methods being Bayesian. See, for example, Viele et al¹ or van Rosmalen et al⁴ for a comprehensive review. Roughly speaking, methods for historical borrowing can be categorized into two types. The first type of methods...
constructs an informative prior for the parameters in the concurrent control arm based on the (down-weighted) likelihood of the historical data. Examples of these methods include the power prior approach\(^5,6\) and the modified power prior approach.\(^7,8\) The second type of methods, such as Neuenschwander et al,\(^9\) Hobbs et al,\(^10,11\) Schmidli et al,\(^12\) Kaizer et al,\(^13\) Lewis et al,\(^14\) and Röver and Friede,\(^15\) borrows strength across concurrent and historical control arms through hierarchical modeling. For example, in Röver and Friede,\(^15\) the authors assumed that the concurrent and historical control parameters are random samples from a common population distribution. As a result, parameter estimates for the concurrent and historical controls shrink toward an overall mean, with the degree of shrinkage adaptively determined according to the heterogeneity across studies. In some cases, informative prior and hierarchical modeling approaches are closely related (see, eg, Chen and Ibrahim\(^16\)). In the pioneering work of Pocock,\(^17\) the author described a series of favorable conditions for historical borrowing to be most reliable and beneficial. For example, the historical control group should have been part of a recent clinical study which contained the same requirements for patient eligibility, and the distributions of important patient characteristics in the group should be comparable with those in the current trial. The use of historical information in medical device trials was discussed by the Food and Drug Administration.\(^18\)

Recently, the increasing accessibility of routinely collected health care data has led to interests in the use of RWD for assessing treatment effects in clinical trials.\(^2,19-21\) It is expected that the patient characteristics in the RWD are different from those in the clinical trial. Therefore, techniques in the causal inference literature, such as propensity score weighting or matching, are commonly employed to adjust for such discrepancy. Examples of recent works on RWD include Ventz et al\(^22\) and Carrigan et al.\(^23\)

In this article, we propose to use Bayesian additive regression trees (BART)\(^24\) for incorporating external data into the analysis of clinical trials. Our approach aims to tackle two issues regarding borrowing external data:

1. The distribution of patient characteristics in the current clinical trial may be different from that in the external data, and
2. Even if patient-level covariates have been adjusted for, there might still be unmeasured confounders which can contribute to the heterogeneity in patient outcomes across data sources.

The first issue has been the focus of much of the RWD literature and is also a main problem in causal inference, while the second issue has been the focus of the historical borrowing literature. By modeling the relationship between patient outcome, covariates, and an indicator of data source using BART, the proposed approach takes into account both issues. As seen in Hill,\(^25\) BART is able to detect interactions and nonlinearities thus can readily identify heterogeneous treatment effects across the covariate space and data sources. On the other hand, for areas of the covariate space in which patient outcomes are relatively homogeneous, BART pools information across data sources to produce more precise estimates (Section 2.2). These features allow BART to adaptively incorporate external information into the analysis of clinical trials.

BART has many attractive features. The implementation of BART has been made easy by the R package BART,\(^26\) which supports continuous, binary, categorical, and time-to-event outcomes and can also perform variable selection in the presence of a large number of covariates.\(^27\) A stream of work has demonstrated the promising theoretical properties of BART (eg, Linero and Yang\(^28\) and Röcková and van der Pas\(^29\)). Lastly, BART has been used in many applications, such as causal inference,\(^25\) survival analysis,\(^30\) subgroup finding,\(^31\) and missing data,\(^32\) with proven good performance. A recent review of BART can be found in Hill et al.\(^33\)

The remainder of this article is organized as follows. In Section 2, we describe the proposed methodology, including an introduction of the treatment effect estimation problem in clinical trials. In Section 3, we present simulation studies and comparisons with a power prior approach,\(^3\) a hierarchical linear model, a normal-normal hierarchical model, the virtual twins method,\(^34\) and methods that ignore external data. In Section 4, we illustrate the application of our method with an acupuncture trial. In Section 5, we apply the proposed method to the planning and design of a colorectal cancer trial. Finally, in Section 6, we conclude with a discussion.

2 | METHODOLOGY

2.1 | Treatment effect estimation in clinical trials

Suppose that in addition to the current clinical trial data, we have access to supplemental data from \(J\) external data sources (which can be historical trial datasets or real-world datasets). Let \(i\) index an individual in the current trial, a historical
study, or a real-world study. Let $S_i$ be an indicator for data source, where $S_i = 0$ indicates that individual $i$ is from the current trial, and $S_i \in \{1, 2, \ldots, J\}$ represents that the individual is from an external dataset. Denote by $T_i = 1$ (or 0) an assignment of individual $i$ to treatment (or control). Without loss of generality, assume that all individuals in the external data received the control, while patients in the current trial are assigned to both the treatment and control arms.

Next, following the notation in the causal inference literature (eg, Rubin35), we denote by $Y_i(1)$ or $Y_i(0)$ the potential outcomes that would have been observed for the same individual $i$ if the individual received treatment or control, respectively. In practice, $Y_i(1)$ and $Y_i(0)$ cannot be observed simultaneously, and we let $Y_i = Y_i(1)T_i + Y_i(0)(1 - T_i)$ denote the observed outcome. At this moment, we consider continuous outcomes and focus on the treatment effect defined by the difference between the potential outcomes, $Y_i(1) - Y_i(0)$. The idea can be easily extended to binary or time-to-event outcomes. Finally, denote by $X_i = (X_{i1}, \ldots, X_{iQ})^T$ the Q patient-level covariates, which are assumed to be measured in both the current trial and external data.

The primary goal of many clinical trials is to estimate the average treatment effect (ATE), which may be defined over the sample or population of the trial. Common estimands include the conditional ATE (CATE) and the population ATE (PATE), defined as

$$\Delta_C = \frac{1}{N_{\text{trial}}} \sum_{i:S_i = 0} E[Y_i(1) - Y_i(0)|X_i, S_i = 0], \quad \text{and}$$

$$\Delta_P = E[Y_i(1) - Y_i(0)|S_i = 0] = E[E[Y_i(1) - Y_i(0)|X_i, S_i = 0]],$$

respectively. Here, $N_{\text{trial}} = \sum_i 1\{S_i = 0\}$ denotes the number of individuals in the current trial. See, for example, Imbens36 or Hill25 for a discussion of different types of estimands. In this article, we focus on the estimation of the CATE but will also discuss how to estimate the PATE. For simplicity, we drop the index $i$ whenever needed.

The distribution of $[Y(t)|X, S]$ is known as the response surface. Under the unconfoundedness condition that $[Y(0), Y(1) \perp T|X, S = 0]$ (which is satisfied for randomized or conditionally randomized trials), we have

$$E[Y(t)|X, S = 0] = E[Y(t)|T = t, X, S = 0] = E[Y|T = t, X, S = 0].$$

As a result,

$$E[Y(1) - Y(0)|X, S = 0] = E[Y|T = 1, X, S = 0] - E[Y|T = 0, X, S = 0] \overset{d}{=} \delta(X),$$

and

$$\Delta_C = \frac{1}{N_{\text{trial}}} \sum_{i:S_i = 0} \delta(X_i), \quad \Delta_P = \int \delta(x)p(x|S = 0)dx,$$

(1)

where $p(x|S = 0)$ is the distribution of patient characteristics over the trial population. The quantity $\delta(x)$ is referred to as the conditional treatment effect.

Incorporation of external data could ideally improve the estimation of $E[Y|T = 0, X, S = 0]$. In the ideal case, the control outcome $Y$ and data source indicator $S$ are conditionally independent given the covariates $X$, meaning $[Y \perp S|T = 0, X]$, hence $[Y|T = 0, X, S = s] \overset{d}{=} [Y|T = 0, X]$, where $\overset{d}{=}$ denotes equality in distribution. Under conditional independence, the current and external control data can be pooled together to estimate $E[Y|T = 0, X]$. In practice, conditional independence may not hold due to unmeasured confounding covariates. Our objective is to capture the discrepancy in $[Y|T = 0, X]$ across data sources by modeling the relationship among $Y$, $X$, and $S$ for the control data. Details on the model specification are presented next in Section 2.2.

### 2.2 Model specification via BART

We specify probability models separately for the control and treatment groups in very general forms,

$$[Y|T = 0, X = x, S = s] = f_0(x, s) + \epsilon_0, \quad \text{and}$$

$$[Y|T = 1, X = x, S = 0] = f_1(x) + \epsilon_1,$$

(2)
where $\varepsilon_0 \sim N(0, \sigma_0^2)$ and $\varepsilon_1 \sim N(0, \sigma_1^2)$ are Gaussian errors. Therefore,

$$\delta(x) = f_1(x) - f_0(x, 0).$$  \hfill (3)

In principle, one may use any method that flexibly estimates $f_0$ and $f_1$. Here we choose BART for its many attractive features discussed in Section 1.

Following the default BART model specification, we model $f_0$ and $f_1$ as sums-of-trees,

$$f_0(x, s) = \sum_{j=1}^{m_0} g(x, s; T_{0j}, M_{0j}) \quad \text{and} \quad f_1(x) = \sum_{j=1}^{m_1} g(x; T_{1j}, M_{1j}),$$  \hfill (4)

where $T_{0j}$ and $T_{1j}$ are binary trees, $M_{0j}$ and $M_{1j}$ are sets of parameters associated with the terminal nodes of the trees, and $g(\cdot)$ is a function that maps $(x, s)$ to a parameter in $\mathcal{M}$ based on $\mathcal{T}$. This will be clear next. We use $f_0$ as an example to explain the sum-of-trees model, and the model for $f_1$ follows the same logic, although information borrowing is not necessary for the treatment arm. It is helpful to establish notation for a single tree model first. Let $T_0$ denote a binary tree. Each interior node of $T_0$ represents a decision rule, through which an $(x, s)$ pair is sent either left or right and eventually to a terminal node. The terminal nodes define a partition of the $(x, s)$ space into subspaces. Next, assume the $k$th terminal node is associated with a parameter $\mu_k$, which represents the mean response of the subgroup of observations that fall in that node. Let $\mathcal{M}_b = \{\mu_0, \mu_0, \ldots, \mu_b\}$ denote the set of such parameters, where $b$ is the number of terminal nodes. Given the tree model $(T_0, \mathcal{M}_b)$ and a pair of observations $(x, s)$, $g(x, s; T_0, \mathcal{M}_b)$ is defined as a single parameter value $\mu$ associated with the terminal node to which $(x, s)$ belongs. The left panel in Figure 1A shows an example of a tree model $(T_0, \mathcal{M}_b)$ with a one-dimensional $x$ and a binary $s$, that is, one covariate and one external data source ($s \in \{0, 1\}$). The decision rules in the figure are the criteria for sending an $(x, s)$ pair to the left branch. In this example, we have $g(0.5, 0; T_0, \mathcal{M}_b) = 0.694$.

The tree model adaptively pools information between the current trial and external data. To see this, we consider two hypothetical trial examples with one covariate and a single external data source. In Example 1, we generate control outcomes (30 in the current trial, and 70 in the external data) as follows: $X | S = 0 \sim N(0.7, 0.2^2)$, $X | S = 1 \sim N(0.3, 0.4^2)$, and $Y(0) | X \sim N(1 - X^2, 0.1^2)$. Here, the distributions of $X$ in the current trial and external data are different. This is typical, as a clinical trial usually has inclusion/exclusion criteria to enroll patients that are more likely to benefit from the new treatment, while the external data may contain observations from a wider population. The control outcome is assumed to be conditionally independent of data source. In Example 2, the only difference is that the control outcomes in the external data are generated from $Y(0) | X, S = 1 \sim N(1.4 - 1.2X^2, 0.1^2)$, indicating the control outcome and data source are not conditionally independent. A simulated dataset under Example 1 is illustrated in Figure 1A, as well as the fitted single tree model. The data source indicator $s$ does not appear in the decision rules, meaning the tree model is able to determine that the control outcome is conditionally independent of data source for all $x$ values. All the $\mu$ values are estimated by pooling the trial and external data. Figure 1B shows a simulated dataset under Example 2. The tree model in this case is able to identify some discrepancy across data sources. For the area of $x$ with the most different control outcomes and a sufficient amount of data, the $\mu$ values are estimated separately for the current trial and external data. For the areas of $x$ with similar control outcomes or less data, the $\mu$ values are still estimated by pooling the trial and external data. In summary, a regression tree model allows partial data pooling, adaptively improving the precision of the parameter estimates.

Compared to a single tree model, a sum-of-trees model usually leads to better model fit and predictive capability. This is why model (4) consists of $m_0$ and $m_1$ trees. The idea is the following: consider first fitting a single tree model to a dataset, denoted by $g(x, s; T_{01}, M_{01})$. The residuals can be calculated from $y - g(x, s; T_{01}, M_{01})$, and one can then fit the next tree model to these residuals. Repeating this procedure $m_0$ times, we get a total of $m_0$ trees. See Chipman et al.\textsuperscript{24} for more details. Since each subtree allows partial information pooling, the sum-of-trees model also allows so. Figure 2 provides an illustration of a sum-of-trees model fit to the simulated dataset in Example 1, which nicely captures the covariate-outcome relationship.

The BART model also consists of a set of regularization priors over the tree parameters, which keeps the effect of each subtree small and further improves its performance. For example, for each binary tree $\mathcal{T}$, the probability that a node at depth $d \in \{0, 1, 2, \ldots\}$ is nonterminal is given by $\rho(1 + d)^{-\kappa}$. By default, $\rho = 0.95$ and $\kappa = 2$, which penalize deep and bushy trees. The distributions on the splitting variable assignment and the splitting rule assignment conditional on the splitting variable are given uniform priors. The numbers of subtrees, $m_0$ and $m_1$, are prespecified with a default value of...
FIGURE 1  Single tree fits to two sets of simulated data. In the conditionally independent case, the tree model automatically pools the trial and external control data. When conditional independence is violated, the tree model automatically performs partial pooling [Colour figure can be viewed at wileyonlinelibrary.com]

200. The μ’s are given normal conjugate priors. Lastly, conjugate inverse-gamma distribution priors are placed on σ_0^2 and σ_1^2, the parameters of which are calibrated based on the residual standard deviations from least squares. Refer to Chipman et al [24] for more details.

In Chipman et al [24] a Markov chain Monte Carlo algorithm is employed to implement posterior inference for a BART model. In particular, the algorithm generates L draws from the joint posterior distribution of the model parameters,

\[ \{(T_{01}^{(c)}, \mathcal{M}_{01}^{(c)}), \ldots, (T_{0m_n}^{(c)}, \mathcal{M}_{0m_n}^{(c)}), \sigma_0^{(c)} | \ell = 1, 2, \ldots, L \} \quad \text{and} \quad \{(T_{11}^{(c)}, \mathcal{M}_{11}^{(c)}), \ldots, (T_{1m_1}^{(c)}, \mathcal{M}_{1m_1}^{(c)}), \sigma_1^{(c)} | \ell = 1, 2, \ldots, L \}. \]

For a specific patient in the current trial (s = 0) with covariate values \( x^* \), the posterior samples of \( f_0(x^*, 0) \) and \( f_1(x^*) \) can be, respectively, calculated based on

\[
\begin{align*}
\hat{f}_0^{(c)}(x^*, 0) &= \sum_{j=1}^{m_0} g(x; s; T_{0j}^{(c)}, \mathcal{M}_{0j}^{(c)}) \\
\hat{f}_1^{(c)}(x^*) &= \sum_{j=1}^{m_1} g(x; T_{1j}^{(c)}, \mathcal{M}_{1j}^{(c)}).
\end{align*}
\]
The posterior samples of the conditional treatment effect at \( x^* \), \( \delta(x^*) \), are given by \( \delta^{(\ell)}(x^*) = f^{(\ell)}(x^*) - f^{(0)}(x^*, 0) \) for \( \ell = 1, 2, \ldots, L \) (see Equation 3). Figure 2 (right panel) shows for a simulated dataset the posterior credible intervals of the conditional treatment effects (vertical line segments) evaluated at the \( x^* \) values of the trial patients.

2.2.1 Estimation of the CATE

Let \( \{x_i^* | i : S_i = 0\} \) denote the set of covariates values for the patients in the current trial. From Equation (1), the posterior samples of \( \Delta_c^{(\ell)} \) can be calculated by \( \Delta_c^{(\ell)} = \sum_{i:S_i=0} \delta^{(\ell)}(x_i^*) / N_{\text{trial}} \). The sample mean of \( \{\Delta_c^{(\ell)} : \ell = 1, \ldots, L\} \) approximates the posterior mean of \( \Delta_c \), and the sample quantile of \( \{\Delta_c^{(\ell)} : \ell = 1, \ldots, L\} \) approximates the quantile of the posterior distribution of \( \Delta_c \).

2.2.2 Estimation of the PATE

If the goal is to estimate the PATE, the distribution of patient characteristics in the trial population, \( [X | S = 0] \), also needs to be modeled. In this case, we propose to use the Bayesian bootstrap prior. We assume that \( X \) can only take the (discrete) values in \( \{x_i^* | i : S_i = 0\} \). Further, let \( \zeta_i \) be the probability associated with \( x_i \), that is, \( \Pr(X = x_i^* | S = 0) = \zeta_i \), and \( \sum \zeta_i = 1 \). With a Dirichlet distribution prior on the vector of \( \zeta_i \)'s, its posterior distribution is also a Dirichlet distribution. By drawing \( L \) posterior samples of the \( \zeta_i \)'s, the posterior samples of \( \Delta_p \) can be calculated by \( \Delta_p^{(\ell)} = \sum_{i:S_i=0} \left[ \zeta_i^{(\ell)} \delta^{(\ell)}(x_i^*) \right] \).

3 SIMULATION STUDIES

We conduct several simulation studies to evaluate the operating characteristics of the proposed BART method. We focus on the estimation of the CATE, because the true PATE can be hard to compute in general as it can involve complicated multiple integral (see Equation 1), making it challenging to check how the estimated PATE deviates from the truth. In Section 3.1, we consider scenarios with a single external data source \( (J = 1) \) under the assumption of conditional independence (of the control outcome and data source). In practice, it is common that only a single external data source is available for borrowing. In Section 3.4, we explore scenarios in which conditional independence is violated. In Section 3.5, we examine the performance of the proposed method with multiple external data sources \( (J > 1) \). In all simulation scenarios, we assume that the individuals in the current study are randomized to treatment and control, and those in the external data are all treated by the control drug.
3.1 Simulation setup

We first consider the following five simulation scenarios, under which the true data-generating models satisfy conditional independence. For each scenario, assume 50 individuals are enrolled in the current study, and data of 200 individuals from a single external data source \((J = 1)\) are available.

3.1.1 Scenario 1: Nonlinear response surfaces, heterogeneous treatment effects

We consider an illustrative example with a one-dimensional covariate \(X\). We assume the distributions of \(X\) in the current trial and external data are different, which is common in practice. Specifically, we generate \(X\) as follows,

\[
X \mid S = 0 \sim N(0.7, 0.2^2) \quad \text{and} \quad X \mid S = 1 \sim N(0.3, 0.4^2).
\]

The treatment assignment in the current trial is random,

\[
T \mid S = 0 \sim \text{Ber}(0.5).
\]

Lastly, we assume the outcome has a nonlinear relationship with \(X\), generated from

\[
Y \mid T, X \sim N \left(1 - 0.16T + T(X - 1)^2 - (1 - T)X^2, \ 0.1^2\right).
\]

The true CATE depends on the generated covariate values, and the true PATE is \(E[E[Y(1) - Y(0) \mid X, S = 0]] = 0.5\). Illustrations of the simulated data can be found in Figures 1 and 2.

3.1.2 Scenario 2: Nonlinear response surface for the control arm, heterogeneous treatment effects

We consider a scenario with \(Q = 4\) covariates, which are generated by first drawing

\[
(X_1, X_2, X_3, X_4) \mid S = 0 \sim N_4(\mu_{X_0}, \sigma_{X_0}^2 \Omega_X),
\]

\[
(X_1, X_2, X_3, X_4) \mid S = 1 \sim N_4(\mu_{X_1}, \sigma_{X_1}^2 \Omega_X),
\]

and then setting \(X_4 \sim \text{Ber}[\Phi(X_4 - 0.5)]\) for both groups, where \(\Phi\) denotes the cumulative distribution function of the standard normal distribution. In this way, we obtain a combination of continuous and binary covariates, similar to the real-data application. Here, \(N_Q(\cdot, \cdot)\) denotes a \(Q\)-variate normal distribution, \(\mu_{X_0} = (0.7, \ldots, 0.7)\), \(\sigma_{X_0} = 0.2\), \(\mu_{X_1} = (0.3, \ldots, 0.3)\), \(\sigma_{X_1} = 0.4\), and \(\Omega_X\) is a correlation matrix with off-diagonal elements randomly sampled from \((0.1, 0.4, 0.7, -0.3)\) with probabilities \((0.4, 0.3, 0.1, 0.2)\). The distributions of \(X\) in the current trial and external data have some overlap but are not identical.

The treatment and control outcomes are generated, respectively, as follows,

\[
Y \mid T = 1, X \sim N \left(X^T \beta_1 + 5, 0.5^2\right),
\]

\[
Y \mid T = 0, X \sim N \left(\exp(X^T \beta_0), 0.5^2\right).
\]

As a result, the conditional treatment effect \(\delta(X) = E[Y \mid T = 1, X, S = 0] - E[Y \mid T = 0, X, S = 0]\) is a nonlinear function of \(X\). This scenario mimics the example in Section 4.1 of Hill\(^{25}\) and is designed to evaluate the performance of BART in the presence of nonlinear and heterogeneous treatment effects. The coefficients in \(\beta_1\) and \(\beta_0\) are randomly sampled from two possible values \((0.1, 0.7)\) with probabilities \((0.3, 0.7)\), respectively. Here, a regression coefficient of 0.1 (or 0.7) represents a relatively weak (or strong) impact of the corresponding covariate on \(Y\). The true CATE depends on the generated covariate values, and the true PATE in this case is hard to compute as it involves complicated multiple integral.
3.1.3 Scenario 3: Nonlinear response surfaces, homogeneous treatment effects

We consider a scenario with the inclusion of ordinal and categorical covariates. Specifically, we first generate

\[
(X_1, \tilde{X}_2, X_{3,0}, \tilde{X}_{3,1}, \tilde{X}_{3,2}) | S = 0 \sim N_5(\mu_{X0}, \sigma_{X0}^2 \Omega_X),
\]

\[
(X_1, \tilde{X}_2, X_{3,0}, \tilde{X}_{3,1}, \tilde{X}_{3,2}) | S = 1 \sim N_5(\mu_{X1}, \sigma_{X1}^2 \Omega_X),
\]

set \( S = I(\tilde{X}_2 \geq 0.2) + I(\tilde{X}_2 \geq 0.6) \), and then draw \( X_3 \in \{0, 1, 2\} \) with \( \Pr(X_3 = k) = \exp(\tilde{X}_{3,k})/\sum_{j=0}^{\text{probabilities}} \exp(\tilde{X}_{3,j}) \), where \( I(\cdot) \) is an indicator function. In this way, we obtain a combination of continuous \((X_1)\), ordinal \((X_2)\), and categorical \((X_3)\) variables. The parameters \( \mu \)'s, \( \sigma \)'s, and \( \Omega \)'s are determined in the same way as in Scenario 2.

The outcomes are generated from

\[
Y | T, X \sim N \left( \tilde{X}^T \beta + \tilde{X}_{\text{int}}^T \beta_{\text{int}} + T, \ 0.3^2 \right).
\]

Here, \( \tilde{X} = (X_1, \sin(3X_1), \tilde{X}_2, X_{3,1}, \tilde{X}_{3,2})^T \), and \( \tilde{X}_{\text{int}} \) includes all possible first-order interactions among the variables in \( \tilde{X} \). The indicator variables \( \tilde{X}_{3,k} \)'s represent the categories of \( X_3 \), that is, \( \tilde{X}_{3,k} = 1 \) if \( X_3 = k \) and 0 otherwise, treating \( X_3 = 0 \) as the reference category. The inclusion of \( \sin(3X_1) \) and \( \tilde{X}_{\text{int}} \) creates nonlinear and nonmonotonic response surfaces and is again meant to test the performance of BART. The coefficients in \( \beta \) are randomly sampled from \((0.1, 0.7)\) with probabilities \((0.3, 0.7)\), and those in \( \beta_{\text{int}} \) are sampled from \((0, 0.4)\) with probabilities \((0.3, 0.7)\). Since the response surfaces are parallel across the treatment and control arms, the treatment effects are homogeneous, and both the true CATE and PATE equal 1.

3.1.4 Scenario 4: Linear response surfaces, homogeneous treatment effects

We consider a scenario where the treatment and control outcomes have a linear relationship with the covariates. First, a combination of continuous, ordinal, and categorical covariates are generated as in Scenario 3. Next, the outcomes are generated from

\[
Y | T, X \sim N \left( 0.2 + 0.1T + \tilde{X}^T \beta, \ 0.1^2 \right),
\]

where \( \tilde{X} = (X_1, \tilde{X}_2, \tilde{X}_{3,1}, \tilde{X}_{3,2})^T \), and \( \tilde{X}_2 \) and \( \tilde{X}_{3,k} \)'s are defined as in Scenario 3. The coefficients in \( \beta \) are randomly sampled from two possible values \((0.1, 0.7)\) with probabilities \((0.3, 0.7)\), respectively. The true CATE and true PATE are both 0.1 and do not depend on the empirical distribution of \( X \).

3.1.5 Scenario 5: Flat response surfaces, homogeneous treatment effects

We further simplify Scenario 4 and consider a scenario where the treatment and control outcomes have no relationship with the covariates, and the distributions of \( X \) are the same between the current trial and external data. The goal of Scenarios 4 and 5 is to assess the loss of efficiency from using an unnecessarily complex modeling approach. Similar to Scenario 2, consider \( Q = 4 \) covariates. For both the current trial and external data, the covariates are generated by first drawing

\[
(X_1, X_2, X_3, \tilde{X}_4) \sim N_4(\mu_X, \sigma_X^2 \Omega_X),
\]

where \( \mu_X = (0.5, \ldots, 0.5) \), \( \sigma_X = 0.5 \), and \( \Omega_X \) is generated in the same way as in Scenario 2. Then, we sample \( X_4 \sim \text{Ber} \left[ \Phi(2\tilde{X}_4 - 1) \right] \). Finally, the outcomes are generated from

\[
Y | T \sim N \left( 0.2 + 0.5T, \ 0.1^2 \right).
\]

The true CATE and true PATE are both 0.5 and do not depend on the empirical distribution of \( X \).
3.2 Competing methods and performance metrics

We compare the proposed BART method for the response surface of the following form:

1. (HLM) A hierarchical linear model for the responses surface of the following form,

\[
\begin{align*}
[Y | T = 0, X = x, S = s] & \sim N(a_{0s} + x^T \beta_{0s}, \sigma_0^2), \\
[Y | T = 1, X = x, S = 0] & \sim N(a_1 + x^T \beta_1, \sigma_1^2).
\end{align*}
\]

The regression coefficients are given priors

\[
\begin{align*}
a_{0s} & \sim N(\bar{a}_0, \tau_a^2), \quad \beta_{0s} \sim N_Q(\hat{\beta}_0, \text{diag}(\tau_{\hat{\beta}_1}^2, \ldots, \tau_{\hat{\beta}_S}^2)), \quad \sigma_0^2 \sim \text{IG}(v, v), \\
\bar{a}_0 & \sim N(0, 10^2), \quad \hat{\beta}_0 \sim N_Q(0, 10^2 I), \quad \tau^2_{\hat{\beta}_1}, \ldots, \tau^2_{\hat{\beta}_S} \sim \text{IG}(v, v), \\
a_1 & \sim N(0, 10^2), \quad \beta_1 \sim N_Q(0, 10^2 I), \quad \sigma_1^2 \sim \text{IG}(v, v),
\end{align*}
\]

where \( v = 10^{-4} \). Posterior inference for the CATE follows a similar procedure as in Section 2.2.

2. (PPLM) A linear regression model of the form

\[
\begin{align*}
[Y | T = 0, X = x, S = 0] & \sim N \left( (1, x)^T \beta_0, \sigma_0^2 \right), \\
[Y | T = 1, X = x, S = 0] & \sim N \left( (1, x)^T \beta_1, \sigma_1^2 \right).
\end{align*}
\]

We place the following priors on the regression coefficients: \( \sigma_0^2 \sim \text{IG}(v, v), \beta_1 \sim N_{Q+1}(0, 10^2 I), \) and \( \sigma_1^2 \sim \text{IG}(v, v) \). For \( \beta_0 \), we construct a power prior\(^3,^6\) from external data. Suppose there is only a single external data source. The power prior for \( \beta_0 \) is given by \( \pi(\beta_0 | D_E, \eta) \propto L(\beta_0 | D_E)^\eta \pi_0(\beta_0) \), where \( D_E = (y_E, X_E) \) denotes the external data, \( L(\cdot | \cdot) \) is the likelihood function for regression coefficients, \( \pi_0(\beta_0) \) is the initial prior, and \( \eta \in [0, 1] \) represents the weight of the external data. It can be shown\(^38\) that by setting \( \pi_0(\beta_0) \propto 1 \),

\[
\pi(\beta_0 | D_E, \eta) = N \left[ (X_E^T X_E)^{-1} X_E^T y_E, \eta^{-1} \sigma_E^2 (X_E^T X_E)^{-1} \right],
\]

where \( \sigma_E^2 \) is the variance parameter in the regression model for the external data and can be easily estimated using ordinary least squares. The power parameter \( \eta \) can be prespecified or estimated from the data. We follow Ibrahim et al\(^38\) and choose an optimal \( \eta \) value by minimizing a penalized likelihood-type criterion. When there are multiple external datasets, application of the power prior approach requires the selection of multiple power parameters, which can be computationally challenging. Therefore, for simplicity, we limit our comparison with the power prior approach to the scenarios where only one external dataset is present.

3. (NNHM) A normal-normal hierarchical model that does not take into account covariates,

\[
\begin{align*}
[Y | T = 0, S = s] & \sim N(a_{0s}, \sigma_0^2), \\
[Y | T = 1, S = 0] & \sim N(a_1, \sigma_1^2).
\end{align*}
\]

The model parameters are given priors

\[
\begin{align*}
a_{0s} & \sim N(\bar{a}_0, \tau_a^2), \quad \bar{a}_0 \sim N(0, 10^2), \quad \tau_a^2 \sim \text{IG}(v, v), \\
\sigma_0^2 & \sim \text{IG}(v, v), \quad a_1 \sim N(0, 10^2), \quad \sigma_1^2 \sim \text{IG}(v, v).
\end{align*}
\]

Inference for the CATE is based on the posterior distribution of \( (a_1 - a_{00}) \).

4. (VT) The virtual twins method, originally proposed by Foster et al\(^34\) to identify subgroups from randomized clinical trial data, can be adopted to serve the purpose of treatment effect estimation.\(^39\) Specifically, for our application, we use a random forest (RF)\(^40\) to regress \( Y \) against \( (T, X, S, X^T) \), predict the counterfactual outcomes for individuals in the current trial, and then calculate the CATE. The inclusion of covariate-treatment interactions \( X^T \) was recommended by Foster et al\(^34\) and was shown to improve results. Note that an interaction between \( S \) and \( T \) is not necessary for the applications in our setting, because we have assumed that all individuals in the external data received the control,
thus \( S \cdot I(T = 0) \equiv S \) and \( S \cdot I(T = 1) \equiv 0 \). We use out-of-bag estimates\(^{34,39}\) whenever possible and use the bootstrap method\(^{41}\) (resampling with replacement) to evaluate the uncertainty of the CATE estimate, such as its confidence interval. The R package randomForestSRC\(^{42}\) is used to implement the RF algorithm. VT and the proposed BART method share some similarities; for example, both employ flexible regression tree ensembles to model the response surface. A notable difference between the two methods is that by default, VT fits a single model to both treatment groups with the inclusion of covariate-treatment interactions, while the proposed BART method fits a separate model to each treatment group. If desirable, the modeling strategy for either method can easily be modified. It was noted by Lu et al\(^{39}\) that fitting a separate model to each treatment group allows for greater adaptivity.

5. For each of the BART, HLM, and NNHM methods, we also consider a version that does not make use of external data. These are denoted by BART−, HLM−, and NNHM−, respectively. For example, BART− models

\[
Y | T = 0, X = x, S = 0 \sim N \left( f_0(x), \sigma^2_0 \right),

Y | T = 1, X = x, S = 0 \sim N \left( f_1(x), \sigma^2_1 \right),
\]

where \( f_0 \) and \( f_1 \) are sums-of-trees similar to Equation (4). Therefore, external data (those with \( S \geq 1 \)) are ignored in this case.

The performance of the Bayesian methods (BART, HLM, PPLM, and NNHM) is evaluated based on the following metrics:

1. Bias and root mean squared error (RMSE) in estimating the CATE, given by

\[
\text{Bias} = \hat{\Delta}_C - \Delta_{true} \quad \text{and} \quad \text{RMSE} = \sqrt{\frac{1}{L} \sum_{L=1}^{L} \left( \Delta_C^{(L)} - \Delta_{true} \right)^2},
\]

respectively, where \( \Delta_C \) is the posterior mean of \( \Delta_C \).

2. Coverage and length of the 95% credible interval (CI) of \( \Delta_C \).

3. Precision in estimation of heterogeneous effects (PEHE),\(^{25}\) operationalized as

\[
\text{PEHE} = \sqrt{\frac{1}{N_{trial}} \sum_{i: S=0} [\hat{\delta}(x^*_i) - \delta_{true}(x^*_i)]^2},
\]

where \( \hat{\delta}(x^*_i) \) is the posterior mean of \( \delta(x^*_i) \). A smaller PEHE indicates a better capture of heterogeneous treatment effects.

4. Results of the hypothesis tests:

- **Test 1:** \( H_{10} : \Delta_C \leq \Delta_{true} \) vs \( H_{11} : \Delta_C > \Delta_{true} \);
- **Test 2:** \( H_{20} : \Delta_C \leq \Delta_{true} - d \) vs \( H_{21} : \Delta_C > \Delta_{true} - d \).

Here, \( H_{10} \) is rejected if \( \Pr(\Delta_C > \Delta_{true} | \text{data}) > 0.95 \), which is a false positive (type I error); \( H_{20} \) is rejected if \( \Pr(\Delta_C > \Delta_{true} - d | \text{data}) > 0.95 \), which is a true positive (for some \( d > 0 \)). The fraction of times \( H_{10} \) is rejected reflects the type I error rate of a method, while that for \( H_{20} \) reflects the power. We set \( d = 0.08 \) for Scenarios 1, 4, and 5, and \( d = 0.25 \) for Scenarios 2 and 3. These values are chosen to facilitate the comparison of the powers for different methods.

For the VT method, the posterior means are replaced by the corresponding point estimates given by RF prediction, the posterior samples are replaced by the bootstrap samples, the credible intervals are replaced by the confidence intervals, and \( H_{10} \) (or \( H_{20} \)) is rejected if the 95% lower one-sided confidence bound for \( \Delta_C \) is greater than \( \Delta_{true} \) (or \( \Delta_{true} - d \)).

### 3.3 Simulation results

For each simulation scenario, we generate 500 datasets and fit the eight models to each dataset. For each method, we run MCMC simulation for 1100 iterations with the first 100 draws discarded as burn-in.
Table 1 summarizes the simulation results. The values are averages over repeated simulations. Under Scenarios 1 and 2, the CATE slightly differs for each simulated dataset, because each time a distinct set of covariate values are generated. The average CATE over repeated simulations is also reported in Table 1. The average CATE, bias, RMSE, CI length, and PEHE have been multiplied by 100 to facilitate comparison between methods.

Scenarios 1 and 2 embody nonlinear response surfaces and heterogeneous treatment effects. Under these scenarios, the BART method has the best overall performance in terms of the lowest RMSE and PEHE, shortest CI length, and highest power. Scenario 3 has nonlinear response surfaces and homogeneous treatment effects, and BART still outperforms the other methods in most aspects under this scenario. The NNHM and NNHM methods have the lowest PEHE under Scenario 1, because their modeling assumption of homogeneous treatment effects is consistent with the simulation truth. Under Scenarios 4 and 5, the response surfaces are linear and parallel across treatment groups, leading to homogeneous treatment effects. The strong parametric assumptions implicit in HLM and PPLM are satisfied under Scenario 4, and those of NNHM are satisfied under Scenario 5. Therefore, the models consistent with the data-generating processes are expected to perform the best. Specifically, PPLM outperforms the other methods, but the performance of BART is still comparable with that of HLM and NNHM. Lastly, VT outperforms BART under Scenario 4 but is worse than BART under the other scenarios.

The CI coverage and type I error rate of BART do not give rise to concerns under any of the five scenarios. An exact match with the nominal frequentist coverage probability is not expected as BART is a Bayesian method. PPLM, however, has much lower than nominal coverage under Scenario 1 and an inflated type I error rate under Scenario 3. In summary, BART has robust performance across scenarios, while the performance of PPLM, HLM, and NNHM is sensitive to violations of modeling assumptions. In practice, if it is believed that the response surface has a particular parametric form (eg, a linear model), the corresponding parametric model can be used. Without such prior knowledge, the BART method is preferable, especially when the response surface is expected to be nonlinear.

Since the current trial is randomized and controlled, methods ignoring external data (BART, HLM, and NNHM) can estimate the CATE with nearly no bias. By adjusting for prognostic and predictive covariates, the BART and HLM methods have higher power in Scenarios 1 to 4 compared to NNHM. Furthermore, since the control outcome is conditionally independent of data source, borrowing from external control data should ideally improve the estimation of the CATE. However, we can see this is only the case for BART but not for HLM and NNHM. First, note that in Scenarios 1 to 4, the control outcome is not marginally independent of data source when not conditioning on the covariates. Therefore, the NNHM method, which does not adjust for covariates, has higher bias and potentially lower power in Scenarios 1 to 4 compared to NNHM. Second, in Scenarios 1 to 3, the relationships between the covariates and control outcomes are nonlinear. Therefore, the HLM method, which shrinks the slope and intercept coefficients based on a linear model, also does not compare favorably to HLM in these scenarios.

### 3.4 Violation of conditional independence

We conduct additional simulation studies to assess the performance of the proposed BART method when the control outcome is not conditionally independent of data source. Specifically, in Scenario 1, we now generate the external control outcome from

\[ Y \mid T = 0, X, S = 1 \sim N \left( 1.4 - 1.2X^2, \ 0.1^2 \right) . \]

In Scenario 2, we use a modified model to generate

\[ Y \mid T = 0, X, S = 1 \sim N \left( \exp[X^\top (\beta_0 + \beta_0^{\text{diff}})], \ 0.5^2 \right) , \]

where \( \beta_0^{\text{diff}} \) introduces discrepancies between current and external control outcomes. When \( \beta_0^{\text{diff}} \neq 0 \), the control outcome is not conditionally independent of data source. We randomly sample the coefficients in \( \beta_0^{\text{diff}} \) from \((0.2, -0.2, 0)\) with probabilities \((0.3, 0.3, 0.4)\), conditioning on \( \beta_0^{\text{diff}} \neq 0 \). In Scenario 3, we now generate

\[ Y \mid T = 0, X, S = 1 \sim N \left( a^{\text{diff}} + X^\top (\beta + \beta^{\text{diff}}) + X^\top \beta_{\text{int}}, \ 0.3^2 \right) , \]
TABLE 1 Simulation results under the five simulation scenarios with a single external data source under the assumption of conditional independence

| Method  | Bias  | RMSE | % Cover | CI length | PEHE | % Rej. 1 | % Rej. 2 |
|---------|-------|------|---------|-----------|------|----------|----------|
| Scenario 1 (Avg. CATE = 50.10) | | | | | | | |
| BART | $-0.49$ | 4.27 | 95.8 | 13.00 | 8.05 | 2.2 | 77.6 |
| HLM | 0.18 | 6.00 | 100.0 | 20.73 | 13.20 | 0.2 | 45.8 |
| PPLM | $-1.74$ | 5.18 | 83.8 | 13.22 | 18.29 | 2.4 | 60.8 |
| NNHM | $-2.52$ | 10.49 | 96.4 | 31.44 | 20.40 | 1.0 | 14.4 |
| VT | $-4.15$ | 6.40 | 78.8 | 14.29 | 11.68 | 0.0 | 12.2 |
| BART− | $-0.53$ | 4.81 | 93.8 | 14.08 | 11.79 | 3.4 | 71.4 |
| HLM− | $-0.45$ | 4.29 | 95.8 | 13.33 | 11.03 | 1.6 | 76.0 |
| NNHM− | $-0.21$ | 9.29 | 96.0 | 28.26 | 20.08 | 2.6 | 26.2 |
| Scenario 2 (Avg. CATE = 152.48) | | | | | | | |
| BART | 0.51 | 20.65 | 94.2 | 56.51 | 35.52 | 6.2 | 55.6 |
| HLM | $-2.45$ | 22.51 | 95.4 | 65.33 | 45.98 | 3.6 | 39.8 |
| PPLM | 4.22 | 23.83 | 97.2 | 70.78 | 55.56 | 5.6 | 52.4 |
| NNHM | 4.71 | 40.57 | 94.4 | 115.33 | 155.10 | 7.0 | 26.6 |
| VT | $-4.01$ | 36.31 | 98.2 | 115.20 | 62.59 | 0.4 | 5.0 |
| BART− | $-0.91$ | 22.43 | 93.6 | 61.30 | 48.98 | 5.6 | 48.2 |
| HLM− | $-1.21$ | 22.35 | 96.0 | 65.88 | 40.59 | 3.8 | 43.0 |
| NNHM− | 1.36 | 47.23 | 98.6 | 150.76 | 154.94 | 2.0 | 10.2 |
| Scenario 3 (Avg. CATE = 100.00) | | | | | | | |
| BART | 0.45 | 15.61 | 95.0 | 45.34 | 28.19 | 5.6 | 71.4 |
| HLM | 1.14 | 22.26 | 97.4 | 66.64 | 36.35 | 3.0 | 45.8 |
| PPLM | 6.69 | 20.01 | 93.0 | 57.19 | 47.83 | 12.0 | 72.2 |
| NNHM | 5.09 | 37.81 | 98.4 | 118.96 | 19.39 | 2.2 | 21.2 |
| VT | $-2.87$ | 20.34 | 92.6 | 55.60 | 28.41 | 2.4 | 37.4 |
| BART− | $-0.28$ | 18.10 | 95.4 | 53.02 | 29.13 | 5.0 | 58.0 |
| HLM− | $-0.73$ | 31.79 | 95.6 | 93.01 | 18.34 | 4.4 | 27.2 |
| NNHM− | 0.02 | 15.29 | 95.0 | 44.65 | 9.00 | 5.2 | 17.0 |
| Scenario 4 (Avg. CATE = 10.00) | | | | | | | |
| BART | 0.19 | 5.87 | 97.0 | 17.18 | 10.84 | 4.8 | 57.2 |
| HLM | 0.12 | 7.82 | 97.2 | 19.54 | 7.62 | 3.2 | 58.2 |
| PPLM | 0.14 | 4.72 | 94.0 | 14.08 | 7.66 | 5.4 | 77.8 |
| NNHM | 1.92 | 17.07 | 97.2 | 51.84 | 9.48 | 4.4 | 14.8 |
| VT | $-0.85$ | 4.78 | 93.8 | 13.56 | 7.31 | 1.8 | 65.8 |
| BART− | $-0.06$ | 5.94 | 94.0 | 17.22 | 11.12 | 6.0 | 56.8 |
| HLM− | $-0.16$ | 5.73 | 96.2 | 17.53 | 8.51 | 4.0 | 57.2 |
| NNHM− | $-0.24$ | 15.29 | 95.0 | 44.65 | 9.00 | 5.2 | 17.0 |
| Scenario 5 (Avg. CATE = 50.00) | | | | | | | |
| BART | 0.10 | 3.77 | 95.0 | 10.63 | 4.33 | 5.2 | 90.4 |
| HLM | 0.09 | 3.98 | 96.6 | 11.84 | 5.58 | 3.2 | 87.0 |
| PPLM | 0.03 | 3.17 | 95.4 | 9.31 | 4.84 | 5.4 | 95.8 |
| NNHM | 0.08 | 3.68 | 96.6 | 10.96 | 2.10 | 3.2 | 90.4 |
| VT | $-1.52$ | 3.83 | 87.2 | 10.05 | 6.02 | 0.6 | 74.8 |
| BART− | 0.09 | 3.84 | 93.2 | 10.68 | 4.83 | 6.4 | 90.2 |
| HLM− | 0.10 | 4.22 | 96.6 | 12.59 | 6.52 | 3.6 | 83.8 |
| NNHM− | 0.10 | 3.99 | 97.2 | 11.77 | 2.31 | 4.2 | 87.6 |

Note: Values shown are averages over 500 repeated simulations. The average CATE, bias, RMSE, CI length, and PEHE have been multiplied by 100 to facilitate comparison between methods. % Rej. 1 and % Rej. 2 represent the percentages of times $H_{10}$ and $H_{20}$ are rejected, respectively.
where $\alpha^{\text{diff}} = 0.03$, and the coefficients in $\beta^{\text{diff}}$ are randomly sampled from (0, 0.04) with probabilities (0.7, 0.3). In this case, the differences between current and external control outcomes are small in compare to the standard deviation of the observations. In Scenario 4, we also consider a new generative model given by

$$Y \mid T = 0, X, S = 1 \sim N(0.2 + \alpha^{\text{diff}} + \hat{X}^T(\beta + \beta^{\text{diff}}), 0.1^2),$$

with $\alpha^{\text{diff}} = -0.03$ and $\beta^{\text{diff}}$ determined similarly as in Scenario 3. Finally, in Scenario 5,

$$Y \mid T = 0, S = 1 \sim N(0.4, 0.1^2).$$

The other simulation settings, including the simulated trial data, are kept unchanged. To quantify the degree of heterogeneity between current and external control data, we calculate the CATE discrepancy by

$$\frac{1}{N_{\text{trial}}} \sum_{i, S=0} (E[Y \mid T = 0, X_i, S = 0] - E[Y \mid T = 0, X_i, S = 1]).$$

A positive (or negative) CATE discrepancy means that the CATE calculated based on the response surface of the external control data is greater (or smaller) than that of the current control data. Therefore, borrowing in the presence of a positive (or negative) CATE discrepancy would likely result in an overestimate (or underestimate) of the CATE.

The average CATE discrepancy over repeated simulations under each scenario is reported in Table 2. Since the current trial data remain unchanged, BART–, HLM–, and NNHM– yield identical inference thus are not included in Table 2. In Scenarios 1, 3, and 5, the average CATE discrepancy is negative. Therefore, we can observe a general reduction in power for most methods compared to Table 1. Interestingly, under Scenarios 1 and 3, BART still has better power compared to BART– even in the nonindependent case (with a negative CATE discrepancy). This is because BART is a sum-of-trees model. In the presence of study heterogeneity, while many trees in the summation may not pool information across data sources, partial information borrowing may still be realized by the other trees. For areas of the covariate space in which the trial and external data are relatively homogeneous (in the case of Scenario 1, for $x$ around $\sqrt{2}$), the degree of borrowing is larger. In Scenarios 2 and 4, the average CATE discrepancy is positive. Specifically, in Scenario 2, the CATE discrepancy is large compared to the standard deviation of the observations, and we can observe a general increase in type I error rate for most methods compared to Table 1. Notably, the type I error rate of PPLM inflates to 55.4% in this scenario due to strong borrowing. However, since BART borrows information in a judicious manner, the amount of type I error rate inflation is not severe.

When the CATE discrepancy is relatively small (Scenarios 3 and 4), the performance of all methods is similar to that under the conditionally independent setting (Section 3.3). The strong parametric assumptions of HLM and PPLM are satisfied under Scenario 4, and those of NNHM are satisfied under Scenario 5. Therefore, these methods generally perform well under the two scenarios. However, due to strong borrowing, the decrease in power for PPLM is substantial under Scenario 5 in the presence of a large negative CATE discrepancy. Lastly, VT performs well under Scenario 4 but is not very promising in the other scenarios. In summary, BART still has favorable performance when the control outcome is not conditionally independent of data source.

### 3.5 Multiple external data sources

We examine the performances of the methods with multiple external data sources ($J = 4$). Assume each external data source has data of 50 individuals. The external control data are generated as follows. For Scenario 1,

$$X \mid S \in \{1, 3\} \sim N(0.7, 0.2^2), \quad X \mid S \in \{2, 4\} \sim N(0.3, 0.4^2),$$

$$Y \mid T = 0, X, S \in \{1, 2\} \sim N(1 - X^2, 0.1^2), \quad \text{and}$$

$$Y \mid T = 0, X, S \in \{3, 4\} \sim N(1.4 - 1.2X^2, 0.1^2).$$

For Scenario 2,

$$(X_1, X_2, X_3, \tilde{X}_4) \mid S \in \{1, 3\} \sim N_4(\mu_{X_0}, \sigma_{X_0}^2 \Omega_X),$$

$$(X_1, X_2, X_3, \tilde{X}_4) \mid S \in \{2, 4\} \sim N_4(\mu_{X_1}, \sigma_{X_1}^2 \Omega_X).$$
### Simulation results under the five simulation scenarios with a single external data source, assuming violation of conditional independence

| Method | Bias | RMSE | % Cover | CI length | PEHE | % Rej. 1 | % Rej. 2 |
|--------|------|------|---------|-----------|------|----------|----------|
| Scenario 1 (Avg. CATE = 50.10, CATE discrepancy = −29.35) |
| BART  | −0.47 | 4.38 | 96.8    | 13.44     | 8.46 | 2.0      | 75.8     |
| HLM   | −0.51 | 6.65 | 100.0   | 23.48     | 11.72| 0.0      | 23.2     |
| PPLM  | −7.81 | 9.43 | 64.0    | 16.13     | 15.33| 0.0      | 19.8     |
| NNHM  | −1.33 | 10.75| 99.0    | 34.56     | 20.15| 0.4      | 12.0     |
| VT    | −7.86 | 9.63 | 35.8    | 15.23     | 14.81| 0.0      | 1.0      |
| Scenario 2 (Avg. CATE = 152.48, CATE discrepancy = 113.91) |
| BART  | 0.94  | 20.94| 91.0    | 55.83     | 40.46| 8.8      | 56.4     |
| HLM   | −1.64 | 21.92| 94.6    | 62.21     | 45.95| 5.2      | 44.6     |
| PPLM  | 39.72 | 48.53| 62.2    | 95.94     | 95.14| 55.4     | 90.6     |
| NNHM  | −4.86 | 37.52| 98.2    | 119.57    | 69.33| 0.4      | 7.2      |
| VT    | −4.39 | 20.27| 91.6    | 54.86     | 28.53| 2.0      | 37.0     |
| Scenario 3 (Avg. CATE = 100.00, CATE discrepancy = −8.54) |
| BART  | 0.40  | 15.59| 95.0    | 45.36     | 28.63| 4.8      | 70.6     |
| HLM   | 1.02  | 22.42| 97.6    | 67.35     | 36.32| 3.0      | 44.0     |
| PPLM  | 4.95  | 19.52| 94.0    | 56.82     | 46.56| 9.6      | 68.4     |
| NNHM  | 5.73  | 38.38| 94.6    | 120.91    | 19.63| 2.0      | 21.0     |
| VT    | −4.39 | 20.27| 91.6    | 54.86     | 28.53| 2.0      | 37.0     |
| Scenario 4 (Avg. CATE = 10.00, CATE discrepancy = 0.20) |
| BART  | 0.18  | 5.95 | 97.0    | 17.92     | 10.93| 4.0      | 54.6     |
| HLM   | 0.19  | 7.90 | 97.4    | 19.89     | 7.82 | 3.0      | 57.2     |
| PPLM  | 0.34  | 4.76 | 93.8    | 14.17     | 8.14 | 5.8      | 78.4     |
| NNHM  | 1.89  | 17.16| 97.8    | 52.32     | 9.46 | 3.6      | 14.2     |
| VT    | −0.79 | 4.80 | 93.8    | 13.64     | 7.34 | 2.4      | 66.8     |
| Scenario 5 (Avg. CATE = 50.00, CATE discrepancy = −20.00) |
| BART  | −0.40 | 3.82 | 93.4    | 10.75     | 4.52 | 3.0      | 86.6     |
| HLM   | −0.16 | 4.14 | 95.8    | 12.18     | 5.78 | 3.0      | 83.8     |
| PPLM  | −19.42| 19.57| 0.0     | 9.38      | 19.97| 0.0      | 0.0      |
| NNHM  | −0.11 | 3.95 | 95.6    | 11.55     | 2.32 | 3.8      | 86.4     |
| VT    | −3.01 | 5.02 | 71.2    | 10.85     | 6.89 | 0.2      | 43.4     |

Note: Values shown are averages over 500 repeated simulations. The average CATE, bias, RMSE, CI length, and PEHE have been multiplied by 100 to facilitate comparison between methods. % Rej. 1 and % Rej. 2 represent the percentages of times $H_{10}$ and $H_{20}$ are rejected, respectively.

\[
Y | T = 0, X, S \in \{1, 2\} \sim N(\exp(X^T \beta_0), \sigma^2) \text{, and} \]
\[
Y | T = 0, X, S \in \{3, 4\} \sim N(\exp(X^T (\beta_0 + \delta_0)), \sigma^2) \text{.}
\]

For Scenario 3,
\[
(X_1, \tilde{X}_2, \tilde{X}_3, X_4, \tilde{X}_5) | S \in \{1, 3\} \sim N_5(\mu_X, \sigma^2_X \Omega), \]
\[
(X_1, \tilde{X}_2, \tilde{X}_3, X_4, \tilde{X}_5) | S \in \{2, 4\} \sim N_5(\mu_{X1}, \sigma^2_X \Omega_X),
\]
\[ Y \mid T = 0, X, S \in \{ 1, 2 \} \sim N \left( \tilde{X}^T \beta + \tilde{X}_{\text{int}}^T \beta_{\text{int}}, 0.3^2 \right), \text{ and} \]
\[ Y \mid T = 0, X, S \in \{ 3, 4 \} \sim N \left( \alpha_{\text{diff}} + \tilde{X}^T (\beta + \beta_{\text{diff}}) + \tilde{X}_{\text{int}}^T \beta_{\text{int}}, 0.3^2 \right). \]

For Scenario 4,
\[ (X_1, \tilde{X}_2, \tilde{X}_{3,0}, \tilde{X}_{3,1}, \tilde{X}_{3,2}) \mid S \in \{ 1, 3 \} \sim N_d(\mu_{X_0}, \sigma^2_{X_0} \mathbf{I}_X), \]
\[ (X_1, \tilde{X}_2, \tilde{X}_{3,0}, \tilde{X}_{3,1}, \tilde{X}_{3,2}) \mid S \in \{ 2, 4 \} \sim N_d(\mu_{X_1}, \sigma^2_{X_1} \mathbf{I}_X), \]
\[ Y \mid T = 0, X, S \in \{ 1, 2 \} \sim N \left( 0.2 + \tilde{X}^T \beta, 0.1^2 \right), \text{ and} \]
\[ Y \mid T = 0, X, S \in \{ 3, 4 \} \sim N \left( 0.2 + \alpha_{\text{diff}} + \tilde{X}^T (\beta + \beta_{\text{diff}}), 0.1^2 \right). \]

Lastly, for Scenario 5,
\[ (X_1, X_2, X_3, \tilde{X}_4) \sim N_d(\mu_X, \sigma^2_X \mathbf{I}_X), \]
\[ Y \mid T = 0, S \in \{ 1, 2 \} \sim N \left( 0.2, 0.1^2 \right), \text{ and} \]
\[ Y \mid T = 0, S \in \{ 3, 4 \} \sim N \left( 0.4, 0.1^2 \right). \]

The other simulation settings, including the simulated trial data, are kept unchanged. From the data-generating process, we can see that \([Y \mid T = 0, X, S = 0] \overset{d}{=} [Y \mid T = 0, X, S = s]\) holds for \(s \in \{1, 2\}\) but not for \(s \in \{3, 4\}\). In this way, we get a mixture of control data that are conditionally independent of data sources and those that are not.

The BART, HLM, NNHM, and VT methods can readily accommodate multiple external data sources. The PPLM method requires additional calibration to handle multiple external data sources thus is not included in the comparison. Table 3 summarizes the simulation results. The performances of the methods remain similar to those under the previous settings. Under Scenarios 1 to 3, BART outperforms the other methods in most aspects. The strong parametric assumptions of HLM and NNHM are satisfied under Scenarios 4 and 5, respectively, thus these methods slightly outperform BART in the corresponding scenarios. Lastly, VT performs well under Scenario 4 but is not very promising in the other scenarios.

### 3.6 Summary

The simulation results presented in Sections 3.3 to 3.5 suggest that BART maintains desirable and robust performance across a variety of scenarios. The CI coverage and type I error rate of BART also do not give rise to concerns in all scenarios. Methods that outperform BART in some scenarios (e.g., PPLM) typically suffer from undesirable CI coverage, power, or type I error rate in other scenarios. To summarize, BART is an appealing and reliable method for external borrowing and is well-suited for real-world applications when there is little knowledge regarding the parametric form of the response surface or whether the control outcome is conditionally independent of data source.

### 4 Application to an Acupuncture Trial

We illustrate the practical application of the proposed method based on the randomized controlled trial of acupuncture in Vickers et al.\textsuperscript{43} The trial used randomized minimization to allocate 401 headache patients to an acupuncture group (205 patients) and a control group (standard care, 196 patients). Patients randomized to acupuncture received acupuncture treatments over three months in addition to standard care. Several outcome measures, such as the headache score on a 0 to 100 scale, were assessed at baseline, 3, and 12 months. A total of 161 patients in the acupuncture arm and 140 patients in the control arm completed the 12-month follow-up. The available baseline characteristics of the patients were age, sex, headache type (tension or migraine), and number of years of headache disorder (chronicity). The patient-level data of this trial were made available by Vickers.\textsuperscript{44}
Table 3 | Simulation results under the five simulation scenarios with four external data sources

| Method | Bias | RMSE | % Cover | CI length | PEHE | % Rej. 1 | % Rej. 2 |
|--------|------|------|---------|-----------|------|----------|----------|
| **Scenario 1 (Trial CATE = 50.10)** | | | | | | | |
| BART | -0.28 | 4.32 | 94.2 | 12.63 | 8.47 | 5.2 | 76.8 |
| HLM | -0.27 | 5.39 | 99.8 | 17.99 | 11.08 | 0.6 | 51.2 |
| NNHM | -1.71 | 9.96 | 98.0 | 30.38 | 20.18 | 2.0 | 15.4 |
| VT | -6.43 | 8.48 | 53.0 | 15.20 | 11.73 | 0.0 | 2.2 |
| **Scenario 2 (Trial CATE = 152.48)** | | | | | | | |
| BART | 0.79 | 20.37 | 92.4 | 56.67 | 36.24 | 7.0 | 56.0 |
| HLM | -0.91 | 21.41 | 95.0 | 62.98 | 45.09 | 3.4 | 43.4 |
| NNHM | 5.95 | 39.56 | 95.0 | 112.96 | 154.42 | 7.6 | 27.6 |
| VT | 18.74 | 34.26 | 97.8 | 101.89 | 51.47 | 5.0 | 36.8 |
| **Scenario 3 (Trial CATE = 100.00)** | | | | | | | |
| BART | 0.45 | 15.34 | 94.0 | 44.33 | 27.62 | 6.2 | 73.2 |
| HLM | 0.11 | 19.08 | 96.2 | 58.02 | 26.75 | 4.0 | 51.0 |
| NNHM | 3.62 | 33.90 | 97.4 | 103.49 | 18.26 | 3.4 | 27.2 |
| VT | -5.47 | 16.55 | 89.8 | 44.11 | 31.44 | 0.8 | 46.8 |
| **Scenario 4 (Trial CATE = 10.00)** | | | | | | | |
| BART | 0.12 | 5.67 | 95.4 | 16.76 | 10.64 | 5.2 | 58.6 |
| HLM | 0.26 | 5.34 | 96.2 | 16.35 | 7.29 | 4.2 | 65.8 |
| NNHM | 1.54 | 15.72 | 96.8 | 46.97 | 8.93 | 4.4 | 18.0 |
| VT | -1.60 | 4.12 | 88.8 | 11.06 | 7.37 | 0.4 | 73.0 |
| **Scenario 5 (Trial CATE = 50.00)** | | | | | | | |
| BART | -0.34 | 3.83 | 92.0 | 10.54 | 4.35 | 5.4 | 85.6 |
| HLM | -0.18 | 4.15 | 92.6 | 11.86 | 5.30 | 3.8 | 80.8 |
| NNHM | -0.17 | 3.97 | 93.8 | 11.39 | 2.36 | 4.6 | 84.0 |
| VT | -2.67 | 4.73 | 70.2 | 10.13 | 6.50 | 0.2 | 50.8 |

Note: Conditional independence holds for only two of these data sources. Values shown are averages over 500 repeated simulations. The average CATE, bias, RMSE, CI length, and PEHE have been multiplied by 100 to facilitate comparison between methods. % Rej. 1 and % Rej. 2 represent the percentages of times $H_{10}$ and $H_{20}$ are rejected, respectively.

For the purpose of our illustration, we consider the decrease in the headache score at 12 months compared to that at baseline as the primary outcome ($Y$). The covariates ($X$) are baseline headache score, age, sex, headache type, and chronicity, where sex and headache type are binary covariates, and the others are continuous. Also, since our focus is not on the handling of missing data, we only consider the 301 complete cases. To demonstrate the effect of external borrowing, we simulate hypothetical external control data. Our reasons for using simulated external control data (instead of real data) are as follows. First, although many acupuncture trials have been conducted and published, patient-level data are generally not publicly available. Second, by generating synthetic data, we can control the degree to which the external and trial data are commensurate. Assume there is a single external data source with 200 patients. We consider the following three scenarios:

1. (Scenario 1) We generate external control data by mimicking the trial control data, resembling a conditional independent case. In particular, we use the synthpop method,\(^45\) which allows one to generate a synthetic dataset that preserves the essential statistical features of an observed dataset.

2. (Scenario 2) We oversample patients with low baseline headache scores and undersample patients with high baseline headache scores, although the outcome values are generated using the synthpop method by mimicking similar
patients in the trial control data. In other words, the distributions of patient characteristics are different in the trial and external data, although the control outcome is conditionally independent of data source.

3. (Scenario 3) We first generate external control data using the `synthpop` method, and then update the outcomes by

\[
[Y | T = 0, X, S = 1] = \bar{Y} + 5 - 0.05 \cdot \text{baseline headache score},
\]

where \( \bar{Y} \) and \( Y \) stand for the originally generated and updated control outcome values, respectively. In this case, the patient population is similar between the trial and external data, but the control outcome is not conditionally independent of data source.

Figure 3 shows the trial data and simulated external control data under each scenario.

We fit the BART model to the dataset under each scenario. For comparison, we also consider a version of BART that does not make use of external data, that is, the model is fitted to the trial data only. The estimated CATE and its 95% credible interval in each scenario are reported in Table 4. As expected, when external data are available, the BART model can borrow information to achieve more precise estimates. When the control outcome is not conditionally independent of data source, borrowing leads to some deviation of CATE estimate from that obtained from the current trial data alone (see estimated CATE for Scenario 3). Such deviation may be viewed as bias, although the actual bias is unknown as the true CATE is unknown in real examples. But since BART borrows information in a judicious manner, the deviation is not substantial.

An ad hoc permutation test can be performed within the BART modeling framework to evaluate the conditional independent assumption of the control outcome and data source. Specifically, we may permute the data source indicator, thereby destroying the relationship between \( S \) and \( Y \) (given that \( X \) is in the model), fit a new BART model from this permuted design matrix and record how the new model fits the data. The BART model fit can be characterized by the
TABLE 5 Summary of the subset of PRIME data for patients who had known RAS mutation status and had tumor measurements at both baseline and week 8

| Arm                  | Panitumumab + FOLFOX4 | FOLFOX4 alone |
|----------------------|------------------------|---------------|
|                      | Wild-type RAS | Mutant RAS | Wild-type RAS | Mutant RAS |
| Number of patients   | 86          | 92         | 92           | 108         |
| Mean tumor shrinkage at week 8 (mm) | 49.94      | 29.57      | 31.88        | 27.13       |
| Standard deviation (mm) | 48.35    | 41.43      | 39.19        | 35.10       |

pseudo-\(R^2\): \(1 - \sum_i (y_i - \hat{y}_i)^2 / \sum_i (y_i - \bar{y})^2\), where \(\hat{y}_i\) denotes the fitted value of \(y_i\). Repeating this permutation procedure many times, we obtain a null distribution of pseudo-\(R^2\)'s. The \(P\)-value can then be defined as the proportion of null pseudo-\(R^2\)'s greater than the pseudo-\(R^2\) of the BART fit to the original dataset. This is a one-sided test. If the \(P\)-value is small, it is likely that the data source indicator \(S\) is an important predictor for \(Y\), after controlling for \(X\). This permutation test can be easily done using the `cov_importance_test` function in the R package `bartMachine`. The \(P\)-value for the permutation test (based on 100 permutation samples) under each scenario is reported in Table 4. From the results, we can see that \(S\) has a strong effect on \(Y\) under Scenario 3 but not under Scenarios 1 and 2. This is consistent with the simulation truth.

5 APPLICATION TO A COLORECTAL CANCER TRIAL

We consider another application of the proposed method to the planning and design of a colorectal cancer trial. Suppose an investigator is interested in conducting a proof-of-concept trial, comparing a novel anti-epidermal growth factor receptor (EGFR) agent in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) to FOLFOX4 alone in patients with previously untreated metastatic colorectal cancer (mCRC). Suppose the investigator would like to further restrict the trial population to patients with RAS (KRAS or NRAS) wild-type tumors. This is because RAS mutation has been recognized as a negative predictive biomarker for anti-EGFR therapy in patients with mCRC. For the illustration of our method, we consider early tumor shrinkage (measured by the decrease in tumor size from baseline) as the primary outcome, which is a continuous variable. Previous studies have shown early tumor shrinkage to be strongly associated with improved progression-free survival and overall survival outcomes in patients with mCRC.

The PRIME study is a good reference for planning this clinical trial. PRIME is a randomized phase III study in patients with previously untreated mCRC. In this study, 1183 patients were enrolled and randomized to panitumumab + FOLFOX4 (treatment arm, 593 patients) and FOLFOX4 alone (control arm, 590 patients). Tumor size was measured by spiral computed tomography scan at baseline and then every 8 weeks until disease progression. Measurements were based on the sum of the longest diameters (in mm) of measurable target lesions, as identified per central radiology review. A subset of the individual patient data from PRIME was made available on Project Data Sphere at https://doi.org/10.34949/1m76-9m69. Specifically, the publicly available dataset contains 521 patients (260 in the treatment arm and 261 in the control arm) who had at least one measurement of tumor size. We focus on tumor shrinkage at week 8. By restricting the PRIME dataset to patients who had known RAS mutation status and had measurements of tumor sizes at both baseline and week 8, the sample size is further reduced to 378 (178 in the treatment arm and 200 in the control arm). Here, the RAS mutation status is determined by whether a patient had mutations in KRAS/NRAS exons 2/3/4. Table 5 provides a summary of this subset of data.

Since the therapies in the control arms of the new trial and PRIME are identical, it is potentially beneficial to incorporate the control arm data of PRIME into the analysis of the new trial. We perform sample size estimation and power analysis for the new trial, assuming external control data will be incorporated using BART. We also consider the possibility of unequal allocation and compare three treatment:control allocation ratios—1:1, 1.5:1, and 2:1. With additional information about the control arm, more resources may be devoted to the new treatment without sacrificing the power. For a proof-of-concept trial, allocating more patients to the treatment arm allows the investigator to learn more about the mechanism and safety profile of the new therapy. In addition to RAS mutation status and baseline tumor size, the following covariates are also included in our analysis: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, and primary tumor type. Here, the ECOG status is an ordinal scale indicating how severely the disease affects...
the daily living abilities of a patient at baseline, and the primary tumor type is a binary variable (colon or rectal). These covariates are available in the PRIME dataset and should also be measured in the new trial.

We use a bootstrap procedure to implement the power calculation (see, eg, Kleinman and Huang). Suppose the investigator believes that the patient characteristics and outcomes in the new trial will be similar to those among RAS wild-type patients in the PRIME study. Assume \( N_1 \) and \( N_0 \) patients will be enrolled to the treatment and control arms, respectively. The bootstrap power calculation proceeds by iterating the following steps many (say, 1000) times.

1. Generate hypothetical treatment arm data for the new trial by sampling with replacement \( N_1 \) covariate-outcome pairs from the treatment arm data among RAS wild-type patients in PRIME.
2. Generate hypothetical control arm data for the new trial by sampling with replacement \( N_0 \) covariate-outcome pairs from the control arm data among RAS wild-type patients in PRIME.
3. Fit the BART model to the hypothetical trial data and PRIME control data. Here, although the trial is restricted to RAS wild-type patients, PRIME control data of both RAS wild-type and RAS mutant patients are included in the model fitting, as BART can automatically adjust for covariates. Record whether the null hypothesis, \( H_0 : \Delta C \leq 0 \), is rejected based on \( \Pr(\Delta C > 0 | \text{data}) > 0.95 \).

The proportion of rejections is the estimated power. Figure 4 shows the power curve given by BART, where the power is maximized with a 1.5:1 allocation ratio. The power analysis provides valuable information for the investigator to determine the appropriate sample size and allocation ratio for the trial. For example, to target a power of 0.8, the investigator can plan to recruit 100 patients with a 1.5:1 allocation ratio. The unequal allocation also allows the investigator to collect more safety data on the new therapy.

For comparison, we also perform power calculations using BART− and Welch’s \( t \)-test. BART− fits BART models to the trial data but ignores PRIME control data. Welch’s \( t \)-test compares the mean tumor shrinkage between the treatment and control groups (PRIME control data are not included) and rejects \( H_0 \) if the one-sided \( P \)-value is less than 0.05. Figure 4 shows the power curves given by these methods. To achieve the same power, BART− and Welch’s \( t \)-test would require a larger sample size. For example, to target a power of 0.8, a sample size of 110 or 140 patients is needed using BART− or Welch’s \( t \)-test, respectively. In addition, BART− and Welch’s \( t \)-test would have a lower power if a 1.5:1 or 2:1 allocation ratio is used. Furthermore, BART− leads to a saving of 30 patients compared to Welch’s \( t \)-test, highlighting the potential of nonparametric methods even in the absence of external data. In general, the gain of BART borrowing can be attributed to (i) the inclusion of external data and (ii) the nonparametric modeling approach. In this application, the nonparametric modeling approach contributes to a large portion of the savings.

6 | DISCUSSION

We have explored the capacity of BART to incorporate external data into the analysis of clinical trials. BART adaptively pools information across data sources to improve the precision of treatment effect estimates. Simulation studies have
shown that the proposed BART method has desirable and robust performance without the need of strong parametric assumptions on the form of the response surface. Even when there are discrepancies between external and trial control data, BART borrowing does not lead to a severe inflation of type I error rate or reduction in power. We have considered continuous outcomes, but the BART package also supports binary and time-to-event outcomes, making it easy to extend the proposed method.

As an anonymous reviewer pointed out, the gain of external borrowing using BART seemed minor in the real applications we have presented. This is because BART (under the default prior setting) borrows information in a judicious manner. If desirable, one could impose stronger borrowing by tuning the prior hyperparameters of BART to achieve more substantial gains. However, it should be noted that stronger borrowing also increases the potential of bias and type I error rate inflation.

We have focused on the estimation of the average treatment effect defined over the sample or population of the current clinical trial. To generalize the results to the population at large or a particular target population (that is different from the trial population), additional assumptions are necessary. See, for example, Stuart et al\textsuperscript{53} for a discussion.

Other flexible regression methods, such as RF\textsuperscript{40} and Gaussian process regression (GPR),\textsuperscript{54} are also suitable for our application. However, we have chosen BART for its several attractive features outlined in Section 1. As shown in the simulation studies, a vanilla RF model performed worse than BART. Nevertheless, refinements of RF can be made to improve its performance and better estimate its variance; see, for example, Wager and Athey\textsuperscript{55} and Lu et al.\textsuperscript{39} On the other hand, GPR suffers from a cubic time complexity and finds it hard to handle a large number of covariates, while empirically we have found that BART is computationally efficient.

In our model specification (Equation 2), we have opted to fit separate models to the treatment and control data. An alternative approach is to fit a single model to both the treatment and control data, treating the treatment assignment as just another covariate (as in the VT method). The pros and cons of the two modeling strategies are worth further investigation. See, for example, Section 5 of Hahn et al\textsuperscript{56} for a discussion.

We have followed the default setting in Chipman et al\textsuperscript{24} for the BART model. An interesting future direction is to further tailor the BART model specifically for our application. For example, the default BART model assumes a uniform prior on the splitting variable assignment. An alternative prior can be specified to discourage (or encourage) selecting the data source indicator as a splitting variable, achieving stronger (or weaker) borrowing across data sources. We have included the data source indicator as a categorical covariate in the BART model (see Equation 2). An alternative model specification\textsuperscript{57} is

\[
[Y \mid T = 0, X = x, S = s] \sim N \left[ f_0(x) + h_0(x, s), \sigma_0^2 \right],
\]

where \( f_0(x) = \sum_{j=1}^{m_0} g(x; \tau_j, M_{0j}) \) is a sum-of-trees model, and \( h_0(x, s) \) is a parametric model, for example, \( h_0(x, s) = a_0s \) or \( h_0(x, s) = a_0 + x^\top \beta_0s \). By tuning the prior parameters for \( a_0s \) and \( \beta_0s \), one can also control the degree of borrowing across data sources. Finally, for simplicity, the error variance (\( \sigma_0^2 \)) has been assumed common across data sources, but this assumption may be relaxed.

ACKNOWLEDGEMENTS
We thank the editor, the associate editor, and two anonymous reviewers for their valuable comments. The simulation studies presented in Section 3 utilized the RMACC Summit supercomputer, which is supported by the National Science Foundation (awards ACI-1532235 and ACI-1532236), the University of Colorado Boulder, and Colorado State University. The RMACC Summit supercomputer is a joint effort of the University of Colorado Boulder and Colorado State University. The individual patient data from the colorectal cancer trial presented in Section 5 were derived from www.projectdatasphere.org, which is maintained by Project Data Sphere. Neither Project Data Sphere nor the owner(s) of any information from the website have contributed to, approved, or are in any way responsible for the contents of this analysis.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are openly available at https://dx.doi.org/10.1186/1745-6215-7-15 and https://doi.org/10.34949/1m76-9m69.

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**How to cite this article:** Zhou T, Ji Y. Incorporating external data into the analysis of clinical trials via Bayesian additive regression trees. *Statistics in Medicine*. 2021;40(28):6421-6442. doi: 10.1002/sim.9191