Personalized Plans with Multiple Treatments

Chathura Siriwardhana, Ph.D.

Department of Bioinformatics and Biostatistics, University of Louisville, Louisville, KY, USA

Meng Zhao

Javelin Marketing Group, Dallas, TX, USA

Somnath Datta, Ph.D.

Department of Biostatistics, University of Florida, Gainesville, FL, USA

K.B. Kulasekera, Ph.D.

Department of Bioinformatics and Biostatistics, University of Louisville, Louisville, KY, USA

Technical Report BST2017-01

Department of Bioinformatics and Biostatistics
School of Public Health and Information Science
University of Louisville
Louisville, KY, USA

Personalized Plans with Multiple Treatments

Chathura Siriwardhana, Meng Zhao, Somnath Datta and K.B. Kulasekera

Department of Bioinformatics and Biostatistics,

University of Louisville, Louisville, Kentucky 40202

Abstract

In this work we propose a method for treatment assignment based on individual covariate information for a patient. Our method covers more than two treatments and it can be applied with a broad set of models and it has very desirable large sample properties. An empirical study using simulations and a real data analysis show the applicability of the proposed procedure.

Key Words: Design variables; Personalized Treatments, Single Index Models

1. Introduction

Designing optimal treatment regimes based on individual patient characteristics has gained a momentum over the last few years (see for example van't Veer and Bernards, 2008; Varquez, 2013). Dynamic treatment regimes that are geared towards the "best" outcome for a patient based on his/her genetic and genomic markers are of high importance. Rather limited literature on this topic mainly deals with deciding between two

treatments based on patient characteristics. Assuming without any loss of generality that a larger outcome is better, the methods developed in the literature essentially determine the larger conditional expectation of the outcome given the set of markers for the patient. Qian and Murphy (2011) discuss a two step procedure that is based on an estimation of a conditional mean followed by a maximization of that mean over a set of possible treatments. Cai et al. (2011) use a smoothed sub-group mean in the comparison of two treatments. Here the subgroups are determined via a set of contours (scores) that define overall similarities among patients. For continuous responses, these scores have been defined via linear models. In a different approach for treatment assignments Zhao et al. (2012) consider an optimization technique to select between two treatments where the binary optimization procedure is within a class of pre-specified model functions. Drawing parallels to the support vector machine technology, these authors show decision optimality of the treatment selection procedure within the binary framework showing that the procedure discussed in Qian and Murphy (2011) is inferior to theirs in the two treatments case. In a more recent article, Zhang et al. (2012) use a robust conditional mean estimation method to alleviate possible wrong model postulation when one estimates the conditional mean for each patient's profile. Schulte et al. (2014) provide details of using Quality learning (Q-learning) and Advantage learning (A-learning) concepts in devising sequential rules based on a set of pre-specified decision points. The optimality of the decision algorithm, based on the conditional sequential mean, has been discussed by these authors. While mathematically and computationally tedious, it gives a sequential decision rule that self updates the changing patient behavior in switching to a different treatment. Additional references on dynamic treatment regimes can be found in Schulte et al. (2014). Treatment selection based on observational studies has been treated by many authors. Readers are referred to Robins et al. (2004, 2008) and references therein for additional details of such procedures.

In many treatment selection situations clinicians have more than two treatments to select from and the decision of assigning the treatment protocol based on individual

patient characteristics is highly desirable. In this work, we discuss the K treatment option ($K \geq 2$) scenario where we compare quantities that are suitable approximations to true conditional probabilities of outcome variable of each treatment dominating other treatments given patient specific scores constructed from covariates. In particular, instead of estimated marginal conditional expectations, we examine estimated conditional probability of each treatment dominating the others based on K independent pairs of outcomes and covariates, one for each treatment. We choose the optimal treatment as the one that has the highest estimated probability of dominating every one else for a given patient score. This allows one to compare treatments for a wide variety of distributions of outcome measures. As seen in our empirical investigations, the performance of this method is comparable to selection using conditional means when responses have finite means. In our approach, scores are defined via a set of Single Index Models (SIMs) or Partially Linear Single Index Models (PLSIMs) and our scoring system simplifies to the same type of scoring as in Cai et al. (2011) if $K = 2$. The method we propose is general where the above SIMs (PLSIMs) used to obtain scores can be quantile regression models rather than mean regression models, thus allowing a broad class of structures to get a suitable score. Empirical evaluations of this new mechanism using a detailed simulation study to assess the accuracy of treatment selection show that the proposed method is comparable with existing methodology in the two treatment option with linear models, it has a higher accuracy in the two treatment case with SIMs and performs very well in the multiple treatment case. Furthermore, we applied our method to an existing dataset with multiple treatment arms to examine the use of treatment assignment based on patient characteristics. The results show that one arm is highly preferred over the others for patients in this study with respect to the primary outcome variable which was a blood count. We also assessed possible gains or losses of patient survival had the patients were assigned according to the rule proposed here. Interestingly our study reveals that there could have been an advantage in terms of survival also to have used our selection method in the treatment assignment.

The remainder of the article is organized as follows. In Section 2, we discuss the proposed methodology. Section 3 includes simulation results followed by a real data illustration. The main body of the paper ends with a discussion in Section 4. Outlines of all proofs are deferred to an Appendix.

2. Treatment Selection

In this section we describe the proposed procedure and list some of its desirable large sample properties. Let $(Y_1^*, ..., Y_K^*)'$ be the hypothetical (counterfactual) responses and $\boldsymbol{X}$ be a vector of r covariates for a patient where larger values of the responses are indicative of better outcomes. Assume further that a patient's covariate value $\boldsymbol{X}$ is used to obtain a lower dimensional composite patient score $U(\boldsymbol{X})$. In practice one cannot observe the whole vector $(Y_1^*, ..., Y_K^*)'$ for a single patient. However, using iid observations of type $(\tilde{Y}_j, \boldsymbol{X}_j, A_j)$, $j = 1, ..., n$ where A_j is the binary treatment indicator for two treatments and $\tilde{Y}_j$ is the observed response for the jth patient, previous authors have proposed the estimated difference in conditional means given a score U to compare two treatments. For example, Zhang et al. (2012) use robust estimators of $E[Y_1^*|A = 0, U(\boldsymbol{X})] - E[Y_2^*|A = 1, U(\boldsymbol{X})]$ where $U(\boldsymbol{X}) = \boldsymbol{X}$ and $A = 0, 1$ assign treatments 1 and 2 respectively.

Here, because we cannot sample from the joint distribution of $(Y_1^*, ..., Y_K^*, \boldsymbol{X})'$, we consider pairs of random variables $(Y_i, \boldsymbol{X}_i)$ drawn from marginal distributions of $(Y_i^*, \boldsymbol{X}), i = 1, ..., K$ respectively, where the ith and lth pairs are independent for $i \neq l$. Then, in methods based on conditional means, one would use $E[Y_i|\boldsymbol{X}_i = \boldsymbol{x}]$ to select the best treatment. However, when $\boldsymbol{X}$ has very high dimension, a natural choice is to use a composite score $U(\boldsymbol{X})$ that has a much smaller dimension. Using such a score function U, in our approach, we extend the treatment selection for K treatments as follows. For

$(Y_i, \boldsymbol{X}_i)$, $i = 1, ..., K$ above, we define a set of probabilities

$$p_i(u) = P[Y_i > \max_{i \neq l} Y_l | U(\boldsymbol{X}_l) = u; l = 1, .., K]; i = 1, ..., K, \tag{1}$$

to select the best treatment. These p_is are considered to be surrogates for

$$p_i^*(u) = P[Y_i^* > \max_{i \neq l} Y_l^* | U(\boldsymbol{X}) = u]; i = 1, ..., K, \tag{2}$$

where, as defined above, $(Y_1^*, ..., Y_K^*)'$ is the vector of counterfactuals and $\boldsymbol{X}$ is the corresponding covariate vector for a patient. When one uses conditional mean as the selection tool, because $E[Y_i^* | \boldsymbol{X} = \boldsymbol{x}] = E[Y_i | \boldsymbol{X}_i = \boldsymbol{x}]$, observing from the marginal distribution of $(Y_i^*, \boldsymbol{X})$ results in the same selection criterion as if one were to observe from the joint distribution ofour data are from marginal distributions of $(Y_i^*, \boldsymbol{X}), i = 1, ..., K$. . This is not necessarily the case if the selection is based on a different parameter and when the data is from marginal distributions as in this formulation.

Because our data is of the form $(Y_i, \boldsymbol{X}), i = 1, ..., K$, we use the condition $U(\boldsymbol{X}_l) = u$, $l = 1, .., K$ in (1). This imposes the requirement of a same score u for possibly different covariate values associated with patients undergoing different treatments. If our data was of the form $(Y_1^*, ..., Y_K^*, \boldsymbol{X})$, then a requirement such as $U(\boldsymbol{X}) = u$ as in (2) would be appropriate. Although the function $p_i(u)$ does not use the joint distribution of $(Y_1^*, ..., Y_K^*, \boldsymbol{X})$ (from which we cannot sample), for a given score value u, we argue that $p_i(u)$ above nevertheless gives a measure of dominance for the ith treatment over the others and hence can be used in selecting the best treatment for a patient with that score. In Section 3, we show that our proposed procedure based on $p_i(u)$s has good performance against a selection based on estimated $p_i^*(u)$s using simulated counterfactual data that were generated using realistic assumptions.

What we propose is an alternative to measures based on conditional expectations which require restrictive moment assumptions on the error distribution for all inference

aspects in a regression context, the natural framework of handling such data. On the other hand, estimation of quantities like p_is can be done using conditional U-statistics with minimal assumptions. In our approach, for a given set of functions $p_1(.), ..., p_K(.)$, we define the best treatment for patients with a score U_0 as the treatment given by

$$k^*(U_0) = \arg \max_{1 \leq i \leq K} \{p_i(U_0)\}. \tag{3}$$

This procedure can be thought of as maximizing a value function that is the joint conditional expectation of an indicator of one treatment dominating the others given the score rather than evaluating $E[Y|U]$ for each treatment and picking the largest. For example, in Zhao et al. (2012), the best treatment was in principle defined as the index corresponding to the larger of $E[Y_1|U]$ and $E[Y_2|U]$ where Y_1 and Y_2 are the responses for each treatment. In practice, we propose to use estimators of $p_i(U_0)$ based on clinical data and then choose the best treatment as the one that is given by the corresponding estimator of $k^*(U_0)$. While it is impossible to gather counterfactual training data in real life, we can simulate such data and estimate $p_i^*(u)$s using those data and then select the best treatment as the one that maximizes estimated $p_i^*(u)$ for a given score u.

The above approach can be meaningfully used for any set of models that is appropriate for relating responses and covariates provided that those models define an ordering of the above p_is for at least one score so that one of the treatments stands out. If several treatments have the same largest p_i value for a given score, one may pick one of those at random. As observed below, one set of models that can provide such an ordering are Single Index Models (SIMs). In the sequel we base our discussions on Single Index Models for observations $(Y_i, \boldsymbol{X}_i)$ for the ith treatment via

$$Y_i = g_i\left(\boldsymbol{\beta}_i' \boldsymbol{X}_i\right) + \epsilon_i \tag{4}$$

for $i = 1, \ldots, K$ where each $\boldsymbol{\beta}_i$ is a r-vector of parameters, g_is are unknown link functions for which we assume some reasonable smoothness conditions to hold, and ϵ_i is an error

term with $E[\epsilon_i|\boldsymbol{X}_i] = 0$. This model can also be taken as a quantile regression model with suitable modifications.

One can actually show (proof not given here) that if the SIM above holds and if $g_i(\boldsymbol{\beta}_i'\boldsymbol{X}) > g_l(\boldsymbol{\beta}_l'\boldsymbol{X})$ for all $i \neq l$, then the corresponding $p_i(u) > p_l(u), i \neq l$ for the realization $U = u$ for our proposed score. Hence, using p_is to choose the best treatment is somewhat more general than using conditional expectations. Although the properties of the proposed approach discussed in the sequel are for mean SIMs, they all also hold for quantile SIMs models. Additionally, those properties extend to PLSIMs as the parameters of the linear part of PLSIMs can be estimated at a $\sqrt{n}$ rate (see for example Liang et al., 2010).

If the model relating Y_i to $\boldsymbol{X}_i$ is not a SIM, we can still implement the same mechanism of obtaining the scores via a single index model approximation to the mean or the median of the responses and then estimate the corresponding p_is. This can be thought of as using a first order Projection Pursuit Regression to model the responses. Since nonparametric estimation of p_is require minimal model assumptions, our approach is applicable for a very wide class of models. For notational simplicity, we only list properties of the procedure for conditions that are appropriate for mean SIMs . Modifications in these conditions needed for other models are minimal.

Our data are then of the following form. Let Y_{ij} indicate the jth responses from a group of n_i individuals under treatment i with covariate values $\boldsymbol{X}_{ij}, j = 1, \ldots, n_i$. The sample sizes n_i are assumed to satisfy the condition that n_i/N tends to a positive number where $N = \sum n_i$. Then, for this data, relationship (4) is written as

$$Y_{ij} = g_i(\boldsymbol{\beta}_i'\boldsymbol{X}_{ij}) + \epsilon_{ij}, j = 1, \ldots, n_i; i = 1, ..., K. \tag{5}$$

Our approach to define an appropriate overall score U is first to use a reasonable model to obtain a treatment specific score for each patient. The score for treatment i

measures how favorable it is for a patient to receive this treatment when compared to if he or she were to receive other treatments. To be specific, we first define

$$S_i(\boldsymbol{X}) = g_i(\boldsymbol{\beta}_i'\boldsymbol{X}) - \max_{k \neq i} \{g_k(\boldsymbol{\beta}_k'\boldsymbol{X})\}.$$

Next, we define the overall score to be the combination of the maximum of these treatment specific scores, and an index that indicates for which treatment the maximum has been achieved for the particular covariate value. That is, we define

$$\begin{aligned} S(\boldsymbol{X}) &= \max_i \{S_i\} \\ \delta(\boldsymbol{X}) &= \arg\max_i \{S_i\}. \end{aligned} \tag{6}$$

Then, for a patient with covariate value $\boldsymbol{X}$ we define the patient score as $U(\boldsymbol{X}) = (S(\boldsymbol{X}), \delta(\boldsymbol{X}))'$. Note that the score $U(\boldsymbol{X})$ reduces to the score used in the two treatment case by Cai et al. (2011) if we restrict gs to be linear. Also, if $K = 2$ and errors are symmetric about 0, δ becomes the index for the treatment with the larger location parameter for a given $\boldsymbol{X}$. However, when $K > 2$, this is not necessarily the case.

In practice one does not know the error distributions and model functions for models defined in (4) and therefore we cannot directly calculate p_is at a given score u. Thus, to apply the proposed selection method, we first need to estimate each p_i using a standard function estimation method. This requires observed Y_{ij} values as well as observed U values corresponding to those responses. However, Us defined above are hypothetical scores for a covariate value $\boldsymbol{X}$ as we do not know g_is and $\boldsymbol{\beta}_i$s. Hence, in estimating p_is, we propose to use "estimated" $U(\boldsymbol{X}_{ij})$ values , $\hat{U}(\boldsymbol{X}_{ij})$, say, corresponding to responses $Y_{ij}, j = 1, ..., n_i; i = 1, ..., K$.

Now, to obtain $\hat{U}(\boldsymbol{X}_{ij})$ values, suitable estimators of link functions g_is and index vectors $\boldsymbol{\beta}_i$s can be used to construct estimators $\hat{S}(\boldsymbol{X})$ and $\hat{\delta}(\boldsymbol{X})$ of $S(\boldsymbol{X})$ and $\delta(\boldsymbol{X})$, respectively. There is a vast literature on estimating the link function and the index

vector of a single index model (see, for example, Hristache et al., 2001, Yu and Ruppert, 2002 and references therein) allowing us to use one out of a several available reasonable estimation methods to estimate the gs and the $\boldsymbol{\beta}$s. We used the procedure given in Hristache et al. (2001) in our simulations and data analysis in the sequel. In the sequel these estimators will be generically denoted by $\hat{g}_i$ and $\hat{\boldsymbol{\beta}}_i$, respectively, for $i = 1, \ldots, K$. In particular, for any given vector $\boldsymbol{x}$, let

$$\begin{aligned}
\hat{S}_i(\boldsymbol{x}) &= \hat{g}_i\left(\hat{\boldsymbol{\beta}}_i'\boldsymbol{x}\right) - \max_{j\neq i}\left\{\hat{g}_j\left(\hat{\boldsymbol{\beta}}_j'\boldsymbol{x}\right)\right\} \\
\hat{S}\left(\boldsymbol{x}\right) &= \max_i\left\{\hat{S}_i(\boldsymbol{x})\right\} \\
\hat{\delta}\left(\boldsymbol{x}\right) &= \arg\max_i\left\{S_i(\boldsymbol{x})\right\} \\
&\quad \text{and} \\
\hat{U}(\boldsymbol{x}) &= \left(\hat{S}\left(\boldsymbol{x}\right), \hat{\delta}\left(\boldsymbol{x}\right)\right)' \qquad (7)
\end{aligned}$$

We randomly select an index $\hat{\delta}$ in the unlikely event that multiple treatments produce the same $\hat{S}$. Now, we construct our estimator for $p_i(u), i = 1, ..., K$ at a given $u = (s, d)'$ as follows. Define

$$\mathcal{J} = \left\{(j_1, \ldots, j_K)\,|j_i \in \{1, \ldots, n_i\}, i = 1, \ldots, K\right\}.$$

and, for $J \in \mathcal{J}$ we let

$$\hat{w}_J\left(s\right) = \prod_{i=1}^{K}\frac{1}{h_i}w\left(\frac{s - \hat{S}\left(\boldsymbol{X}_{ij_i}\right)}{h_i}\right)$$

where w is a kernel function with $w \geq 0$ and $\int w(t)dt = 1$, and h_is are a set of smoothing parameters. Also, let

$$\hat{\eta}_J\left(d\right) = \prod_{l=1}^{K} I\left(\hat{\delta}\left(\boldsymbol{X}_{lj_l}\right) = d\right).$$

Now, taking an approach similar to the construction of conditional U-statistics (Stute,

1991), an estimator of $p_i(u), i = 1, ..., K$ can be defined as

$$\hat{p}_i(u) = \frac{\sum_{J \in \mathcal{J}} I\left[Y_{ij_i} > \max_{k \neq i}\{Y_{kj_k}\}\right] \hat{w}_J(s)\, \hat{\eta}_J(d)}{\sum \hat{w}_J(s)\, \hat{\eta}_J(d)}. \tag{8}$$

For a realization $\boldsymbol{x}_0$ of the covariate $\boldsymbol{X}$, if we knew the corresponding realization of the score, $u_0 = (S(\boldsymbol{x}_0), \delta(\boldsymbol{x}_0))'$, we can estimate $p_i(u_0)$ by $\hat{p}_i(u_0)$. However, due to the aforementioned reasons, we can only find an estimate $\hat{u}_0$ of u_0 using (7) above. Thus, we use $\hat{p}_i(\hat{u}_0)$ as our estimate of $p_i(u_0)$ for $i = 1, ..., K$. Finally, the estimated best treatment for a patient with estimated score $\hat{u}_0$ is defined as

$$\hat{k^*} = \arg \max_{1 \leq i \leq K} \{\hat{p}_i(\hat{u}_0)\}. \tag{9}$$

Due to the complicated estimation structure it is very difficult to assess inferential properties of the estimator $\hat{k^*}$. However, under reasonable assumptions (not listed here but available from the authors) we can show that

$$\hat{p}_i(\hat{u}_0) \to p_i(u_0) \tag{10}$$

in probability for each i. Hence, if for some k^*, $p_{k^*}(u_0) > \max_{i \neq k^*}\{p_i(u_0)\}$, then the treatment selection procedure described above is consistent since the best treatment is defined as the treatment corresponding to the largest p_i and, given the property $\hat{p}_i(\hat{u}_0) \to p_i(u_0)$, our procedure selects the best treatment with probability tending to one. The ordering of the p_is depends on models that relate the responses and the covariates.

Bandwidth selection for estimating the link functions and p_is is a challenging issue. Method suggested in Wand and Jones (1995) seemed to perform reasonably well in our simulations and data analysis. However, these choices may not be optimal. We do not investigate the optimal bandwidth selection issue in this work.

3. Empirical Studies

In this section we present a detailed simulation study that investigates the properties of the proposed procedure in finite samples.

We conducted a series of simulations with the proposed procedure under various settings. Our primary focus is to compare accuracy of correct treatment selection using p_i against the correct selection using p_i^*, which is impossible to estimate in practice.

While we are unable to do it in real life, we can simulate counterfactual training data to estimate $p_i^*(u)$s and use those estimates to assess the correct assignment frequency for new (test) cases. In this case, the estimation of $p_i^*(u)$ is done using an estimator (see below) that captures and reflects the sampling scheme of obtaining counterfactual data.

We also generate separate training data in the form of K independent samples of size n from each marginal distribution of $(Y_i^*, \boldsymbol{X}), i = 1, ..., K$ to estimate $p_i(u)$s using (8) and then use the same test data to calculate the selection accuracy via the estimated p_is. Our goal is to illustrate that the accuracy of correct treatment selection using p_is does not drop off significantly from that of using p_i^*s in all simulated settings.

This simulation study was performed for both the two and multiple ($K > 2$) treatment groups cases. Results for the two groups cases were compared with the corresponding results for existing methods. However, such comparisons were not possible with multiple treatments since there is currently no other method covering more than two treatments. We select our model sets such that each model in a set dominates other competing models for some combination of covariate values; in other words, none of considered models fully dominate other models within the whole covariate space.

Although impossible to obtain counterfactual data in real life we can simulate them under reasonable assumptions. In this simulation study, we first generated samples from the joint distribution of $(Y_1^*, ..., Y_K^*)'$ in the following fashion. First for each $j = 1, ..., n$,

we generate the covariate $\boldsymbol{X}_j$. Then, we generate a multivariate random vector $\mathbf{e}_j^* = (e_{1j}^*, ..., e_{Kj}^*)'$ of size K with mean $(0, ..., 0)$ where the ilth entry of the covariance matrix is given by $\sigma^2\rho; i, l = 1, ..., K$, for a range of values σ and ρ. Now, the jth observation $(Y_{1j}^*, ..., Y_{Kj}^*)'$ is generated by $\mathbf{e}_j^* + (g_1(\boldsymbol{\beta}_1'\boldsymbol{X}_j), ..., g_K(\boldsymbol{\beta}_K'\boldsymbol{X}_j))'$. On the other hand, to mimic real data situations, for each $i = 1, ..., K$, we first generated n covariate values $\boldsymbol{X}_{ij}$, $j = 1, ..., n$. This was followed by generating n iid copies e_{ij} $j = 1, ..., n$ of a mean zero random variable e_i with a dispersion parameter σ to define $Y_{ij} = g_i(\boldsymbol{\beta}_i'\boldsymbol{X}_{ij}) + e_{ij}$ for $j = 1, ..., n$.

While we use the method described in Section 2 to estimate p_is, in estimating $p_i^*, i = 1, ..., K$ using observations $(Y_{1j}^*, ..., Y_{Kj}^*, \boldsymbol{X}_j)$, $j = 1, ..., n$, we use

$$\hat{p}_i^*(u) = \frac{\sum_{j=1}^n I[Y_{ij}^* \geq max_{k\neq j}\{Y_{kj}^*\}] w\Big(\frac{s-\hat{S}(\boldsymbol{X}_j)}{h_i}\Big) I[\hat{\delta}(\boldsymbol{X}_j) = d]}{\sum_{j=1}^n w\Big(\frac{s-\hat{S}(\boldsymbol{X}_j)}{h_i}\Big) I[\hat{\delta}(\boldsymbol{X}_j) = d]}; i = 1, ..., K$$

Here $\hat{S}(\boldsymbol{X}_j)$s are obtained from the same formulas as in (7) except that, for a given j, the covariate value $\boldsymbol{X}_j$ is coupled with Y_{ij}^* for every $i = 1, ..., K$, rather than using pairs $(Y_{ij}, \boldsymbol{X}_{ij})$ $j = 1, ..., n_i$; $i = 1, ..., K$ when estimating the link functions and associated index vectors.

Here we used a sample size n ($n = 50$ or $n = 100$). The components of the r dimensional covariate vectors $\boldsymbol{X}$ were generated independently from a $U(-1, 1)$ distribution, where r ranged from 3 to 8. Using various link functions and index vectors, where a selected few are listed in Tables 1-4, we obtained the treatment responses Y_{ij}^*s and Y_{ij}s above. Here the vector e^* was taken to follow a multivariate normal distribution using the R package MASS (Venables and Ripley, 2002) and multivariate double exponential distribution using the R package LaplacesDemon (Hall et al., 2106) while the errors e_{ij}s were generated from $N(0, \sigma^2)$ and $DE(0, \sigma)$ where the dispersion parameter σ was chosen from the set $\{0.1, 0.2, 0.3, 0.4, 0.5, 1.0\}$ and three values were used for ρ; $\rho = 0, 0.5, 0.9$. We have considered the performance under both linear and nonlinear regression models.

We discuss additional details of the structures of these models in the sequel.

Once samples were generated, we estimated the corresponding SIMs using the procedure given in Hristache et al. (2001) using Epanechnicov kernels (see Polzehl, 2013). Then, a new covariate value $\boldsymbol{X}_0$ was generated in the same manner as previous covariates above, and for its corresponding estimated score $\hat{u}_0$, we calculated both $\hat{p}_i^*(\hat{u}_0)$ and $\hat{p}_i(\hat{u}_0)$ for $i = 1, ..., K$. The kernel function in this estimation was taken to be a $U(-1, 1)$ probability density function (pdf). We chose the bandwidths by the algorithm given by Wand and Jones (1995) for each $i, i = 1, ..., K$. Then, corresponding to this $\boldsymbol{X}_0$, we generated a K dimensional random vector $(Y_1^*, ..., Y_K^*)'$ with equi-correlated (same ρ as above) components, where Y_i^* has mean $g_i(\boldsymbol{\beta}_i'\boldsymbol{X}_0)$ and variance σ^2 for $i = 1, ..., K$. We define the treatment assignment to be correct if

$$\arg\max_i\{\hat{p}_i^*(\hat{u}_0)\} = \arg\max_i\{Y_i^*\}.$$

in case of using the estimated p_i^* values and if

$$\arg\max_i\{\hat{p}_i(\hat{u}_0)\} = \arg\max_i\{Y_i^*\}.$$

if we are using independent pairs of observations, which will be the case in a real life situation.

We repeated this procedure 1000 times for several models for different sample sizes n. In the multiple treatment groups case ($K = 3$ and 4) we used a variety of models generated from several nonlinear model families. All considered cases produced results that are generally anticipated in a study of this nature. Our discussion in the sequel focuses on two model families

$$g_i\Big\{\pi k_i + \pi\big(\boldsymbol{\beta}'\boldsymbol{X}\big)\Big\} \quad i = 1, ..., K, \quad \text{(Type I)},$$

and

$$g_i\Big\{\pi k_i + \pi\big(\boldsymbol{\beta}_i'\boldsymbol{X}\big)\Big\} \;\; i = 1, ..., K, \qquad \text{(Type II)}.$$

In each type above, g_i is either a *sine* or a *cosine* function. In Type I models, the same single index vector $\boldsymbol{\beta}$ has been used for all treatment groups where the g_i function varies across the groups. In our simulations we chose this common vector to be $\boldsymbol{C'} = \big(1/\sqrt{r}, ..., 1/\sqrt{r}\big)_{1\times r}$ (see tables 2). In Type II models we used a variety of $\boldsymbol{\beta}_i$ index vectors whose components were selected in an arbitrary fashion. These components are given in Table 5. For example, in the three treatment case with $r = 3$, these vectors were $\boldsymbol{\beta}_1 = \big(1.5, 1.6, 0.9\big)'$, $\boldsymbol{\beta}_2 = \big(0.8, 0.6, 0.7\big)'$, and $\boldsymbol{\beta}_3 = \big(1.8, 2.1, 0.8\big)'$.

In the first few tables, Tables 1-3, we provide correct selection frequencies using estimated p_i^* values agianst the correct selection frequency using estimated p_is. While selction using estimated p_i^* values have higher correct selection frequiencies compared with those using estimated p_is, we notice that the drop off in selection accuracy when using $\hat{p}_i$ is not substantial in almost all examined cases. Given that, one cannot obtain data for estimating p_i^* in real life, we argue that the use of the measure p_i, which can be estimated using observations from marginal distributions of $(Y_i^*, \boldsymbol{X})$, is a reasonable technique to select the optimal treatment.

As observed from these tables, cases involving highly nonlinear curves with minor differences in mean functions performed somewhat poorly compared with cases where the nonlinearity is less severe or the differences between the signals is higher. If several models are close to each other within the whole covariate domain, a high classification error (i.e., incorrect treatment assignment) can be expected due to the lack of separation between model functions. In general, the behavior of a multi covariate nonlinear model cannot be easily visualized. Type-I models used here have relatively substantial differences in their mean functions compared to some Type II models for each K. Tables 2

and 3 show the correct assignment frequencies for a representative set of multi-groups cases. Again, the results for all examined cases were very similar to the few presented here.

Examination of the results reveal high assignment accuracy for large sample sizes and low error variability. In general, we observed fairly high accuracies for low covariate dimensions. The presented simulation results are based on *sine* and *cosine* functions which are bounded in (-1, 1). Hence, an increment in σ by 0.1 adds a relatively large noise to a model. Consequently, as expected, we observed a decline in the correct assignment frequency as σ is increased. The results for the three groups case for both Type I and II models are somewhat comparable whereas the results for Type II models for four groups case were lower compared to those corresponding to Type I models. As indicated in the previous paragraph, we believe these differences are due to relative lack of separation in the model functions.

Since we are only going to be able to use estimated p_is in practice, in the case of two groups, we compared the selection accuracy using $\hat{p}_i$ with corresponding correct selection frequencies for the two groups assignment methods proposed by Cai et al. (2011), Zhang et al. (2012), and Zhao et al. (2012). We chose to compare only with these three methods because these methods highly differ in their approaches and also dominate all other existing methods available in the literature for the two groups case. In Table 4 we report the number of cases in which the selection by each of the above three competing methods for the two groups case (using the highest conditional mean) matched with the group with the largest response. Here, we highlighted the settings in which those methods underperformed against our method (using $\hat{p}_i$) by an asterisk sign. Out of 48 examined cases, the method based on $\hat{p}_i$ competed well with the existing methods in 40 cases. Clearly, our method has a high accuracy in nonlinear models compared to the three existing treatment selection methods for two groups. In the case of linear models, which is represented by Model 1 in Table 4, the new method performed

Models (regression functions)	σ	n	$\hat{p}(u)$	$\hat{p}^*(u)$		
				$\rho = 0$	$\rho = 0.5$	$\rho = 0.9$
(1) $(1.5X_1 - 0.1X_2 + 2X_3 + 2X_4 - 1.5X_5 - 1.6X_6)/\sqrt{15.07}$: Group 1 $(2X_1 + 1.6X_2 + 2.2X_3 + 3.5X_4 + 1.2X_5 + 1.5X_6)/\sqrt{27.34}$: Group 2	0.1	50	864	915	933	975
		100	891	922	938	980
	0.2	50	794	834	886	957
		100	825	845	902	954
(2) $\sin\{\pi(X_1 - 0.3X_2 - X_3)/\sqrt{2.09}\}$: Group 1 $\sin\{\pi/4 + \pi(X_1 + X_2 + X_3)/\sqrt{3}\}$: Group 2	0.1	50	900	920	936	951
		100	891	924	940	963
	0.2	50	860	883	887	928
		100	853	891	906	933
(3) $\sin\{\pi(0.8X_1 + 1.1X_2 + 0.9X_3 + X_4 + 0.9X_5 + 1.1X_6)/\sqrt{5.68}\}$: Group 1 $\sin\{\pi/2 + \pi(1.8X_1 - 1.3X_2 + 0.8X_3 + X_4 - 1.2X_5 - X_6)/\sqrt{9.01}\}$: Group 2	0.1	50	880	912	911	922
		100	911	925	930	960
	0.2	50	839	864	884	896
		100	868	856	908	943
(4) $\sin\{\pi(X_1 + X_2 + X_3)/\sqrt{3}\} + X_1^2$: Group 1 $\sin\{\pi/2 + \pi(X_1 + X_2 + X_3)/\sqrt{3}\} + 0.7X_1^2$: Group 2	0.1	50	920	940	934	950
		100	935	951	958	961
	0.2	50	908	898	910	941
		100	924	915	933	945

Table 1: Frequencies of correct treatment assignments in 1000 test cases using estimated $p(u)$ and $p^*(u)$ with Normally distributed errors. Here $p^*(u)$ is estimated for different values of ρ.

comparably to the best method. Model 4 in Table 4 was chosen to demonstrate the robustness of the proposed method, where the requirement of SIM's is violated. Even in these cases, the accuracy remained fairly high, showing that the proposed method is rather robust. Reassuring the robustness property, we observed similar results for a more complex treatment selection scenario, using another set of perturbed SIM models. We provide this result in Supplementary Table 4.

We provide additional simulation results for treatment selection with the proposed procedure in the supplementary material. Since our simulations indicate that that the performance of treatment selection using $\hat{p}_i(u)$'s is competitive with the use of $\hat{p}_i^*(u)$'s, which are based on hypothetical counterfactual data, these additional studies were conducted using $\hat{p}_i(u)$'s only. Supplementary Tables 1 and 2 provide details.

4. ACTG-175 HIV Clinical Trial

In this section we illustrate our proposed method using a real clinical trial dataset. Obviously, in this situation we have samples from marginal distributions of pairs $(Y_i^*, \boldsymbol{X})$

Models (regression functions)	Dimension r	σ	n	Normal Error				D.E. Error			
				$\hat{p}(u)$	$\hat{p}^*(u)$			$\hat{p}(u)$	$\hat{p}^*(u)$		
					$\rho=0$	$\rho=0.5$	$\rho=0.9$		$\rho=0$	$\rho=0.5$	$\rho=0.9$
$\sin\Big\{\pi(\boldsymbol{C'X})\Big\}$: Group 1 $\cos\Big\{\frac{\pi}{6}+\pi(\boldsymbol{C'X})\Big\}$: Group 2 $\sin\Big\{\frac{7\pi}{5}+\pi(\boldsymbol{C'X})\Big\}$: Group 3	3	0.1	50	937	961	968	979	929	959	971	980
			100	946	960	973	990	936	959	971	987
		0.3	50	868	904	948	857	892	913	940	804
			100	891	910	957	866	894	931	955	846
		0.5	50	733	782	835	896	649	798	816	896
			100	766	814	859	930	720	834	863	925
	5	0.1	50	934	953	946	966	922	957	960	972
			100	973	954	970	986	949	966	975	984
		0.3	50	861	891	923	843	883	906	928	818
			100	871	918	957	916	882	932	965	843
		0.5	50	761	780	831	874	682	756	840	877
			100	796	801	869	931	728	799	857	944
	8	0.1	50	897	912	914	932	883	912	914	929
			100	962	970	975	982	950	961	957	985
		0.3	50	823	855	859	816	828	840	864	726
			100	881	905	966	875	879	924	953	839
		0.5	50	707	700	722	765	563	691	713	748
			100	784	806	854	919	739	781	859	916
$\sin\Big\{\pi(\boldsymbol{C'X})\Big\}$: Group 1 $\sin\Big\{\frac{\pi}{2}+\pi(\boldsymbol{C'X})\Big\}$: Group 2 $\sin\Big\{\frac{-\pi}{2}+\pi(\boldsymbol{C'X})\Big\}$: Group 3 $\sin\Big\{\pi+\pi(\boldsymbol{C'X})\Big\}$: Group 4	3	0.1	50	904	919	943	973	890	924	943	964
			100	939	931	957	979	909	942	969	975
		0.3	50	810	868	903	799	827	859	908	699
			100	841	868	920	822	847	880	924	773
		0.5	50	653	656	746	831	529	653	723	838
			100	714	690	778	874	625	729	777	877
	5	0.1	50	895	931	953	957	878	934	933	954
			100	946	929	954	971	910	936	959	967
		0.3	50	808	839	899	775	808	812	883	699
			100	842	876	923	827	836	870	927	752
		0.5	50	640	633	733	835	518	654	736	784
			100	687	663	755	884	608	751	789	872
	8	0.1	50	853	881	900	918	836	906	894	920
			100	926	938	949	966	903	945	950	967
		0.3	50	708	747	808	720	746	774	802	644
			100	829	889	901	809	827	863	910	717
		0.5	50	549	509	593	665	438	563	587	681
			100	689	674	742	857	577	729	785	843

Table 2: Frequencies of correct treatment assignments in 1000 test cases using estimated $p(u)$ and $p^*(u)$, for Type I nonlinear regression models, with $\boldsymbol{C'} = \big(1/\sqrt{r}, ...1/\sqrt{r}\big)_{1\times r}$. Here $p^*(u)$ is estimated for different values of ρ.

Models (regression functions)	Dimension r	σ	n	Normal Error				D.E. Error			
				$\hat{p}(u)$	$\hat{p}^*(u)$			$\hat{p}(u)$	$\hat{p}^*(u)$		
					$\rho=0$	$\rho=0.5$	$\rho=0.9$		$\rho=0$	$\rho=0.5$	$\rho=0.9$
$\sin\left\{\frac{\pi}{\|\beta_1\|}(\boldsymbol{\beta}_1'\boldsymbol{X})\right\}$: Group 1 $\cos\left\{\frac{\pi}{6}+\frac{\pi}{\|\beta_2\|}(\boldsymbol{\beta}_2'\boldsymbol{X})\right\}$: Group 2 $\sin\left\{\frac{7\pi}{5}+\frac{\pi}{\|\beta_3\|}(\boldsymbol{\beta}_3'\boldsymbol{X})\right\}$: Group 3	3	0.1	50	956	957	964	981	924	956	970	981
			100	970	967	956	978	948	968	970	988
		0.3	50	878	874	897	950	818	887	912	957
			100	896	881	898	956	844	917	910	957
		0.5	50	766	806	827	894	688	779	854	894
			100	796	790	860	927	737	833	862	931
	5	0.1	50	930	944	957	957	926	938	940	964
			100	947	959	977	974	942	957	976	980
		0.3	50	865	855	887	933	802	874	908	935
			100	897	877	920	950	838	897	934	964
		0.5	50	762	761	818	854	694	763	834	881
			100	802	802	870	919	741	834	864	922
	8	0.1	50	889	885	913	919	862	914	910	921
			100	947	963	970	968	942	961	967	977
		0.3	50	801	805	830	860	736	801	827	872
			100	881	863	892	940	812	880	921	942
		0.5	50	649	668	709	756	537	685	715	750
			100	791	804	843	881	724	772	843	889
$\sin\left\{\frac{\pi}{\|\beta_1\|}(\boldsymbol{\beta}_1'\boldsymbol{X})\right\}$: Group 1 $\cos\left\{\frac{\pi}{8}+\frac{\pi}{\|\beta_2\|}(\boldsymbol{\beta}_2'\boldsymbol{X})\right\}$: Group 2 $\cos\left\{\frac{-\pi}{6}+\frac{\pi}{\|\beta_3\|}(\boldsymbol{\beta}_3'\boldsymbol{X})\right\}$: Group 3 $\sin\left\{\pi+\frac{\pi}{\|\beta_4\|}(\boldsymbol{\beta}_4'\boldsymbol{X})\right\}$: Group 4	3	0.1	50	830	866	889	909	772	863	909	917
			100	884	893	881	939	819	903	908	950
		0.3	50	652	699	761	816	602	737	765	816
			100	738	753	773	842	673	776	818	881
		0.5	50	562	586	625	700	464	589	641	717
			100	616	615	690	785	513	639	705	809
	5	0.1	50	727	806	836	840	731	827	846	856
			100	822	881	872	901	791	872	891	894
		0.3	50	595	659	687	753	558	691	681	771
			100	697	692	758	837	645	727	750	828
		0.5	50	508	559	594	641	410	558	593	656
			100	557	566	647	781	508	639	660	753
	8	0.1	50	725	775	787	772	685	729	774	784
			100	823	865	888	899	802	864	870	901
		0.3	50	586	559	577	688	486	610	634	677
			100	657	679	734	805	599	697	740	818
		0.5	50	447	467	481	553	381	478	506	551
			100	549	554	646	709	490	580	667	715

Table 3: Frequencies of correct treatment assignments in 1000 test cases using estimated $p(u)$ and $p^*(u)$, for Type II nonlinear regression models. Table 5 provides $\boldsymbol{\beta}$ vectors used in this case. Here $p^*(u)$ is estimated for different values of ρ.

Models(regression function)	σ	n	Proposed Method	Cai's Method	Zhao's Method	Zhang's Method
(1) $(1.5X_1 - 0.1X_2 + 2X_3 + 2X_4 - 1.5X_5 - 1.6X_6)/\sqrt{15.07}$: Group 1 $(2X_1 + 1.6X_2 + 2.2X_3 + 3.5X_4 + 1.2X_5 + 1.5X_6)/\sqrt{27.34}$: Group 2	0.1	50	864	889	800*	899
		100	891	906	856*	902
	0.2	50	794	817	773*	801
		100	825	840	821*	844
(2) $\sin\{\pi(X_1 - 0.3X_2 - X_3)/\sqrt{2.09}\}$: Group 1 $\sin\{\pi/4 + \pi(X_1 + X_2 + X_3)/\sqrt{3}\}$: Group 2	0.1	50	900	683*	676*	683*
		100	891	722*	698*	728*
	0.2	50	860	670*	691*	693*
		100	853	708*	683*	718*
(3) $\sin\{\pi(0.8X_1 + 1.1X_2 + 0.9X_3 + X_4 + 0.9X_5 + 1.1X_6)/\sqrt{5.68}\}$: Group 1 $\sin\{\pi/2 + \pi(1.8X_1 - 1.3X_2 + 0.8X_3 + X_4 - 1.2X_5 - X_6)/\sqrt{9.01}\}$: Group 2	0.1	50	880	605*	633*	678*
		100	911	680*	671*	700*
	0.2	50	839	606*	603*	672*
		100	868	672*	652*	664*
(4) $\sin\{\pi(X_1 + X_2 + X_3)/\sqrt{3}\} + X_1^2$: Group 1 $\sin\{\pi/2 + \pi(X_1 + X_2 + X_3)/\sqrt{3}\} + 0.7X_1^2$: Group 2	0.1	50	920	743*	694*	804*
		100	935	794*	764*	842*
	0.2	50	908	741*	703*	796*
		100	924	774*	740*	834*

Table 4: Frequencies of correct treatment assignments in 1000 test cases by four competing algorithms in the two groups case with Normally distributed errors. Cases where the proposed method (ours) outperformed a competing method is denoted by *.

for multiple groups, $i = 1, ..., K$. Hence our analysis is based on estimated p_is

The data resulted from the ACTG 175 clinical trial (Hammer et al. 1996). This trial was a randomized, double-blinded, placebo-controlled clinical trial that was conducted for comparing antiviral medications for HIV-1 patients whose T-cell CD4 counts were in the range of 200 to 500 per cubic millimeter. The dataset (Juraska et al. 2012) contains information on 2136 HIV-1 infected individuals who were randomized into four treatment arms; those treated with Zidovudine (arm-0), combination of Zidovudine and Didanosine (arm-1), combination of Zidovudine and Zalcitabine (arm-2), Didanosine (arm-3). Arms 0, 1, 2, and 3 contain 532, 519, 524, and 561 patients, respectively. The severity of HIV progression is measured through a decline in CD4 counts. This trial periodically measured a patient's CD4 count as the clinical outcome. In our analysis, we considered the log transformed CD4 count of a patient after 20 weeks of treatment as the clinical response. As covariates, we used log-CD4 and log-CD8 counts at baseline, age, weight, and the number of months a patient received pre-antiviral therapy.

We applied the proposed treatment assignment strategy to the data from all four arms

Treatment groups	Group	Number of covariates	β_1	β_2	β_3	β_4	β_5	β_6	β_7	β_8
Three	1	3	1.5	1.6	0.9					
		5	1.5	1.6	0.9	1.2	1.4			
		8	1.5	1.6	0.9	1.2	1.4	-1.5	1.2	1.6
	2	3	1.0	1.4	0.8					
		5	1.0	1.4	0.8	0.8	0.6			
		8	1.0	1.4	0.8	0.8	0.6	-1.1	0.8	0.6
	3	3	1.3	1.7	0.7					
		5	1.3	1.7	0.7	0.9	1.1			
		8	1.3	1.7	0.7	0.9	1.1	-1.3	-0.1	0.9
Four	1	3	0.8	0.6	0.7					
		5	0.8	0.6	0.7	0.5	0.6			
		8	0.8	0.6	0.7	0.5	0.6	0.8	0.7	0.5
	2	3	1.2	1.4	0.9					
		5	1.2	1.4	0.9	1.5	0.9			
		8	1.2	1.4	0.9	1.5	0.9	1.1	1.4	1.2
	3	3	0.2	0.3	0.8					
		5	0.2	0.3	0.8	0.6	0.3			
		8	0.2	0.3	0.8	0.6	0.3	0.1	0.4	0.6
	4	3	1.8	2.1	0.8					
		5	1.8	2.1	0.8	0.7	0.9			
		8	1.8	2.1	0.8	0.7	0.9	1.3	1	1.3

Table 5: $\boldsymbol{\beta}$ vectors for Type II models, for model dimensions (r) 3, 5, and 8.

of the study. We also provide an illustration to compare with several existing two-treatment methods, . In each situation, we randomly selected 200 patients from each arm as "training" data to estimate the SIMs. Remaining patients were considered as new (test) patients. After fitting SIMs to training data we estimated the scores for the test cases and estimated the corresponding p_i functions using Gaussian kernels at corresponding scores to assign each test patient to the best treatment suggested by the largest estimated p_i value.

We report the results for the two group comparisons first. When we used the proposed method, out of 651 test patients, only 3 were assigned to arm-0, suggesting that possibly a large number of patients would have experienced a more favorable outcome from arm-1. We also applied the two-group assignment methods proposed by Cai et al. (2011), Zhao et al. (2012), and Zhang et al. (2012), for the same training and test data. These methods also assigned lesser number of patients to arm 0, than the actual

assignment by the randomized trial. We present these results in Table 6. For example, in Table 6, the (1, 0) cell for the Proposed Method indicates that only 2 out of 319 patients who were actually treated in arm-1 would have been assigned to arm-0 had we used the proposed method.

Orginal Assignment	New Assignment							
	Proposed Method		Cai's Method		Zhao's Method		Zhang's Method	
	Arm-0	Arm-1	Arm-0	Arm-1	Arm-0	Arm-1	Arm-0	Arm-1
Arm-0	1	331	13	319	0	332	28	304
Arm-1	2	317	11	308	0	319	25	294
Total	3	648	24	627	0	651	53	598

Table 6: Two groups treatment assignment summary for ACTG-175 trial by four methods.

In the multiple treatments assignment setting, we have a total of 1336 patients in the test set. Among them, we assigned the majority: 828 to arm-1 whereas 306 and 186 patients are assigned to arms 2 and 3, respectively. Similar to the two group assignment, the new method assigns only few patients to arm-0, seemingly suggesting that one of the other arms almost always dominate arm 0 with respect to our scoring mechanism. These results are summarized in Table 7. We noticed that, a large number of patients (1023) are proposed to be assigned to a different treatment arm than their actual assignment. Based on these allocations, it appears that the majority of patients in the study would have benefited from arm 1.

4.1 Examination of the survival aspect

The proposed treatment selection method above is an attempt to assign patients to receive the optimal outcome based on their score. Given that the above analysis shows that the optimal assignments based on patient characteristics are different from actual assignments towards a higher CD4 count, it might be the case that such an assignment

Original Assignment	Proposed Assignment			
	Arm-0	Arm-1	Arm-2	Arm-3
Arm-0	2	211	70	49
Arm-1	2	193	77	47
Arm-2	5	201	73	45
Arm-3	5	223	88	45
Total	14	828	308	186

Table 7: Four groups treatment assignment summary for ACTG-175 clinical trial by the proposed method.

rule could also improve the expected value of the related survival time conditional on the score. To explore whether such an implication might hold, we proceed as follows.

In the dataset, there are three types of events: (i) when an individual's CD4 count drops less than 50% of his/her pretreatment count, (ii) an event indicating progression to AIDS, (iii) death. Thus, the term "survival time" would denote an event time in the above sense. In addition, there was right censoring present in the data. Now, consider the i th subject in the test set with covariate value $\boldsymbol{X}_i$ who is assigned to a particular arm by an assignment mechanism. Suppose the individuals estimated score is $\hat{u}_i = \left\{\hat{S}(\boldsymbol{X}_i), \hat{\delta}(\boldsymbol{X}_i)\right\}$. Let k_i^* be the group the procedure would assign this patient based on his/her estimated score $\hat{u}_i$ and let k_i be the treatment group he was assigned in the original trial. Conditional on $\hat{u}$, we estimated the difference in the survival times in the two groups, as

$$\Delta_i = E(t_{k_i^*}|\hat{u}_i) - E(t_{k_i}|\hat{u}_i).$$

We obtain a suitable estimate $\hat{\Delta}_i$ for Δ_i using the following method. For a fixed k, we consider a symmetric neighborhood of width $2h$ centered around $\hat{S}(\boldsymbol{X_i})$,

$$N_h = \left\{\hat{S}(\boldsymbol{X}_i) - h, \hat{S}(\boldsymbol{X}_i) + h\right\},$$

where h was the bandwidth chosen by the procedure given in Wand and Jones (1995) for scores for all patients. Next, we selected a subgroup of patients from the whole set

(training and test), whose covariate values $\boldsymbol{X}$ satisfy (i) patient was originally treated in arm k and (ii) $\hat{S}(\boldsymbol{X}) \in N_h$ and (iii) the score satisfies $\hat{\delta}(\boldsymbol{X}) = \hat{\delta}(\boldsymbol{X_i})$. If the size (d, say) of the above subgroup is less than 30, we increased the width of the neighborhood N_h in multiples of h (i.e., $3h$, $4h$ etc.) to make $d \geq 30$. After that the Kaplan Meier estimator was calculated using the survival times of those individuals in N_h.

Our estimator of the expected survival time for each group, i.e., $E(t_{k_i}|\hat{u}_i)$, $k_i = 1, ..., K$, was the area covered under the corresponding Kaplan-Meier curve. For a given $\hat{u}_i$, we then find the estimated survival gain $\hat{\Delta}_i$ from the proposed selection as the difference between the two estimated expectations, $\hat{E}(t_{k_i^*}|\hat{u}_i) - \hat{E}(t_{k_i}|\hat{u}_i)$. Finally we estimate the overall treatment selection efficiency as the averaged $\hat{\Delta}_i$s for all test patients,

$$\phi = \frac{1}{N} \sum_{i=1}^{N} \hat{\Delta}_i, \tag{11}$$

where N is the number in the test set. Note that a positive value for ϕ indicates an overall effective treatment selection. Table 8 gives these ϕ values for the proposed procedure with two and multiple treatments cases along with the resulting estimated survival gains for methods proposed by Cai et al. (2011), Zhao et al. (2012), and Zhang et al. (2012), for the two-groups application.

	Two Groups Assignments				Four Groups Assignments by Proposed Method
	Proposed Method	Cai's Method	Zhao's Method	Zhang's Method	
ϕ	76.1	73.0	77.2	66.0	56.3
ϕ_m	62.5	58.5	63.1	53.0	32.2

Table 8: Obseved ϕ and ϕ_m by four treatment selection methods under different treatment possibilities.

Additionally, we consider the marginal survival functions and define,

$$\Delta_i^{'} = E(t_{k_i^*}) - E(t_{k_i}),$$

where $E(t_{k_i^*})$ and $E(t_{k_i})$ are corresponding marginal expected survival times of new (k_i^*) and actual (k_i) arms. Again using the area under the marginal Kaplan Meier estimates, we calculate estimated values of $\Delta_i^{'}$, $i = 1, ..., N$. Similar to (11), we obtain ϕ_m using these marginal estimates. Corresponding ϕ_m's are also reported in Table 8. Since the proposed treatment selection is based on a scoring scheme, we argue that examining the score dependent survival outcome would be a more reliable approach. This is confirmed by the fact $\phi_m \leq \phi$ in all cases.

5. Discussion

In this article we proposed a novel personalized treatment plan to select the optimal treatment from a set of multiple treatments. This method is a single step procedure which can be easily applied. The proposed method is based on semi parametric Single Index Models which, add great flexibility in modeling real life situations. Furthermore, this method can also be used for quantile regression SIMs providing additional model flexibility compared with existing methods based on conditional expectations. Our empirical studies show that the proposed method based on an attainable sampling scheme performs very satisfactorily in selecting the optimal treatment in a multiple treatment setting compared with a selection concept that is based on a sampling scheme that one would desire yet unachievable . Also, our proposed method outperforms existing methods for the two treatment case for more practically realistic non-linear models and our simulations showed that the method is rather robust against departures from SIMs. Our analysis of a real clinical trials dataset which has the multiple treatment option reveals a possible connection between optimal treatment selection and a gain in patient survival.

This article deals with complete responses. However, censoring is very common in practice. An extension of the proposed methodology to a covariate dependent censoring setting and various lifetime aspects such as multi state models is forthcoming. Our

study is addressing the optimal treatment selection based on a single response. However, there are numerous circumstances where the optimality is desired with respect to multiple criteria. For example, a treatment may have to be selected to maximize the survival rates but minimize after effects and maximize the quality of life in terms of temporary side effects. In such cases we have a multi criteria optimization problem. This opens up another interesting future research avenue.

Bibliography

1. Cai, T., Tian, L., Wong, P. H., and Wei, L. J. (2011),"Analysis of Randomized Comparative Clinical Trial Data for Personalized Treatment Selections", *Biostatistics*, pp. 270-282.

2. Hall, B., Hall, M., Statisticat, L. L. C., Brown, E., Hermanson, R., Charpentier, E., and Singmann, H. (2016), "LaplacesDemon: a complete environment for Bayesian inference within R, R package version 16.0.1.

3. Hammer, S. M., Katzenstein, D. A., Hughes, M. D., Gundacker, H., Schooley, R. T., Haubrich, R. H., Henry, W. K., Lederman, M. M., Phair J. P., Niu M., Hirsch M. S., and Merigan T. C. (1996), "A Trial Comparing Nucleoside Monotherapy with Combination Therapy in HIV-Infected Adults with CD4 Cell Counts from 200 to 500 per Cubic Millimeter", *New England Journal of Medicine*, pp. 1081-1090.

4. Hristache, M., Juditsky, A., Polzehl, J., and Spokoiny, V. (2001), "Structure Adaptive Approach for Dimension Reduction", *The Annals of Statistics*. pp. 1537-1566.

5. Juraska, M., Gilbert, P. B., Lu, X., Zhang, M., Davidian, M., and Tsiatis, A. A. (2012), "speff2trial: Semiparametric Efficient Estimation for a Two-Sample Treatment Effect". R package version 1.0.4.

6. Liang, H., Liu, X., Li, R., amd Tsai, C-H. (2010), "Estimation and Testing for Partially Linear Single Index Models", *Annals of Statistics*, pp. 3811-3836.

7. Polzehl, J. (2013),"EDR: Estimation of the effective dimension reduction (EDR) space", R package version 0.6-5.1.

8. Qian, M., and Murphy, S. A. (2011), "Performance Guarantees for Individualized Treatment Rules." *The Annals of Statistics*, pp. 1180-1210.

9. Schulte, P.J., Tsiatis, A.A., Laber, E.B., and Davidian, M. (2014), "Q- and A-learning Methods for Estimating Optimal Dynamic Treatment Regimes", *Statistical Science*, To Appear.

10. Robins, J. (2004), "Optimal structured nested models for optimal sequential decisions", In: Lin DY, Heagerty PJ, editors. *Proceedings of the Second Seattle Symposium on Biostatistics. New York: Springer*, pp. 189-326.

11. Robins, J., Orellana, L., and Rotnitzky, A. (2008), "Estimation and extrapolation of optimal treatment and testing strategies", *Statist. Med.*, pp. 4678-4721

12. Stute, W. (1991), "Conditional U-Statistics", *Annals of Probability*, pp. 812-825.

13. van't Veer, L.J. and Bernards, R. (2008), "Enabling Personalized Cancer Medicine Through Analysis of Gene-Expression Patterns", *Nature*, Apr 3;452(7187), pp. 564-70.

14. Vazquez, A. (2013), "Optimization of Personalized Therapies for Anticancer Treatment", *BMC Systems Biology*, pp. 7-31

15. Venables, W. N., Ripley, B. D. (2002) Modern Applied Statistics with S. Fourth Edition. Springer, New York.

16. Wand, M. P. and Jones, M. C. (1995), "Kernel Smoothing", *Chapman and Hall*, London.

17. Wang, L. and Yang, L. (2009), "Spline Estimation of Single Index Models", *Statistica Sinica*, 19, pp 765-783

18. Yu, Y. and Ruppert, D. (2002), "Penalized Spline Estimation for Partially Linear Single-Index Models", *Journal of the American Statistical Association*, pp. 1042-1054.

19. Zhang, B., Tsiatis A. A., Laber, E. B., and Davidian, M. (2012), "A Robust Method for Estimating Optimal Treatment Regimes", *Biometrics*, pp. 1010-1018.

20. Zhao, Y., Donglin, Z., Rush, A. J., and Kosorok, M. K. (2012), "Estimating Individualized Treatment Rules Using Outcome Weighted Learning", *Journal of the American Statistical Association*, pp. 1106-1118.